Efficacy and safety of preoperative 5-fluorouracil, cisplatin, and mitomycin C in combination with radiotherapy in patients with resectable and borderline resectable pancreatic cancer: a long-term follow-up study

Yutaka Endo 1, Minoru Kitago 1*, Koichi Aiura 2, Masahiro Shinoda 1, Hiroshi Yagi 1, Yuta Abe 1, Go Oshima 1, Shutaro Hori 1, Yutaka Nakano 1, Osamu Itano 2, Junichi Fukada 4, Yohei Masugi 5 and Yuko Kitagawa 1

Abstract

Background: We aimed to evaluate the efficacy and safety of 5-fluorouracil-based neoadjuvant chemoradiotherapy (NACRT) in patients with resectable/borderline resectable pancreatic ductal adenocarcinoma (PDAC).

Methods: This retrospective study investigated the clinicopathological features and > 5-year survival of patients with T3/T4 PDAC who underwent NACRT at our institute between 2003 and 2012.

Results: Seventeen resectable and eight borderline resectable patients were included. The protocol treatment completion and resection rates were 92.0% and 68.0%, respectively. Two patients failed to complete chemotherapy owing to cholangitis or anorexia. Common grade 3 toxicities included anorexia (12%), neutropenia (4%), thrombocytopenia (4%), anemia (4%), and leukopenia (12%). Pathologically negative margins were achieved in 94.1% of patients who underwent pancreatectomy. Pathological response according to Evans’ classification was grade IIA in 10 patients (58.8%), IIB in 5 patients (29.4%), and IV in 2 patients (11.8%). Postoperative pancreatic fistulas were observed in four patients (23.5%), delayed gastric emptying in one patient (5.9%), and other operative morbidities in four patients (23.5%). The 1-, 2-, 5-, and 10-year overall survival rates were 73.9%, 60.9%, 60.9%, and 39.1%, respectively (median follow-up period, 80.3 months).

Conclusions: NACRT is tolerable and beneficial for resectable/borderline resectable PDAC, even in the long-term.

Keywords: Chemoradiotherapy, Follow-up studies, Neoadjuvant therapy, Pancreatic carcinoma

Introduction

Pancreatic cancer, especially pancreatic ductal adenocarcinoma (PDAC), is a devastating disease that is associated with poor prognosis and low resectability rates (15.0–20.0%) [1]. When possible, surgical resection is the only curative treatment available. However, approximately 80.0% of patients experience recurrence after a short time interval, with a median survival of approximately 20 months [2]. Because of the minimal survival benefit of surgery alone, adjuvant and neoadjuvant treatment strategies for PDAC are being actively investigated. There have been several reports regarding the efficacy of adjuvant therapies for resected pancreatic cancer [3, 4]. However, the ideal neoadjuvant treatment protocol and its significance for prognosis remain unclear [5].

One rationale for using neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (NACRT) is to achieve negative resection margins (R0) because survival rates are poor in patients with positive resection margins (R1/R2). Another reason is its more effective delivery, compared to...
adjuvant chemotherapy, without potential delays caused by surgical complications. The proposed benefits of chemotherapy in pancreatic cancer are local disease control and improved rates of complete resection [6–8]. Katz et al. [9] reported that preoperative chemoradiotherapy was associated with a median survival of 40 months in resected patients. However, the overall survival (OS) benefits of NACRT remain unclear.

We have administered NACRT using 5-fluorouracil (5-FU), cisplatin, and mitomycin C in combination with radiotherapy since the early 2000s. The rationale for our regimen was that there were several reports concerning the anti-tumor effect of mitomycin C and cisplatin in the combination of 5-FU [10, 11]. However, there have been no reports concerning the long-term effects of NACRT for PDAC. Therefore, we aimed to evaluate the short-term safety and long-term efficacy of NACRT for potentially resectable PDAC in a long-term follow-up study.

Methods
Twenty-five patients who underwent NACRT and subsequent surgery at Keio University Hospital (Tokyo, Japan) between May 2003 and August 2012 were retrospectively analyzed to evaluate the efficacy and safety of NACRT. NACRT was selectively administered to a limited number of patients with T3/T4 PDAC according to the Tumor-Node-Metastasis classification, seventh edition, who agreed with this treatment. In addition, selected patients had a performance status of 0–1, were 20–80 years of age, and had adequate organ function (defined by no abnormal laboratory findings for chemotherapy). Prior to NACRT and surgery, all patients underwent staging investigations to examine evidence of distant metastasis by contrast-enhanced computed tomography (CT) or magnetic resonance imaging. Preoperative cytologic confirmation was not mandatory if the patients’ lesions were highly suspected to be pancreatic cancer. PET scan and laparoscopy were not used for staging. We conducted a retrospective observational study and used the “opt-out” method as a way to obtain informed consent from patients. The study was approved by the Human Experimentation Committee of our institution (no. 20120279).

The NACRT regimen consisted of a combination of 4 cycles of chemotherapy (continuous administration of 5-FU; cisplatin on day 5, 12, 19, and 26; mitomycin C on day 6, 13, 20, and 27; and heparin infusion) and radiotherapy (planned total dose, 40.0 Gy of external beam radiation therapy [40.0 Gy per 20 fractions]). After completing NACRT, patients underwent restaging CT to determine resectability. Approximately 1–2 weeks after completing NACRT, patients without evidence of disease progression and who were medically fit were taken into the operating room for subsequent curative surgery. All adverse events experienced during the study were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Radiological responses in patients who underwent NACRT were evaluated by CT using the Response Evaluation Criteria in Solid Tumors [12].

Surgery, which included pylorus-preserving or subtotal stomach-preserving pancreatoduodenectomy or distal pancreatectomy accompanied by extensive lymphatic and connective tissue clearance in combination with or without postoperative liver perfusion chemotherapy and adjuvant chemotherapy, was performed as described previously [13]. The postoperative morbidity rate included all complications following surgery (classified according to the Clavien-Dindo classification [14]) up to the day of discharge. A postoperative pancreatic fistula (POPF) was defined according to the criteria of the International Study Group on Pancreatic Fistula [15], and delayed gastric emptying was defined according to the criteria of the International Study Group of Pancreatic Surgery [16]. A POPF of grade B/C was considered a clinically significant complication.

Pathological responses in patients who underwent NACRT were evaluated based on the proportion of residual viable tumor cells according to the classification proposed by Evans et al. [17]. Pathological data obtained also included the Tumor-Node-Metastasis classification, the surgical margin status, the presence or absence of microscopic lymphovascular and perineural invasion, the tumor differentiation, and the presence or absence of major vascular invasion. The surgical margin represented either the pancreatic or bile duct stump or the dissected plane around the pancreas. If viable microscopic cancer cells were detected at the edge of these sites, the surgical margin status was considered positive [18, 19].

After surgical resection of the PDAC, each patient received the standard postoperative follow-up. Recurrence was defined by definitive evidence of recurrence, which was confirmed with radiographic findings, with or without elevated serum cancer antigen 19-9 levels. Physical examinations, toxicity assessments, complete blood cell counts, serum chemistry profiles, and chest-abdominal CT scans were performed approximately every 4–6 months for the first 12 months and every 6 months thereafter.

Statistical analyses
Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. OS was defined as the time interval between the date of commencing preoperative therapy and the date of death from any cause or last follow-up. For patients who underwent surgical resection, recurrence-free survival was defined as the time interval between the date of surgery and the date of first recurrence (local, distant, or
both) or death, whichever occurred first. All statistical analyses were conducted using JMP 12 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

Table 1 summarizes the patients’ clinical characteristics before the commencement of NACRT. Twenty-five patients with potentially resectable (n = 17) or borderline resectable (n = 8) pancreatic cancer were investigated. The eight borderline resectable patients included six patients with portal vein invasion and two patients with arterial abutment.

Treatment responses

The radiological responses to NACRT are shown in Fig. 1. The waterfall plot of the maximum percentage change of the primary site from baseline during NACRT identified 16 patients (16/25, 64.0%) with stable disease, 5 patients (5/25, 20.0%) with partial response, and 4 patients (4/25, 16.0%) with progressive disease. Four patients with progressive disease, who developed liver metastases that were detected during preoperative assessment with multidetector CT and surgery, did not undergo resection. Two patients with macroscopic peritoneal dissemination during surgery did not undergo resection. One patient with local disease progression underwent gastrojejunal bypass surgery. One patient with reduced performance status did not undergo resection.

Of the 17 patients (17/25, 68.0%) who underwent tumor resection, 13 (13/17, 76.4%) patients underwent pancreatoduodenectomy and 4 (4/17, 23.5%) patients underwent distal pancreatectomy. None of the patients underwent total pancreatectomy. Portal vascular resection was performed in four patients (4/17, 23.5%). None of the patients underwent hepatic or celiac artery resection. The median operative time for pancreatoduodenectomy was 678 (range, 372–1032) min, with a median estimated blood loss of 785.0 (range, 120.0–2390.0) mL. The median operative time for distal pancreatectomy was 437 (range, 387–648) min, with a median estimated blood loss of 217.5 (range, 100.0–1210.0) mL.

Toxicity and complications during NACRT and subsequent surgery

NACRT-related toxicities are summarized in Table 2. During NACRT, there was no NACRT-related mortality. Grade 3 neutropenia, leukopenia, anemia, thrombocytopenia, and anorexia occurred in zero, three, one, zero, and two patients, respectively. The protocol treatment completion and resection rates were 92.0% (23/25) and 68.0% (17/25), respectively (Table 1). Two patients failed to complete chemotherapy owing to cholangitis (1/25, 4.0%) or anorexia (1/25, 4.0%). All patients received the planned dose of radiotherapy. Among the 17 patients who underwent resection, clinically significant POPFs were observed in 4 patients (4/17, 23.5%), delayed gastric emptying was observed in 1 patient (1/17, 5.9%), and other operative morbidities (Clavien-Dindo grade IIIa or higher) were observed in 4 patients (4/17, 23.5%). None of the patients required further surgery. Furthermore, 8 of the patients who underwent resection (8/17, 47.0%) received portal vein infusion for 4 weeks immediately after surgery, 2 (2/17, 11.8%) patients received adjuvant chemotherapy (5-FU, etc.), and 5 (5/17, 29.4%) patients received both.

Pathological findings of NACRT

The pathological findings in the 17 patients who underwent resection are summarized in Table 3. Pathological evaluation revealed that all patients had PDAC. Five patients had node-positive disease, and two patients had portal vein invasion. None of the patients had major arterial invasion. Pathological response according to Evans’ classification was grade IIA in 10 patients (10/17, 58.8%), IIB in 5 patients (5/17, 29.4%), and IV in 2 patients (2/17, 11.8%).

Table 1 Patients’ characteristics

| Characteristic           | Patients (n = 25) |
|-------------------------|------------------|
| Age (years), median (range) | 66 (51–80)       |
| Tumor size (mm), median (range) | 28 (12–40)       |
| Sex, n (%)              |                  |
| Male                    | 16 (64.0)        |
| Female                  | 9 (36.0)         |
| Primary tumor location, n (%) |              |
| Head/neck               | 18 (72.0)        |
| Body                    | 6 (24.0)         |
| Tail                    | 1 (4.0)          |
| NCCN resectability, n (%) |                 |
| Resectable              | 17 (68.0)        |
| Borderline resectable    | 8 (32.0)         |
| BR-PV                   | 6 (24.0)         |
| BR-A                    | 2 (8.0)          |
| Completion of NACRT, n (%) | 23 (92.0)        |
| Completion of RT, n (%)  | 25 (100.0)       |
| Completion of CT, n (%)  | 23 (92.0)        |
| Resection rate, n (%)    | 17 (68.0)        |
| Reason for protocol failure, n (%) |           |
| Cholangitis             | 1 (4.0)          |
| Neutropenia             | 1 (4.0)          |

Abbreviations: CT chemotherapy, NACRT neoadjuvant chemoradiotherapy, NCCN National Comprehensive Cancer Network, BR-PV borderline resectable-portal vein, BR-A borderline resectable-artery, RT radiotherapy.
Survival analyses

The 1-, 2-, 5-, and 10-year OS rates for all patients combined were 73.9%, 60.9%, 60.9%, and 39.1%, respectively, with a median follow-up period of 80.3 (range, 2.6–145.0) months. The 1-, 2-, 5-, and 10-year survival rates for the resected cases were 82.3%, 76.5%, 76.5%, and 49.2%, respectively, for OS and 64.7%, 58.8%, 52.9%, and 19.6%, respectively, for recurrence-free survival (Fig. 2a–b). Recurrence was noted in 10 (52.9%) of the 17 patients who underwent resection. Patterns of recurrence included distant metastasis in seven patients (70.0%), local recurrence in two patients (20.0%), and remnant pancreatic cancer in one patient (10.0%). Ten patients (10/25, 40.0%) survived for ≥5 years; four patients (4/25, 16.0%) survived for >5 years without any signs of recurrence.

Discussion

This study is the first to evaluate the short-term safety and long-term efficacy of NACRT using 5-FU, cisplatin, and mitomycin C in combination with radiotherapy for 5 years or more. We observed a relatively high survival rate after subsequent surgery with low toxicity. The overall toxicity profile of this regimen was fully acceptable without any grade 4 toxicities. However, the incidence of postoperative complications, especially POPF grade B/C (4/17, 23.5%), was relatively high compared to that of previous reports [20, 21], which demonstrated an 11–17% rate of POPF. There is one potential explanation for this finding. Compared to the early 2000s when the operation in this analysis was performed, there has been notable progress in the pancreatic anastomosis procedure and in both intra- and postoperative management.

Table 2 Toxicity profiles

| Toxicity                  | Grade (CTCAE v4.0) | 1 | 2 | 3 | 4 | All | G3 |
|---------------------------|--------------------|---|---|---|---|-----|----|
| Hematological             |                    |   |   |   |   |     |    |
| Leukopenia                |                    | 1 | 12| 3 | 0 | 16  | 3  |
| Neutropenia               |                    | 0 | 2 | 0 | 2 | 0   | 0  |
| Anemia                    |                    | 4 | 2 | 1 | 0 | 7   | 1  |
| Thrombocytopenia          |                    | 0 | 1 | 0 | 0 | 1   | 0  |
| Non-hematological         |                    |   |   |   |   |     |    |
| Elevated creatinine       |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Elevated AST/ALT          |                    | 2 | 0 | 0 | 0 | 2   | 0  |
| Hyperbilirubinemia        |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Hyponatremia              |                    | 2 | 0 | 0 | 0 | 2   | 0  |
| Alopecia                  |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Anorexia                  |                    | 3 | 2 | 2 | 0 | 7   | 2  |
| Constipation              |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Diarrhea                  |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Edema                     |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Fever                     |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Nausea                    |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Rash                      |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Stomatitis                |                    | 0 | 0 | 0 | 0 | 0   | 0  |
| Vomiting                  |                    | 0 | 0 | 0 | 0 | 0   | 0  |

Abbreviations: AST aspartate aminotransferase, ALT alanine aminotransferase, CTCAE Common Terminology Criteria for Adverse Events, G grade, v version
These recent advances may account for the discrepancy between the POPF rate in our study and those of our recent surgical results.

Since we had followed the patients analyzed in this study for > 5 years, we were able to calculate actual 5-year survival rates. In the present study, 10 patients (10/25, 40.0%) survived for ≥ 5 years and 4 patients (4/25, 16.0%) survived for > 5 years without any signs of recurrence. Compared to previous studies [23–25], the actual 5-year survival rates in our study seemed to be favorable.

Table 3 Pathological characteristics

| Characteristic                        | Patients (n = 17) |
|---------------------------------------|-------------------|
| Histology (PDAC), n (%)               | 17 (100.0)        |
| T stage, n (%)                        |                   |
| T0                                    | 0 (0.0)           |
| Tis                                   | 0 (0.0)           |
| T1                                    | 4 (23.5)          |
| T2                                    | 1 (5.9)           |
| T3                                    | 12 (70.6)         |
| N stage, n (%)                        |                   |
| N0                                    | 12 (70.6)         |
| N1                                    | 5 (29.4)          |
| TNM stage, n (%)                      |                   |
| 0                                     | 0 (0.0)           |
| IA                                    | 3 (17.6)          |
| IB                                    | 1 (5.9)           |
| IIA                                   | 8 (47.1)          |
| IIb                                   | 5 (29.4)          |
| Negative microscopic resection margins, n (%) |        |
| R0                                    | 16 (94.1)         |
| R1                                    | 1 (5.9)           |
| Differentiation, n (%)                |                   |
| Well-moderate                         | 6 (35.3)          |
| Moderate-poor                         | 10 (58.8)         |
| Other                                 | 1 (5.9)           |
| Portal vein invasion status, n (%)    | 2 (11.8)          |
| Microscopic lymphovascular invasion, n (%) | 8 (47.1)       |
| Microscopic perineural invasion, n (%) | 5 (29.4)          |
| Evans’ classification, n (%)          |                   |
| I                                     | 0 (0.0)           |
| II A                                  | 10 (58.8)         |
| II B                                  | 5 (29.4)          |
| III                                   | 0 (0.0)           |
| IV                                    | 2 (11.8)          |

Abbreviations: PDAC pancreatic ductal adenocarcinoma, TNM tumor-node-metastasis

Endo et al. World Journal of Surgical Oncology (2019) 17:145 Page 5 of 8
metastatic disease. However, considering this transition in radiographic modality, there is still room for improvement in our NACRT regimen. Recent studies [38, 39] have demonstrated that more active combinations, such as FOLFIRINOX (leucovorin, 5-FU, irinotecan, and oxaliplatin) or gemcitabine and nab-paclitaxel, have strong anti-tumor effects. Therefore, these may be candidates for improving preoperative therapy and resection rates.

This study has several limitations. First, the study was retrospective in nature and had a single-center design; therefore, the results lacked external validity. Second, the number of enrolled patients was limited. Third, there is a possibility that our analyzed patients had indolent diseases, and therefore, our relatively favorable survival rate might be affected by selection bias. Therefore, this study was not designed to prove the survival benefit of NACRT. Further, multicenter studies with proper patient selection and larger sample sizes are warranted to achieve a robust conclusion.

In conclusion, preoperative administration of 5-FU, cisplatin, and mitomycin C in combination with radiotherapy is well tolerated and safe. This is the first study to evaluate the efficacy and safety of NACRT using 5-FU, cisplatin, mitomycin C, and heparin in combination with radiotherapy in the long-term. Our protocol achieved a relatively high survival rate after subsequent surgery.

Fig. 2 Kaplan-Meier curves of (a) overall survival in patients receiving neoadjuvant chemoradiotherapy and (b) recurrence-free survival in patients who underwent surgical resection.
Abbreviations
NACRT: Neoadjuvant chemoradiotherapy; PDAC: Pancreatic ductal adenocarcinoma; POPF: Postoperative pancreatic fistula

Acknowledgements
We would like to thank Editage (https://www.editage.com/) for the English language editing.

Authors’ contributions
YE, MK, and KA participated in the research design. YE, MK, MS, HY, YA, GO, SH, YN, JF, and YM participated in the data curation. YE participated in the writing of the paper. YE and MK participated in the performance of the research. YE contributed the analytic tools. YE participated in the data analysis. MK, KA, OL, and YK participated in the review of the paper. YK supervised the research. All authors read and approved the final manuscript.

Funding
There is no funding for this work.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
We conducted a retrospective observational study and used the “opt-out” method as a way to obtain informed consent from patients. The study was approved by the Human Experimentation Committee of our institution (no. 201102279).

Consent for publication
We have obtained the consent for publication from all patients.

Competing interests
Yuko Kitagawa received a designated donation from Kyowa Hakko Kirin Co., Ltd., Otuska Pharmaceutical Co., Ltd. and Yakult Honsha Co., Ltd. His institution has an endowed chair from Yakult Honsha Co., Ltd. The other authors declare that they have no competing interests.

Author details
1Department of Surgery, Keio University School of Medicine, Tokyo, Japan. 2Department of Surgery, Kawasaki City Hospital, Kanagawa, Japan. 3Department of Gastrointestinal Surgery, International University of Health and Welfare, Chiba, Japan. 4Department of Radiology, Keio University School of Medicine, Tokyo, Japan. 5Department of Pathology, Keio University School of Medicine, Tokyo, Japan.

Received: 14 April 2019 Accepted: 6 August 2019

Published online: 16 August 2019

References
1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89.
2. Egawa S, Toma H, Ohigashi H, et al. Japan Pancreatic Cancer Registry; 30th year anniversary. Japan Pancreas Society. Pancreas. 2012;41(7):985-92.
3. Oettle H, Neuhaus P, Hochhaus A, Hartmann J, Gellert K, Riedwliki K, Niedergesthmann M, Zulke C, Fachle J, Aming MB et al. Adjuvant chemotherapy with gemcitabine and long-term outcome among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(1):42-49.
4. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kano T, Shimizu Y, Nakamoto S, Sakamoto H et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2013;388(10041):2247-58.
5. Verna V, Li J, Lin C. Neoadjuvant Therapy for Pancreatic Cancer: Systematic Review of Postoperative Morbidity, Mortality, and Complications. Ann J Clin Oncol. 2016;39(3):302-13.
6. Varadharajah GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Abdalla E, Wang H, Staerkel GA et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(21):3487-95.
7. Ohigashi H, Ishikawa O, Eguchi H, Takahashi H, Gotoh K, Yamada T, Yano M, Nakazumi A, Uehara H, Tomita Y et al. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg. 2009;250(1):88-95.
8. Liu W, Fu XL, Yang JY, Liu DJ, Li J, Zhang JF, Hsu YM, Yang MW, Hua R, Sun YW. Efficacy of Neo-Adjuvant Chemoradiotherapy for Resectable Pancreatic Adenocarcinoma: A PRISMA-Compliant Meta-Analysis and Systematic Review. Medicine (Baltimore). 2016;95(15):e3009.
9. Katz MH, Wang H, Balachandran A, Bhsale P, Crane CH, Wang X, Pisters PW, Lee JE, Vauthey JN, Abdalla EK et al: Effect of neoadjuvant chemoradiation and surgical technique on recurrence of localized pancreatic cancer. J Gastrointest Surg. 2012;16(6):1688-78.
10. Takada T, Armano H, Yassuda H, Nimura Y, Matsuhiro T, Kato H, Nakagawa T, Nakayama T, Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas. The P. Biliary T. Is postoperative adjuvant chemotherapy useful for gallbladder cancer? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002;95(8):1685-95.
11. Krousge T, Kuchi T, Maki K, Kakize T, Japanese Study Group of Adjuvant Therapy for Pancreatic C. A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Jpn J Clin Oncol. 2006;36(3):159-65.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
13. Aiura K, Takahashi S, Matsui J, Ueda M, Kitagawa Y. Beneficial effects of 5-Fluorouracil and heparin-based portal infusion chemotherapy combined with mitomycin C and cisplatin after curative resection of pancreatic cancer. Pancreatology. 2010;10(2):250-8.
14. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6366 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
15. Bassi C, Marchegianni G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asburn HJ, Bessellink MG et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula. 11 Years After. Surgery. 2017;161(3):8-13.
16. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbricki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761-8.
17. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, Charnsangavej C, Fenoglio CJ, Ames FC. Preoperative chemoradiation and pancreatectoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127(11):1335–9.
18. Staley CA, Cleary KR, Abbruzzese JL, Lee JE, Ames FC, Fenoglio CJ, Evans DB. The need for standardized pathologic staging of pancreatectoduodenectomy specimens. Cancer. 1996;12(4):373-80.
19. Isai S. Revised 7th edition of the General Rules for the Study of Pancreatic Cancer by Japan Pancreas Society - revised concepts and updated points. Nihon Shokakibyo Gakkai Zasshi. 2017;117(4):617-26.
20. Cooper AB, Parmar AD, Riall TS, Hall BL, Katz MH, Aloia TA, Pitt HA. Does the use of neoadjuvant therapy for pancreatic adenocarcinoma increase postoperative morbidity and mortality rates? J Gastrointest Surg. 2015;19(1):2416-23.
21. Okano K, Suto H, Oshima M, Maeda E, Yamamoto N, Kakinoki K, Kamada H, Masaki T, Takahashi S, Shibata T et al: A Prospective Phase II Trial of Neoadjuvant S-1 with Concurrent Hypofractionated Radiotherapy in Patients with Resectable and Borderline Resectable Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol. 2017;24(9):2777-84.
22. Nahm CB, Connor SJ, Samra JS, Mittal A. Postoperative pancreatic fistula: a review of traditional and emerging concepts. Clin Exp Gastroenterol. 2018;11:105-18.
23. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinico-pathologic analysis of 5-year survivors. Ann Surg. 1996;223(3):273-9.
24. Katz MH, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, Varadharajah G, Abbruzzese JL, Crane CH, Krishnan S et al: Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol. 2009;16(4):836-47.
25. Kimura K, Amano R, Nakata B, Yamazoe S, Hirata K, Murata A, Miura K, Nishio K, Hirakawa T, Ohira M, et al. Clinical and pathological features of five-year survivors after pancreatectomy for pancreatic adenocarcinoma. World J Surg Oncol. 2014;12:360.

26. Fujii-Nishimura Y, Nishiyama R, Kitago M, Masugi Y, Ueno A, Alura K, Kawachi S, Kawai M, Abe Y, Shinoda M et al. Two Cases of Pathological Complete Response to Neoadjuvant Chemoradiation Therapy in Pancreatic Cancer. Keio J Med. 2015;64(2):26-31.

27. Chun YS, Cooper HS, Cohen SJ, et al. Significance of pathologic response to preoperative therapy in pancreatic cancer. Ann Surg Oncol. 2011;18(13):3601-7.

28. Christians KK, Heimler JW, George B, et al. Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy. Surgery. 2016;159(3):893-900.

29. Mellon EA, Strom TJ, Hoffe SE, et al. Favorable perioperative outcomes after resection of borderline resectable pancreatic cancer treated with neoadjuvant stereotactic radiation and chemotherapy compared with upfront pancreatectomy for resectable cancer. J Gastrointest Oncol. 2016;7(4):547-55.

30. Nakano Y, Kitago M, Shinoda M, et al. Clinical predictive factors of long-term survival after curative resection of pancreatic cancer: a retrospective study. Cancer Med. 2017;6(10):2278-86.

31. Kuderer NM, Ontel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. J Clin Oncol. 2009;27(29):4902-11.

32. Schorn S, Demir IE, Reyes CM, et al. The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma - A systematic review and meta-analysis. Cancer Treat Rev. 2017;55:96-106.

33. Pisters PW, Abbiruzzese JL, Janjan NA, et al. Rapid-fractionation preoperative chemoradiation, pancreatectoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. J Clin Oncol. 1998;16(12):3843-50.

34. Takai S, Sato S, Yanagimoto H, et al. Neoadjuvant chemoradiation in patients with potentially resectable pancreatic cancer. Pancreas. 2008;36(1):e26-32.

35. Turini O, Viert F, Moureau-Zabotto L, et al. Neoadjuvant 5 fluorouracil-cisplatin chemoradiation effect on survival in patients with resectable pancreatic head adenocarcinoma: a ten-year single institution experience. Oncology. 2009;76(6):413-9.

36. Papalezova KT, Tyler DS, Blazer DG, 3rd, et al. Does preoperative therapy optimize outcomes in patients with resectable pancreatic cancer? J Surg Oncol. 2012;106(1):111-8.

37. Motoi F, Ishida K, Fujishima F, et al. Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective multi-institutional phase 2 trial. Ann Surg Oncol. 2013;20(12):3794-801.

38. Conroy T, Gavoille C, Samalin E, Ychou M, Ducreux M. The role of the FOLFIRINOX regimen for advanced pancreatic cancer. Curr Oncol Rep. 2013;15(2):182-9.

39. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.