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Name of Journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 80623

Manuscript Type: REVIEW

**Comprehensive multimodal management of borderline resectable pancreatic cancer:
current status and progress**

management of borderline resectable pancreatic cancer

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Abstract

Borderline resectable pancreatic cancer (BRPC) is a complex clinical entity with specific biological features. Criteria for resectability need to be assessed in combination with tumor anatomy and oncology. Neoadjuvant therapy (NAT) for BRPC patients is associated with additional survival benefits. Research is currently focused on exploring the optimal NAT regimen and more reliable ways of assessing response to NAT. More attention to management standards during NAT, including biliary drainage and nutritional support, is needed. Surgery remains the cornerstone of BRPC treatment and multidisciplinary teams (MDTs) can help to evaluate whether patients are suitable for surgery and provide individualized management during the perioperative period, including NAT responsiveness and the selection of surgical timing.

Key Words: Borderline resectable pancreatic cancer; Neoadjuvant therapy; Resectability; Surgery; Multimodality treatment; Multidisciplinary teams.

Wu HY, Li JW, Li JZ, Zhai QL, Ye JY, Zheng SY, Fang K. Comprehensive multimodal management of borderline resectable pancreatic cancer: current status and progress. *World J Gastrointest Surg* 2022; In press

Core Tip: Borderline resectable pancreatic cancer (BRPC) is a type of pancreatic cancer with specific biological characteristics. To date, there is no unified comprehensive management for this disease. Thus, an evaluation of BRPC resection and neoadjuvant therapy (NAT) is needed. This review summarizes new resection methods and different NAT schemes, including treatment efficacy evaluation and management. This study also discusses the current progress of surgical treatment and the use of multidisciplinary teams (MDTs) to provide comprehensive multimodal management of BRPC treatment.

INTRODUCTION

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Pancreatic cancer (PC) has the poorest prognosis of all common cancers with a 5-year relative survival rate of only 11%. In the US, the PC incidence rate ranked 10th among males and 8th among females in 2022^[1]. Even with recent advances in treatment, survival has not improved significantly in the last 10 years^[2]. The only potentially curative treatment for this disease is surgical resection, however, 80–85% of patients are not candidates for resection due to nonspecific symptoms and a lack of early diagnostic methods^[3].

It is critical to identify specific BRPC patients who could be eligible for radical surgery. This disease is currently classified into four types for clinical management:

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resectable pancreatic cancer (RPC), borderline resectable pancreatic cancer (BRPC), and unresectable pancreatic cancer, including locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer. BRPC is further divided into pancreatic cancer with arterial invasion (BR-A) and pancreatic cancer with superior mesenteric vein/portal vein invasion only (BR-PV)^[15]. The indications for surgery have expanded over the past few decades with advances in surgical techniques and improved preoperative imaging precision. The term “borderline resectable” was first introduced by the MD Anderson Cancer Center group in 2006^[4]. Although surgery is technically feasible because it is localized and does not metastasize, BRPC carries a high risk of positive margins due to vascular infiltration^[5, 6]. In other words, the microscopic/macroscopic residual (R1/R2) resection rate is high while the margin-negative resection (R0) rate is significantly associated with poor prognosis and early recurrence^[7]. The preferred treatment for BRPC is neoadjuvant therapy (NAT) and reassessment for possible curative resection. NAT has an early clinical benefit against PC but there is no consensus on the optimal regimen for patients with BRPC. In addition, patient responsiveness to NAT and the optimal protocol for biliary drainage and nutritional support requires further study. Over the past decade, there has been a lack of consensus about the optimal timing of surgery after NAT, the extent of lymph node dissection and arterial resection and reconstruction, and the need for intraoperative

adjuvant therapy. Since BRPC patient management involves several medical fields, multidisciplinary teams (MDTs) are needed to assure the different treatment modalities are connected to maximize their benefit.

REAPPRAISAL OF RESECTABILITY CRITERIA

Historically, the resectability of pancreatic cancer has been dependent on the contiguous relationship between the celiac axis (CA), the superior mesenteric artery/vein (SMA/SMV), the portal vein (PV), and the common hepatic artery (CHA). Improvements in surgical methods and post-surgical care have meant that tumor infiltration of the SMV/PV, SMA, HA, or CA is no longer a surgical contraindication. With the development of surgical techniques, especially increase in safety of vessel reconstruction, the range of resectability as defined by anatomy has expanded over the past 20 years^[8-11]. The National Comprehensive Cancer Network (NCCN) guideline is the most widely used standard for the resectability of anatomy for BRPC patients because it distinguishes between pancreatic body/tail and pancreatic head/uncinate process tumors^[12]. To assure uniformity and standardization in reporting and trial enrollment, this standard also eliminates the anatomically ambiguous terminology previously used to describe the interface between the tumor and nearby blood vessels (such as vascular “abutment,” “encasement,” “occlusion,” and “impingement”), in favor of defining $\geq 180^\circ$ as a detailed degree of the interface between the tumor and each vessel^[13].

BRPC is shown to be a particularly aggressive disease that may not benefit from upfront surgery. Biological parameters are used to evaluate resectability^[14]. Some patients have no peripheral vascular invasion and imaging results indicate that the lesions can be resected and preoperative CA19-9 Levels are significantly increased. Other patients have positron emission tomography/computed tomography (PET/CT) results that indicate that the regional lymph nodes (LN) are suspicious and positive. Thus, a new international consensus on BRPC classification was suggested by the International Association of Pancreatology (IAP) in 2017^[15].

IAP-BR-criteria added biological factors including CA19-9 ≥ 500 IU/mL and regional LN metastasis by biopsy or PET/CT into the BRPC definition based on anatomic criteria (BRPC type-a), defined as BRPC type-b. BRPC type-a with the addition of conditional factors such as Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 or more is defined as BRPC type-c. In a cohort of 369 patients with RPC, Kato *et al* compared IAP-BR-criteria and NCCN-BR-criteria and found that IAP-BR-criteria were more effective at predicting prognosis^[16].

In 2021, potential modifications to the current resectability classification based on IAP-BR-criteria, including additional candidate factors, were discussed at the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS)^[17]. At this meeting, further candidate factors were proposed. ¹ PET/CT maximum standardized uptake values (SUVmax) of the primary tumor were suggested for use as biological indicators to evaluate resectability and therapy response after NAT, while CEA, CA125, or DUPAN-2 were proposed for use as surrogate tumor markers in Lewis antigen-negative patients. For conditional host-related factors, age, Charlson-Dayo comorbidity, and markers of the ⁴ systemic inflammatory response such as the modified Glasgow Prognostic Score (mGPS) or the neutrophil/Lymphocyte ratio (NLR) were also suggested for evaluating the resectability. More interestingly, new prognostic “genomic” markers that include ⁴ germline DNA damage repair (DDR) mutations such as S100A2, S100A4, KRAS, and therapeutic target markers, including microsatellite instability (MSI), BRCA1, BRCA2, and other homologous recombination deficiency (HRD) gene mutations, were also considered to have application potential and to be of value for further research.

Several genomic, transcriptomic, morphological, proteomic, metabolomic, and immune subtyping methods for PC were reviewed by Huang *et al*^[18], of which the immune and morphological subtypes are associated with prognosis. Wartenberg *et al* used immunohistochemical staining of immune cells in the tumor microenvironment to classify pancreatic cancer into three types: immune-escape, immune-rich, and immune-exhausted. The immune-rich subtype was associated with a better prognosis^[19].

Kalimuthu *et al* classified PC into gland-forming and non-gland forming subtypes by histopathology and reported that patients with <40% non-gland forming subtypes had superior overall survival (OS)^[20]. The other classification subtypes were primarily used to predict the feasibility of chemotherapy and the efficacy of immunotherapy or targeted therapies.

In summary, resectability aims to make resection “meaningful” and promote a more favorable prognosis rather than maintaining a single focus on the resection rate. The various subtyping approaches for pancreatic cancer should be integrated and simplified using multiomics. Current studies still rely solely on the anatomical definition of BRPC (Figure 1). Future research needs to consider BRPC biological factors and use standardized resectability evaluation criteria to ensure that findings are comparable across studies.

NEOADJUVANT THERAPY FOR BRPC

To date, ~20% of PC patients are surgical candidates at the moment of diagnosis, 30% are BRPC or LAPC, and 50% have metastatic disease and are ineligible for surgery^[3]. The architectural features of BRPC are such that even after extensive dissection of the nerve plexus along arteries, upfront surgery without NAT frequently results in a high R1 resection rate^[5, 6]. The current standard for BRPC treatment typically starts with preoperative chemotherapy or chemoradiotherapy, because NAT could degrade the stage and improve the R0 resection rate^[21-25]. In addition to controlling local disease, the absence of tumor progression following NAT is a selection criterion for identifying tumors that are less biologically invasive or respond well to systemic therapy. Thus, this treatment can help to identify optimal surgical candidates. Moreover, because many postoperative patients cannot accept adjuvant therapy due to complications, NAT can help to reduce the incidence of pancreatic fistula and increase the completion rate of multimodality therapy. In summary, NAT is primarily used to select suitable surgery candidates and improve the tolerance of preoperative treatment^[6, 26, 27].

Long-term results of the PREOPANC trial were published in 2022^[27]. The findings revealed a significant difference in the OS of patients who received NAT (3 cycles of neoadjuvant gemcitabine + 2 cycles of radiotherapy with 36 Gy) and those who received upfront surgery. At a median follow-up of 59 mo, the neoadjuvant chemoradiotherapy group had a median survival time (MST) of 15.7 mo, while the upfront surgery group had a MST of 14.3 mo (HR, 0.73; 95%CI, 0.56–0.96; $P = .025$). Moreover, the 5-year OS rate for patients who underwent NAT or upfront surgery was 20.5% and 6.5%, respectively. The NAT group also had a higher R0 resection rate than the upfront surgery group (72 vs. 43%, $P < 0.001$). Although single gemcitabine is no longer a standard treatment for PC patients, the PREOPANC trial showed that gemcitabine combined with NAT, surgery, and adjuvant chemotherapy was effective against BRPC. Jacob *et al* conducted a meta-analysis and subgroup analysis of 5 RCTs in which BRPC was included and found that NAT was associated with higher OS of patients with BRPC (HR 0.61, 95%CI 0.44–0.85; $P = 0.004$; $I^2 = 59\%$). Both neoadjuvant chemotherapy (NACT) (HR 0.54, 95%CI 0.34–0.87; $P = 0.01$; $I^2 = 64\%$) and neoadjuvant chemoradiation (NACRT) resulted in a higher OS than upfront surgery (HR 0.74, 95%CI 0.58–0.95; $P = 0.02$; $I^2 = 7\%$)^[28]. Since NAT improves the R0 resection rate and OS, European Society of Medical Oncology (ESMO)^[29] and NCCN guidelines^[12] recommend NAT over upfront surgery for BRPC.

Neoadjuvant chemotherapy or neoadjuvant chemoradiation therapy?

Due to the lack of RCT data, there is no consensus on a preferred neoadjuvant therapy regimen. However, NCCN guidelines^[12] recommend fluorouracil-leucovorin-irinotecan-oxaliplatin/modified fluorouracil-leucovorin-irinotecan-oxaliplatin (FOLFIRINOX/mFOLFIRINOX) ± radiation or gemcitabine/nab-paclitaxel (GNP) ± radiation as the first-line regimens^[12]. A SWOG-1505 preliminary analysis was reported more recently. This study evaluated mFOLFIRINOX and GNP in the NAT setting of RPC and found that the GNP arm was associated with a higher median disease-free survival (DFS) (14.2 vs 10.9 mo, $P = 0.87$) and a complete or moderate pathological

response (42% *vs* 25%) than the mFOLFIRINOX arm. However, the resection rate, R0 resection rate, and 2-year OS ¹⁹ did not differ between the groups^[30]. Of note, there was no significant difference in the toxicity profile of the GNP and mFOLFIRINOX groups in this research. A phase II study conducted by Kondo *et al* included 47 patients with BRPC-arterial contact (BRPC-A) who received six cycles of a neoadjuvant gemcitabine, nab-paclitaxel plus S-1 (GAS) regimen. The R0 rate was 86%, and ¹ the 2-year OS rate and median OS time among 47 eligible patients were 70.1% and 41.0 mo, respectively^[31]. More RCTs are needed to compare these two first-line neoadjuvant chemotherapy regimens.

For PC patients with known BRCA1/2 or PALB2 mutations, NCCN guidelines recommend FOLFIRINOX/mFOLFIRINOX or GNP plus platinum complex treatment^[12]. Similar to breast cancer, key proteins involved in homologous recombination during PC include BRCA1 and BRCA2, and PALB2 is a critical regulator of BRCA2 function^[32-34]. Prior studies have shown that platinum-based treatment increases the OS of patients with advanced PC who have germline mutations in BRCA1, BRCA2, or PALB2 ^[35-37]. A retrospective study found that patients with these mutations had an overall response rate (ORR) of 58% while those in the control group had an ORR of 21% ($P = 0.0022$). In addition, the real-world progression-free survival (PFS) ⁸ was 10.1 mo for patients with these mutations and 6.9 mo for controls (HR 0.43; 95%CI 0.25–0.74; $P = 0.0068$)^[38].

The role of radiation or chemoradiation during NAT for BRPC remains unclear^[39]. NACRT uses radiotherapy to sterilize tumor boundaries that are in contact with vasculature and chemotherapy to treat any undiagnosed micro-metastatic disease. Intensity-modulated radiation therapy (IMRT), stereotactic body ¹⁸ radiation therapy (SBRT), three-dimensional conventional radiation therapy (3D-CRT), and intraoperative radiation therapy (IORT), have all been used for patients with BRPC^[40]. Retrospective evidence suggests that NACRT may be associated with a higher proportion of margin-negative resections than NACT^[41].

Studies have further divided the current NACRT regimen into concurrent chemoradiotherapy with or without induction chemotherapy (Table 1). Until now, RCTs that directly compare NACRT and NACT are lacking in patients with BRPC. A021501 study enrolled 126 patients with BRPC, of whom 70 (55.6%) and 56 (44.4%) were randomized into an NACT arm and an NACRT arm, respectively. The NACT arm received eight doses of mFOLFIRINOX while the NACRT arm received eight doses of mFOLFIRINOX followed by a hypofractionated protocol that uses SBRT 33-40 Gy or image-guided radiotherapy (RT) with 25 Gy. After NAT, patients without disease progression underwent a pancreatectomy along with four additional doses of oxaliplatin-calcium-folate-fluorouracil (FOLFOX6). Of the first 30 patients in each arm, the R0 rate was achieved in 10 (33%) and 17 (57%) patients in the NACRT and NACT arms, respectively, resulting in the closure of the NACRT arm and continuation of the NACT arm. The 18-month OS rates were 66.7% and 47.3% in the NACT and NACRT arms, respectively, while the median OS of patients was 29.8 and 17.1 mo in the NACT and NACRT arms, respectively. These findings suggested that NACT alone was associated with a more favorable prognosis than NACRT among patients with BRPC^[42].

ESPAC-5F is a four-arm, multicenter, phase II trial that evaluated different approaches to NAT among patients with BRPC. Ninety patients were randomly assigned to four arms: upfront surgery, two cycles of gemcitabine + capecitabine followed by surgery, four cycles of FOLFIRINOX followed by surgery, and NACRT with 50.4 Gy over 28 fractions with concurrent capecitabine followed by surgery. There was no statistical difference in R0 rates between the arms (14%, 17%, 18%, and 37% for the upfront surgery, gemcitabine + capecitabine arm, FOLFIRINOX, and NACRT arms, respectively). There was a trend toward a higher R0 rate in the NACRT arm, but the intention-to-treatment (ITT) R0 rate was 19%, which was like the ITT R0 rates of the other three arms. It is worth noting that patients in the NAT arms had a higher 1-year OS than those in the upfront surgery arm (77% *vs* 42%, HR = 0.27; *p* < 0.001), but the NACRT arm did not confer a more prominent survival benefit than other arms^[43]. Multiple single-institution retrospective studies have evaluated the efficacy of

neoadjuvant SBRT for BRPC and LAPC, showing excellent R0 resection rates and promising OS^[44-46]. These results contradict the A021501 study, potentially because the A021501 study had low rates of pancreatectomy (35%) and treatment completion (18%). It is worth mentioning that SBRT has a theoretical synergy with emerging immunotherapies, the effectiveness and safety of which have been confirmed by previous basic research and clinical studies^[47, 48].

In conclusion, the superiority of NACT and NACRT for BRPC remains unclear and there is still controversy about the most appropriate NAT regimen. Current research findings suggest that the clinical benefit of NAT over upfront surgery is tentatively certain. BRPC patients could actively participate in NACRT/SBRT/IMRT-related clinical trials but all radiotherapy procedures should be performed in a large experienced pancreatic center. A robust NAT study would ideally compare NACT with NACRT including 3D-CRT, IMRT, or SBRT.

Total neoadjuvant therapy for BRPC

Most trials for BRPC have performed ³ surgical resection between short-course neoadjuvant therapy (SNT) and adjuvant therapy. As the biological behavior of PC has become better understood, some researchers have proposed a new modality called total neoadjuvant therapy (TNT). TNT was designed to provide postoperative adjuvant therapy in a preoperative setting and includes concurrent chemoradiotherapy delivered before or after systemic chemotherapy^[159]. The theoretical advantages of TNT over SNT include its ability to (1) reduce the risk of delayed chemotherapy for postoperative patients and (2) improve patient compliance and tolerance and ensure drug dose and intensity. A retrospective study found that TNT increased the surgical resection and R0 rates among BRPC and LAPC patients^[49]. However, another study reported that while TNT improved the complete pathological remission rate, there was no statistical difference in the median OS between the two groups compared with the SNT mode^[50]. In the SWOG-1505 trial, less than half of the patients completed systematic treatment, causing some doubt about whether TNT can help patients to receive the maximum

amount of systemic therapy^[30]. The use of the TNT mode for PC patients is still in its initial stages. The problems associated with TNT are the same as those of NAT, and this treatment modality still lacks a highly accurate and effective evaluation mechanism.

Response assessment of BRPC after neoadjuvant therapy

While findings from RCTs of adjuvant chemotherapy given to patients receiving upfront surgery have suggested that the ideal time frame for perioperative systemic chemotherapy is 6 mo^[51], there is no agreement on the length and cycle of NAT for BRPC patients. To make this decision, NAT endpoints will need to be defined to assess responsiveness and tumor re-staging during treatment. NAT patients are typically evaluated every 2 mo to measure treatment toxicity and assess objective clinical, radiologic, biochemical, or metabolic responses. However, there are few effective biomarkers or imaging techniques available to monitor treatment responses among patients with pancreatic neoplasms^[50, 52].

CA19-9 and Computed Tomography (CT) are the only techniques widely used to assess objective response rates following NAT due to the absence of relevant high-quality study findings. However, there is a growing consensus that CT has important limitations including its inability to distinguish between the tumor and fibrosis or inflammation or to accurately determine tumor responsiveness to NAT^[53, 54]. Studies indicate that a significant proportion of unresectable patients, assessed by CT using the RECIST criteria following NAT, finally achieve an R0 resection^[55, 56].

Several radiologic approaches are being used to evaluate NAT responses including dual-energy CT (DECT), ¹⁸Ffluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT), endoscopic ultrasound (EUS), and diffusion-weighted magnetic resonance imaging-MRI (DWI-MRI). Since variations in standard uptake values (SUVs) may represent the metabolic response of cancer to chemotherapy and FDG uptake is highly correlated with tumor load and viability, FDG-PET/CT is used to evaluate NAT efficacy toward a variety of solid malignancies^[57-59]. The metabolic response observed by FDG-PET/CT offers a functional assessment of tumor responsiveness compared

to RECIST criteria. Akita *et al*^[57] demonstrated that maximal SUVs and tumor size were dramatically reduced following NACRT in BRPC and RPC patients. However, pancreatic tissues incorporate lots of stroma and a high infiltration of inflammatory cells such as macrophages and neutrophils and NAT can further promote both inflammatory cell infiltration and fibrosis. As a result, posttherapy SUV may not accurately reflect the pathological response. In addition, Akita *et al* found that a favorable period for FDG-PET/CT assessment is 8 wk post-radiation. A histological inspection of the resected specimens at that time did not reveal inflammatory alterations in the peripancreatic tissues^[57].

The differentiation of tumor composition can be discriminated by DECT which uses simultaneous scanning with special stages of electricity. DECT can precisely differentiate between PC and continual mass-forming chronic pancreatitis. Moreover, the iodine concentration for the duration of DECT can differentiate between pancreatic patients who successfully respond to chemotherapy and those who don't. This finding suggests that DECT may be used to identify fibrosis caused by NAT^[60, 61].

DWI-MRI can recognize tissue diffusivity characteristics and be used to perform quantitative and qualitative tumor evaluations. Cuneo *et al*^[62] reported that tumor apparent diffusion coefficient (ADC) values of DWI-MRI were specifically linked to the amount of tumor cell destruction. Responders and non-responders had different pretreatment ADC values, suggesting that the ADC values of DWI-MRI prior to NAT can predict the histologic response of BRPC patients.

EUS is rarely used to evaluate NAT response in pancreatic cancers. The influence of stroma is weak so the value of elastography for chemotherapy and radiation therapy remains unknown^[63].

Radiomics is a quantitative image analysis technology that mines the in-depth features of images, allowing for the extraction of data on tumor intensity, shape, size, or volume from digital images. This technique is used as a biomarker for disease diagnosis, grading, prognosis evaluation, and responses to treatment and can both support personalized clinical decisions and improve individualized treatment

options^[64]. The role of radiomics to evaluate NAT responsiveness has been studied extensively in other solid tumors. Braman *et al* found that a combined intratumoral and peritumoral radiomic feature identified by contrast-enhanced MRI can predict the complete response of breast cancer patients following NAT^[65]. Several studies have assessed the use of radiomics to aid PC prognosis and NAT responsiveness (Table 2). Ciaravino *et al* reported that 17 LAPC or BRPC patients reached the resectable stage after NAT, and CT texture analysis showed that there was a statistically significant difference between kurtosis before and after NAT ($P = 0.0046$)^[66]. A prospective study by Borhani *et al* included 39 patients with RPC or BRPC, all of whom had completed surgery after NAT. This study reported that the histologic response could be assessed by ¹ pretreatment mean positive pixel (MPP) at a fine- and medium-level filtration, pretreatment kurtosis at a medium-level filtration and changes in kurtosis, and higher MPP was related to favorable histologic response (OR 1.06; 95% CI, 1.002-1.12)^[67].

Currently, artificial intelligence (AI) technologies, including deep learning and machine learning, are also being developed to evaluate NAT efficacy in PC patients. One study divided 81 pancreatic cancer patients receiving NAT into a response group (333 images) and a non-response group (443 images). A model using only the deep learning (convolutional neural network, CNN) had an area under the curve (AUC) of 0.738, while a combined model incorporating CA19-9 and deep learning had an AUC of 0.785^[68]. Not only does the discrimination and accuracy of this model need to be improved, but also small sample size, and heterogeneity caused by different NAT receptors, resectability, and CT slice thicknesses limited the generalizability of the study. New research has combined radiomics with AI. ³ Delta radiomics is a quantitative approach used to assess the treatment-induced net change of radiomic features in a set of longitudinal images. This technique could theoretically be used for the early prediction of NAT treatment responsiveness. Nasief *et al* analyzed ³ 28 daily CT sets collected during routine CT-guided CRT along with pathological treatment response data from 90 patients with RPC or BRPC to obtain delta-radiomic features related to therapy response^[69]. The results showed that 13 delta-radiomic

features (DRFs) passed the T-test and linear-mixed-effects models and changed significantly after 2–4 wk of treatment. The best-performing machine learning model for differentiating good *vs* poor responders was designed using the ¹⁷normalized-entropy-to-standard-deviation-difference (NESTD), kurtosis, and coarseness. The AUC of this model was 0.94, but due to the limitation of sample size and the lack of biological interpretability of machine learning model, delta radiomics model distance to practical clinical application, additional studies are needed to validate the reproducibility of the model and to address the issues of model interpretability as well as visualization applications.

While CA19-9 is typically used to track the effectiveness of NAT among patients with BRPC, the predictive value of this marker remains limited. The relevance of a NAT-induced decrease in CA19-9 Levels has not been clearly defined, and the cut-off CA19-9 value for diagnosing NAT responders remains controversial. Prior studies have shown that a 20–50% drop in CA19-9^[70-73] or an absolute value of 72–400 (U/mL) CA19-9 after NAT^[74-76] was associated with resectability or a favorable prognosis following resection. In addition, among patients who are Lewis antigen expression negative or have abnormal bilirubin levels due to cholestasis, serum CA19-9 is inapplicable. Thus, more accurate and focused biomarkers are required to evaluate NAT responsiveness^[77-79]. While circulating cell-free deoxyribonucleic acid (cf-DNA), circulating tumor cells (CTCs), exosomes, and ephrin typeA receptor 2 in tumor-derived extracellular vesicles (EphA2EV) all show good correlations with NAT responsiveness, larger sample RCTs are required to validate their roles^[80-82]. For BRPC patients who received gemcitabine and S1 followed by radiotherapy, the augmentation of partial response rates after NAT was associated with positive expression of human equilibrative nucleoside transporter 1 (hENT1) and negative expression of thymidylate synthase^[83]. Moreover, Glazer *et al* demonstrated that the neutrophil/Lymphocyte ratio (NLR) is associated with the OS of BRPC patients who undergo surgical resection after NAT^[84].

Non-invasive and accurate tumor restaging after NAT may be possible through AI approaches such as machine learning and deep learning, combined with different

device-based radiomics and novel biomarkers. This will inform the choice of timing for post-NAT surgery among BRPC patients.

Nutritional support for BRPC patients during neoadjuvant therapy

Malnutrition is a common problem among PC patients, two-thirds of whom are diagnosed with anorexia at the first visit^[85]. NAT significantly alters the nutritional status of patients with esophageal and gastric cancer, which impacts postoperative recovery and surgery rates^[86]. However, there is a lack of high-level evidence-based studies on the changes in nutritional status among BRPC patients during NAT as well as the optimal strategy for nutritional status assessment and support.

A retrospective study published in 2020 showed that the preoperative nutritional risk, an independent prognostic factor for OS (HR 5.24, $P = 0.013$), was significantly higher among patients receiving NAT ($P = 0.026$)^[87]. Moreover, Kim *et al* found that the average pre-NACT prognostic nutritional index (PNI) was higher than the post-NACT PNI, with a difference of 2.98. Moreover, if the change value of PNI, obtained by pre-NAT PNI minus post-NAT PNI, is lower than -1.94, it is a risk factor for the OS of PC patients following NAT^[88]. Thus, a nutritional evaluation of BRPC patients should be routinely performed, especially those who have received NAT.

In addition to scoring using conventional nutritional screening tools, CT-based body composition analysis is being increasingly used to evaluate the nutritional status of patients with PC. Several studies of body composition have shown that sarcopenia, defined by a reduction in the skeletal muscle index (SMI) of the third lumbar spine, and an increase in the visceral fat area (VFA) and subcutaneous fat area (SFA), are high-risk factors for postoperative pancreatic leakage and can affect the long-term prognosis of PC patients^[89-93]. Sandini *et al* found that patients with BRPC or LAPC who received NAT had a significant loss of adipose tissue. However, there was little reduction in lean body mass. This study also showed that NAT-induced increases in muscle mass were a reliable indicator of respectability^[94].

At present, there is no unified standard management for the nutritional support of BRPC patients during NAT. An expert consensus from Spain in 2021^[95] recommended that BRPC patients receiving NAT should (1) receive a nutritional screening by Malnutrition Universal Screening Tool (MUST) before NAT, (2) receive nutrition support with a MUST score ≥ 1 , and (3) be taking oral nutritional supplements (ONS). A position paper from the International Study Group on Pancreatic Surgery (ISGPS) for nutritional support and therapy in pancreatic surgery^[96] recommended that when one of the following criteria is met, nutritional support for patients with PC during NAT should be seriously considered: (1) weight loss $>15\%$, (2) a BMI $<18.5 \text{ kg/m}^2$, (3) a subjective global assessment score C or nutritional risk score >5 , or (4) a serum albumin $<30\text{g/L}$ (no evidence of liver or renal dysfunction).

Nutritional therapy during NAT for BRPC patients should be individualized to each patient's performance status. New nutritional screening tools should be designed to incorporate body composition analysis and corresponding cutoffs should be developed for clinical application.

Preoperative biliary drainage during neoadjuvant therapy

Most pancreatic tumors are located in the head of the pancreas, which is prone to malignant biliary obstruction (MBO) and affects hepatic function, coagulation, and fibrinolysis. While it remains unknown whether early preoperative biliary drainage (PBD) or straightforward surgery is the better option^[97-99], it is reasonable for BRPC patients to choose PBD. Since NAT is routinely required for patients with BRPC and the NAT period is generally 2–6 mo^[100], PBD should be performed to ensure that chemotherapy can be safely completed without interruption from cholangitis or hepatic insufficiency while waiting for surgery^[101].

There are two critical types of PBD: percutaneous biliary drainage (PTBD) and endoscopic retrograde biliary drainage (ERBD), including endoscopic biliary stenting (EBS) and endoscopic naso-biliary drainage (ENBD)^[102]. Before the introduction of ERBD, PTBD was the preferred type of biliary drainage. However, retrospective studies

from Japan showed lower survival and higher rates of peritoneal recurrence among patients treated with PTBD than those receiving ERBD^[103, 104]. In addition, in a retrospective study of patients undergoing PTBD or ERBD, the PTBD group had significantly higher hepatic metastasis, more wound infections, and lower OS^[99]. Sasahira *et al* found that ENBD was associated with much less dysfunction than EBS in MBO^[105]. However, ENBD may not be suitable for long-term preoperative cure because of its impact on patient quality of life and disruptions in the enterohepatic circulation of bile salts^[106].

Thus, EBS is repeatedly used when PBD is performed, and the used stents can be extensively divided into plastic stents (PS) and self-expandable metal stents (SEMS), including full-covered self-expandable metal stents (FCSEMS), partially covered self-expandable metal stents (PCSEMS) and uncovered self-expandable metal stents (USEMS). Some studies have found that FCSEMS is more effective than PS for MBO among BRPC patients receiving NAT. Several RCTs have verified that the median patency of SEMS is 4–9 mo or more, which is notably longer than that of PS^[107–110]. A recent RCT from Japan which included patients with BRPC who required PBD before gemcitabine plus nab-paclitaxel (GNP) based NAT, illustrated that the rate of stent dysfunction was drastically lower in the FCSEMS arm than in the PS arm (18.2% vs. 72.8%, $P = 0.015$), and showed that FCSEMS and PS had a similar safety profile and medical costs^[111]. A retrospective study of 749 patients with MBO found that covered self-expandable metal stents (CSEMS) and USEMS had similar rates of clinical success in bile-duct obstruction treatment and patency duration. However, the USEMS arm was associated with less tumor growth than the CSEMS arm (76% vs. 9%, $P < 0.001$)^[112]. While no studies have directly compared PCSEMS and FCSEMS, a decision on the choice of biliary stents for BRPC patients receiving NAT would ideally be made following a joint evaluation by a surgeon and a pathologist.

EUS-guided biliary drainage (EUS-BD) has emerged as a positive approach for biliary drainage when ERCP is unsuccessful and can reduce the likelihood of pancreatitis, injury to the pancreatic tissue, and irritation. However, due to the risk of potential bile

leakage and the high demand at the endoscopist level, more studies are needed to compare the efficacy and safety of EUS-BD with other methods for preoperative biliary drainage^[113].

While study findings remain insufficient, available data suggest that SEMS is more suitable in PBD for patients with BRPC during NAT. However, the choice of PS is most suitable when the window period for preoperative therapy is short. More high-quality studies are required to demonstrate the most appropriate method for PBD during NAT.

UPDATE ON INTRAOPERATIVE STRATEGIES FOR BRPC

Lymph node dissection and vascular reconstruction

Lymph node recurrence is an important part of the postoperative recurrence of PC^[114]. There remains some controversy about the scope of surgical lymph node dissection, and most researchers believe that expanding regional lymph node dissection cannot improve patient prognosis. However, a few studies indicate that there is value in expanding dissection^[115, 116]. Lymph nodes in the arterial and portal regions are the main sites for the local recurrence of PC^[117]. A series of meta-analyses showed no significant increase in ⁵ the median survival time and 1-, 3-, and 5-year survival rates of patients receiving extended lymphadenectomy in pancreaticoduodenectomy (EPD) versus standard lymphadenectomy in pancreaticoduodenectomy (SPD) and an increased risk of complications^[118, 119]. The standard ¹⁴ lymph node dissection ranges are ⁵, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b for pancreatic head cancer. For cancers of the pancreatic body and tail, dissection of stations 10, 11, and 18 is standard and dissection of station 9 is only recommended for patients with cancer of the pancreatic body^[120]. No definitive studies have illustrated the benefit of expanded lymph node dissection for BRPC patients. The concept of Heidelberg triangle surgery was proposed by the University of Heidelberg in Germany^[121]. In addition to conventional lymph node dissection, all lymph nodes, vessels, and nerve tissue in the Heidelberg triangle can be dissected.

One study found that about one in five patients who received pancreatoduodenectomy (PD), distal pancreatectomy (DP), or distal pancreatectomy with abdominal axis resection (DP-CAR) for pancreatic tumors had lymph node recurrence. Of these, peri-pancreatic head (peri-Ph), para-aortic, and SMA lymph node recurrences were the most common, accounting for 12%, 11%, and 10%, respectively^[122]. The precise type of lymph node dissection should be chosen according to the tumor's location and other characteristics.

BRPC is often associated with the invasion of important vessels such as the celiac trunk and common hepatic artery, resulting in low clinical resection rates. Studies illustrate that combined external pancreatic atherectomy (AR) in patients with tumor invasion of SMA, CA, and HA is often associated with more postoperative complications and higher mortality rates and has no impact on survival. Thus, reconstructive pancreatic resection with arterial invasion is not recommended for this patient population^[123, 124]. However, some recent studies have questioned these results, suggesting that in highly specialized pancreatic centers, even atherectomy can be performed safely and promote long-term outcomes similar to standard surgery for radical cure^[125, 126]. Distal pancreatectomy with abdominal axis resection (DP-CAR) or modified Appleby resection improves the safety of BRPC combined with atherectomy. Since this technique allows en block resection of the celiac axis and the common hepatic artery, arterial reconstruction is not required. However, the feasibility and effectiveness of this procedure remain to be evaluated in future clinical studies.

Many studies have focused on how to increase the rate of radical resection and thus improve survival among patients with BRPC. The depth of arterial tumor invasion has a greater impact on radical resection than the circumferential size of the tumor invasion^[127]. Arterial wall invasion in PC is often confined to the arterial epithelium and rarely breaks through the outer elastic layer of dense connective tissue. Some studies have proposed the concept of "arterial sheath debridement," using the loose tissue between the arterial epithelium and the outer elastic layer as the anatomical plane to debride the peri-arterial nerve fiber connective tissue, to obtain radical resection while

avoiding severe complications associated with arterial resection^[128]. However, the current understanding of treatment for junctional resectable patients and the common use of preoperative radiotherapy have shown an increase in peri-arterial tissue inflammation and fibrosis. This has made it difficult to free the affected artery and completely debride peri-arterial tissue invaded by the tumor during surgery.

Most PC patients have SMV-PVax involvement. However, radical surgery combined with vein resection and reconstruction is shown to be safe and feasible with a good prognosis in several studies^[129, 130]. Dua *et al* propose various vascular anastomoses such as longitudinal vascular suture, transverse vascular suture, end-to-end vascular anastomosis, vessel wall patch repair, and autograft or artificial vascular reconstruction^[131]. The most appropriate approach is chosen based on the circumference and length of the invading vessels. There is no consensus about the best mechanism for revascularization, but direct suturing, patch repair, and autograft are preferred because of the increased risk of thrombosis associated with artificial implants.

SURGERY COMBINED WITH INTRAOPERATIVE RADIOTHERAPY

Patients who undergo pancreatic tumor resection are prone to local recurrence and distant metastasis after surgery. Local control of the tumor is essential to prolonging survival and improving quality of life. Previous studies have shown that neoadjuvant chemotherapy, radiotherapy, and extracorporeal irradiation therapy can improve local and regional control and survival. However, EBRT is limited in its clinical application by the challenge of delivering sufficient doses of radiation. In contrast, intraoperative radiation therapy (IORT) has the unique advantage of delivering the maximum dose of ionizing radiation precisely to the tumor, tumor bed, surrounding lymph node area, superior mesenteric margin, portal vein, and areas at high risk for recurrence, while surgically removing radiation-sensitive organs such as the small intestine from the radiation field to minimize damage to surrounding normal tissue. In addition, the surgeon and radiation therapist can coordinate intraoperatively under direct vision to determine the exact location and extent of the irradiated target area to avoid missing

risk areas. Simultaneous completion of surgery and radiotherapy can significantly shorten the treatment course of patients. IORT patients have a median survival time of 19.1 mo, a 2-year survival rate of 42.1%, and a 2-year local control rate of 83.7% after resection, which are all higher than patients in the control group. In addition, the pain relief rate after IORT is 94.9%^[132]. Harrison *et al* found that after FOLFIRINOX-based NAT, survival rates at 12, 24, 48 and 60 mo were 99%, 79%, 47%, and 28%, respectively, for all forms of resection plus IORT (10 Gy). For patients who only received IORT (20 Gy), the survival rates at 12, 24, 48, and 60 mo were 98%, 49%, 13%, and 9%, respectively^[133]. The overall complication rate of IORT was 26.7%, including gastroparesis, gastrointestinal bleeding, pancreatic leakage, and celiac leakage. Clinical and experimental studies have shown that IORT at 10–20 Gy is still well tolerated by organs, even in patients with combined revascularisation^[134]. These findings suggest that patients with postoperative pathology showing residual tumors visible to the naked eye at the margins or positive margins on frozen pathology, or patients with moderate or severe pain and ineffective pain relief, can improve their prognosis and quality of survival following combined IORT.

Radioactive Particle Implantation

¹²⁵I particle implantation directly implants particles into tumor tissues to achieve precise treatment of tumor. Gamma rays released by these particles reach tumor cells with reduced decay and a high effective dose, causing tumor tissues to receive more radiation and undergo higher levels of necrosis. The gamma-ray irradiation distance is short so most of the energy can be absorbed by tumor tissues, minimizing the damage to surrounding normal tissues. In addition, toxic side effects, including radiation-induced inflammation, seed displacement, pancreatic fistula, bleeding, and gastrointestinal obstruction are minimal^[135]. A refined and standardized treatment approach with reasonable preoperative planning of the particle number and distribution and accurate prediction of energy distribution will improve treatment efficacy and reduce the incidence of acute adverse effects. By maximizing the radiation

dose to the tumor and reducing radiation damage to the surrounding normal tissues, local invasion of the tumor is significantly inhibited and patient OS is increased. However, there is still a lack of corresponding research to support whether BRPC patients will benefit from this treatment.

Intraoperative cryoablation therapy and intraoperative combined cryoablation and hyperthermia

Intraoperative cryoablation therapy (IOCT) is a tumor treatment technique based on the idea that physical action kills cells. Lesion tissue is repeatedly frozen and thawed, tumor cells appear to be dehydrated and burst, and the microstructure inside the broken tumor cells can activate the immune system to control tumor progression. In addition, platelets in the blood vessels around the tumor accumulate and form thrombi to destroy the blood supply to the tumor, thus indirectly killing the tumor cells. Compared with other solid tumors, PC cryoablation treatment is more difficult because the anatomical location of the pancreas is deeper and the path selection is smaller, making it a challenge to cover a satisfactory treatment area. Some studies have also shown that intraoperative combined cryoablation and hyperthermia (ICCH) can complement the advantages of cold and heat ablation. Compared with cryoablation alone, combined cold and heat ablation is associated with improved surgical efficiency, tumor control, and complication rates^[136, 137].

Irreversible electroporation

Irreversible electroporation (IRE), also known as NanoKnife, is a new non-thermal physical ablation technique. By applying short and high pulse voltages between two electrodes made of unique materials, the original membrane potential of the cell is altered, creating irreversible nanoscale pores in the lipid bilayer of the membrane and causing disruption of cellular homeostasis that leads to cell death.

This ablation method only causes cell death in a specific area while preserving the integrity of the tissue scaffold and the fibrous structure of the cells. In contrast, the

adjacent tissues, including blood vessels and surrounding normal tissues are not damaged, avoiding the "heat sink effect" in the ablation area and facilitating tissue repair. IRE is used to achieve local ablation by disrupting cellular homeostasis and destroying or controlling tumor growth. This technique is more selective to tissues and cells than other modalities and can protect the surrounding blood vessels, bile ducts, and other important tissues, and cause the physiological death of cells in the ablation area to avoid excessive tissue necrosis and increase the body's immune burden. The addition of IRE to conventional therapy promotes significantly longer patient survival than that of historic controls^[138]. Papoulas *et al* showed that intraoperative IRE and PD can be used successfully in appropriate BRPC patients to achieve clear microdissection margins^[139], minimizing the risk of local recurrence and improving outcomes.

MULTIDISCIPLINARY BRPC PATIENT TEAMS

Multidisciplinary teams (MDTs) have become a popular way to guarantee the best care for cancer patients and reliably improve the diagnosis and treatment of PC^[140-142]. Unfortunately, there is a lack of data on the role and criteria of MDTs in PC. Syed *et al* found that the multidisciplinary pancreas conference (MDPC) ¹⁵ led to a significantly higher rate of adjuvant chemotherapy initiation than has been previously reported^[143]. Hansen *et al* analyzed 7,015 patients with diagnosed or suspected pancreatic and duodenal tumors who received MDTs and compared the results from similar patients seen at the same hospital before the implementation of MDTs^[144]. In this study, patients with advanced stages of disease who received MDTs had a higher rate of surgery, including vascular reconstruction, and there was no increase in morbidity and mortality. Neither study identified long-term survival benefits of MDTs for PC patients.

As discussed previously, there is no broad consensus on the standard of care for BRPC, so the core task of MDTs is diagnosis and assessment for resectability and treatment, including the selection of a surgical scheme and NAT regimen and the evaluation of NAT responsiveness^[145]. The MDT mode established around BRPC should (1) build on the outpatient department of MDTs and involve experts from

different clinical specialties and subspecialties, including but not limited to pancreatic surgery, gastroenterology, radiology, medical oncology, pathology, nutriology, therapeutic radiology, and anesthesiology, (2) ensure that specialist nurses in the clinic serve as the hub for various experts, (3) ensure stability and communication between team core members, (4) require that medical records are quantitatively evaluated and a long-term follow-up system is established, and (5) ensure that MDT time, personnel, location, and equipment are fixed (Figure 2). MDTs can formulate a regular review plan for patients, dynamically evaluate treatment effects and adverse events, adjust the treatment plan as needed, and terminate treatment if necessary. The MDT can also carry out multidisciplinary research, including clinical trials.

A 2019 study found that MDTs from different centers varied substantially in resectability rates for non-metastatic PC^[145]. The researchers suggested that for patients with PC, uniform MDT patterns and criteria require further exploration. Large sample-sized and multicenter studies are required. In addition, it is necessary to reduce the heterogeneity that results from differences in the equipment used across centers.

CONCLUSION

BRPC management has entered the era of multimodality therapy with a single surgical treatment. In the past 20 years, more studies have identified that surgical treatment for PC is insufficient. Even extensive surgery is a local treatment, while cancer, especially PC, is a systemic disease. Thus, appropriate management for BRPC should not only focus on improving surgical rates but also assess how to maximize the survival benefit of radical surgery through the rational selection of patients along with individualized neoadjuvant regimens and surgical modalities.

This review provides a comprehensive discussion of current multimodality treatment regimens for patients with BRPC, including the assessment of resectability, the overall management of neoadjuvant therapy, advances in surgical modalities, and preliminary exploration of MDTs. Several clinical trials are exploring optimal NAT regimens, which confer a long-term survival benefit for BRPC patients, the results of

these trials can be followed in the future. Using precision medicine, the assessment of resectability at the molecular and genetic levels becomes possible, suggesting that molecular targeted therapy or immunotherapy could be a breakthrough for BRPC treatment. The combination of AI and multiomics, including genomic, transcriptomic, and radiomics emerges as a promising tool that could be used to develop personalized management for patients with BRPC. However, large clinical trials are required to establish more clearly defined protocols.

Radical resection is currently the cornerstone of PC treatment, and intraoperative adjuvant therapy regimens continue to evolve. The first step to maximize the benefits of surgery is to accurately select “suitable surgical candidates.” MDTs need to focus on the full personalized management of patients with BRP, using radiology combined with tumor biology and general status to assess and evaluate resectability and multimodality treatment options.

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