

# Optimal resection area for superior mesenteric artery nerve plexuses after neoadjuvant chemoradiotherapy for locally advanced pancreatic carcinoma

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## Abstract

Recently, several reports demonstrated the efficacy of neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACRT) for patients with borderline resectable (BRPC) and locally advanced unresectable pancreatic carcinoma (LAPC). The aim of this study was to evaluate the treatment response after NACRT, especially for nerve plexuses, and the optimal resection area for superior mesenteric artery nerve plexuses in BRPC and LAPC patients after NACRT.

A total of 17 patients with BRPC and LAPC received preoperative gemcitabine-based NACRT. The numbers of BRPC and LAPC patients were 13 and 4, respectively. We evaluated nerve plexus invasion by CT before and after NACRT, decided on the resection area of plexus invasion in SMA before NACRT, and compared the preoperative evaluation and clinicopathological findings.

In the plexus of the supra-mesenteric artery (pl-SMA), arterial nerve plexus invasion, in cases  $<90^\circ$ , all patients showed the absence of residual cancer in the resected specimen after NACRT. In cases between  $90^\circ$  and  $180^\circ$ , 1 of 2 patients (50%) showed nerve plexus invasion. In cases over  $180^\circ$ , all patients showed nerve plexus invasion. We could perform R0 resection in all 10 cases, and pl-SMA invasion disappeared in 6 of 7 BRPC patients.

We demonstrated the relationship between the angle of nerve plexus tumor invasion and treatment effect after NACRT. We could perform R0 resection in all pl-SMA invasion cases, deciding on the resection area of pl-SMA based on CT before NACRT.

**Abbreviations:** BRPC = borderline resectable, CT = computed tomography, LAPC = locally advanced unresectable pancreatic carcinoma, MRI = magnetic resonance imaging, NAC = neoadjuvant chemotherapy, NACRT = neoadjuvant chemoradiotherapy, PDAC = pancreatic ductal adenocarcinoma, pl-SMA = the plexus of the supra-mesenteric artery, RECIST = Response Evaluation Criteria in Solid Tumor.

**Keywords:** NACRT, pancreatic cancer, the plexus of the supra-mesenteric artery

## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the United States.<sup>[1]</sup> Despite recent advances in diagnostic and therapeutic techniques, PDAC remains one of the most lethal malignancies. The 5-year survival rate of patients with primary PDAC, even after complete

resection, is lower than 15%,<sup>[2]</sup> and the overall 5-year survival rate of patients with inoperable PDAC is very low, ranging from 0.4% to 4%.<sup>[3,4]</sup> Surgery with a curative intent remains the only therapeutic option with the potential for cure.<sup>[5,6]</sup> However, PDAC often invades major arteries and the portal vein system, and this makes surgical resection complicated and technically demanding. Therefore, a new treatment strategy for these patients is required.

Recently, several reports showed the efficacy of neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACRT) for patients with borderline resectable (BRPC) and locally advanced unresectable pancreatic carcinoma (LAPC).<sup>[7-11]</sup> However, it is difficult to decide on the appropriate area for R0 resection, especially when nerve plexuses invasion are near the supra-mesenteric artery (SMA) after NACRT.

The aim of this study was to evaluate the treatment response after NACRT, especially for nerve plexuses invasion in BRPC and LAPC patients, and to validate our surgical strategy on the dissection area of superior mesenteric artery nerve plexuses.

## 2. Materials and methods

### 2.1. Study design

This retrospective study reviewed all patients with BRPC or LAPC treated at Hokkaido University Gastroenterological

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Surgery I with gemcitabine-based NACRT between January 2005 and December 2014. The study was approved by the institutional review board of Hokkaido University.

**2.2. Eligibility criteria**

All protocols were performed after obtaining informed consent from all patients in accordance with the approved procedure at our hospital. Potential candidates for entry into this study underwent radiographic evaluation before treatment, including thin-slice abdominal computed tomography (CT) and magnetic resonance imaging (MRI). Patients were confirmed to meet the following criteria before the initiation of therapy: no radiographic evidence of metastatic disease, older than 20 years, radiographic evidence of tumor extension beyond the pancreas, resection criteria based on the NCCN guidelines 2016 version 2,<sup>[12]</sup> confirmed PDAC, based on pathological or cytological examination, before NACRT.

**2.3. Neoadjuvant CRT**

The NACRT regimen consisted of radiation therapy (50.4 gray in 28 fractions) combined with systemic chemotherapy, involving the intravenous administration of gemcitabine (150 mg/m<sup>2</sup>), concurrently initiated on days 1, 8, 15, 22, 29, and 36. After NACRT, we performed restaging imaging including CT to explore distant metastasis or the operative indication (Fig. 1).

**2.4. Response assessment**

Restaging was carried out 4 weeks after the end of NACRT by CT. Evaluation of the treatment efficiency for pancreatic cancer was performed according to Response Evaluation Criteria in Solid Tumor (RECIST).<sup>[13]</sup> Patients with a complete or partial response or stable disease with no distant metastasis underwent

surgical exploration to determine whether the tumor was resectable.

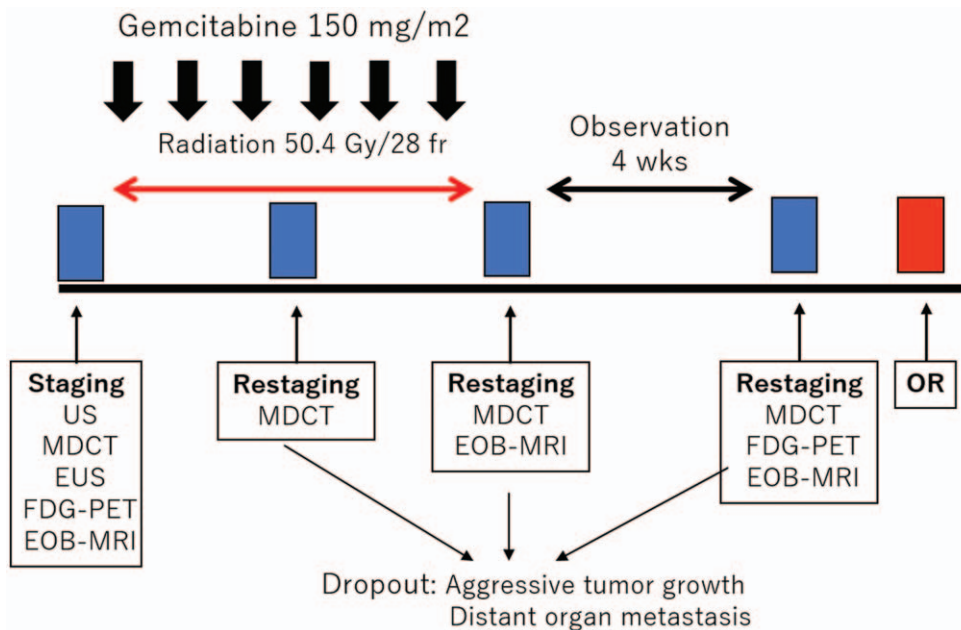
**2.5. Surgery**

Surgical exploration was performed 5 to 6 weeks after the completion of NACRT. The first step of surgery involved total exploration of the abdominal cavity to rule out contraindications to resection, such as hepatic or peritoneal metastasis. After ruling them out, pancreatectomy and systematic lymphadenectomy were performed with a curative intent. Superior mesenteric vein and/or portal vein resection was carried out in cases with possible or definitive tumor invasion. Basically, we performed hemi-circumferential dissection of the plexus of the supra-mesenteric artery (pl-SMA). The right side dissection was performed for pancreas head tumor, and the left side dissection for pancreas body and tail tumor. If the tumor showed an abutment exceeding 180° of the circumference of the SMA wall, the resection area was decided on the basis of CT before NACRT (Fig. 2A and B). In principle, combined arterial resection was not performed. All operations were conducted by the same surgical team, and all operative procedures were carried out in the same manner throughout the study period.

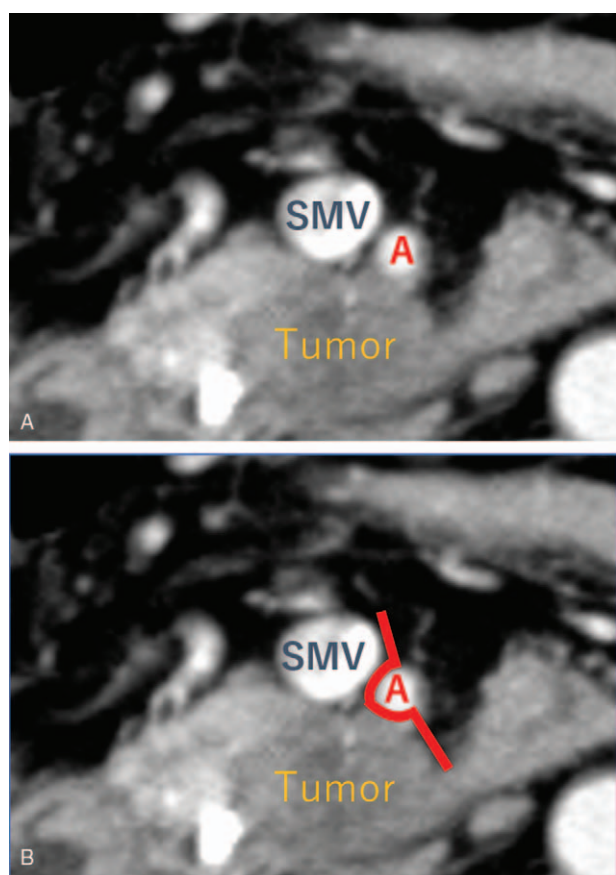
Adjuvant chemotherapy was basically applied unless contraindicated by the patient's condition. In short, the patients received treatments according to the protocols available at the time of treatment. Thus, the patients were given gemcitabine<sup>[14]</sup> or S-1.<sup>[15]</sup> Chemotherapy was initiated at <2 months after the operation in all patients who were considered eligible for the treatment.

**2.6. Pathologic examination**

Macroscopic and microscopic examinations were performed of every pancreatic specimen according to the same procedure. Each



**Figure 1.** The treatment protocol of NACRT for BRPC and LAPC patients. Radiation was administrated at a total radiation dose of 50.4 Gy, 5 times per week. The intravenous administration of gemcitabine (150 mg/m<sup>2</sup>) was initiated on days 1, 8, 15, 22, 29, and 36. BRPC = borderline resectable pancreatic carcinoma, LAPC = unresectable pancreatic carcinoma, NACRT = neoadjuvant chemoradiotherapy.



**Figure 2.** Representative example of how to decide on the resection area of pl-SMA. A BRPC patient. (A) A pancreatic head tumor showed an abutment not exceeding 180° of the circumference of the SMA wall, from 4 to 9 o'clock. (B) We decided on a resection area from 4 to 11 o'clock (bold line). BRPC= borderline resectable pancreatic carcinoma, pl-SMA=the plexus of the supra-mesenteric artery.

specimen was oriented based on anatomic structures and surgical marks. Before cutting the specimen, sections of the margins were submitted. We produced shave sections of the bile duct margin, pancreatic margin, and retroperitoneal margin. Then, the specimen was cut into 5-mm slices, parallel to this first section. All specimens were fixed with 10% buffered formalin, and embedded in paraffin. Deparaffinized sections were stained with hematoxylin-eosin and examined by light microscopy.

**2.7. Statistical analysis**

Patient records were prospectively entered into our database and completed by information obtained from a retrospective review of hospital and physician’s records. Analysis was performed using EZR.

**3. Results**

**3.1. Patient demographics and tumor characteristics before NACRT**

The mean patient age was 59.7 years old (SD, ±8.2 years). Nine patients were men and 8 were women. The location of the tumor was the pancreatic head in 15 patients and the body and/or tail in

**Table 1**

**Patient demographics before NACRT.**

	<b>N = 17</b>
Median age (age ± 2 SD)	59.7 ± 8.2
Sex (Male: Female)	9:8
Location (Ph: Pbt)	15:2
Arterial invasion (positive: negative)	6:11
Portal vein invasion (positive: negative)	12:5
Nerve plexus invasion (positive: negative)	15:2
Resectability BRPC: LAPC	13:4

BRPC= borderline resectable pancreatic carcinoma, LAPC=unresectable pancreatic carcinoma, NACRT=neoadjuvant chemoradiotherapy, SD=standard deviation.

2. Twelve cases were portal vein and/or supra-mesenteric vein invasion-positive and 5 were negative. Fifteen patients were nerve plexus invasion-positive and 2 were negative. Thirteen patients had BRPC, and 4 patients had LAPC (Table 1).

**3.2. Treatment response after NACRT**

Of the 17 patients planned to receive neoadjuvant chemoradiotherapy, a median of 5 cycles (range: 3–6) of neoadjuvant gemcitabine were administered. No serious adverse effects associated with neoadjuvant chemotherapy and no treatment-related deaths occurred.

Radiological responses included partial remission in 6 patients, stable disease in 5 patients, and progressive disease in 2 patients among BRPC patients, and stable disease in 4 LAPC patients. No patient achieved complete remission (Table 2).

**3.3. Comparison with CT evaluation of pre-NACRT and pathological findings**

Comparisons with CT evaluation of pre-NACRT and clinico-pathological factors with PDAC patients who received NACRT are shown in Table 3. Among the 17 patients, 5 of the 13 BRPC patients showed downstaging and 2 of the 4 LAPC patients showed downstaging. Only 4 patients had positive lymph nodes. BR patients showed lower rates of nerve plexus invasion. Seven (53.8%) of the BRPC patients were Evans classification IIb, and 3 (75%) of the LAPC patients were Evans classification IIb or III.

**3.4. CT evaluation and pathological response in pl-SMA patients**

Ten patients, 7 BRPC and 3 LAPC patients, showed pl-SMA invasion before NACRT. Based on our resection strategy for pl-SMA, we performed R0 resection in all cases, and pl-SMA

**Table 2**

**Treatment response after NACRT.**

<b>RECIST</b>	<b>BRPC (N = 13)</b>	<b>LAPC (N = 4)</b>	<b>Total (N = 17)</b>
PD	2	0	2 (11.8%)
SD	5	4	9 (52.9%)
PR	6	0	6 (35.3%)
CR	0	0	0

BRPC= borderline resectable pancreatic carcinoma, LAPC=unresectable pancreatic carcinoma, NACRT=neoadjuvant chemoradiotherapy, RECIST=PR at least 30% decrease, PD at least 20% increase, SD Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

**Table 3**

**Comparison with CT evaluation of pre-NACRT and pathological findings.**

	BRPC (N = 13)		LAPC (N = 4)	
	Pre-NACRT	Pathological findings	Pre-NACRT	Pathological findings
Stage IA/IIA/IIIB/IIIV (UICC 7th edition)	0/8/2/3/0	1/8/4/0/0	0/2/1/1/0	0/4/0/0/0
Positive lymph node metastasis	4 (30.7%)	4 (30.7%)	2 (50%)	0 (0%)
Positive nerve plexus invasion	11 (84.6%)	4 (30.7%)	4 (100%)	3 (75%)
Evans classification I/IIa/IIb/IIIV		1/5/7/0/0		0/1/1/2/0

BRPC = borderline resectable pancreatic carcinoma, LAPC = unresectable pancreatic carcinoma, NACRT = neoadjuvant chemoradiotherapy, Evans classification: tumor cell destruction Grade I < 10%, Grade IIa 10%–50%, Grade IIb 50%–90%, Grade III 90%+, Grade IV no viable cells.

invasion disappeared in 6 of the 7 BR patients. Three of the 10 patients survived with no recurrence (Table 4).

**3.5. Arterial pl invasion between CT before NACRT and pathological findings in pl-SMA invasion-positive patients after NACRT**

Fifteen of the 10 patients showed SMA contact before NACRT: 5 patients <90°, 2 patients between 90° and 180°, and 3 patients over 180°. In cases of <90°, all patients showed the absence of residual cancer in the resected specimens after NACRT. In the cases between 90° and 180°, 1 of the 2 patients (50%) showed pl-SMA invasion. In the cases over 180°, all patients showed pl invasion (Table 5). As shown in Figure 3, a 63-year-old female suffered from pancreatic head carcinoma that had contact with SMA of 120° before NACRT (Fig. 3A). After NACRT, the radiological tumor response was stable disease, and the tumor contact with SMA did not show any change (Fig. 3B). The macroscopic appearance of PDAC following NACRT can be seen in only small clusters within 2.1 cm. There is no tumor in pl-SMA. The initial size of the tumor is unidentifiable (Fig. 3C). Microscopically, extensive fibrosis is present surrounding the

neural band. In addition, there are monocytes that invade the fibrosis (Fig. 3D).

**4. Discussion**

This is the first report to describe the clinicopathological treatment effect of NACRT regarding pl-SMA invasion. We showed the relationship between the angle of nerve plexus tumor invasion before NACRT and the treatment effect after NACRT. And, we could perform R0 resection for all pl-SMA invasion cases, if the pl-SMA resection area was decided on the basis of CT before NACRT.

Several reports showed that patients who underwent complete pancreatic cancer resection had a favorable survival rate in comparison with surgical margin-positive cases.<sup>[16–18]</sup> However, surgery for BRPC and LAPC in contact with a major artery including the hepatic artery and SMA is highly controversial. The survival of patients who underwent combined resection and reconstruction of major arteries was reported to be significantly correlated with higher mortality rates.<sup>[19–21]</sup> More patients would be indicated for surgical treatment if tumor removal without co-resection of the arteries

**Table 4**

**CT Evaluation and pathological response in pl-SMA patients.**

	BRPC/LAPC	pl-SMA invasion pre → post NACRT	RECIST	pPL	Evans classification	R0/1/2	First site of recurrence
Case 1	BRPC	90° → 0°	PR	–	IIa	R0	Lung
Case 2	BRPC	90° → 0°	PR	–	IIa	R0	Liver
Case 3	BRPC	90° → 0°	SD	–	IIb	R0	Lung
Case 4	BRPC	90° → 60°	PR	–	IIa	R0	Lung, local
Case 5	BRPC	45° → 45°	SD	–	IIa	R0	Liver failure 3Y11M
Case 6	BRPC	120° → 120°	SD	–	IIb	R0	Lung
Case 7	BRPC	160° → 120°	PR	+	IIb	R0	Lung
Case 8	LAPC	210° → 210°	SD	+	IIb	R0	–
Case 9	LAPC	360° → 360°	SD	+	III	R0	–
Case 10	LAPC	210° → 210°	SD	+	IIa	R0	–

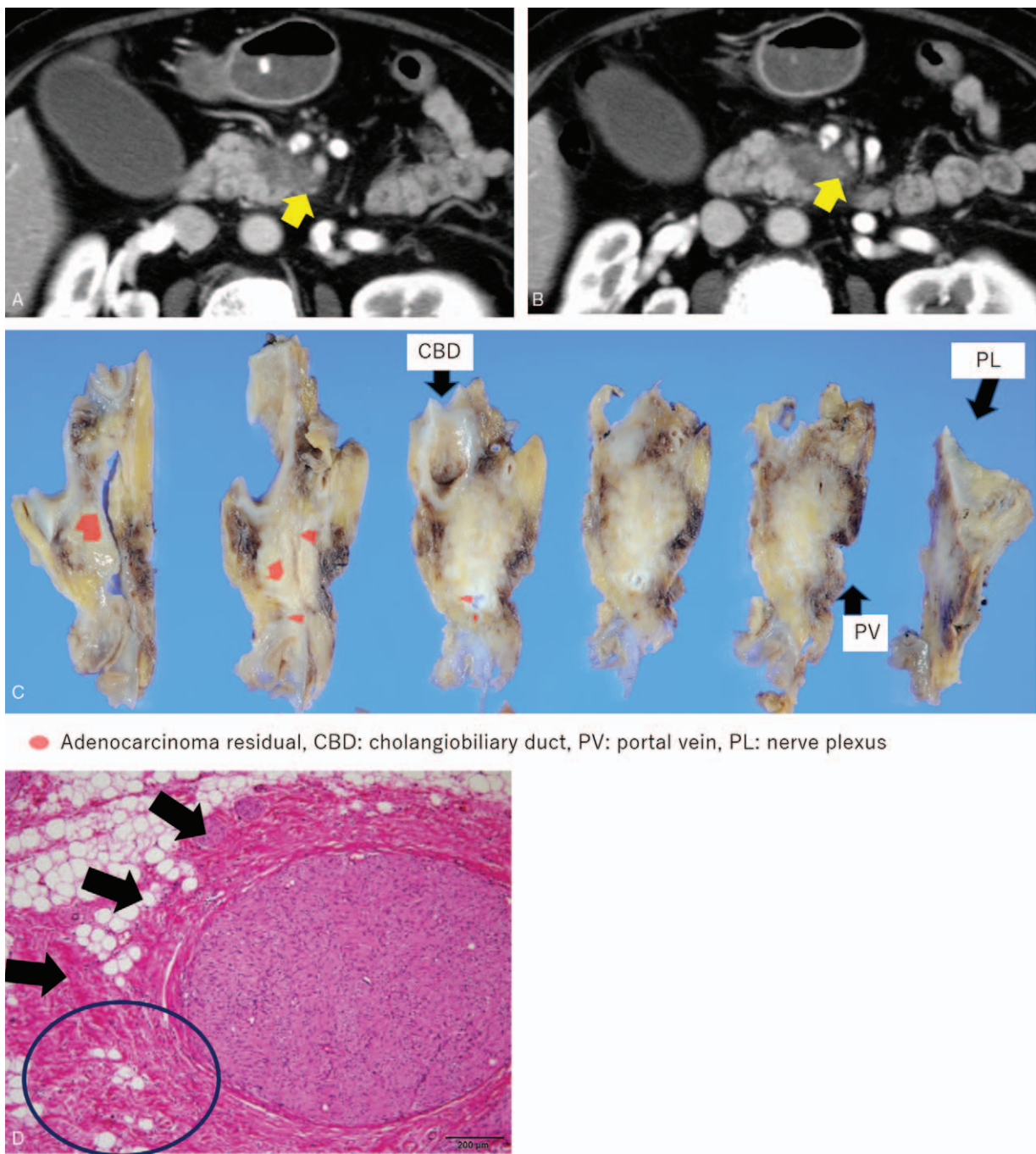
BRPC = borderline resectable pancreatic carcinoma, LAPC = unresectable pancreatic carcinoma, pl-SMA = the plexus of the supra-mesenteric artery, RECIST = PR at least 30% decrease, PD at least 20% increase, SD Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, pPL: pathological plexus invasion.

**Table 5**

**Nerve plexus invasion between CT before NACRT and pathological findings in pl-SMA invasion-positive patients after NACRT.**

pl-SMA invasion before NACRT by CT	N = 10	Pathological findings		pl invasion site
		pl invasion (+)	pl invasion (–)	
0 < <90°	5	0	5	
90° ≤ <180°	2	1	1	1 pl-SMA
180° ≤	3	3	0	1 phl, 2 pl-SMA

NACRT = neoadjuvant chemoradiotherapy, phl = pancreatic head nerve plexus first portion, pl invasion = nerve plexus invasion, pl-SMA = plexus of supra-mesenteric artery.



**Figure 3.** Representative case of BRPC, case 6, a 63-year-old female, pancreatic head carcinoma that had contact with SMA of 120° before NACRT (A). After NACRT, the tumor size was stable, and contact with the SMA remained unchanged (B). The macroscopic appearance of PDAC following NACRT can be seen only in small clusters within 2.1 cm. There is no tumor in pl-SMA. The initial size of the tumor is unidentifiable (C). Microscopically, extensive fibrosis is present surrounding the neural band. In addition, there are monocytes that invade the fibrosis (circled area in [D]). BRPC=borderline resectable pancreatic carcinoma, NACRT = neoadjuvant chemoradiotherapy, PDAC=pancreatic ductal adenocarcinoma, pl-SMA=the plexus of the supra-mesenteric artery, SMA=the plexus of the supra-mesenteric artery.

could be deemed oncologically feasible. Recently, neoadjuvant chemotherapy or chemoradiotherapy has been advocated for patients with BRPC and LAPC by several investigators.<sup>[7,22-25]</sup> Higher R0 resection rates after NACRT for patients with BRPC and LAPC have been reported.<sup>[7-10,26,27]</sup> A higher R0 resection rate might have contributed to the better overall survival of patients with arterial contact who received NACRT. However, little information is available on treatment strategies

including artery-preserving surgery for BRPC and LAPC in contact with major arteries. The typical findings associated with this factor are the presence of reticular opacities abutting the arteries, and the grainy appearance of dense periarterial tissue on tri-phasic contrast-enhanced MDCT. According to our results, we can perform R0 resection of pl-SMA in all cases if we decide on the resection area based on CT before NACRT

Nerve plexus dissection has been routinely advocated in Japan for achieving margin-negative resection, because pancreatic cancer tends to extend along the nerve plexus. The 2 important issues are achieving the resection margin, especially to the SMA, and preserving pl-SMA at least to the hemicycle to avoid uncontrollable postoperative diarrhea. Inoue et al<sup>[28]</sup> reported that following right hemicyrcum-ferential pl-SMA dissection, 29% of patients suffered from diarrhea, which could be controlled successfully using opioids. Nimura et al<sup>[29]</sup> reported the results of a randomized controlled trial, which found that postoperative weight loss associated with severe diarrhea for more than 6 months was more frequently encountered in patients undergoing an extended surgical procedure than in those undergoing a standard procedure. Furthermore, postoperative adjuvant chemotherapy improves the survival of patients with resected pancreatic cancer.<sup>[15,30]</sup> It is important for patients to undergo R0 resection and receive adjuvant chemotherapy to achieve improved survival. So, balanced resection may be required to allow patients to successfully complete the planned dose of adjuvant chemotherapy. To achieve R0 and balanced resection, our findings indicate that we can reduce the resection area of pl-SMA based on intraoperative frozen-section analysis of the resection margin after NACRT.

The tumor size and stage after NACRT are key indicators of the therapeutic effect. However, RECIST criteria may not accurately reflect the tumor response.<sup>[7,31]</sup> In this study, radiographic downstaging of disease in patients with BRPC and LAPC after NACRT was rare. The replacement of the tumor with fibrosis, which is observed on the histologic examination of resected patients, and radioinduced edema, may explain why the radio response to NACRT is modest and does not correlate well with the histologic response.<sup>[32–35]</sup> Therefore, we recommend the aggressive use of surgery in patients who have BRPC and LAPC with a suitable performance status, fully controlled comorbidities, and an absence of metastatic disease after NACRT.

In conclusion, we have demonstrated the relationship between the angle of nerve plexus tumor invasion and treatment effect after NACRT. We could perform R0 resection in all patients with pl-SMA invasion.

## Author contributions

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**Supervision:** Toshiya Kamiyama, Yusuke Uchinami, Tomoko Mitsuhashi, Akinobu Taketomi.

**Writing – original draft:** Takahiro Einama.

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