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ORIGINAL ARTICLE – PANCREATIC TUMORS

Clinical Impact of Neoadjuvant Chemotherapy and Chemoradiotherapy in Borderline Resectable Pancreatic Cancer: Analysis of 884 Patients at Facilities Specializing in Pancreatic Surgery

Yuichi Nagakawa, MD, PhD, FACS[1], Yatsuka Sahara, MD[1], Yuichi Hosokawa, MD[1], Yoshiaki Murakami, MD[2], Hiroki Yamaue, MD[3], Sohei Satoi, MD[4], Michiaki Unno, MD[5], Shuji Isaji, MD[6], Itaru Endo, MD[7], Masayuki Sho, MD[8], Tsutomu Fujii, MD[9], Chie Takishita, MD[1], Yosuke Hijikata, MD[1], Shuji Suzuki, MD[10], Shigeyuki Kawachi, MD[11], Kenji Katsumata, MD[1], Tetsuo Ohta, MD[12], Takukazu Nagakawa, MD[12], and Akihiko Tsuchida, MD[1]

[1]Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University, Shinjuku, Tokyo, Japan; [2]Department of Surgery, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; [3]Department of Gastroenterological Surgery, Wakayama Medical University, Wakayama, Japan; [4]Department of Surgery, Kansai Medical University, Moriguchi, Osaka, Japan; [5]Department of Hepatobiliary-Pancreatic Surgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan; [6]Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine, Tsu, Mie, Japan; [7]Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan; [8]Department of Surgery, Nara Medical University, Kashihara, Nara, Japan; [9]Department of Surgery and Science, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan; [10]Department of Gastroenterological Surgery, Tokyo Medical University Ibaraki Medical Center, Inashiki, Ibaraki, Japan; [11]Digestive and Transplantation Surgery, Tokyo Medical University Hachioji Medical Center, Hachioji, Tokyo, Japan; [12]Department of Gastroenterological Surgery, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa, Japan

ABSTRACT

Background. The efficacy of neoadjuvant therapy (NAT), including neoadjuvant chemotherapy (NAC) and neoadjuvant chemo-radiotherapy (NACRT), for patients with borderline resectable pancreatic cancer (BRPC) has not been elucidated. This study aimed to clarify the efficacy of NAC and NACRT for patients with BRPC.

Methods. The study analyzed the treatment outcomes of 884 patients treated for BRPC from 2011 to 2013. Treatment results were compared between upfront surgery and NAT and between NAC and NACRT using propensity score-matching analysis. Overall survival (OS) was calculated via intention-to-treat analyses.

Results. The overall resection rates for the patients who underwent NAT were significantly lower than for the patients who underwent upfront surgery (75.1% vs 93.3%; $p < 0.001$). However, the R0 resection rate was significantly higher for NAT than for upfront surgery ($p < 0.001$). Additionally, the OS for the patients who received NAT was significantly longer than for those who underwent upfront surgery (median survival time [MST], 25.7 vs 19.0 months; $p = 0.015$). The lymph node rate for the patients with NACRT was significantly lower than for those who underwent NAC ($p < 0.001$). However, the resection rate for the NACRT cases was significantly lower than for the NAC cases ($p = 0.041$). The local recurrence rate for the NACRT cases was significantly lower than for the NAC cases ($p = 0.002$). However, OS did not differ significantly between NAC and NACRT (MST, 29.2 vs 22.5 months; $p = 0.130$).

Conclusions. The study showed that NAT has potential benefit for patients with BRPC. Compared with NAC,

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Y. Nagakawa, MD, PhD, FACS
e-mail: naga@tokyo-med.ac.jp

NACRT decreased the rates for lymph node metastasis and local recurrence but did not improve the prognosis.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines[1] classifies pancreatic ductal adenocarcinoma as resectable, unresectable, or borderline resectable. Although borderline resectable pancreatic cancer (BRPC) may be technically resectable, it poses particularly high risks of margin-positive resection and postoperative recurrence.[2,3] Therefore, the NCCN guidelines and expert consensus statement recommend neoadjuvant therapy (NAT) for patients with BRPC.[1,2] However, due to the limited number of patients with BRPC, few large studies have shown the efficacy of NAT. Small studies have described the effectiveness of neoadjuvant chemotherapy (NAC) and combined neoadjuvant chemoradiotherapy (NACRT) for patients with BRPC.[4–8]

Combined radiotherapy with chemotherapy is reported to be effective as a local treatment method for pancreatic ductal adenocarcinoma (PDAC).[9,10] However, patients with BRPC are at high risk for recurrence after resection, with distant metastasis being the most common type.[10] Therefore, whether local treatment using combined radiotherapy improves the treatment results of BRPC needs to be clarified. However, whether NAC or NACRT is more effective for patients with BRPC is unclear.

This study aimed to clarify the clinical impact of NAC and NACRT on patients with BRPC through a multi-institutional cohort study conducted in collaboration with facilities specializing in pancreatic surgery.

METHODS

The study enrolled 63 member institutions of the Japanese Society of Pancreatic Surgery (JSPS) that specialize in pancreatic surgery. All patients treated for BRPC from January 2011 to December 2013 at each participating institution were registered in a common database.

To ascertain the validity of image diagnosis, we required all facilities to supply proof of BRPC diagnosis via multidetector computed tomography. Additionally, we validated the data by randomly inspecting selected institutions. Before our analysis, the final database was carefully checked for clerical errors by three physicians (Y.N., Y.H., and Y.S.).

All analyses were performed under the supervision of a statistician at Tokyo Medical University. The study was performed in accordance with the ethics standards stated in the 1964 Declaration of Helsinki and its later amendments. The ethics board of the JSPS and Tokyo Medical University approved this study and waived the requirement for informed consent due to the retrospective nature of this study.

Definition of Borderline Resectable Pancreatic Cancer

Resectability was assessed using multidetector computed tomography with a multiphase contrast-enhanced technique based on the Japanese Classification of Pancreatic Carcinoma stipulated by the Japan Pancreas Society.[11] Pancreatic tumors were classified as resectable if there was (1) no arterial tumor contact with the celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA) and (2) no tumor contact with the superior mesenteric vein or portal vein, or $\leq 180°$ contact without vein contour irregularity.

BRPC was defined as (1) solid tumor contact of $\leq 180°$ with the SMA or CA but no arterial stenosis and/or contour irregularity or (2) solid tumor contact or infiltration into the CHA with an intact and uninvolved CA and/or proper hepatic artery or $\geq 180°$ solid tumor contact with, infiltration into, and/or occlusion of the portal or superior mesenteric vein without extension toward the lower border of the duodenum but no arterial contact with the SMA, CA, and/or CHA. A diagnosis of BRPC was determined for patients if their tumor extended the CA and CHA but allowed performance of safe and complete resection via distal pancreatectomy with CA resection.[12,13]

Data Collection

The following factors were examined: pretreatment factors (sex, age, tumor location, serum albumin, CA19-9, performance status, NAT, and resection), tumor response after NAT based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (complete response [CR], partial response [PR], no change [NC], stable disease [SD], or progressive disease [PD]), operation methods (pancreaticoduodenectomy, total pancreatectomy), pathologic diagnosis (lymph node status, portal vein involvement, surgical margin status), and initial recurrence patterns.

Data including the date of the first treatment, surgery, and last follow-up visit were collected for each patient. Overall survival time was calculated from the time of the first treatment, including NAT and surgery, to the last follow-up visit or death (intention-to-treat analyses).

Statistical Analysis

Treatment results between upfront surgery and NAT and between NAC and NACRT were compared using propen-

sity score-matching (PSM) analysis to reduce bias from factors influencing treatment outcomes. The factors used for matching were age, sex, tumor location, and preoperative albumin, CA19-9, and performance status. A propensity score was calculated for each patient using a logistic regression model, and one-to-one-matched study groups were created using complete matching without replacement. Match tolerance was set at zero. Data for continuous variables are expressed as median (range). Dichotomous variables were evaluated using Chi-square tests. Kaplan–Meier curves were generated to estimate overall survival, and comparisons between groups were performed using log-rank (Mantel–Cox) tests. A p value lower than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics, version 24 (IBM Corp, Armonk, NY, USA).

RESULTS

Clinicopathologic Characteristics

A total of 844 patients were registered (Fig. 1). The patient characteristics are summarized in Table 1. Neoadjuvant therapy was administered to 530 patients (60%), including 211 patients (23.9%) receiving NAC and 319 patients (36.1%) receiving NACRT. The NAC protocols used were gemcitabine (Gem) + S-1 (n = 165), Gem alone (n = 26), S-1 alone (n = 13), and others (n = 7). In the NAC group, chemotherapy was administered 30 days or fewer for 36 patients (17.1%), 31–60 days for 90 patients (46.7%), 61–90 days for 34 patients (16.1%), and 90 days or longer for 51 patients (24.2%).

The NACRT protocols performed as concurrent chemoradiotherapy were Gem + S-1 + radiotherapy (n = 127), S-1 + radiotherapy (n = 117), Gem + radiotherapy (n = 59), and other (n = 16). Radiotherapy was performed using the following total radiation doses: less than 30 Gy (n = 1, 0.3%), 30–39 Gy (n = 45, 14.1%), 40–49 Gy (n = 66, 20.7%), 50–59 Gy (n = 203, 63.6%), and 60 Gy or more (n = 4, 1.3%). Furthermore, for the 30 patients (9.4%) in the NACRT group, neoadjuvant

TABLE 1 Patient characteristics

	Total (n = 884)
Age: years[a]	68.0 (35–86)
Sex	
Male	483 (54.6)
Female	401 (45.4)
Tumor location	
Head	682 (77.1)
Body	202 (22.9)
Pretreatment albumin: g/dl	3.9 (1.9–8.4)
Pretreatment CA19-9 levels: U/ml	180 (0.0–41,650)
Performance status	
0	716 (81.0)
≥ 1	168 (19.0)
Neoadjuvant therapy	
Yes	530 (60.0)
No	354 (40.0)
NAC or NACRT	
NAC	211 (39.8)
NACRT	319 (60.2)
Resection	
Yes	715 (80.9)
No	169 (19.1)

NAC neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy

[a]Data are expressed as median (range) or as n (%)

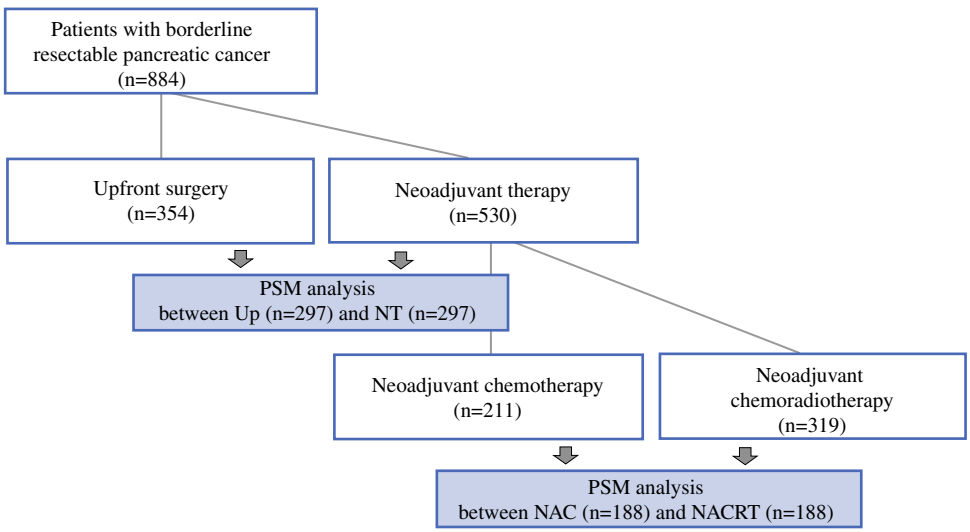

FIG. 1 Flow diagram of patient enrollment

systemic chemotherapy (Gem alone [$n = 5$], Gem + S-1 [$n = 22$], others [$n = 3$]) was performed before concurrent chemoradiotherapy was introduced.

Resection was performed for 715 patients (80.1%). Resection was not performed ($n = 169$) (1) in the upfront surgery group ($n = 29$) due to detection of distant metastases during surgery ($n = 24$, 82.8%) and tumor determined to be unresectable PDAC because of local progression ($n = 5$, 17.2%); (2) in the NAC group ($n = 41$) due to occurrence of distance metastasis ($n = 20$, 48.8%), local progression ($n = 17$, 41.5%), adverse event of chemotherapy ($n = 1$, 2.4%), or comorbidity ($n = 3$, 7.3%); and (3) in the NACRT group ($n = 99$) due to occurrence of distance metastasis ($n = 53$, 53.5%), local progression ($n = 28$, 28.3%), adverse event of chemoradiotherapy ($n = 4$, 4.0%), comorbidity, or other reasons including patient preference ($n = 14$, 14.1%).

Comparison Between Upfront Surgery and NAT in the PSM Analysis

The treatment results of upfront surgery and NAT were compared using PSM analysis. A total of 594 (67.2%) patients were matched from each group. The overall resection rates for the patients who underwent NAT were significantly lower than for those who underwent upfront surgery (75.1% vs 93.3%; $p < 0.001$). However, the rates of R0 resection ($p < 0.001$) and negative lymph nodes and portal vein involvement ($p = 0.023$) for the patients who underwent NAT were significantly higher than for those who underwent upfront surgery (Table 2). Additionally, the overall survival for the patients who received NAT was significantly longer than for those who underwent upfront surgery (median survival time [MST], 25.7 vs 19.0 months; $p = 0.015$) (Fig. 2a).

Overall survival was analyzed for the upfront surgery and NAT groups whether they underwent resection or not (Fig. 2b). The MST for the patients who received NAT and underwent resection was significantly longer than for the patients who received NAT and did not undergo resection (29.8 vs 13.0 months; $p < 0.001$). Notably, the MST for the patients who did not undergo resection was significantly worse in the upfront surgery group than that in the NAT group (6.6 vs 13.0 months; $p < 0.001$).

Comparison Between NAC and NACRT in the PSM Analysis

The treatment results for NAC and NACRT were compared using PSM analysis. A total of 376 patients (63.7%) were matched. The rates of the negative lymph nodes for the patients with NACRT were significantly higher than for the patients with NAC (62.2% vs 34.0%; $p < 0.001$), but the overall resection rates for the patients with NACRT were significantly lower than for the patients with NAC (70.7% vs 80.3%; $p < 0.041$). The local recurrence rates for the patients who underwent NACRT were significantly lower than for those who underwent NAC (20.4% vs 44.6%; $p = 0.002$) (Table 3). However, overall survival did not differ significantly between the NAC and NACRT groups (MST, 29.2 vs 22.5 months; $p = 0.130$; Fig. 2c).

DISCUSSION

To date, few large studies on optimal strategies for the management of BRPC have been conducted due to the small number of BRPC cases. Therefore, we conducted a PSM using 884 patients from facilities specializing in pancreatic surgery. To our knowledge, this is the largest number of cases included in a study of this topic to date. We showed that NAT was associated with better overall survival than upfront surgery. Additionally, the NAT group had a significantly better R0 rate than the upfront surgery group. These results indicate that NAT is important for improving survival outcomes in BRPC.

In 2013, Kato et al.[14] conducted a retrospective study with a large number of PDAC patients, including 624 patients with BRPC who underwent resection from 2002 to 2007 at institutions similar to those included in our study, suggesting that valid comparisons can be made between the two studies. They reported an MST of only 12.6 months.[14] At the time of that study, NAT for BRPC was not commonly administered. Therefore, only 63 (10%) of the 624 patients with BRPC received NAT.

In our study, 530 (60%) of the 884 patients received NAT. Thus, the number of patients undergoing NAT for BRPC has recently increased in line with the NCCN guidelines. In addition, the MST of the NAT group in our study was 25.7 months, and thus our findings show significant improvement compared with those from the study by Kato et al.[14]

Furthermore, we found that although the R0 rate and prognosis were significantly improved with NAT versus upfront surgery, the overall resection rate was worse in the former group (75.1% vs 93.3%; $p < 0.001$). Katz et al.[15] published the largest retrospective report to date, which evaluated 160 patients with BRPC from 1999 to 2006. In their cohort, 125 patients (78%) completed preoperative therapy, and only 66 (41%) underwent resection, suggesting that the absence of effective chemotherapy at the time was reflected in the low resection rate. However, analysis of the patients who did not undergo resection in our study showed that the MST was only 6.6 months for upfront surgery and significantly longer for NAT (13 months).

TABLE 2 Univariable outcomes for propensity score-matched patients undergoing upfront surgery or neoadjuvant therapy between 2011 and 2013

	Before matching					After matching				
	UP (n = 354)		NT (n = 530)		p value	UP (n = 297)		NT (n = 297)		p value
	n	%	n	%		n	%	n	%	
Age (years)										
≥ 68	149	42.1	266	50.2	**0.018**	133	44.8	133	44.8	
< 68	205	57.9	264	49.8		164	55.2	164	55.2	
Sex										
Male	193	54.5	290	54.7	1.000	161	54.2	161	54.2	
Female	161	45.5	240	45.3		136	45.8	136	45.8	
Tumor location										
Head	294	83.1	388	73.2	**0.001**	245	82.5	245	82.5	
Body	60	16.9	142	26.8		52	17.5	52	17.5	
Pretreatment albumin (g/dl)										
≥ 3.9	166	46.9	180	34.0	< **0.001**	121	40.7	121	40.7	
< 3.9	188	53.1	350	66.0		176	59.3	176	59.3	
Pretreatment CA19-9 levels (U/ml)										
≥ 180	165	46.6	283	53.4	0.055	140	47.1	140	47.1	
< 180	189	53.4	247	46.6		157	52.9	157	52.9	
Performance status										
0	260	73.4	456	86.0	< **0.001**	247	83.2	247	83.2	
≥ 1	94	26.6	74	14.0		50	16.8	50	16.8	
Resection										
Yes	325	91.8	390	73.6	< **0.001**	277	93.3	223	75.1	< **0.001**
No	29	8.2	140	26.4		20	6.7	74	24.9	
Surgical margin										
R0	227	69.8	329	84.4	< **0.001**	195	70.4	191	85.7	< **0.001**
R1/2	98	30.2	61	15.6		82	29.6	32	14.3	
Lymph node metastasis										
Negative	68	20.7	198	49.0	< **0.001**	60	21.4	106	45.7	< **0.001**
Positive	261	79.3	206	51.0		220	78.6	126	54.3	
Portal vein involvement										
Negative	169	52.0	240	61.5	**0.012**	144	52.0	139	62.3	**0.023**
Positive	156	48.0	150	38.5		133	48.0	84	37.7	
Initial recurrence pattern										
Local recurrence	107	42.5	88	33.1	0.028	95	42.4	58	36.7	0.263
Only local recurrence	68	27.0	55	20.7		62	27.7	43	27.2	
With distant metastasis	39	15.5	33	12.2		33	12.6	15	9.6	
Distant metastasis	145	57.5	178	66.9		129	57.6	100	63.3	

UP upfront surgery, *NT* neoadjuvant therapy

Thus, NAT may improve survival for patients without resection. In addition, the introduction of NAT is useful for identifying patients whose prognosis will improve after the resection. However, the low resection rate among NAT cases may be a critical issue. If a patient who experiences the development of unresectable PDAC after NAT had undergone upfront surgery without NAT, a long-term survival might have been expected. However, we could not clarify the issue in this study, and it needs to be studied further.

The improved prognosis in our study may have been attributable to the NAT protocols used. In particular, combination therapy with gemcitabine and S-1 (GS) was used in 74.6% of the NAC and 39.8% of the NACRT cases.

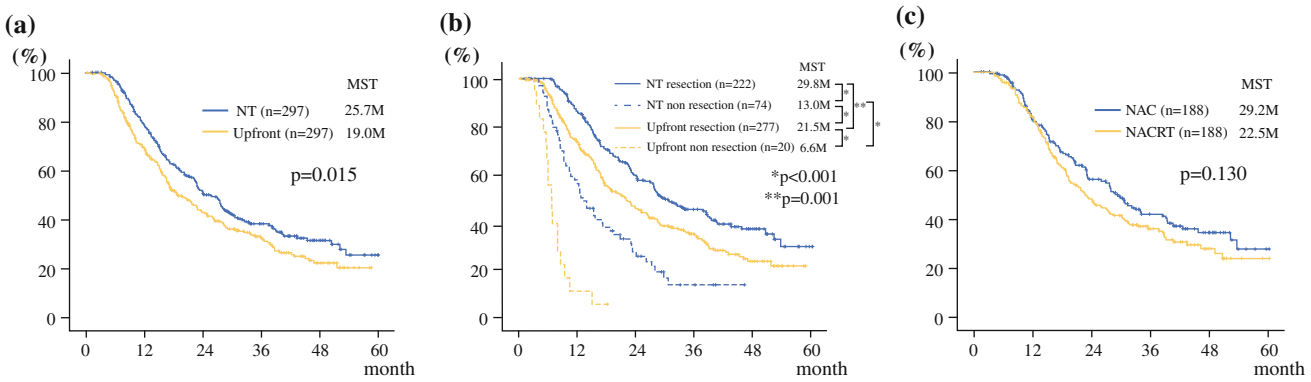

FIG. 2 **a** Comparison of overall survival for the intention-to-treat population based on upfront surgery and neoadjuvant therapy using PSM analysis. **b** Overall survival analyzed for upfront surgery and neoadjuvant therapy patients whether they underwent resection or not. **c** Comparison of overall survival for the intention-to-treat population based on neoadjuvant chemotherapy and combined neoadjuvant chemoradiotherapy using PSM analysis

A previous randomized trial comparing the effectiveness of gemcitabine alone, S-1 alone, and GS for unresectable PDAC showed that although survival did not differ significantly between treatments, the response rate was significantly better for GS than for gemcitabine alone.[16] Furthermore, Motoi et al.[17] conducted a multi-institutional phase 2 study with NAC using GS and showed that patients who underwent resection had an increased MST (34.7 months). Murakami et al.[18] also reported a longer prognosis for patients who received neoadjuvant GS chemotherapy for BRPC (MST, 27.1 months). Thus, neoadjuvant GS therapy may be a suitable treatment option for downstaging BRPC, although its effectiveness still needs to be evaluated in further clinical trials.

The advantage of combined radiotherapy as NAT remains unclear.[19,20] Radiation may increase the risk of bleeding in case of arterial resection. Therefore, it is important to clarify the advantage of NACRT over NAC. Our results showed that NACRT significantly reduced the rates of lymph node metastasis and local recurrence compared with NAC. However, the overall survival rate did not differ between the NAC and NACRT groups. Although radiotherapy is effective as a local treatment method for PDAC, BRPC is considered to be a systemic disease with microscopic distant metastasis.[8] Systemic control using systemic chemotherapy may be more important for improving the survival of patients with BRPC.

Recently, the advantage of multi-agent chemotherapy before performance of concurrent chemoradiotherapy to suppress recurrence of distant metastasis has been reported.[20,21] In our study, only 9.4% of the patients in the NACRT group underwent systemic chemotherapy before concurrent chemoradiation. In addition, the resection rate in the NACRT cases was significantly lower than in the NAC cases, and 53.5% of the patients in the NACRT group did not undergo resection due to distant metastasis. Concurrent chemoradiation has more adverse events, particularly gastrointestinal side effects, than systemic chemotherapy.[22] Therefore, the chemotherapy dose should be reduced when concurrent chemoradiation is introduced. Thus, an inadequate chemotherapy dose may have led to the low resection rate in this study. Therefore, systemic chemotherapy with a full dose may be needed before concurrent chemoradiotherapy to improve treatment outcomes in NACRT.

This study had several limitations. First, the study did not examine the reason for selection of NAT. Various factors may have caused ineligibility for surgery for the patients who selected NAT, including a comorbidity, and this may have resulted in the low resection rate for the NAT group. Second, data from some low-volume centers were included in this study, and patient volume may have affected the results. Third, it has been reported that the rate of R0 resections after NAT may be more closely related to a reduction in tumor cell density than to a real reduction in tumor diameter.[23,24] Thus, the evaluation of surgical margin after NAT may not have been exactly similar to that of upfront surgery. Fourth, various regimens for NAT were included, and the administration period varied for each patient. Therefore, regimens that help to improve the resection and survival rates need to be investigated in future studies.Despite these limitations, this study was the largest retrospective study to examine the clinical impact of NAC and NACRT.

In conclusion, this study showed the potential benefit of NAT for patients with BRPC. Our findings support the use of NAT for patients with BRPC. However, the survival benefit of combined radiotherapy with chemotherapy was not clarified. An appropriate regimen with effective systemic chemotherapy should be developed to improve the resection and survival rates after NAT.

TABLE 3 Univariable outcomes for propensity score-matched patients undergoing neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy between 2011 and 2013

	Before matching					After matching				
	NAC (n = 211)		NACRT (n = 319)		p value	NAC (n = 188)		NACRT (n = 188)		p value
	n	%	n	%		n	%	n	%	
Age (years)										
≥ 68	108	51.2	156	48.9	0.657	95	50.5	95	50.5	
< 68	103	48.8	163	51.1		93	49.5	93	49.5	
Sex										
Male	116	55.0	174	54.5	0.929	105	55.9	105	55.9	
Female	95	45.0	145	45.5		83	44.1	83	44.1	
Tumor location										
Head	158	74.9	230	72.1	0.485	147	78.2	147	78.2	
Body	53	25.1	89	27.9		41	21.8	41	21.8	
Pretreatment albumin (g/dl)										
≥ 3.9	145	68.7	205	64.3	0.304	134	71.3	134	71.3	
< 3.9	66	31.3	114	35.7		54	28.7	54	28.7	
Pretreatment CA19-9 levels (U/ml)										
≥ 180	107	50.7	140	43.9	0.131	89	47.3	89	47.3	
< 180	104	49.3	179	56.1		99	52.7	99	52.7	
Performance status										
0	182	86.3	274	85.9	1.000	169	89.9	169	89.9	
≥ 1	29	13.7	45	14.1		19	10.1	19	10.1	
Response rate										
CR/PR	51	24.2	71	22.3	0.673	47	25.0	44	23.4	0.810
SD/PD	160	75.8	248	77.7		141	75.0	144	76.6	
Resection										
Yes	170	80.6	220	69.0	**0.003**	151	80.3	133	70.7	**0.041**
No	41	19.4	99	31.0		37	19.7	55	29.3	
Surgical margin										
R0	140	82.4	189	85.9	0.399	127	84.1	116	87.2	0.501
R1/2	30	17.6	31	14.1		24	15.9	17	12.8	
Lymph node metastasis										
Negative	55	32.0	143	61.6	< **0.001**	52	34.0	89	62.2	< **0.001**
Positive	117	68.0	89	38.4		101	66.0	54	37.8	
Portal vein involvement										
Negative	95	55.9	145	65.9	0.047	84	55.6	90	67.7	0.039
Positive	75	44.1	75	34.1		67	44.4	43	32.3	
Initial recurrence pattern										
Local recurrence	54	44.6	34	23.4	< **0.001**	54	44.6	20	20.4	**0.002**
Only local recurrence	35	28.9	20	13.8		35	28.9	14	14.3	
With distant metastasis	19	15.7	14	9.7		19	15.7	6	6.1	
Distant metastasis	67	55.4	111	76.6		67	55.4	78	79.6	

NAC neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy

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DISCLOSURES There are no conflicts of interest.

ETHICAL STANDARDS This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was also approved by the relevant institutional review boards.

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