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ORIGINAL ARTICLE

Significance of neoadjuvant therapy for borderline resectable pancreatic cancer: a multicenter retrospective study

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Abstract

Purpose Neoadjuvant therapy (NAT) is increasingly used to improve the prognosis of patients with borderline resectable pancreatic cancer (BRPC) albeit with little evidence of its advantage over upfront surgical resection. We analyzed the prognostic impact of NAT on patients with BRPC in a multicenter retrospective study.

Methods Medical data of 165 consecutive patients who underwent treatment for BRPC between January 2010 and December 2014 were collected from ten institutions. We defined BRPC according to the National Comprehensive Cancer Network guidelines, and subclassified patients according to venous invasion alone (BR-PV) and arterial invasion (BR-A).

Results The rates of NAT administration and resection were 35% and 79%, respectively. There were no significant differences in resection rates and prognoses between patients in the BR-PV and BR-A subgroups. NAT did not have a significant impact on prognosis according to intention-to-treat analysis. However, in patients who underwent surgical resection, NAT was independently associated with longer overall survival (OS). The median OS of patients who underwent resection after NAT (53.7 months) was significantly longer than that of patients who underwent upfront (17.8 months) or no resection (14.9 months). The rates of superior mesenteric or portal vein invasion, lymphatic invasion, venous invasion, and lymph node metastasis were significantly lower in patients who underwent resection after NAT than in those who underwent upfront resection despite similar baseline clinical profiles.

Conclusions Resection after NAT in patients with BRPC is associated with longer OS and lower rates of both invasion to the surrounding tissues and lymph node metastasis.

Keywords Chemotherapy · Chemoradiotherapy · Metastasis · Resection

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Introduction

Pancreatic cancer (PC) is one of the most lethal malignancies; patients with this disease have a 5-year survival rate of only 7% [1]. Surgical resection is the only potentially curative therapy for PC; however, local invasion to the surrounding vessels and organs owing to rapid locoregional growth as well as the early systemic spread of cancer cells often preclude curative resection [2].

The National Comprehensive Cancer Network (NCCN) guidelines define borderline resectable (BR) PC as a tumor that exhibits intermediate radiographical findings that fall between resectable and unresectable status [3]. BRPC differs from resectable PC in that it carries a higher risk of positive surgical resection margins and requires more extensive surgery [4]. The positive resection margin rates and overall median survival times (MSTs) after upfront surgery for BRPC are reported to be 36–64% and 13–15 months, respectively [5, 6]. To improve the curative resection rates and prognoses, a variety of neoadjuvant therapies (NATs) have been adopted for patients with BRPC [7–12]. The goals of NAT include achieving R0 resection following the locoregional control of the primary tumor, sterilization of metastatic lymph nodes, early treatment for occult distant metastases, and selection of patients who are likely to benefit from surgical resection [13]. Moreover, a neoadjuvant setting ensures a higher chemotherapy completion rate than adjuvant treatment.

The NCCN guidelines recommend NAT for BRPC treatment [3]. However, there is little medical evidence of the benefit of NAT in patients with BRPC; this is partly because of the lack of standardization of clinical trial designs that are optimized for BRPC owing to its rarity (it accounts for 10% of non-metastatic PCs), and also because of the lack of a common definition for BRPC [14]. Recent meta-analyses did not demonstrate a definitive survival benefit when using NAT for BRPC [15, 16]. High-quality prospective studies aimed at comparing survival outcomes following NAT for BRPC to those following upfront surgery are challenging to perform because NAT has been increasingly administered to patients with BRPC to improve their poor survival rates after upfront surgery. In the clinical setting, therapeutic strategies for BRPC vary greatly among institutions. It is important to analyze the differences in the prognoses of patients with BRPC according to therapeutic methods such as upfront surgery and NAT during the same period. In this multicenter study, we compared the outcomes of patients with BRPC who received upfront surgical resection to those who underwent preoperative NAT at multiple institutions in Kyushu Island, Japan. Furthermore, we compared the pathological findings in patients of both groups.

Materials and methods

Patient enrollment

In this multicenter study, data were collected from consecutive patients who underwent treatment for BRPC at ten institutions on Kyushu Island, Japan, between January 2010 and December 2014. The study was approved by the ethics review board of each participating institution. Imaging examinations including computed tomography and magnetic resonance imaging were performed to diagnose BRPC; only patients with confirmed pathological diagnoses of pancreatic adenocarcinoma or adenosquamous carcinoma were included. Patients underwent upfront surgery or NAT based on each institution's preferred therapeutic strategy. S-1 (TS-1, Taiho Pharmaceutical Co., Ltd. Tokyo, Japan) or gemcitabine (GEM)-based chemotherapy was used as the postoperative adjuvant therapy. All resected specimens were examined histologically according to the seventh tumor-node-metastasis (TNM) classification system [17].

Definition of BRPC

The NCCN guideline (version 2.2017) defines BRPC based on the tumor's venous (superior mesenteric vein [SMV] and portal vein [PV]) and arterial (common hepatic artery [CHA], celiac axis [CA], and superior mesenteric artery [SMA]) characteristics [3]. We divided BRPC into BR-PV (suggestive of invasion to the SMV/PV alone) and BR-A (suggestive of invasion to the SMA/CHA/CA) based on the "Classification of Pancreatic Carcinoma" (Fourth English Edition, Japan Pancreas Society) [18]. The criteria for BR-PV are as follows: a tumor with no evidence of contact with the SMA, CA, and CHA; or a tumor contacting the SMV/PV at 180° or greater—or causing occlusion of the SMV/PV—that does not exceed the inferior border of the duodenum for safe reconstruction. The criteria for BR-A are as follows: a tumor contacting the SMA and/or CA at less than 180° with no evidence of stenosis or deformity, or a tumor contacting the CHA without contacting the proper hepatic artery and/or the CA. Cases of contact are classified as BR-A for both the portal venous and arterial systems.

Data collection

We reevaluated the computed tomography and magnetic resonance imaging scans of the enrolled patients to diagnosis BRPC according to the above definitions. The following variables were extracted: age, sex, Eastern Cooperative Oncology Group performance status score, tumor position, tumor size, BR classification, pretreatment serum CA 19-9 levels, NAT administration, date of surgery, type of surgery, pathological PV/SMV invasion, pathological T status, lymph node status,

surgical margin status, adjuvant therapy, date of recurrence, and survival status. We evaluated the tumor response rate after NAT according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

Statistical analysis

Associations between different categorical variables were assessed using the χ^2 test or Fisher's exact test. The multivariate regression model was used to estimate the odds ratio (OR) and corresponding 95% confidence intervals (CIs) using factors found to be significant on univariate analysis as covariates. Survival curves were plotted using the Kaplan–Meier method and analyzed using the log-rank test. Overall survival (OS) was calculated as the interval between initial treatment (NAT or surgery) and death by any cause. The multivariate Cox proportional hazards model was used to estimate the adjusted hazard ratios (HRs) and corresponding 95% CIs using factors found to be significant on univariate analysis as covariates. P values < 0.05 indicated statistical significance. Statistical evaluation was performed using SigmaPlot version 12.5 for Windows (HULINKS Inc., Tokyo, Japan).

Results

Patient characteristics

During the study period, 165 patients who were diagnosed with BRPC at the ten institutions were enrolled (Supplementary Table 1). The baseline demographic and clinical data of all patients are summarized in Table 1. NAT was administered to 58 (35%) of all patients. NAT included neoadjuvant chemoradiotherapy (NACRT) and neoadjuvant chemotherapy (NAC) that were administered to each of 29 patients, respectively. Patients in the NACRT group received radiotherapy at a dose of 50–58 Gy over 4 weeks with S-1 at a dose of 80 mg/m^2 for the first 21 days. One month after radiotherapy completion, S-1 was administered for 2 weeks followed by a 2-week rest period. Patients in the NAC group received GEM or S-1 based chemotherapy; GEM plus S-1 was the most common regimen (17 of 29 patients), followed by GEM alone ($n = 9$) and S-1 alone ($n = 3$). In patients receiving the GEM plus S-1 regimen, GEM was administered at a dose of 1000 mg/m^2 on days 1 and 8 of each cycle. S-1 was administered orally at a dose of 80 mg/m^2 for the first 14 consecutive days followed by a 7-day rest period. Each cycle was repeated every 21 days. No patient experienced side effects that prevented the completion of the NAT regimens. The median duration of NAT administration was 5.0 months (interquartile range, 2.8–7.0 months). Of the 58 patients who underwent NAT, 17 (29%), 19 (33%), and 22 (38%) showed a partial response, stable disease, and progressive disease according to the RECIST criteria, respectively. Of the 58 patients who underwent NAT, 32 (55%) did not undergo surgical resection. The most common reason was distant metastasis ($n = 13$) followed by local progression ($n = 9$), refusal of surgical resection ($n = 5$), peritoneal dissemination at laparotomy ($n = 3$), severe comorbidity ($n = 1$), and unknown ($n = 1$). The median follow-up duration was 15.6 months (mean, 20.8 months).

Table 1 Characteristics of patients with borderline resectable pancreatic cancer ($n = 165$)

Factors		Total ($n = 165$)	BR-PV ($n = 103$)	BR-A ($n = 62$)	P value (PV vs. A)
Age	Median value (interquartile range)	69.0 years (61.0–74.5)	69.0 years (61.0–75.0)	66.5 years (60.8–73.3)	0.489
Sex	Male	87 (53%)	54 (52%)	33 (53%)	0.951
	Female	78 (47%)	49 (48%)	29 (47%)	
Performance status score	0/1	149 (90%)	92 (89%)	57 (92%)	0.781
	2	16 (10%)	11 (15%)	5 (8%)	
Tumor location	Head	132 (80%)	89 (86%)	43 (69%)	0.014
	Body/tail	33 (20%)	14 (14%)	19 (31%)	
Tumor size	≤ 20 mm	16 (10%)	13 (13%)	3 (5%)	0.176
	> 20 mm, ≤ 40 mm	119 (72%)	74 (72%)	45 (73%)	
	> 40 mm	30 (18%)	16 (16%)	14 (23%)	
Pretreatment serum CA 19–9	Median value (interquartile range)	184.0 U/mL (24.7–524.7)	149.9 U/mL (14.5–404.7)	250.9 U/mL (49.6–1113.8)	0.058
NAT	No	107 (65%)	68 (66%)	39 (63%)	0.812
	Yes	58 (35%)	35 (34%)	23 (37%)	
Resection	No	35 (21%)	20 (19%)	15 (24%)	0.596
	Yes	130 (79%)	83 (81%)	47 (76%)	

BR-A, borderline resectable (arterial invasion); *BR-PV*, borderline resectable (superior mesenteric vein/portal vein invasion alone); *CA 19-9*, carbohydrate antigen 19-9; *NAT*, neoadjuvant therapy

Association between clinical factors and prognoses in all patients

Female sex and resection were significant factors associated with longer OS on univariate analysis (Table 2). We divided the ten institutes into three high-volume centers that registered ≥ 25 patients and seven low-volume centers that registered < 25 patients. There was no significant difference in the OS between the high and low-volume centers. Only resection was an independent prognostic factor on multivariate analysis. The MSTs of patients who underwent upfront surgery and NAT were 16.7 (95% CI, 11.4–22.0) and 22.0 (95% CI, 16.2–27.8) months, respectively. NAT had no significant impact on prognosis according to intention-to-treat (ITT) analyses of all patients (Fig. 1a).

Association between clinical factors and prognoses in patients who underwent surgical resection

Of the 130 patients who underwent surgical resection, 104, 22, and 4 underwent pancreatoduodenectomy, distal pancreatectomy, and total pancreatectomy, respectively. Resection of the SMV and CHA/CA was performed in 102 (78%) and 10 (8%) of the patients, respectively. None of the patients underwent resection of the SMA. Table 3 shows the relationships between various clinical factors and OS in patients who underwent surgical resection. Univariate analysis revealed that female sex, adjuvant therapy, and NAT were significant predictors of better prognosis; all three factors were also independently associated with better prognosis on multivariate analysis. Patients who underwent surgical resection after NAT showed markedly longer OS; their MST of 53.7 months was significantly better than that of patients who underwent upfront surgical resection ($P = 0.019$) or did not undergo surgical resection ($P < 0.001$, Fig. 1b). In contrast, the MST of patients who underwent upfront surgical resection (17.8 months) was not significantly better than that of patients who did not undergo surgical resection (14.9 months) ($P = 0.084$).

Comparison of pathological findings between patients who underwent upfront surgical resection and resection after NAT

The baseline clinical profiles of patients who underwent upfront surgical resection and resection after NAT were similar (Supplementary Table 2). Postoperative adjuvant therapy was administered to 74 (71%) of the 104 patients who underwent

Table 2 Association between clinical factors and overall survival in patients with borderline resectable pancreatic cancer ($n = 165$)

		Univariate analysis		Multivariate analysis	
Factor (n)		MST (months) (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (years)	< 75 (126)	19.9 (14.6–25.2)	0.686		
	≥ 75 (39)	16.2 (10.1–22.3)			
Sex	Male (87)	14.6 (11.4–17.8)	0.022	0.688	0.059
	Female (78)	23.0 (13.8–32.3)		(0.466–1.015)	
PS	0/1 (149)	20.1 (15.7–24.5)	0.366		
	2 (16)	9.9 (2.3–17.5)			
Tumor location	Head (131)	18.0 (13.4–22.7)	0.187		
	Body/tail (33)	23.4 (15.3–31.5)			
Tumor size	≤ 40 mm (135)	19.9 (14.6–25.2)	0.791		
	> 40 mm (30)	15.6 (8.1–23.1)			
Pretreatment serum CA 19-9	≤ 500 U/mL (122)	19.3 (15.2–23.5)	0.857		
	> 500 U/mL (43)	18.9 (8.5–29.3)			
BR classification	BR-PV (103)	18.0 (13.8–22.3)	0.296		
	BR-A (62)	22.5 (9.5–35.5)			
NAT	No (107)	16.7 (11.4–22.0)	0.318		
	Yes (58)	22.0 (16.2–27.8)			
Institute	7 LVC (59)	15.2 (12.4–17.9)	0.134		
	3 HVC (106)	20.8 (15.9–25.6)			
Resection	No (35)	14.9 (12.0–17.8)	0.012	0.632	0.037
	Yes (130)	20.8 (14.9–26.7)		(0.411–0.974)	

BR, borderline resectable; *CA 19-9*, carbohydrate antigen 19-9; *CI*, confidence interval; *HR*, hazard ratio; *HVC*, high-volume center; *LVC*, low-volume center; *MST*, median survival time; *NAT*, neoadjuvant therapy; *PS*, performance status

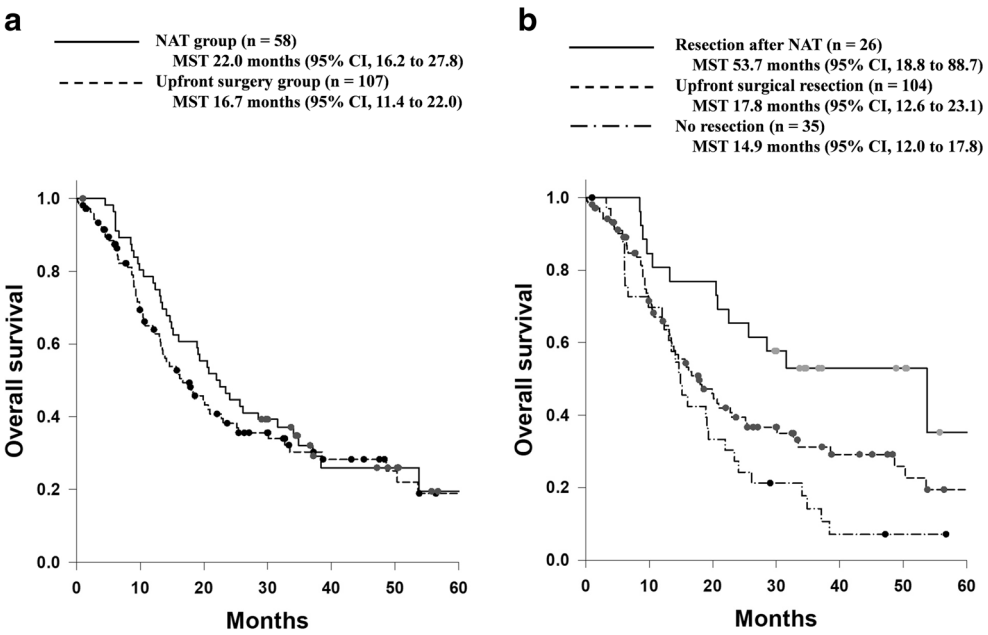

Fig. 1 Kaplan–Meier survival curves showing the overall survival from the time of initial treatment. **a** There was no significant difference in the overall survival (depicted as MST) between the NAT and upfront surgery groups in intention-to-treat analysis ($P = 0.318$). **b** Patients who underwent resection after NAT showed significantly longer overall survival (depicted as MST) than those who underwent upfront surgical resection ($P = 0.019$) or no resection ($P < 0.001$). CI confidence interval, MST median survival time, NAT neoadjuvant therapy

upfront surgical resection and 21 (81%) of the 26 patients who underwent resection after NAT. The rates of pathological invasion into the SMV/PV, lymphatic invasion, venous invasion, and lymph node metastasis were significantly lower in patients who underwent resection after NAT than in those who underwent upfront surgical resection (Supplementary Table 3). Patients who underwent resection after NAT showed a higher R0 resection rate.

Discussion

Adjuvant therapy following surgical resection is a standard therapeutic strategy for radiographically resectable PC [19]. On the other hand, various NATs have been administered to improve the prognosis of patients with BRPC, as this disease is characterized by more advanced local progression and a higher risk of occult distant metastases than resectable PC

Table 3 Association between clinical factors and overall survival in patients who underwent surgical resection ($n = 130$)

		Univariate analysis		Multivariate analysis	
Factor (n)		MST (months) (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (years)	< 75 (99)	20.9 (13.9–28.0)	0.723		
	≥ 75 (31)	20.8 (9.3–32.3)			
Sex	Male (66)	13.5 (9.2–17.9)	0.010	0.447	< 0.001
	Female (65)	28.5 (16.1–40.9)		(0.279–0.716)	
Tumor location	Head (107)	20.1 (16.0–24.2)	0.136		
	Body/tail (23)	53.6 (10.4–96.8)			
Tumor size	≤ 40 mm (104)	20.9 (14.7–27.2)	0.778		
	> 40 mm (26)	15.6 (2.2–29.0)			
BR classification	BR-PV (83)	20.1 (15.6–24.6)	0.586		
	BR-A (47)	22.7 (12.7–32.8)			
Pretreatment serum CA 19-9	≤ 500 U/mL (98)	19.9 (15.5–24.3)	0.715		
	> 500 U/mL (32)	30.1 (17.9–42.3)			
NAT	No (104)	17.8 (12.6–23.1)	0.019	0.508	0.030
	Yes (26)	53.7 (18.8–88.7)		(0.276–0.935)	
Institute	7 LVC (51)	15.9 (11.1–20.6)	0.072		
	3 HVC (79)	30.1 (18.5–41.7)			
Adjuvant therapy	No (35)	13.5 (8.7–18.2)	0.004	0.421	< 0.001
	Yes (95)	25.7 (15.3–36.1)		(0.252–0.703)	

BR, borderline resectable; *CI*, confidence interval; *HR*, hazard ratio; *HVC*, high-volume center; *LVC*, low-volume center; *MST*, median survival time; *NAT*, neoadjuvant therapy

[4]. NAT has several potential advantages over postoperative adjuvant therapy, such as a higher therapy completion rate that enables tumor down-staging to achieve a higher R0 resection rate, enabling early treatment for radiographically occult distant metastases, and facilitating the selection of patients who are most likely to benefit from surgical resection [20]. NAT has been administered to patients with BRPC with little medical evidence of its benefit compared to upfront surgery. Recently, the first prospective randomized controlled trial demonstrated the oncological benefit of GEM-based NACRT compared to upfront surgery in patients with BRPC [21]; the surgical resection and R0 rates were 63% and 52%, respectively. The 2-year survival rate and MST were significantly better in the NACRT group (40.7% and 21 months) than in the upfront surgery group (26.1% and 12 months).

In this multicenter retrospective study, various treatment approaches including NAC, NACRT, and upfront surgical resection were selected for treating BRPC according to the therapeutic strategy of each participating institution. NAT was not significantly associated with longer OS on ITT analysis of all patients; however, those who underwent resection after NAT showed significantly longer OS (MST, 53.7 months) than those who underwent upfront surgical resection (MST, 17.8 months) or no resection (MST, 14.9 months). In contrast, OS rates did not significantly differ between patients who underwent upfront surgical resection and those who did not undergo resection. On multivariate analysis in patients who underwent surgical resection, NAT was an independent factor associated with better prognosis. It was reported that extended pancreatectomy involving the resection of additional organs or relevant vascular structures did not improve the prognoses of patients with BR and locally advanced PC [2]. Our data suggest that NAT selected patients who could benefit from surgical resection. In contrast, it is considered difficult for patients undergoing upfront surgery to attain a long OS even if they could undergo surgical resection. Patients who developed distant metastasis or local progression after NAT or at laparotomy did not undergo surgical resection. The resection rate in patients who underwent NAT was relatively low at 45%. Patients with aggressive tumors that produce early distant metastases or local progression are generally considered ineligible for surgical resection.

Several previous studies demonstrated that BRPC patients with arterial involvement showed worse prognoses than those with venous involvement following upfront surgery [5, 22]. Kato et al. reported significant differences between patients with arterial involvement vs. those with venous involvement in terms of R0 resection rates (55.3% vs. 72.6%, respectively) and 5-year survival rates (9.9% vs. 16.1%, respectively) [22]. In the present study, there were no significant differences in the rates of NAT administration or of resection between BR-PV- and BR-A-group patients; moreover, there were no differences in prognosis between these groups. Ramacciato et al. performed a multicenter study encompassing 406 patients who underwent en bloc SMV and/or PV resection for PC [23]. They found that the median OS was 24 months and that histological venous invasion was independently associated with poor prognosis. Their results demonstrated that the OS of patients with histological invasion to the SMV/PV was significantly shorter than that of patients without such invasion. BR-PV is thought to have more aggressive oncological features than radiographically resectable PC. Sho et al. reported that NAT was associated with longer OS in patients with venous involvement but not those with arterial involvement [24]. Hence, NAT administration should be considered not only for BR-A but also for BR-PV.

In terms of surgical resection, we found no significant differences in the clinical profiles of patients who underwent upfront surgical resection vs. those who underwent resection after NAT. When comparing pathological findings between the two patient groups, those who underwent resection after NAT showed significantly lower rates of invasion to the SMV/PV, lymphatic invasion, venous invasion, lymph node metastasis, and non-R0 resection despite having similar baseline clinical features. These pathological findings may account for the partly better prognoses in patients who underwent resection after NAT. NAT may exhibit a similar antitumor effect against radiographically occult distant metastases if their biological behaviors are similar to those of the cancer cells present in the lymphatic/blood vessels and metastasized lymph nodes. Barnes et al. demonstrated that administering postoperative adjuvant therapy to patients who underwent resection after NAT for BRPC had a significant protective effect in those with lymph node metastases but not in those without [25]. Their study may support the theory that NAT has similar effects on both lymph node metastasis and occult distant metastasis.

This study had several limitations owing to its retrospective nature. First, selection bias may have existed in both the upfront surgery and NAT groups, although the baseline clinical profiles of these two groups were comparable. Second, the NAT regimen and duration were not uniform across institutions. Third, the resection rate after NAT was relatively low; a reason for this and for failure to improve the OS on ITT analysis may be the low intensity of the NAT regimens used to treat BRPC in this study. Recent studies demonstrated that NAT using FOLFIRINOX [26, 27] or nab-paclitaxel [6] improved both the resection rates and prognoses in patients with advanced PC; hence, it is possible that more aggressive NAT using FOLFIRINOX or nab-paclitaxel may produce greater oncological benefit in patients with BRPC. Nevertheless, our study demonstrated that NAT is useful to select patients with BRPC who benefit from surgical resection, as patients who underwent resection after NAT in our study achieved a markedly long OS. Notably, we collected data based on a strict definition of BRPC from multiple centers. Nevertheless,

several issues remain to be elucidated in prospective studies, including (1) the most optimal regimen with which to obtain the highest resection rate and most favorable prognosis, (2) the optimal duration of NAT administration, and (3) the benefit of administering radiotherapy in addition to chemotherapy. Furthermore, the biological, conditional, and anatomical factors of patients with BRPC [28] should be considered when planning therapeutic strategies and further trials.

Conclusions

In patients with BRPC, NAT produced OS advantage among those who underwent surgical resection compared to those who underwent upfront surgery. NAT was associated with lower rates of pathological invasion to the SMV/PV, lymphatic/blood vessel invasion, lymph node metastasis, and non-R0 resection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals 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. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65:5–29
2. Hartwig W, Gluth A, Hinz U, Koliogiannis D, Strobel O, Hackert T, Werner J, Büchler MW (2016) Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. Br J Surg 103:1683–1694
3. Tempero MA, Malafa MP, Al-Hawary M et al (2017) Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 15:1028–1061
4. Evans DB, George B, Tsai S (2015) Non-metastatic pancreatic cancer: Resectable, borderline resectable, and locally advanced-definitions of increasing importance for the optimal delivery of multimodality therapy. Ann Surg Oncol 22:3409–3413
5. Yamada S, Fujii T, Sugimoto H, Nomoto S, Takeda S, Kodera Y, Nakao A (2013) Aggressive surgery for borderline resectable pancreatic cancer: evaluation of National Comprehensive Cancer Network guidelines. Pancreas 42:1004–1010
6. Ielpo B, Caruso R, Duran H, Diaz E, Fabra I, Malavé L, Ferri V, Alvarez R, Cubillo A, Plaza C, Lazzaro S, Kalivaci D, Quijano Y, Vicente E (2017) A comparative study of neoadjuvant treatment with gemcitabine plus nab-paclitaxel versus surgery first for pancreatic adenocarcinoma. Surg Oncol 26:402–410
7. Yoo C, Kang J, Kim KP, Lee JL, Ryoo BY, Chang HM, Lee SS, Park DH, Song TJ, Seo DW, Lee SK, Kim MH, Park JH, Hwang DW, Song KB, Lee JH, Kim SC (2017) Efficacy and safety of neoadjuvant FOLFIRINOX for borderline resectable pancreatic adenocarcinoma: improved efficacy compared with gemcitabine-based regimen. Oncotarget 8:46337–46347
8. Takahashi H, Akita H, Tomokuni A, Kobayashi S, Ohigashi H, Fijiwara Y, Yano M, Sakon M, Ishikawa O (2016) Preoperative gemcitabine-based chemoradiation therapy for borderline resectable pancreatic cancer: impact of venous and arterial involvement status on surgical outcome and pattern of recurrence. Ann Surg 264:1091–1097
9. Katz MH, Shi Q, Ahmad SA et al (2016) Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for clinical trials in oncology trial A021101. JAMA Surg 151:e161137
10. Rose JB, Rocha FG, Alseidi A, Biehl T, Moonka R, Ryan JA, Lin B, Picozzi V, Helton S (2014) Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising post-operative outcomes and survival. Ann Surg Oncol 21:1530–1537
11. Christians KK, Tsai S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, Kelly T, Erickson B, Wang H, Evans DB, George B (2014) Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? Oncologist 19:266–274
12. Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, Rich TA, Adams RB, Bauer TW (2011) Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. Ann Surg Oncol 18:619–627
13. Katz MH, Pisters PW, Lee JE, Fleming JB (2011) Borderline resectable pancreatic cancer: what have we learned and where do we go from here? Ann Surg Oncol 18:608–610
14. Takahashi S, Ohno I, Ikeda M et al (2017) Neoadjuvant S-1 with concurrent radiotherapy followed by surgery for borderline resectable pancreatic cancer: study protocol for an open-label, multicentre, prospective phase II trial (JASPAC05). BMJ Open 7:e018445
15. Tang K, Lu W, Qin W, Wu Y (2016) Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. Pancreatology 16:28–37
16. Festa V, Andriulli A, Valvano MR, Uomo G, Perri F, Andriulli N, Corrao S, Koch M (2013) Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. JOP 14:618–625
17. Sobin LH, Gospodarowicz MK, Wittekind C, International union against Cancer (2010) TNM classification of malignant tumours, 7th edn. Wiley-Blackwell, Chichester

18. Japan Pancreas Society (2017) Classification of Pancreatic Carcinoma, Fourth English edn. Kanehara & Co., Ltd, Bunkyo-ku
19. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H (2013) Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 310: 1473–1481
20. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J (2010) Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 7:e1000267
21. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, Oh DY, Chie EK, Lee JM, Heo JS, Park JO, Lim DH, Kim SH, Park SJ, Lee WJ, Koh YH, Park JS, Yoon DS, Lee IJ, Choi SH (2018) Oncological benefits of neoadjuvant chemoradiotherapy with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg 268:215–222
22. Kato H, Usui M, Isaji S, Nagakawa T, Wada K, Unno M, Nakao A, Miyakawa S, Ohta T (2013) Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multiinstitutional survey by the Japanese Society of Pancreatic Surgery. J Hepatobiliary Pancreat Sci 20:601–610
23. Ramacciato G, Nigri G, Petrucciani N, Pinna AD, Ravaioli M, Jovine E, Minni F, Grazi GL, Chirletti P, Tisone G, Napoli N, Boggi U (2016) Pancreatectomy with mesenteric and portal vein resection for borderline resectable pancreatic cancer: multicenter study of 406 patients. Ann Surg Oncol 23:2028–2037
24. Sho M, Akahori T, Tanaka T, Kinoshita S, Nagai M, Tamamoto T, Ohbayashi C, Hasegawa M, Kichikawa K, Nakajima Y (2015) Importance of resectability status in neoadjuvant treatment for pancreatic cancer. J Hepatobiliary Pancreat Sci 22:563–570
25. Barnes CA, Krepline AN, Aldakkak M, Clarke CN, Christians KK, Khan AH, Hunt BC, Ritch PS, George B, Hall WA, Erickson BA, Evans DB, Tsai S (2017) Is adjuvant therapy necessary for all patients with localized pancreatic cancer who have received neoadjuvant therapy? J Gastrointest Surg 21:1793–1803
26. Barenboim A, Lahat G, Geva R, Nachmany I, Nakache R, Goykhman Y, Brazowski E, Rosen G, Isakov O, Wolf I, Klausner JM, Lubezky N (2018) Neoadjuvant FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer: an intention to treat analysis. Eur J Surg Oncol 44:1619–1623
27. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, Blaszkowsky LS, Kwak EL, Allen JN, Clark JW, Faris JE, Zhu AX, Goyal L, Lillemoe KD, DeLaney TF, Fernández-del Castillo C, Ferrone CR, Hong TS (2018) Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. JAMA Oncol 4:963–969
28. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL (2018) International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 18:2–11