Review Article

A patient-centered, multidisciplinary approach to treating borderline resectable pancreatic adenocarcinoma

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Abstract: The cancer-related death rate for pancreatic ductal adenocarcinoma (PDAC) has shown little improvement over the past decade, and PDAC is expected to be the second leading cause of cancer-related deaths by 2030. This is partly because most patients with PDAC present with metastatic (40%) or locally advanced (40%) disease, and only a minority of patients (20%) present with resectable or borderline resectable (BR) PDAC and are considered potential candidates for pancreatectomy, the only curative treatment available. Borderline resectability is a unique category within pancreatic cancer staging that represents tumors that are technically resectable, with or without vascular resection and reconstruction, but that are at high risk of harboring occult metastases at the time of diagnosis or positive margins if pancreatectomy is performed *de novo*. It assesses multiple dimensions of resectability including anatomy, biology, and condition. A multidisciplinary approach is essential to optimize each dimension and improve outcomes among patients with BR pancreatic adenocarcinoma. Here, we outline the evolution of the pancreatic cancer staging system as it pertains to surgical resectability, describe the influence this staging system has had on treatment, and review the evidence that guides a multidisciplinary approach to workup, staging, and treatment of patients with BR PDAC.

Keywords: Borderline resectable pancreatic cancer (BR pancreatic cancer); multidisciplinary; treatment; evidence

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths in the United States but accounts for only 3% of new cancer diagnoses (1). Although the cancer-related death rate for many other solid organ malignancies has declined, the cancer-related death rate for PDAC has not shown similar improvement over the past decade, and PDAC is expected to be the second leading cause of cancer-related deaths by 2030 (2). This is partly because most patients with PDAC present with metastatic (40%) or locally advanced (40%) disease (3). A minority of patients (20%) present with resectable or borderline resectable (BR) PDAC and are considered potential candidates for pancreatectomy, the only curative treatment available. Here, we outline the evolution of the pancreatic cancer staging system as it pertains to surgical resectability, describe the influence this staging system has had on treatment, and review the evidence that guides a multidisciplinary approach to workup, staging, and treatment of patients with BR PDAC.

Defining BR PDAC: an evolving staging system

Anatomic origin

Historically, PDAC was considered resectable if it appeared radiographically localized without involvement of adjacent mesenteric vessels—the celiac axis, common hepatic artery, superior mesenteric artery and vein, and portal vein. Involvement of these vessels represented a high risk for positive margins at surgery and poor oncologic outcomes following it. Some surgeons recognized that complete resection could be achieved with vascular resection and reconstruction in highly selected patients (4,5). Enhanced selection through the use of first-line chemotherapy subsequently broadened the potential for complete resection and was hypothesized to improve longevity (4,6-8). As such, "borderline resectable" became a term to signify tumors that are technically resectable, with or without vascular resection and reconstruction, but that are at high risk of harboring occult metastases at the time of diagnosis or positive margins if pancreatectomy is performed *de novo* (9,10).

At its inception, "marginally resectable" (as it was reported in literature published in 2001) represented an entirely anatomic designation, and this concept became the foundation for the first clinical classification of BR PDAC outlined by the National Comprehensive Cancer Network in 2006 (9-12). BR PDAC staging now differentiates pancreatic head/uncinate process tumors from pancreatic body/tail tumors. Staging has also evolved to omit confusing nomenclature (e.g., "abutment", "encasement", "occlusion", and "impingement") used in prior classification systems to describe the tumor-vessel interface, or the relationship between the tumor and the adjacent blood vessels, in favor of a detailed descriptor of the degree of tumor-vessel interface between the tumor and each vessel (<180° or ≥180°) to help standardize radiologists' reporting and trial enrollment inclusion.

Over the past two decades, several pancreatic oncology societies and cancer centers have outlined their preferred anatomic definitions, including those proposed by the Americas Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, the Society for Surgery of the Alimentary Tract (13,14), the Alliance for Clinical Trials in Oncology (15), The University of Texas MD Anderson Cancer Center (9,14), and Medical College of Wisconsin (16). Each group of definitions is designed to outline objective radiographic criteria to inform treatment decisions. *Table 1* provides a review of the anatomic differences among the more commonly used criteria to define resectable, BR, and locally advanced PDAC.

Beyond anatomy: BR PDAC dimensional staging

The University of Texas MD Anderson Cancer Center proposed that borderline resectability should not be limited to a solely anatomic designation but should also reflect the biologic thumbprint of an individual cancer and the baseline physiologic capacity of each patient. This model is a much more patient-centric approach to staging compared with the original tumor-centric approach. This comprehensive definition was first introduced in 2008 and was included in the guidelines for potentially curable pancreatic cancer by the American Society of Clinical Oncology (ASCO). This definition was also the foundation for the international consensus criteria for BR PDAC in 2017 (15,17).

Three distinct dimensions of disease are captured within this system: BR-anatomic (BR-A), BR-biology (BR-B), and BR-condition (BR-C). Anatomic factors include the historic criteria for tumor-vessel interface as outlined in *Table 1*. Biologic factors include potentially resectable disease based on anatomic criteria but with clinical findings suspicious for, but without radiographic confirmation of, distant metastases or regional lymph node metastases diagnosed by biopsy or positron emission tomography. Biologic factors also include elevated (>500 units/mL) serum carbohydrate antigen 19-9 (CA 19-9), the most widely used serologic tumor marker in PDAC. Conditional factors include potentially resectable disease based on anatomic and biologic criteria but Eastern Cooperative Oncology Group (ECOG) performance status of two or more, making resection a riskier treatment option.

The definition of BR PDAC can be unidimensional or multidimensional (e.g., A, B, C, AB, AC, BC, or ABC). By incorporating anatomy, biology, and condition into a staging system, it is possible to stratify a patient's unique clinical phenotype into a nomenclature that is understandable among all oncologists. This approach to staging has resulted in a shift in the way oncologists view pancreatic cancer: it is readily accepted that occult disease is present in most patients and, therefore, pancreatectomy is considered more cautiously, the unique role that each dimension has on resectability is critically assessed, and there is greater

Table 1 Anatomic definitions based on TVI of resectable, BR, and locally advanced PDAC as proposed by the AHPBA/SSAT/SSO, the Alliance Group, The University of Texas MDACC, and the MCW

Vessel	Group definition	AHPBA/SSAT/SSO (13,14)	Alliance (15)	MDACC (9,14)	MCW (16)
CA	Resectable	Clear fat planes, no involvement	No extension	No extension	No evidence of TVI
	BR	TVI <180° without stenosis or deformity	TVI <180°	TVI <180° without stenosis or deformity; periarterial stranding forming a convexity	TVI <180°
	Locally advanced	TVI ≥180°	TVI ≥180°	TVI ≥180° and no technical option for reconstruction	Type A: TVI ≥180° but does not extend to aorta and amenable to reconstruction. Type B: TVI ≥180° with extension beyond bifurcation of PHA
SMA	Resectable	Clear fat planes, no involvement	No extension	No extension; normal fat plane between the tumor and the artery	No evidence of TVI
	BR	TVI <180° without stenosis or deformity	TVI <180°	TVI <180° without stenosis or deformity; periarterial stranding forming a convexity against the vessel	TVI <180°
	Locally advanced	TVI ≥180°	TVI ≥180°	TVI ≥180°	Type A: TVI ≥180° but <270°. Type B: ≥270°
CHA	Resectable	Clear fat planes, no involvement	No extension	No extension	No evidence of arterial abutment
	BR	Short segment TVI <180° without tumor contact with the PHA; GDA TVI ≥180° with short segment TVI ≥180° at CHA without CA involvement	Short segment TVI (of any degree) amenable to resection and reconstruction	Short segment TVI of any degree that is amenable to reconstruction, typically at the GDA	TVI <180° or short segment TVI ≥180° without extension to CA or PHA
	Locally advanced	Involvement not amenable to reconstruction	Non-reconstructible involvement	Encased and no technical option for reconstruction	Type A: TVI ≥180° with extension to CA and amenable to reconstruction. Type B: TVI ≥180° with extension beyond the PHA
SMV/PV	Resectable	No evidence of TVI, distortion, tumor thrombus, or venous encasement	TVI <180°, without occlusion	Patent	Tumor-induced narrowing of ≤50%
	BR	TVI of any degree with or without occlusion and amenable to reconstruction	TVI ≥180° and/or short-segment occlusion of the SMV-PV amenable to reconstruction	TVI ≥180° with or without occlusion; amenable to reconstruction	Tumor-induced narrowing of >50% amenable to reconstruction
	Locally advanced	Any non-reconstructible involvement or major venous thrombosis extending several centimeters	Any non-reconstructible involvement	Occluded and no technical option for reconstruction	Occlusion without obvious option for reconstruction

TVI, tumor-vessel interface; BR, borderline resectable; PDAC, pancreatic ductal adenocarcinoma; AHPBA, Americas Heapto-Pancreato-Biliary Association; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology; MDACC, MD Anderson Cancer Center; MCW, Medical College of Wisconsin; CA, celiac axis; PHA, proper hepatic artery; SMA, superior mesenteric artery; CHA, common hepatic artery; GDA, gastroduodenal artery; SMV, superior mesenteric vein; PV, portal vein.

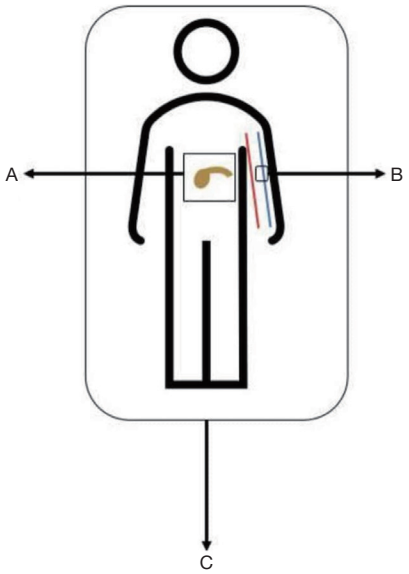

Figure 1 Three dimensions that cumulatively define borderline resectability in PDAC. A, anatomy; B, biology; C, condition. PDAC, pancreatic ductal adenocarcinoma.

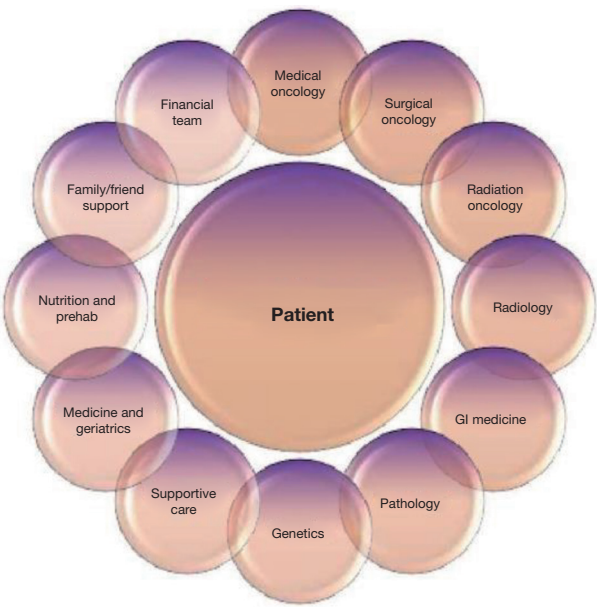

Figure 2 A patient-centered, multidisciplinary approach to management of BR PDAC. BR, borderline resectable; PDAC, pancreatic ductal adenocarcinoma; GI, gastrointestinal.

reliance on input from all medical disciplines as to the best strategy to optimize treatment success. *Figure 1* illustrates the multidimensional staging of BR PDAC.

The multidisciplinary team: identifying and engaging key members

When starting a clinical journey with a patient who is diagnosed with BR PDAC, it is essential to recognize that the path should be founded on the individual. The best treatment plan is ultimately defined by the patient: their symptoms; their unique clinical, serologic, and radiographic staging; their family history; and with their goals of care in mind.

The most important conversation is the first one. This conversation should collect valuable information about each patient's clinical symptoms, baseline function and lifestyle, familial support, and goals of care. The conversation should also provide an opportunity to outline the treatment options and introduce the multidisciplinary team members integral to the proposed treatment.

Figure 2 displays an approach to patient-centered care and depicts some of the key members necessary to deliver the highest level of multidisciplinary care. Data suggests that there is an objective value in engaging a multidisciplinary team. A multidisciplinary strategy for patients with pancreatic cancer allows more accurate diagnosis and staging, a higher receipt of guideline-concordant treatment, and higher accrual to clinical trials (18-21). Johns Hopkins reported that a multidisciplinary clinic resulted in change of management in 24% of patients and enrolled 78% of patients in the National Familial Pancreas Tumor Registry (19). Gardner *et al.* also demonstrated that patients who were treated in a multidisciplinary setting had a significantly shorter duration to first treatment and shorter total number of clinic consultations prior to initiating therapy (18).

Establishing a diagnosis and developing a treatment plan

In the simplest terms, the steps that should be taken when faced with a new pancreatic mass are as follows: (I) name it, (II) stage it, and (III) treat it.

Name it: pathologic confirmation and parallel treatment preparation

Diagnostic confirmation is dependent on tissue biopsy. Esophagogastroduodenoscopy with endoscopic ultrasound (EUS) is most often used to establish the diagnosis (22). EUS uses a high-frequency transducer at the tip of the endoscope that facilitates the generation of high-resolution images of the pancreas through the stomach or duodenum (23).

EUS is regarded as the most sensitive imaging modality for the detection of pancreatic lesions, with a pooled sensitivity rate of 94% (24-42). This modality is specifically useful for the detection and confirmation of small (<3 mm) pancreatic lesions and is superior to the detection offered by computed tomography or magnetic resonance imaging (93% for EUS, 67% for computed tomography, and 53% for magnetic resonance imaging) (26). On EUS, most solid pancreatic lesions are depicted as heterogeneous, hypoechoic masses that can be biopsied with fine-needle aspiration or core needle biopsy to provide pathologic confirmation (23).

Furthermore, endoscopy allows simultaneous endoscopic retrograde cholangiopancreatography-guided biliary decompression in patients who present with obstructive jaundice (43). Preoperative endoscopic retrograde cholangiopancreatography-guided biliary stenting is also a prophylactic tool and is the preferred approach for patients with non-obstructed pancreatic head masses who plan to undergo neoadjuvant chemotherapy and thus will experience delay surgical bypass (44). This procedure is often performed with sphincterotomy followed by trans-papillary placement of a metal or plastic stent over a guidewire. Metal stents are preferred over plastic stents owing to a lower risk of complications such as stent dysfunction and cholangitis (45,46). Although plastic stents are cheaper, technically more compliant, and easier to deploy, they result in more frequent replacements with a patency on the order of 3 months compared with 6–9 months or longer for metal stents (47).

Stage it: a multidimensional approach to local and systemic staging

Anatomy

A pancreatic protocolled computed tomography study of the abdomen and pelvis is the best modality to identify the anatomic relationship of a tumor to the surrounding vasculature. Intravenous iodinated contrast at a volume of 150 mL should be rapidly infused at a rate of 5 mL/second, slices should be constructed at <3 mm with overlap, and at least two postcontrast acquisitions should be included: a late arterial and venous phase. In the late arterial phase, the tumor is discernable as a hypodense mass in a background of pancreatic parenchyma. The venous phase is generally the best for determining the relationship of the tumor with surrounding vasculature and assessing the liver for hepatic metastases. Coronal and sagittal views are reformatted and aid in determining arterial and venous vascular involvement (48).

Biology

CA 19-9 is measured in every patient who presents with PDAC. Although serum CA 19-9 has little use in the 10% of patients who are nonproducers and is difficult to comprehend in patients with biliary obstruction, CA 19-9 is the only US Food and Drug Administration–approved biomarker in PDAC (49,50). Normal values range from 0 to 37 U/dL. Although most patients with PDAC present with elevated values of CA 19-9, a value ≥500 U/mL is generally considered the threshold for defining borderline resectability at MD Anderson. This value is founded on clinical observation but is statistically arbitrary.

Owing to the limitations of CA 19-9 as a reliable biomarker in nonproducers, there is growing enthusiasm for the use of circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) as universal serologic biomarkers in PDAC. ctDNA and CTCs can be collected from the peripheral and portal venous blood to potentially quantify systemic disease burden (51-56). Given the added benefit of assessing the tumor mutational profile, it is also realistic to anticipate the forthcoming ability to predict response to therapy by the presence and volume of a tumor's ctDNA or CTCs (57,58).

Condition

ECOG performance status is used to assess each patient at the time of presentation with PDAC. Any patient who has an ECOG performance status of ≥2 is considered to have BR PDAC according to conditional criteria (15).

Age is not captured within the ECOG performance score but is an important component of condition among patients with PDAC. Because PDAC affects a predominately elderly population, with a median age at diagnosis of 70 years, it is important to engage a geriatrician, when appropriate, who can provide useful information such as the predicted non-cancer survival at 5 and 10 years based on comorbidity, functional, and mental status. This information can be

helpful in making treatment decisions (59,60).

Treat it: neoadjuvant therapy and dynamic metrics to follow response

All patients with BR PDAC, when defined using the criteria outlined above, should be considered for neoadjuvant therapy according to ASCO guidelines for potentially curable pancreatic cancer (17). Although this is founded on low-quality evidence, it is considered a strong recommendation (17).

Two trials, the PREOPANC I and a Korean trial by Jang *et al.*, have compared neoadjuvant therapy with surgery *de novo* in this setting. These two trials used chemoradiation as the neoadjuvant treatment arm, and no subsequent trials have compared contemporary systemic regimens with surgery *de novo* (61,62). Contemporary regimens include 5-fluorouracil (5-FU)/leucovorin/oxaliplatin/irinotecan (FOLFIRINOX) or gemcitabine with abraxane (nanoparticle albumin-bound paclitaxel; GemAb) and are the current first-line regimens used to treat PDAC, with proven efficacy in more advanced disease. Two recent phase II studies, the SWOG S1505 and the Alliance A021501, included these regimens in their neoadjuvant trial design but did not include a primary resection arm (63,64).

Extrapolating data from best-available trials has resulted in expert consensus that neoadjuvant chemotherapy is advantageous in patients with BR PDAC (17,65). Prioritizing a systemic or combined systemic and local therapy–first approach in the management of BR PDAC has the potential to optimize each dimension of treatment of BR PDAC, as outlined below.

Anatomy

Some prospective evidence supporting the potential of neoadjuvant therapy to optimize anatomic dimensions of resectability compared with surgery *de novo* can be found in the PREOPANC I and Jang trials (61,62). The PREOPANC I trial randomized patients with resectable and BR PDAC to surgery *de novo* or neoadjuvant gemcitabine-based chemoradiotherapy and reported a higher R0 resection rate in the neoadjuvant treatment cohort (63% compared with 31%, P<0.01) (61). In a smaller study by Jang *et al.*, the findings were similar: the R0 resection rate was significantly higher in the neoadjuvant chemoradiation group than in the surgery *de novo* group (52% compared with 26%, P<0.01) (62).

The recently published Alliance A021501 trial suggested an R0 resection advantage with the use of a neoadjuvant systemic therapy-only approach, reporting a higher R0 resection rate with neoadjuvant modified FOLFIRINOX (mFOLFIRINOX) than with neoadjuvant mFOLFIRINOX followed by hypofractionated radiotherapy (mFOLFIRINOX + RT) (42% compared with 25%, P<0.01) (64). Additionally, a single-institution trial from MD Anderson showed that a tumor-parenchymal interface response to neoadjuvant mFOLFIRINOX and chemoradiation was a reliable anatomic biomarker and could be used to predict R0 resection (66). The details of these studies will be discussed below.

The available evidence suggests that neoadjuvant therapy has the potential to show a radiographically meaningful response on restaging imaging and improve the rate of R0 resection (61,62,66,67).

Biology

There is a high rate of distant failure following surgery *de novo* among patients with BR PDAC, validating the hypothesis that micrometastases are present even in a seemingly localized stage of disease (9,10). A retrospective study from MD Anderson showed that among CA 19-9 producers, the overwhelming majority (>90%) of patients who had a pathologic major response (pMR) had normalization of their elevated baseline CA 19-9 following neoadjuvant therapy, demonstrating the value of CA 19-9 as a biologic readout during treatment (68).

The University of Pittsburgh Medical Center reported that a pre-treatment to post-treatment CA 19-9 reduction of >50% was highly predictive of R0 resection. Additionally, they reported that 29% of patients who had a pre-treatment to post-treatment CA 19-9 reduction experienced a complete pathologic response (69).

In a recent study, more than 95% of patients with resectable PDAC had CTCs in their peripheral blood. The dynamic changes of CTCs following first-line chemotherapy were strongly associated with disease progression or response. Thus, CTCs and ctDNA offer tools to study the systemic burden of disease. Further work is needed to determine how to incorporate such tests into neoadjuvant management algorithms (70).

Condition

A neoadjuvant approach provides the opportunity for all patients to optimize the management of medical comorbidities or functional limitations that may portend poorer outcomes following pancreatectomy. All potential

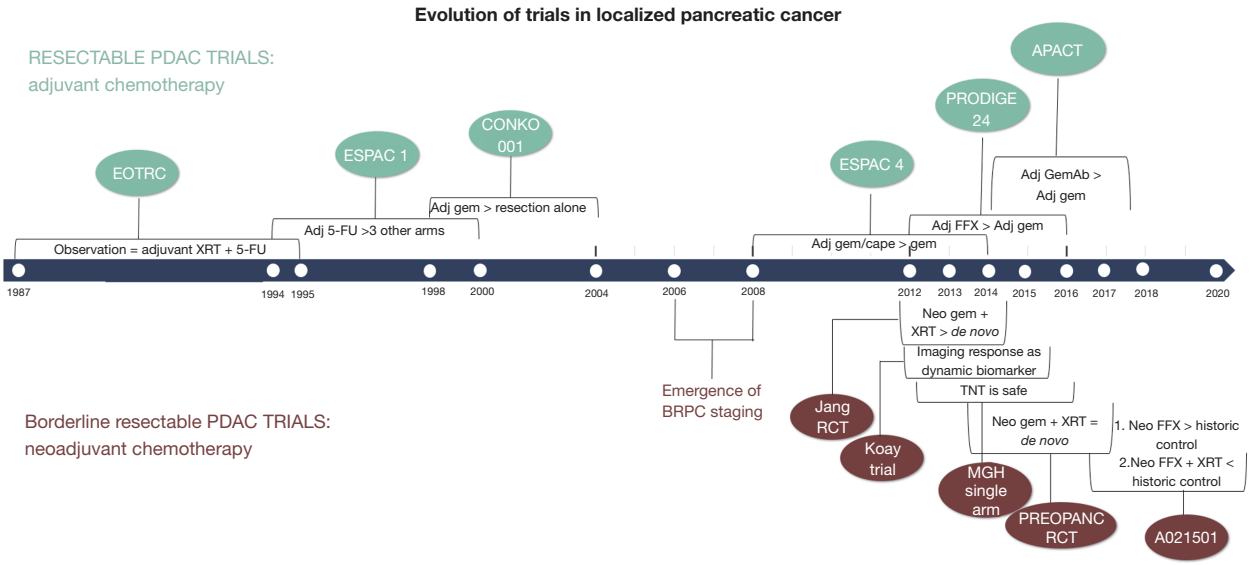

Figure 3 Evolution of clinical trials in localized PDAC over the past three decades. Green indicates trials in patients with resectable PDAC. Red indicates trials in patients with BRPC and/or resectable PDAC (61,62,64,66,67,77-81). EORTC, European Organization for Research and Treatment of Cancer; XRT, radiotherapy; 5-FU, 5-fluorouracil; ESPAC, European Study Group for Pancreatic Cancer; adj, adjuvant; CONKO-001, Charite Onkologie 001; gem, gemcitabine; BRPC, borderline resectable PDAC; PDAC, pancreatic ductal adenocarcinoma; cape, capecitabine; PRODIGE, Partenariat de Recherche en Oncologie Digestive; FFX, FOLFIRINOX (5-FU/leucovorin/oxaliplatin/irinotecan); APACT, Adjuvant Pancreatic Adenocarcinoma Clinical Trial; GemAb, gemcitabine with abraxane; neo, neoadjuvant; *de novo*, surgery *de novo*; RCT, randomized controlled trial; TNT, total neoadjuvant.

surgical candidates should consult with a general practitioner to optimize the management of comorbidities and a dietician to improve nutrition, as well as enroll in a prehabilitation program during their neoadjuvant therapy (71). The chemotherapy period allows an opportunity to declare improvement or decompensation from baseline while receiving systemic therapy. Just as radiographic and serologic response to therapy have important prognostic readouts, the functional dynamics that are observed during prehabilitation may help predict which patients will experience significant complications following surgery (71-73).

These data illustrate the value of neoadjuvant systemic therapy in not only managing anatomic barriers to surgical clearance, treating occult metastatic disease, and conditioning a patient for proposed pancreatectomy, but also guiding the multidisciplinary team in its understanding of each patient's unique phenotypic profile. Furthermore, a neoadjuvant treatment strategy improves multimodal treatment completion; about 25% to 50% of patients who undergo surgery *de novo* never begin adjuvant therapy because of postoperative complications, failure to regain performance status sufficient to permit therapy, or rapid development of progressive disease (74-76).

Evidence-based treatment: borderline staging as an impetus for a shift in trial design

The initial multimodal clinical trials in PDAC established the use of adjuvant therapy following pancreatectomy for patients with resectable PDAC. After BR PDAC was introduced, a neoadjuvant approach was incorporated into trial designs, reflecting how BR PDAC staging conceptually influenced the approach to treating PDAC. *Figure 3* outlines the evolution of clinical trial design before and after the emergence of BR PDAC staging.

Resectable PDAC: adjuvant therapy trials

Early trials studied the efficacy of adjuvant therapies in patients with resectable PDAC and cumulatively established the multimodal strategy of resection and chemotherapy with or without radiation to be superior to resection alone in curative-intent treatment.

Between 1987 and 1995, the European Organization for

Research and Treatment of Cancer (EORTC) trial enrolled 218 patients and randomized them to surgery *de novo* followed by observation or surgery with adjuvant 5-FU and radiotherapy. The study showed no significant difference in the primary endpoint of overall survival (OS), with a median OS of 24 months in the treatment arm and 19 months in the observation arm (P=0.21) (77).

In 2004, the European Study Group for Pancreatic Cancer (ESPAC)-1 trial compared four arms: adjuvant 5-FU-based chemoradiotherapy alone, adjuvant 5-FU-based chemoradiotherapy followed by 5-FU, adjuvant 5-FU alone, and observation (78). This trial was not powered for direct comparisons between the four cohorts but did show that patients who received systemic chemotherapy survived longer than patients who did not (median OS 20 months compared with 16 months, P=0.009). Additionally, patients who received adjuvant chemoradiotherapy experienced inferior survival (median OS 16 months compared with 18 months for 5-FU alone, P=0.05) (78).

In 2013, the Charite Onkologie 001 (CONKO-001) trial compared adjuvant gemcitabine with observation and reported a significantly improved 5-year OS rate of 21% for patients treated with adjuvant gemcitabine compared with 10% for patients who received observation only (P=0.01) (79).

In 2017, the ESPAC-4 trial compared adjuvant gemcitabine with gemcitabine plus capecitabine (80). The median OS was 26 months for patients treated with gemcitabine alone and 28 months for patients treated with gemcitabine plus capecitabine (P 0.032).

In 2018, the Partenariat de Recherche en Oncologie Digestive (PRODIGE) 24 trial compared adjuvant gemcitabine with mFOLFIRINOX and showed a robust survival advantage with the implementation of adjuvant mFOLFIRINOX (81). The median OS of patients treated with mFOLFIRINOX was 54 months compared with 35 months for patients treated with gemcitabine (P<0.01). As such, mFOLFIRINOX has become the gold standard adjuvant chemotherapy choice for patients who undergo surgery *de novo*.

In 2019, the results from the phase III Adjuvant Pancreatic Adenocarcinoma Clinical Trial (APACT) trial comparing adjuvant GemAb with gemcitabine alone were reported at the annual ASCO meeting: a survival advantage was observed in the GemAb arm compared with the gemcitabine arm (median OS 41.8 months compared with 37.7 months, P=0.01) (82).

BR PDAC: neoadjuvant therapy trials

The wide adoption of borderline resectability as a unique stage of PDAC introduced new ways of approaching treatment and inspired clinical trial design that investigated the potential role of neoadjuvant approaches in the management of localized pancreatic cancer.

One of the first neoadjuvant trials published was a 2012 Korean study by Jang *et al.* This trial randomized patients with BR PDAC to receive neoadjuvant gemcitabine with radiotherapy or surgery *de novo*. The primary endpoint was OS at 2-year follow-up, and the neoadjuvant arm had a longer median OS of 21 months compared with 12 months in the surgery *de novo* arm (P=0.03) (62).

From 2012 to 2015, a trial from MD Anderson enrolled 33 patients with BR PDAC and measured radiographic response to neoadjuvant mFOLFIRINOX and 50 Gy chemoradiation with concurrent gemcitabine using the anatomic tumor-parenchymal interface (66). The authors proposed a new radiographic biomarker in which tumors at the time of presentation were categorized using computed tomography by the Hounsfield unit difference between the visualized tumor and normal pancreatic parenchyma (66). Low-delta tumors were those that did not exhibit a change in Hounsfield units between the tumor and the parenchyma, and high-delta tumors were those that did exhibit an abrupt change in Hounsfield units between the tumor and parenchyma. Following neoadjuvant therapy, a type I interface response was described as one that remained stable or became more defined, and a type II interface response was described as one that became less defined. In total, 17 patients exhibited a type I interface response and 16 patients exhibited a type II interface response. Patients with high-delta PDAC were more likely to experience a type II interface response than were those with low-delta PDAC (P=0.026) (66). Patients with a type II interface response were more likely to have an R1 resection margin than were those who exhibited a type I response (P<0.001). Patients with low-delta tumors had significantly better OS than those with high-delta tumors (median OS not reached compared with 17 months, P<0.01), and patients with a type I response also had significantly better OS than those with a type II response (median OS 30 months compared with 14 months, P<0.01) (66). These data suggest that a novel imaging-based biomarker may exist, and that the tumor-parenchymal interface response of PDAC may be used to

gauge anatomic response to neoadjuvant therapy and better select patients for pancreatectomy.

Concurrently, a single-center, single-arm trial from Massachusetts General Hospital investigated the primary outcome of R0 resection rate in patients who received 8 cycles of neoadjuvant chemotherapy with multi-agent FOLFIRINOX followed by short-course radiotherapy; a 97% R0 resection rate was observed. The initial design of this trial was to give 4 cycles of therapy preoperatively and 4 cycles postoperatively, but the study was amended to allow patients without progression on the restaging computed tomography scan to receive an additional 4 cycles of FOLFOIRINOX prior to radiotherapy (for a total of 8 cycles of neoadjuvant FOLFIRINOX) and no adjuvant chemotherapy. The authors termed this approach a "total neoadjuvant" approach, and the results showed that such an approach is safe, with favorable oncologic outcomes, including a median OS of 38 months (67).

The Dutch group's PREOPANC phase III trial randomized patients to receive either 2 cycles of neoadjuvant gemcitabine concurrently with 15 Gy chemoradiation followed by resection and 4 cycles of adjuvant gemcitabine, or surgery *de novo* followed by 6 cycles of gemcitabine. The rate of resection was 61% in the neoadjuvant chemotherapy group and 72% in the surgery *de novo* group, although this was not statistically significant (P=0.06). In an intention-to-treat analysis, the median OS was similar between those who received neoadjuvant chemoradiation and those who received primary resection (16 months compared with 14 months, P=0.10). However, more patients in the neoadjuvant therapy cohort underwent an R0 resection (72% compared with 40%, P<0.001). In the subset of patients who underwent resection and started adjuvant therapy, there was improved OS in the neoadjuvant chemoradiation cohort compared with the surgery *de novo* cohort (median OS 35 months compared with 20 months, P=0.03). Although the trial was a negative study and did not show a benefit of neoadjuvant therapy using the defined endpoints, subsequent long-term analysis did show a statistically longer median OS among patients treated with neoadjuvant chemoradiation (hazard ratio 0.73, P=0.03) (61,83).

The Alliance A021501 trial randomized patients to receive either 8 cycles of neoadjuvant mFOLFIRINOX or 7 cycles of mFOLFIRINOX + RT (64). Each cohort was then eligible to receive pancreatectomy followed by 4 cycles of adjuvant mFOLFIRINOX. The primary endpoint was 18-month OS rate, and each arm was compared with a historical control of 50%. The mFOLFIRINOX cohort had an 18-month OS rate of 67%, and the mFOLFIRINOX + RT cohort had an 18-month OS rate of 47%, which did not meet the predefined historic threshold. The study also showed that the rate of R0 resection was 43% for mFOLFIRINOX and 25% for mFOLFIRINOX + RT. The mFOLFIRINOX + RT arm closed at interim analysis owing to the low R0 rate, but the mFOLFIRINOX arm was accrued to full enrollment with a median OS of 30 months. This trial established an 8-cycle mFOLFIRINOX regimen as the contemporary reference neoadjuvant regimen for BR PDAC (64).

Inclusion of neoadjuvant therapy in resectable PDAC trial design

Published in 2020, the SWOG S1505 trial compared two multi-agent neoadjuvant regimens in patients with resectable PDAC: FOLFIRINOX and GemAb. The primary outcome was 2-year OS rate, with similar rates of 41.6% for FOLFIRINOX and 48.8% for GemAb and a median OS of 22 months for FOLFIRINOX and 24 months for GemAb (P=0.40) (63). This trial established these two neoadjuvant regimens to be equally effective (63).

The global view: a guide to dynamic response interpretation and integration of response into treatment decisions

Neoadjuvant chemotherapy administration allows time to better understand the phenotypic profile and longitudinal behavior of an individual PDAC. Although an initial clinical stage gives a single snapshot of the appearance and predicted natural history of a tumor, the integration of longitudinal treatment response provides a panoramic view of a tumor's behavior over time and a more reliable metric of long-term outcomes, thus guiding subsequent treatment choice.

Response can be divided into three unique domains: serologic, radiographic, and pathologic response to neoadjuvant therapy. *Figure 4* is a flow diagram showing an example of the integration of dynamic changes of response into treatment decisions.

Data suggest that these measures of response are reliable prognosticators. In a retrospective study from MD Anderson that included 485 patients treated with either induction FOLFIRINOX or GemAb, patients who experienced a pMR had a significantly higher median reduction in tumor volume radiographically in the restaging

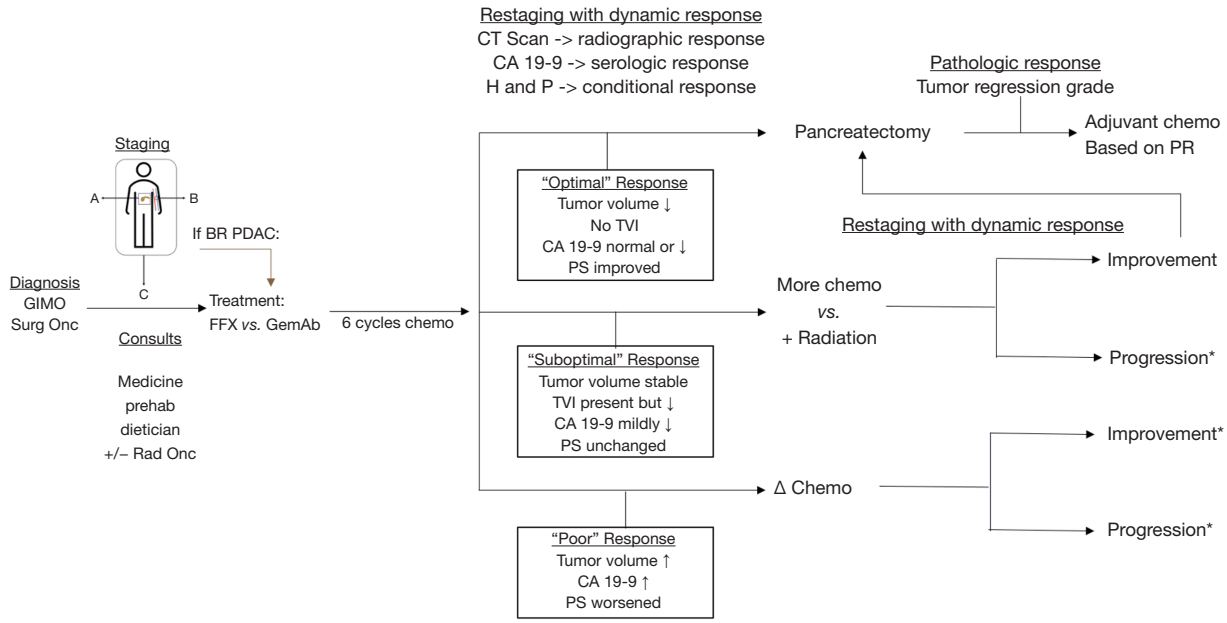

Figure 4 Flow diagram of the workup, multidisciplinary treatment, and response categories to help better guide dynamic response integration into clinical decision making. *, denotes clinical scenarios that would benefit from dedicated multidisciplinary consensus regarding next steps in treatment. A, anatomy; B, biology; C, condition. GIMO, gastrointestinal medical oncology; Surg Onc, surgical oncology; BR, borderline resectable; PDAC, pancreatic ductal adenocarcinoma; FFX, FOLFIRINOX (5-fluorouracil/leucovorin/oxaliplatin/irinotecan); GemAb, gemcitabine with abraxane; Prehab, prehabilitation; Rad Onc, radiation oncology; CT, computed tomography; CA 19-9, carbohydrate antigen 19-9; H and P, history and physical examination; TVI, tumor-vessel interface; PS, performance status; PR, pathologic response.

period following neoadjuvant therapy compared with patients who did not experience a pMR (68% compared with 34% tumor volume reduction, P<0.001) (84). Additionally, decrease and normalization of CA 19-9 levels were associated with significantly higher rates of pMR: 71% of patients who experienced a pMR had normalization of their elevated baseline CA 19-9, 25% of patients had a low baseline CA 19-9, and only 4% had a mildly elevated CA 19-9 following neoadjuvant chemotherapy (84). These are worthwhile data because they predict long-term survival. Patients who experienced a pMR had a median OS that was not reached compared with 40 months for patients without a pMR (P<0.01) (84).

Deciding to whom and when to offer pancreatectomy is a diagnostic challenge and should be a collective decision among the multidisciplinary team. Including longitudinal treatment response data enhances treatment precision among practitioners.

Authors' reflections on type of neoadjuvant regimen and approach to BR PDAC

The data presented here have shown that patients can tolerate and often benefit from neoadjuvant chemotherapy and subsequently undergo successful pancreatectomy without prohibitive perioperative complications. Current guidelines recommend the administration of neoadjuvant multi-agent chemotherapy regimens, either first-line FOLFIRINOX or GemAb, for a total of 4–6 months with consideration of subsequent radiotherapy for most patients with resectable PDAC or BR PDAC (17). This is followed by pancreatectomy and adjuvant chemotherapy.

A dynamic approach to the treatment of BR PDAC allows for an enhanced feedback system to optimize outcomes. Serologic, radiographic, physiologic, and pathologic measures of response can provide real-time readouts of the effectiveness of treatment and act to predict

subsequent treatment success or failure. Integration of these putative markers into the treatment strategy allows a flexible, individualized framework. Data suggest that a total neoadjuvant therapy approach without adjuvant therapy is a safe strategy, but it is important to recognize that such an approach restricts the integration of pathologic response into adjuvant regimen decisions and limits the opportunity for dynamic response data to guide therapy (67).

Concluding remarks

The introduction of the multidimensional BR PDAC staging system has transformed the approach to management of BR PDAC. The inception of this staging system resulted in multiple neoadjuvant trials that sought to understand the role that neoadjuvant therapy may play in improving outcomes for this complex diagnosis, and evidence suggests that neoadjuvant therapy has the potential to improve each of the three dimensions of borderline resectability. Understanding the individual phenotype of a patient with BR PDAC is critical. By definition, these patients are at high risk of treatment failure following surgery *de novo*, so it is critical to understand the unidimensional or multidimensional barriers that are likely to hinder success, use the available evidence for neoadjuvant treatment in an effort to target and optimize all dimensions of borderline resectability, and become fluent in the dynamic metrics of response that can help select patients who would benefit from pancreatectomy.

All decisions in the management of BR PDAC should be done in the setting of a multidisciplinary conversation and only after consensus is obtained. Treatment recommendations should be founded on the multidimensional staging of BR PDAC and integrate longitudinal, dynamic data into decisions. Each individual patient and their goals should act as the foundation for all recommendations, and the proposed plan should be carried out within a broad and diverse multidisciplinary team.

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