Randomized Controlled Trial

Results of a phase II study on the use of neoadjuvant chemotherapy (FOLFIRINOX or gemcitabine with nab-paclitaxel) for borderline-resectable pancreatic cancer (NUPAT-01).

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Disclosure: The authors declare that no conflicts of interest exist regarding this study.

Running title: Neoadjuvant FOLFIRINOX or GEM/nab-PTX

Mini-abstract

Although the development of multidrug chemotherapy regimens has improved the survival outcomes of patients with unresectable pancreatic cancer, the benefits of these treatments in the neoadjuvant setting remain controversial. The results of this study indicate that neoadjuvant chemotherapy with FOLFIRINOX or GEM/nab-PTX is feasible and well tolerated, achieving an R0 resection rate of 67.4%. The survival of patients was even found to be favorable in the intention-to-treat analysis.

Abstract

Objective: Given the frequent adverse events with multidrug chemotherapy, not only the survival benefit but also the feasibility of using neoadjuvant chemotherapy to treat pancreatic cancer need to be clarified.

***Summary background data*:** Although the development of multidrug chemotherapy regimens has improved the survival outcomes of patients with unresectable pancreatic cancer, the benefits of these treatments in the neoadjuvant setting remain controversial.

***Methods*:** Patients with borderline-resectable pancreatic cancer were enrolled and randomly assigned to receive neoadjuvant chemotherapy with either FOLFIRINOX or gemcitabine with nab-paclitaxel (GEM/nab-PTX). After the completion of chemotherapy, patients underwent surgical resection when feasible. This study (NUPAT-01) was a randomized phase II trial, and the primary endpoint was the R0 resection rate.

***Results*:** Fifty-one patients were enrolled in this study (FOLFIRINOX (n=26) and GEM/nab-PTX (n=25)). A total of 84.3% (n=43/51) of the patients eventually underwent surgery, and R0 resection was achieved in 67.4% (n=33/51) of the patients. Adverse events (grade >3) due to neoadjuvant treatment were observed in 45.1% of the patients (n=23/51), and major surgical complications occurred in 30.0% (n=13/43), with

no mortality noted. The intention-to-treat analysis showed that the 3-year overall survival rate was 54.7%, with a median survival time of 39.4 months, and a significant difference in overall survival was not observed between the FOLFIRINOX and GEM/nab-PTX groups.

***Conclusions*:** These results indicate that neoadjuvant chemotherapy with FOLFIRINOX or GEM/nab-PTX is feasible and well tolerated, achieving an R0 resection rate of 67.4%. The survival of patients was even found to be favorable in the intention-to-treat analysis.

Key Words: pancreatic cancer, borderline resectable, neoadjuvant chemotherapy, FOLFIRINOX, gemcitabine, nab-paclitaxel

INTRODUCTION

Pancreatic cancer is a lethal malignant disease and is expected to become the second leading cause of cancer-associated mortality within the next few decades (1). Surgical resection remains the only option for cure; however, the surgical outcomes of resection are not satisfactory due to frequent recurrence after potential curative resection (2, 3). Surgical resection followed by postoperative adjuvant chemotherapy is the current standard of care with definitive evidence of its benefit (4-7), whereas the role of neoadjuvant chemotherapy remains to be clarified. Recently, therapeutic strategies for unresectable pancreatic cancer have changed dramatically along with the advancement of multidrug chemotherapy, especially after the introduction of the FOLFIRINOX and gemcitabine with nab-paclitaxel (GEM/nab-PTX) regimens (8, 9). Since these chemotherapies have improved the survival of metastatic pancreatic cancer patients, evaluation of their benefit in a neoadjuvant setting is warranted, especially for patients with borderline-resectable pancreatic cancer (10, 11).

Although previous studies (11-17) have indicated the benefit of neoadjuvant chemotherapy for pancreatic cancer, most of these studies were retrospective in nature and analyzed only patients who underwent surgery. Patients who failed to proceed to surgery due to toxicity, disease progression, or the presence of metastatic or

unresectable disease at exploratory surgery were excluded from these studies; thus, high-quality evidence in support of neoadjuvant chemotherapy is still lacking. While recent randomized-controlled trials revealed the survival benefit of neoadjuvant chemotherapy for resectable pancreatic cancer (18, 19), chemotherapeutic regimens have changed, and there is no consensus on the optimal regimen to use in the neoadjuvant setting, especially for borderline-resectable pancreatic cancer. Since the approval of FOLFIRINOX and GEM/nab-PTX, general interest has focused on whether these treatments improve the survival of patients in a neoadjuvant setting; however, given that adverse events from these regimens are common, not only the survival benefit but also the feasibility of this regimens remain to be clarified. We therefore designed a randomized phase II trial to assess the clinical feasibility of FOLFIRINOX and GEM/nab-PTX for the treatment of borderline-resectable pancreatic cancer in a neoadjuvant setting. Patient outcomes were analyzed by intention-to-treat analysis to exclude selection bias and reveal the actual benefit of neoadjuvant chemotherapy.

METHODS

Study design

NUPAT-01 is an investigator-initiated, multicenter, nonblinded phase II trial investigating the outcomes, feasibility, possibility and safety of two neoadjuvant chemotherapy regimens for borderline-resectable pancreatic cancer. The study protocol was approved by the Ethics Committee of Nagoya University Graduate School of Medicine (approved number: 2015-0172) and registered in the University Hospital Medical Information Network (registration ID 000017718) and ClinicalTrials.gov (registration ID NCT02717091).

The diagnosis of borderline-resectable pancreatic cancer was made according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma, version 2.2015. Briefly, pancreatic head tumors in contact with the common hepatic artery (CHA), superior mesenteric artery (SMA) (<180°), or portal vein (PV)/superior mesenteric vein (SMV) (>180°) and pancreatic body/tail tumors in contact with the celiac artery (CA) (<180°) or PV/SMV (>180°) were regarded as borderline resectable. Inclusion criteria included (1) a diagnosis of borderline-resectable pancreatic cancer; (2) no distant metastasis; (3) age between 20 and 75; (4) Eastern Cooperative Oncology Group (ECOG) performance

status of 0 or 1; (5) no other treatment for the disease; (6) no other simultaneous malignancies; (7) no major organ failure as assessed by laboratory examination; and (8) agreement to participate in this trial after providing informed consent.

Patients were excluded from this trial if they had (1) a history of severe allergy; (2) active concomitant malignancies; (3) active infectious disease; (4) grade 2 or higher neuropathy; (5) received atanazavir sulfate or tegafur, gimeracil, oteracil potassium (S1); (6) gastrointestinal obstruction; (7) severe ascites or pleural effusion; (8) comorbidities such as severe diabetes, severe hypertension, liver cirrhosis, renal failure, recent history of cardiac infarction, and interstitial pneumonia; (9) pregnancy; (10) mental health issues that hindered their participation; (11) severe diarrhea; and (12) homozygosity for UGT1A1*28 (*28/*28), UGT1A1*6 (*6/*6) and heterozygosity for both UGT1A1*28 and *6 (*28/*6).

After enrollment, patients were randomly assigned (1:1) to either the FOLFIRINOX group or GEM/nab-PTX group through a computer-generated randomization system by controlling for the following measures: location of the tumor (pancreatic head or body/tail) and vascular invasion (PV/SMA or SMA/CHA/CA). The primary endpoint was the R0 resection rate, and the secondary endpoints were the chemotherapy completion rate, relative dose intensity, frequency of adverse events,

efficacy of chemotherapy (as determined by Response Evaluation Criteria in Solid Tumors; RESIST), changes in imaging studies, including the maximum standardized uptake value (SUV max) on positron-emission tomography (PET) images, major complications after surgery, disease-free survival and overall survival.

Administration of neoadjuvant therapy

The FOLFIRINOX regimen consisted of oxaliplatin at a dose of 85 mg/m^2 administered via a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 200 mg/m^2 administered via a 2-hour intravenous infusion, with the addition of irinotecan after 30 minutes at a dose of 180 mg/m^2 administered via a 90-minute intravenous infusion. This treatment was immediately followed by fluorouracil at a dose of 400 mg/m^2 administered by an intravenous bolus, followed by a continuous intravenous infusion at a dose of 2400 mg/m^2 over a 46-hour period. On day 4, pegfilgrastim (3.6 mg/body) were injected subcutaneously. The GEM/nab-PTX regimen consisted of a 30-minute intravenous infusion of nab-paclitaxel at a dose of 125 mg/m^2, followed by an infusion of gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15. Patients were treated with FOLFIRINOX every 2 weeks for a total of 4 cycles or

GEM/nab-PTX every 4 weeks for a total of 2 cycles, and surgery was performed 2 to 8 weeks after the last cycle of neoadjuvant chemotherapy.

Surgical procedures

Imaging examination was performed within 4 weeks after neoadjuvant chemotherapy, and subsequent surgical procedures were determined at the meeting of the attending hepatopancreatobiliary surgeons: in general, subtotal stomach preserved pancreatoduodenectomy (SSPPD) was indicated for pancreatic head tumors, distal pancreatectomy (DP) for pancreatic body/tail tumors, and total pancreatectomy (TP) for pancreatic body tumors if necessary. After exploration of the abdominal cavity, standard pancreatectomy with D2 lymph node dissection was conducted. Resection in combination with portal vein resection was conducted only when the portal vein adhered to and could not be detached from the tumor during the procedure. All operations were performed by an experimental surgical team at every institution, and operative procedures were performed in the same manner throughout the study period.

Postoperative adjuvant chemotherapy was performed if the patient's condition allowed. Generally, the patients received oral S-1 for 6 months (80 mg/m^2/day from days 1 to 14, followed by a one-week interval). For patients who relapsed, additional

chemotherapy such as FOLFIRINOX, GEM/nab-PTX, gemcitabine, or S-1 was administered according to the disease and patient's condition.

Statistical analysis

According to previous studies (11-13), calculation of the sample size for the current study was based on a threshold R0 ratio of 30% and an expected R0 ratio of 60% using an alpha error of 0.05 and beta error of 0.2. The planned sample size was 25 patients for both groups, allowing for five dropouts, with an enrollment period of 5 years followed by an additional follow-up period of 3 years.

Continuous variables were compared using the Mann-Whitney test, and categorical variables were analyzed using the chi-square test. Survival curves of the patients were generated by the Kaplan-Meier method, and differences in survival curves were compared using the Wilcoxon test. Univariate and multivariate analyses were performed to identify prognostic factors for survival using the Cox proportional hazards model. All statistical tests were 2-sided, and *P*-values < 0.050 were considered significant. All statistical analyses were performed using SPSS software (version 28, IBM Japan, Tokyo, Japan).

RESULTS

Primary and secondary endpoints

Patients

The CONSORT diagram is shown in Figure 1. Between October 2015 and January 2020, 51 patients from three departments were enrolled in this study and randomized, resulting in 26 patients in the FOLFIRINOX group and 25 patients in the GEM/nab-PTX group. Among them, 84.3% (n=43/51; FOLFIRINOX group (n=23) and GEM/nab-PTX group (n=20)) completed neoadjuvant chemotherapy and underwent surgical resection. The median follow-up period of all patients was 25.5 months (range 1 to 69.5 months). Eight patients who did not undergo surgical resection were also included, comprising patients with progressive disease during chemotherapy (n=2 and 1; FOLFIRINOX and GEM/nab-PTX, respectively), patients who abandoned chemotherapy due to severe adverse events (n=1 (grade 4 neutropenia) and 1 (abscess development in the tumor)), patients who withdrew from the study due to personal reasons (n=0 and 2), and a patient whose general condition deteriorated before the initiation of chemotherapy (n=0 and 1 (anaphylaxis of uncertain cause)) (Figure 1). The demographics of all patients in both groups are shown in Table 1A. No significant

difference in any characteristics, including age, sex ratio, CA19-9, and radiologic findings, was found between the two groups.

Neoadjuvant chemotherapy: outcome and toxicity

The outcomes of neoadjuvant chemotherapy are shown in Table 1B. R0 resection was achieved in 64.7% of the patients (n=33/51), including 19/26 (73.1%) patients in FOLFIRINOX and 14/25 (56.0%) patients in GEM/nab-PTX (*P*=0.202). The relative dose intensity was significantly higher in the FOLFIRINOX group than in the GEM/nab-PTX group (median values of 100% and 83.3%, respectively). Adverse grade 3 and higher events were significantly less frequent in the FOLFIRINOX group than in the GEM/nab-PTX group (median values of 30.4% and 70.0%, respectively). The most common adverse events were neutropenia (37.5%; n=18/48 (4 and 14 in FOLFIRINOX and GEM/nab-PTX group, respectively)), followed by thrombopenia (8.3%; n=4/48 (2 and 2)), nausea (8.3%; n=4/48 (4 and 0)), and diarrhea (4.2%; n=2/48 (2 and 0)). Other outcomes, including the radiological response, decrease in CA19-9, and SUV max, did not show significant differences between the two groups.

Survival

The overall survival rates after registration were 54.7% and 31.7% (3-year and 5-year survival, respectively), with a median survival time of 39.4 months (Figure 2A). Survival was compared between the two groups, and the results showed no significant difference between the FOLFIRINOX and GEM/nab-PTX groups, with 3-year survival rates of 55.3% and 54.4%, respectively (Figure 2B). In the univariate and multivariate analyses of prognostic factors for overall survival, sex (female) and resection status (R0 resection) were associated with good survival, whereas neoadjuvant chemotherapy, vascular invasion and tumor location were not statistically significant prognostic factors (Table 2).

Post hoc analysis

Next, the patients who completed neoadjuvant chemotherapy and underwent surgical resection were analyzed. Similar to the results of the intention-to-treat analysis, the characteristics of the patients were not significantly different between the two groups, except for the relative dose intensity and the ratio of adverse events (Supplemental Table 1). Regarding surgical characteristics and outcomes, no significant differences were found between the FOLFIRINOX and GEM/nab-PTX groups, including surgical procedure, operation time, blood loss, histologic type, Evans grade

(histologic grade of residual tumor), R status, recurrence rate and major complications (Table 3). Of note, pathological node-positive cases were found less frequently in the FOLFIRINOX group, but this difference was not significant (*P*=0.101). Major postoperative complications included pancreatic fistula (20.0%; n=6/43), delayed gastric emptying (4.7%; n=2/43), hepatic necrosis (4.7%; n=2/43), intra-abdominal bleeding (2.3%; n=1/43), intra-abdominal abscess (2.3%; n=1/43), enterocolitis due to clostridium difficile (2.3%; n=1/43), and chylorrhea (2.3%; n=1/43). Of note, a case of pathological complete remission (Evans grade 4) was found in both groups. R0 resection was achieved in 76.7% (n=33/43) of the surgically resected patients.

The overall survival rates were 58.7% and 36.6% (3-year and 5-year survival, respectively), with a median survival time of 38.6 months (Figure 3A). When comparing the two groups (Figure 3B, C), no significant difference in overall survival was found, but the FOLFIRINOX group had better disease-free survival (*P*=0.044). In the multivariable analysis of prognostic factors for overall survival (Supplemental Table 2), pathological node status and R status were associated with survival, whereas in the univariate analysis, the Evans grade was associated with prognosis. On the other hand, sex, neoadjuvant chemotherapy regimen, vascular invasion, tumor location, RECIST,

surgical procedure, portal vein resection, blood loss, and postoperative adjuvant chemotherapy were not found to be prognostic factors.

Discussion

In this study, we evaluated the outcomes of neoadjuvant chemotherapy by performing a randomized phase II trial. The procedure, which included both chemotherapy and surgery, was successfully completed and well tolerated in the majority of patients, and the survival outcomes show promise for the future application of neoadjuvant chemotherapy in patients with borderline-resectable pancreatic cancer.

The R0 rate reached 64.7% (n=33/51), which met the primary endpoint and was better than expected based on previous reports (11-13). In addition, 84.3% (n=43/51) of the patients successfully underwent the procedure—not only neoadjuvant chemotherapy but also surgical resection. As mentioned, most studies on the use of neoadjuvant chemotherapy for pancreatic cancer were based on retrospective data from surgically resected pancreatic cancer patients, and thus, possible bias cannot be excluded. The results of this prospective study and intention-to-treat analysis indicate that a neoadjuvant FOLFIRINOX or GEM/nab-PTX regimen is feasible, at least for patients with borderline-resectable pancreatic cancer.

The median overall survival time reached 39.4 months. This result is relatively better than that of upfront surgery for borderline-resectable pancreatic cancer (11.6 to 13.1 months) (20-22) and substantially better when compared to the survival times

reported in previous studies evaluating neoadjuvant treatment plus surgery (reportedly ranging from 21.2 to 27.7 months with FOLFIRINOX and from 9 to 27.9 months with GEM/nab-PTX) (13, 23-29) for borderline resectable or locally advanced pancreatic cancer. Although the precise reason for this precedence is not clear, the adherence to the FOLFIRINOX regimen in the current study was high and might have contributed to these results. Nevertheless, disease relapse after surgery was detected in up to 72.1% (n=31/43) of the patients, which is far from ideal. Thus, we must continue to seek a more appropriate option, including neoadjuvant chemotherapy combined with radiotherapy (NACRT), to improve this outcome (30-33).

As mentioned, it remains unclear whether neoadjuvant chemotherapy confers survival benefits due to a lack of high-quality data. However, a few recent randomized-controlled trials have demonstrated a survival benefit; PACT-15 study (18) revealed an advantage in patients administered perioperative PEXG (cisplatin, epirubicin, capecitabine and gemcitabine) for resectable pancreatic cancer, with a median survival time of 38.2 months, and the PREOPANC trial revealed that a neoadjuvant chemoradiotherapy regimen consisting of three cycles of gemcitabine combined with radiotherapy contributed to better overall survival in both resectable and borderline-resectable pancreatic cancer patients (34). While these are important studies that show

the superior survival benefit of neoadjuvant therapy compared to upfront surgery, the median survival time of the neoadjuvant group remained at 15.7 months in the PREOPANC trial, and one can assume that the administration of a recently developed multidrug chemotherapy could prolong their survival further. In this regard, the SWOG1505 trial intended to show the benefit of perioperative mFOLFIRINOX and GEM/nab-PTX for resectable pancreatic cancer (35). Although the R0 resection rate reached 85% (among surgical cases), neither arm met the prespecified overall survival threshold, with median survival times of 23.2 and 23.6 months, respectively. While SWOG1505 showed some similarities with our study (including the resection rate and treatment efficacy), one of the main differences is the higher completion rate of adjuvant chemotherapy (81.4%; n=35/43, consists of mostly S1) in our study. These results suggest that multidrug chemotherapy is too toxic for postoperative patients and that neoadjuvant chemotherapy is more beneficial for borderline-resectable patients than for resectable patients, as has been indicated previously (19).

The unique aspect of this study is its dual-option chemotherapeutic design. In this study, unlike SWOG1505, the FOLFIRINOX group had a higher relative dose intensity, and the rate of patients with grade 3 or 4 adverse events was significantly lower than that of the GEM/nab-PTX group. This is probably due to the preventive

administration of pegfilgrastim, which was not administered to patients receiving GEM/nab-PTX, indicating that pegfilgrastim might have contributed to the feasibility and intensity of FOLFIRINOX. In terms of survival benefit, there was no significant difference in overall survival based on the intention-to-treat analysis, suggesting the equality of FOLFIRINOX and GEM/nab-PTX in a neoadjuvant setting. On the other hand, when analyzing only surgically resected cases, the superiority of FOLFIRINOX was indicated in several aspects, including the disease-free survival rate after surgery and pathological node-positive status.

The limitations of this study are its small sample size and short follow-up period, which underpower the analysis. Additionally, this is a phase II trial and was not designed to compare the difference between two groups or to reveal the survival superiority of neoadjuvant chemotherapy over upfront surgery. Thus, these results do not necessarily guarantee the superiority of neoadjuvant FOLFIRINOX over GEM/nab-PTX or upfront surgery. Nonetheless, it can be assumed that a subset of the patients might have accepted the desirable benefits conferred by neoadjuvant FOLFIRINOX.

In conclusion, this study investigated the feasibility and outcomes of neoadjuvant chemotherapy using two regimens, FOLFIRINOX or GEM/nab-PTX, for borderline-resectable pancreatic cancer. The results indicate that these regimens are

feasible and well tolerated, with an R0 resection rate of 67.4%. In addition, the survival of patients was even found to be favorable in the intention-to-treat analysis. Further research efforts are essential to clarify the most appropriate option for neoadjuvant treatment to improve the survival of these patients.

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913-21.
2. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol. 2018;15(6):333-48.
3. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022.
4. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. The Lancet. 2017;389(10073):1011-24.
5. Sinn M, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. J Clin Oncol. 2017;35(29):3330-7.
6. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, 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. 2016;388(10041):248-57.
7. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018;379(25):2395-406.
8. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-25.
9. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703.
10. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg. 2015;261(1):12-7.
11. Boone BA, Steve J, Krasinskas AM, Zureikat AH, Lembersky BC, Gibson MK,

et al. Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. J Surg Oncol. 2013;108(4):236-41.
12. Hosein PJ, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012;12:199.
13. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol. 2015;22(4):1153-9.
14. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105(8):946-58.
15. Zhan HX, Xu JW, Wu D, Wu ZY, Wang L, Hu SY, et al. Neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of prospective studies. Cancer Med. 2017;6(6):1201-19.
16. Yang L, Bai Y, Li Q, Chen J, Liu F, Weng X, et al. Analysis of the Curative Effect of Neoadjuvant Therapy on Pancreatic Cancer. Front Oncol. 2021;11:695645.
17. Damm M, Efremov L, Birnbach B, Terrero G, Kleeff J, Mikolajczyk R, et al. Efficacy and Safety of Neoadjuvant Gemcitabine Plus Nab-Paclitaxel in Borderline Resectable and Locally Advanced Pancreatic Cancer-A Systematic Review and Meta-Analysis. Cancers (Basel). 2021;13(17).
18. Reni M, Balzano G, Zanon S, Zerbi A, Rimassa L, Castoldi R, et al. Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2-3 trial. Lancet Gastroenterol Hepatol. 2018;3(6):413-23.
19. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol. 2020;38(16):1763-73.
20. Fujii T, Yamada S, Murotani K, Kanda M, Sugimoto H, Nakao A, et al. Inverse Probability of Treatment Weighting Analysis of Upfront Surgery Versus Neoadjuvant Chemoradiotherapy Followed by Surgery for Pancreatic Adenocarcinoma with Arterial Abutment. Medicine (Baltimore). 2015;94(39):e1647.
21. Kato H, Usui M, Isaji S, Nagakawa T, Wada K, Unno M, et al. Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multi-

institutional survey by the Japanese Society of Pancreatic Surgery. Journal of hepato-biliary-pancreatic sciences. 2013;20(6):601-10.
22. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, Nakagawa N, et al. Survival impact of neoadjuvant gemcitabine plus S-1 chemotherapy for patients with borderline resectable pancreatic carcinoma with arterial contact. Cancer chemotherapy and pharmacology. 2017;79(1):37-47.
23. Yoo C, Lee SS, Song KB, Jeong JH, Hyung J, Park DH, et al. Neoadjuvant modified FOLFIRINOX followed by postoperative gemcitabine in borderline resectable pancreatic adenocarcinoma: a Phase 2 study for clinical and biomarker analysis. Br J Cancer. 2020;123(3):362-8.
24. Katz MH, Shi Q, Ahmad SA, Herman JM, Marsh Rde W, Collisson E, et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg. 2016;151(8):e161137.
25. Li X, Guo C, Li Q, Wei S, Zhang Q, Chen Y, et al. Association of Modified-FOLFIRINOX-Regimen-Based Neoadjuvant Therapy with Outcomes of Locally Advanced Pancreatic Cancer in Chinese Population. Oncologist. 2019;24(3):301-e93.
26. Philip PA, Lacy J, Portales F, Sobrero A, Pazo-Cid R, Manzano Mozo JL, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. Lancet Gastroenterol Hepatol. 2020;5(3):285-94.
27. Templeton S, Moser M, Wall C, Shaw J, Chalchal H, Luo Y, et al. Outcomes of Patients with Borderline Resectable Pancreatic Cancer Treated with Combination Chemotherapy. J Gastrointest Cancer. 2021;52(2):529-35.
28. Miyasaka Y, Ohtsuka T, Kimura R, Matsuda R, Mori Y, Nakata K, et al. Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel for Borderline Resectable Pancreatic Cancer Potentially Improves Survival and Facilitates Surgery. Ann Surg Oncol. 2019;26(5):1528-34.
29. Reni M, Zanon S, Balzano G, Passoni P, Pircher C, Chiaravalli M, et al. A randomised phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma. Eur J Cancer. 2018;102:95-102.
30. Fujii T, Satoi S, Yamada S, Murotani K, Yanagimoto H, Takami H, et al. Clinical benefits of neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreatic head: an observational study using inverse probability of treatment weighting. J Gastroenterol. 2017;52(1):81-93.

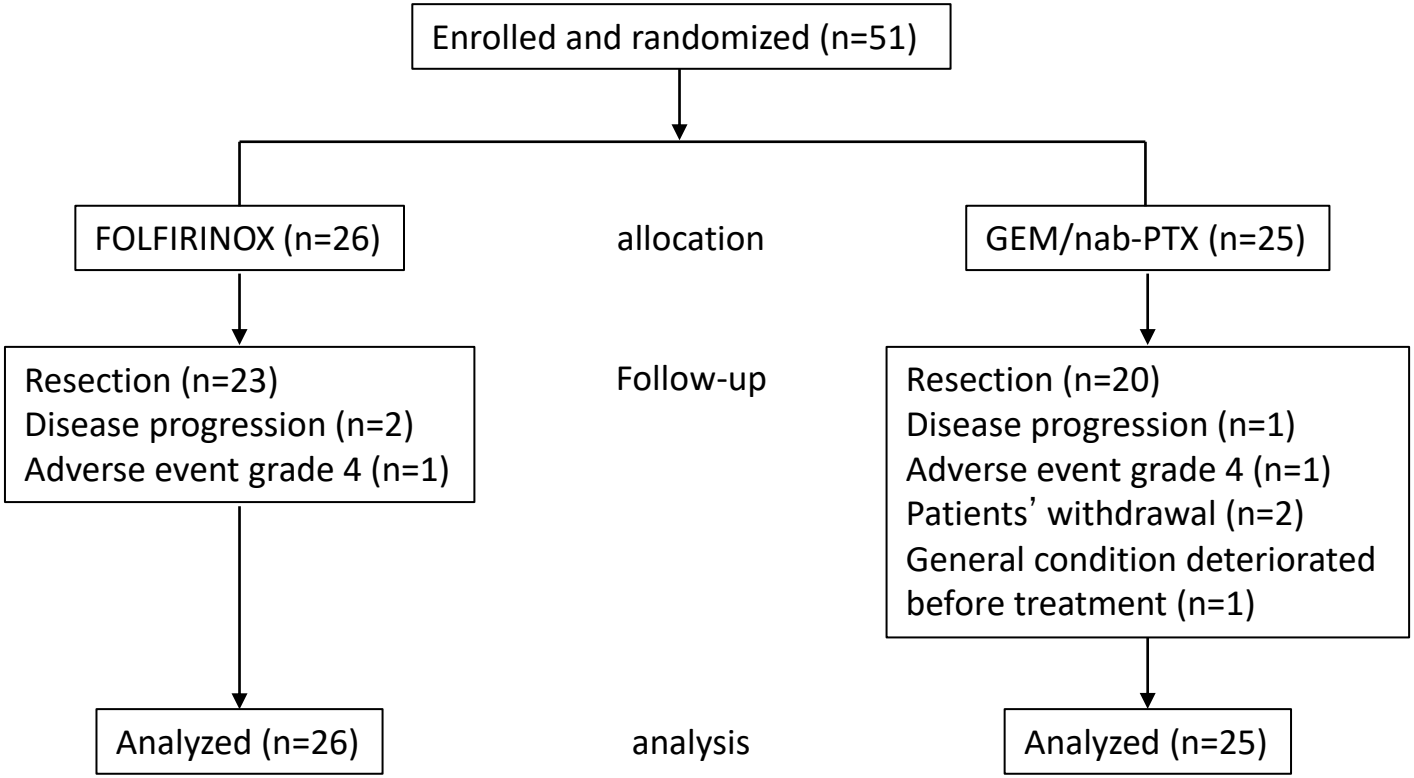
31. Murphy JE, Wo JY, Ryan DP, Clark JW, Jiang W, Yeap BY, et al. Total Neoadjuvant Therapy With FOLFIRINOX in Combination With Losartan Followed by Chemoradiotherapy for Locally Advanced Pancreatic Cancer: A Phase 2 Clinical Trial. JAMA Oncol. 2019;5(7):1020-7.
32. Eguchi H, Takeda Y, Takahashi H, Nakahira S, Kashiwazaki M, Shimizu J, et al. A Prospective, Open-Label, Multicenter Phase 2 Trial of Neoadjuvant Therapy Using Full-Dose Gemcitabine and S-1 Concurrent with Radiation for Resectable Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol. 2019;26(13):4498-505.
33. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol. 2018;4(7):963-9.
34. Versteijne E, van Dam JL, Suker M, Janssen QP, Groothuis K, Akkermans-Vogelaar JM, et al. Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial. J Clin Oncol. 2022:JCO2102233.
35. Sohal DPS, Duong M, Ahmad SA, Gandhi NS, Beg MS, Wang-Gillam A, et al. Efficacy of Perioperative Chemotherapy for Resectable Pancreatic Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021;7(3):421-7.

Figure legends

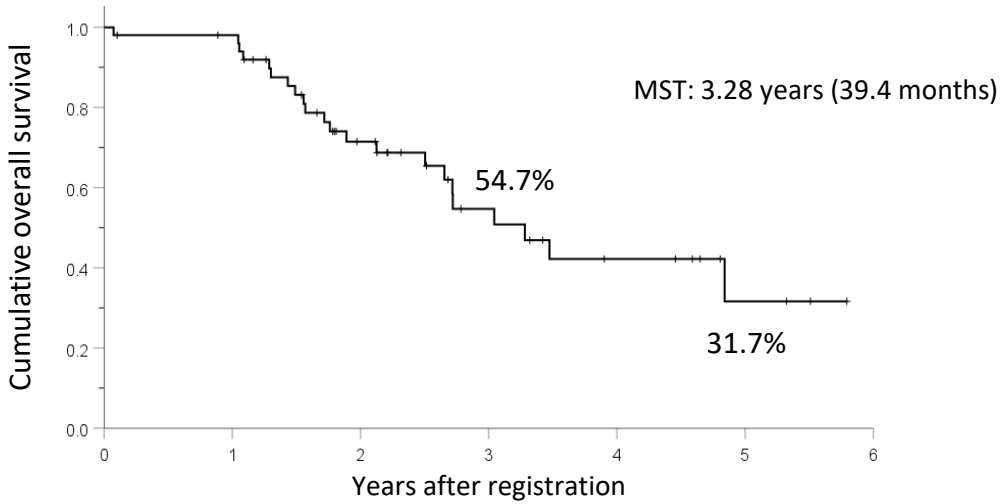
Figure 1: CONSORT diagram of the patients enrolled in NUPAT-01.

Figure 2: Overall survival of the patients by intention-to-treat analysis. (A) Survival of all patients. (B) Survival of the patients according to the neoadjuvant chemotherapy regimen administered.

Figure 3: Survival of the patients who underwent surgical resection. (A) Survival of all patients, (B) overall survival of the patients, and (C) disease-free survival of the patients according to the neoadjuvant chemotherapy regimen administered.


Enrolled and randomized (n=51)
FOLFIRINOX (n=26)
allocation
GEM/nab-PTX (n=25)
Resection (n=23)
Disease progression (n=2)
Adverse event grade 4 (n=1)
Follow-up
Resection (n=20)
Disease progression (n=1)
Adverse event grade 4 (n=1)
Patients' withdrawal (n=2)
General condition deteriorated before treatment (n=1)
Analyzed (n=26)
analysis
Analyzed (n=25)

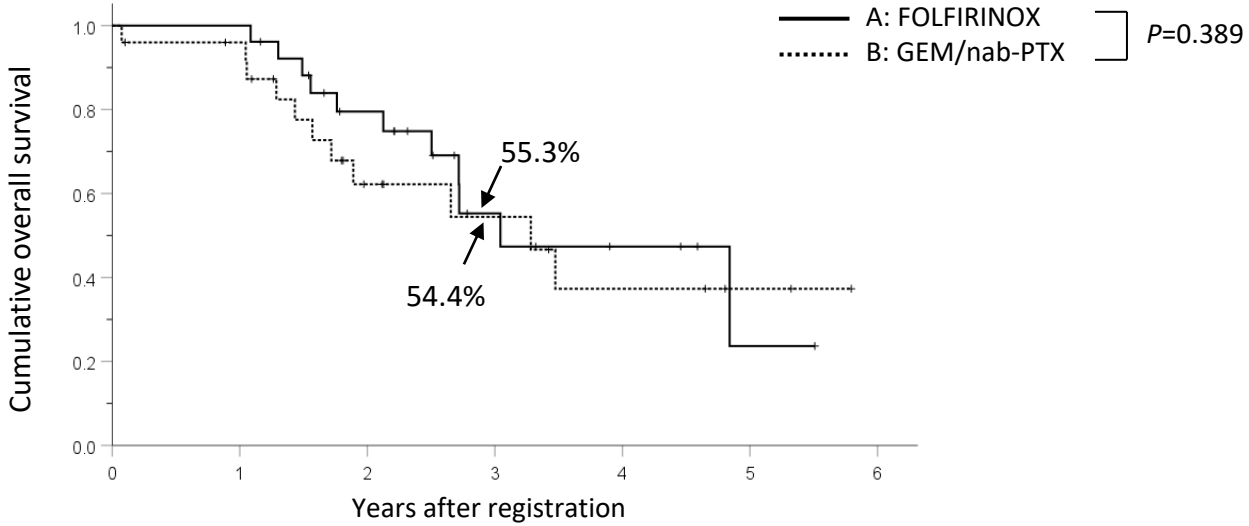
A



No. at risk

51	48	14	3

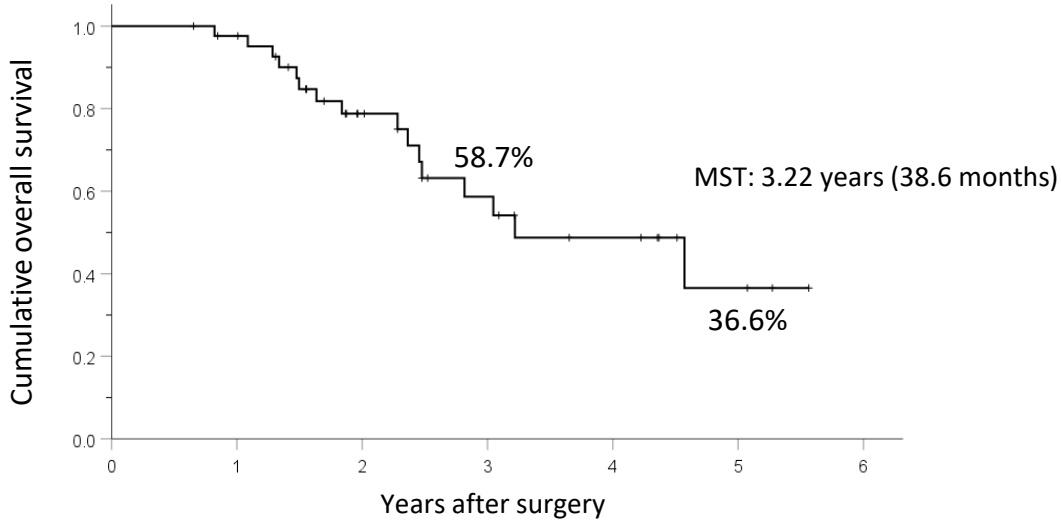
B



No. at risk

A: 26	25	7	1
B: 25	21	7	2

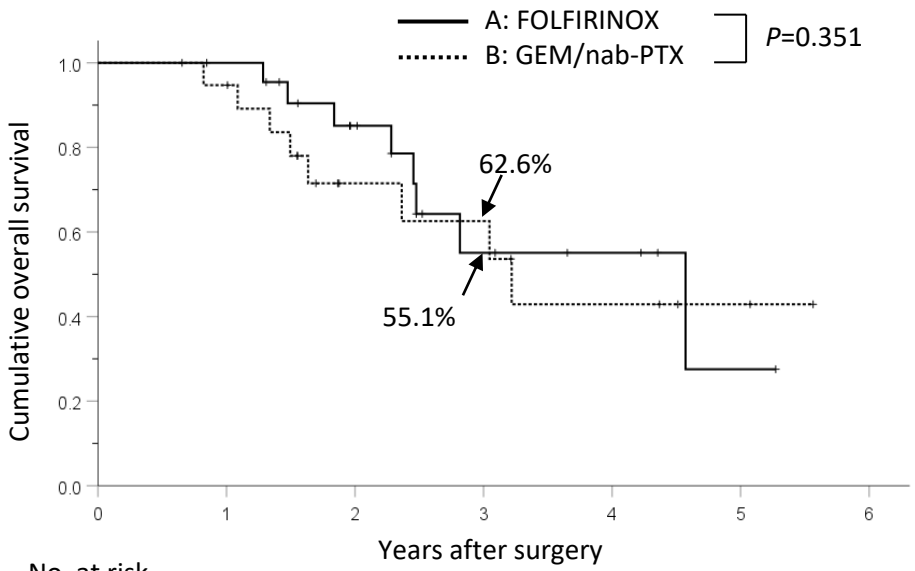
A



No. at risk

43	40	13	3	

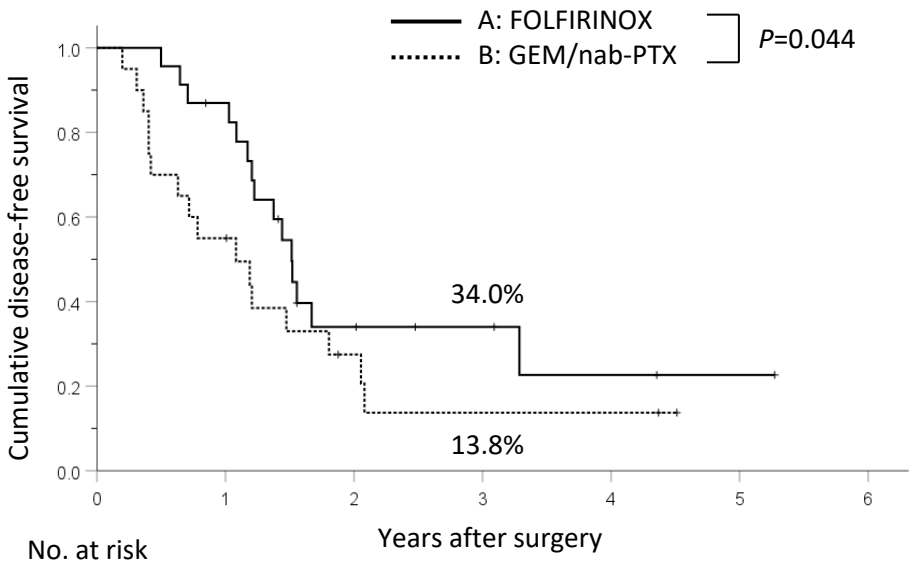
B



No. at risk

A: 23	21	6	1	
B: 20	17	7	2	

C



No. at risk

A: 23	19	4	1	
B: 20	10	2		

Table 1. Patient characteristics and chemotherapy outcomes

Group	FOLFIRINOX (n=26)	GEM/nab-PTX (n=25)	p value
A. Clinical characteristics of the patients			
Age (years), median (quartile)	66 (58-73)	66 (58-71)	0.485
Sex ratio (Male:Female)	16:10	13:12	0.343
CA19-9 (U/ml), median (quartile)	312.5 (54-971)	104 (5-353)	0.122
Radiologic findings at referral			
Tumor diameter (mm), median (quartile)	27.4 (21.8-32.0)	28.5 (23.0-33.7)	0.488
Tumor location (Ph: Pbt)*	19:7	19:6	0.811
Vascular invasion (artery: portal vein)	14:12	13:12	0.895
SUV max, median (quartile)	5.6 (4.2-7.2)	7.2 (5.1-8.3)	0.406
B. Chemotherapy outcomes			
Complete resection (yes: no)**	19:7	14:11	0.202
Relative dose intensity, median (quartile)	100.0 (94.7-100.0)	83.3 (66.7-100.0)	0.014
Adverse events, grade >3 (%)	30.4	70	0.010
RECIST (SD:PR)***	15:8	14:6	0.758
Decrease in the CA19-9 ratio (%)****, median (quartile)	34.3 (19.1-60.1)	46.0 (34.5-61.8)	0.158
SUV max (after chemotherapy), median (quartile)	3.6 (3.1-4.5)	3.4 (3.1-4.8)	0.621

Values in the table represent the number of patients (percentage) unless indicated otherwise.

*Ph, pancreatic head; Pbt, pancreatic body or tail. **Defined as R0 resection.

***Response to chemotherapy according to RECIST criteria. SD, stable disease; PR, partial response.

****Calculated by the CA19-9 value after chemotherapy divided by the initial value.

Table 2. Univariate and multivariate Cox regression analyses of overall survival (intention to treat)

		Univariate		Multivariate	
Characteristics	No. of patients	HR (95% CI)	p value	HR (95% CI)	p value
Sex					
Female	22	1		1	
Male	29	2.477 (1.038-5.914)	0.041	5.017 (1.895-13.280)	0.001
Neoadjuvant chemotherapy					
FOLFIRINOX	26	1		1	
GEM/nab-PTX	25	0.787 (0.340-1.822)	0.576	0.946 (0.391-2.289)	0.902
Vascular invasion					
Artery	27	1		1	
Portal vein	24	1.241 (0.509-3.028)	0.635	0.525 (0.181-1.527)	0.237
Tumor location					
Ph	38	1		1	
Pbt	13	1.493 (0.544-4.095)	0.525	0.582 (0.173-1.961)	0.382
Complete resection					
Yes (R0)	33	1		1	
No	18	6.925 (2.707-17.721)	<0.001	19.287 (5.140-72.363)	<0.001

Table 3. Surgical procedure and outcomes

Group		FOLFIRINOX (n=23)	GEM/nab-PTX (n=20)	p value
	Surgical procedure (PD:DP:TP)	16:5:2	14:4:2	0.982
	Operation time (min), median (quartile)	487 (425-577)	483 (427-608)	0.851
	Portal vein resection (%)	73.9	75.5	0.935
	Blood loss (ml), median (quartile)	1295 (605-1799)	831 (650-1256)	0.486
	Histological type (well:mod:por:other)	1:19:1:2	1:16:2:1	0.869
	Evans Grade (1a:1b:2:3:4)*	5:14:3:0:1	7:9:3:0:1	0.749
	Pathological node positivity (%)	56.5	80	0.101
	R (0:1)	19:4	14:6	0.329
	Recurrence (%)	65.2	80	0.281
	Major complications (%)**	34.8	25	0.486

Values in the table represent the number of patients (percentage) unless indicated otherwise.

*Histologic grading of the residual carcinoma

**Postoperative complications of grade 3 or higher according to the Clavien–Dindo criteria