Multimodality management of borderline resectable pancreatic adenocarcinoma

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Abstract: Patients with borderline resectable pancreatic adenocarcinoma have primary tumors within the pancreas that involve the mesenteric vasculature to a limited degree. Their tumors are nonetheless at high-risk for a microscopically positive surgical resection margin and/or early treatment failure when pancreatectomy is performed de novo. The optimal treatment strategy for these patients has not been established; however, relatively favorable outcomes can be achieved with systemic chemotherapy and radiation therapy (RT) prior to intended resection. In this article, we discuss the modalities used to stage localized pancreatic cancer, the concept of borderline resectable pancreatic cancer (BRPC), the rationale for the use of preoperative therapy, and review recent publications, placing special emphasis on the necessity of appropriate patient selection and coordinating multimodality management to maximize outcomes.

Keywords: Borderline resectable pancreas cancer; neoadjuvant therapy; preoperative therapy; pancreatectomy; pancreatic ductal adenocarcinoma (PDAC); adjuvant therapy

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Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers. Despite developments in both detection and management of this disease over the past three decades, the 5-year overall survival (OS) rate of all patients diagnosed with it remains less than 8% (1). The poor prognosis of PDAC is mainly attributed to an inability to diagnose it at an early stage, a natural history characterized by relatively rapid disease progression and a responsiveness to current chemotherapeutic regimens that is generally poor (2,3). Surgical resection of the primary tumor and regional lymph nodes is often cited as the only treatment modality that is potentially curative, and surgery de novo followed by 6 months of systemic chemotherapy represents the standard of care for patients with tumors that appear to be technically resectable. However, the survival benefit associated with this strategy is severely compromised if cancer cells remain following resection, whether within the tumor bed or at distant systemic sites.

Borderline resectable pancreatic cancer (BRPC) represents a distinct clinical stage of PDAC. Patients with BRPC are at high-risk for a microscopically positive surgical resection and/or early treatment failure after an initial surgical approach due to a variety of tumor and/or patient related factors (4-6). Although the optimal sequence, duration and mode of preoperative therapy for this group of patients remains disputed due to the inherent limitations of previously published studies, consensus guidelines have recommended a multimodality approach to care that typically incorporates systemic chemotherapy followed by consolidative chemoradiation and radical resection (7-10).
Definition

The first definition of BRPC was an exclusively radiographic one. Tumors with an absence of a perivascular fat plane over 180° of the superior mesenteric artery (SMA) and/or superior mesenteric vein and/or portal vein (SMV/PV) persisting for a length of greater than 1 cm on cross-sectional imaging studies were considered “marginally resectable” (11). The concept of BRPC has since evolved. Despite differences in definitions that persist, the general focus has remained tumor anatomy—specifically the relationships between the primary tumor and the central mesenteric vasculature. At MD Anderson Cancer Center, however, we have established and use a comprehensive classification of “borderline resectable” disease that reflects derangements in the cancer’s anticipated behavior and the patient’s physiologic profile in addition to tumor anatomy (12). We categorize patients with BRPC into anatomic (type A), biologic (type B) and conditional (type C) variants.

BRPC type A, as we initially described, included patients with tumors characterized anatomically by one or more of the following: (I) tumor vessel interface (TVI) of ≤180° of the circumference of the SMA or celiac axis; (II) TVI of any degree of the circumference of a short segment of the hepatic artery, typically at the origin of the gastroduodenal artery; (III) short-segment occlusion of the SMV, PV or SMV-PV confluence that is amenable to vascular resection and reconstruction due to patent SMV and PV below and above the area of tumor-related occlusion (13) (Figure 1).

Although other anatomic definitions are currently used, there is agreement that some significant degree of reconstructable mesenteric vessel involvement by the tumor is the critical anatomic feature that positions BRPC between anatomically resectable and unresectable (locally advanced) tumors in the spectrum of localized disease (14). However, the anatomic definition utilized at MD Anderson differs slightly from the criteria proposed by investigators in the Alliance for Clinical Trials in Oncology, National Comprehensive Network, and the Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO) with respect to the degree to which apparent venous involvement discriminates between resectable and borderline resectable disease (10,12).

Patients with BRPC type B have clinical findings suspicious but not diagnostic for metastatic disease. These include indeterminate lesions on imaging in the liver or suspicious distant lymph nodes, serum carbohydrate antigen 19-9 (CA 19-9) level ≥1,000 U/mL in the setting of a normal bilirubin level or biopsy-proven involvement of regional lymph nodes (13).

BRPC type C patients require extensive assessment and optimization to undergo a major surgical procedure due to advance age (≥80 years old) or severe reversible pre-existing comorbidities or depressed performance status [Eastern Cooperative Oncology Group (ECOG) ≥2] (13,15).

A single patient may have features of one or more of these three variants.

Staging

At MD Anderson, all patients undergo an extensive history/physical examination and review of laboratory studies as part of a comprehensive evaluation at presentation to aid in identification of patients who are marginally resectable or inoperable based on anatomic or clinical criteria (16). Assessment of performance status is conducted using ECOG definitions (17) and comorbidities that may be a potential deterrent to a major abdominal surgery are identified (18,19).

Advances in cross-sectional imaging have led to a better assessment of TVI and disease extension and therefore resectability. The most commonly used modality is computed tomography (CT) with a standardized pancreatic protocol of the entire abdomen and pelvis to assess disease burden (20) with pre-contrast, late arterial and portal
venous phases of enhancement that provide the ability to analyze the TVI (21). Enhanced magnetic resonance imaging (MRI) with gadolinium-based intravenous (IV) contrast administration is also effective in detecting local extension and TVI and is often superior to CT in detecting small liver lesions (22). However, due to higher cost, relative unavailability and expertise required for interpretation, MRI is typically used as a secondary modality in presence of liver lesion or CT contrast allergy or when CT cannot identify or characterize the pancreatic mass (4). Endoscopic ultrasound (EUS) is used to obtain tissue for diagnosis with fine-needle aspiration which is a pre-requisite for initiation of preoperative therapy and may actually be more sensitive for detection of small tumors, but we do not typically use it for staging purposes (23). Positron emission tomography (PET)-CT although not ideal for determining local tumor resectability, can be helpful to determine whether equivocal extra-pancreatic lesions truly represent metastases (24). During surgical exploration, occult metastatic disease has been reported in around 30% of patients with resectable disease on imaging, therefore staging laparoscopy is an important tool in preventing unnecessary pancreatic resection (25). It can be performed before initiation of therapy or in the preoperative setting either as a separate procedure or immediately before laparotomy under the same anesthetic (16,26). Selective use of staging laparoscopy has shown to be cost effective in high-risk patients (27).

CA 19-9 level of ≥150 U/L and tumor size of ≥3 cm with radiographically localized disease has shown to be significant independent risk factors for unresectability (28,29). Since the peritoneum is one of the most frequent sites of failure in PDAC, it has been hypothesized that free cancer cells are present in the peritoneal cavity that later cause tumors to spread throughout the peritoneum (30), therefore in absence of other visible metastatic disease on imaging, examination of intraoperative peritoneal lavage cytology (PLC) may serve in identifying these. PLC has shown to be an independent prognostic factor for patients undergoing resection (31), with patients with positive PLC having similar survival as other patients with metastatic disease (32).

Response assessment

Serum CA 19-9 is the most commonly assayed tumor marker in clinical management of PDAC. Elevation of CA 19-9 is associated with poor survival, unresectability (33-35) and tumor stage (36). Previously, our group has shown that although the positive predictable value of a normal pre-treatment CA 19-9 value (<37 U/mL) for completion of neoadjuvant therapy and undergoing resection is close to 90%, its clinical utility is compromised by a low negative predictive value (33%) (37). Recently, we have shown CA 19-9 to be a dynamic marker of tumor biology and response to therapy, with strong association between a decrease of CA 19-9 following preoperative therapy and longer median OS among both unresected and resected patients (38). Additionally in the clinical setting, a ≥5% rise in CA 19-9 after 2 cycles of chemotherapy may serve as a negative predictive marker (39).

The 18F-fluorodeoxyglucose (FDG)-PET is a functional imaging method that is specific to metabolically active cancer cells which aid in predicting clinical outcomes based on baseline metabolic tumor activity and identifying response to treatment by assessing the viability of cancer cells following treatment (35,40-43). Radiographic response and progression is routinely evaluated using Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 guidelines. These define complete response (CR) as the disappearance of visible tumor, partial response (PR) as at least a 30% reduction in tumor load and progressive disease (PD) as at least a 20% increase in tumor load or the appearance of a new lesion. Disease that does not meet the criteria for CR, PR or PD is defined as stable disease (SD) (44).

Radiographic downstaging has shown to be rare, although it may become more common as systemic chemotherapeutics and radiation regimens improve. Indeed, a prior study found only a 12% incidence of response meeting RECIST criteria after the administration of preoperative therapy (45). Furthermore, TVI may not change in a meaningful way after neoadjuvant therapy (46) and may persist even in patients with radiographic response (21). Patients with adequate functional status should be considered for surgery following the administration of preoperative therapy on the basis of lack of radiographic evidence for local or distant disease progression, even in the absence of downstaging or persistence of TVI (16).

Multimodality management

At MD Anderson, the general algorithm used in treatment of BRPC has historically been induction systemic chemotherapy with close monitoring for toxicity (47) followed by administration of chemoradiation (CXRT). Changes in either the radiographic findings or the patient’s
clinical condition at the time of restaging necessitate a reassessment and revision of the treatment plan (14). In the absence of disease progression or decline in performance status at restaging after completion of CXRT, patients are taken to the operating room with intent of resection. Pancreatectomy is often followed by postoperative chemotherapy (48) (Figure 2). Patients are treated on clinical trials whenever possible.

Preoperative therapy
Reasonable rates of OS with use of preoperative therapy in patients with anatomically advanced PDAC when compared to patients receiving surgery first has been shown by multiple single institution retrospective review as well as an intention to treat analysis using the National Cancer Database (5,13,16,49-52). Selected studies highlighting current practices are illustrated in Table 1.

An animal study demonstrated that tagged pancreatic epithelial cells could be detected in the bloodstream and liver of mice with pre-invasive pancreatic lesions (57), suggesting that metastases may develop very early in the course of the disease—prior even to the growth of the primary tumor to a detectable size (14). This theory is further substantiated by the presence of radiographically occult metastatic disease found during laparotomy or laparoscopy in around 30% of patients (25) and high early recurrence rates even after margin-negative resections. In this context, perhaps the most important role of preoperative therapy is in providing a time interval in which to identify patients with suboptimal physiologic status and aggressive tumor biology, to avoid a pancreatectomy that is associated with little survival benefit.

A meta-analysis reported approximately one-third of patients who were deemed unresectable at initial staging may undergo neoadjuvant therapy and get “downstaged” to operable candidates while maintaining similar survival estimates as those initially deemed resectable (58). Additionally, reduction in the anatomical extent of tumor may help in facilitating a negative margin resection, which is widely accepted to strongly predict recurrence and survival (59-63). The presence of metastatic disease in peri-pancreatic lymph nodes has been shown to have an impact on survival (7,64). The lymph node ratio (LNR), defined as the number of lymph nodes with metastatic disease among the total number of lymph nodes retrieved, has been validated as a useful prognostic indicator and receiving neoadjuvant therapy has shown to be associated with reduced LNR in patients (65).

Chemotherapy
The rationale for use of systemic chemotherapy, commonly consisting of gemcitabine or 5-fluorouracil (5-FU) based regimens, includes early treatment of micrometastatic disease, possible downstaging and tumor response. Given the significant improvement in survival and response rates of 32% compared to 10% for gemcitabine alone with introduction of oxaliplatin and irinotecan to fluorouracil (FOLFIRINOX) in patients with metastatic disease (66), it has been a rational choice for induction therapy in patients with advanced non-metastatic disease and adequate performance status (50,53,54,67,68). A multicentric prospective study conducted by 20 centres analysing...
Table 1: Selected studies of borderline resectable pancreatic adenocarcinoma published between 2015 and 2017

<table>
<thead>
<tr>
<th>Study</th>
<th>Type and dates of study</th>
<th>Staging system</th>
<th>All patients (n)</th>
<th>Neo-adjuvant regimen</th>
<th>Neo-adjuvant RT</th>
<th>Resected</th>
<th>R0</th>
<th>Vascular resection</th>
<th>Adjuvant therapy</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz 2016 (9)</td>
<td>Multi-centric prospective, May 2013–Feb 2014</td>
<td>ALLIANCE</td>
<td>22</td>
<td>mFOLFIRINOX</td>
<td>EBRT 50.4 Gy/28 fr + cape, 21 (95%)</td>
<td>15 (68%)</td>
<td>14 (93%)</td>
<td>12 (80%)</td>
<td>Gem, 10 (67%)</td>
<td>21.7 (95%) CI 15.7 to not reached</td>
</tr>
<tr>
<td>Christians 2014 (53)</td>
<td>Single institution retrospective review, Jul 2010–Dec 2012</td>
<td>MCW</td>
<td>18</td>
<td>FOLFIRINOX</td>
<td>Variable</td>
<td>12 (67%)</td>
<td>12 (100%)</td>
<td>10 (83%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blazer 2015 (54)</td>
<td>Single institution retrospective review, Jan 2011–Aug 2013</td>
<td>AHPBA/SSAT/SSO</td>
<td>18‡</td>
<td>mFOLFIRINOX</td>
<td>36 Gy/5 fr + gem ± ox 8 (44%)</td>
<td>11 (61%)</td>
<td>9* (82%)</td>
<td>1 (9%)</td>
<td>Variable, 17 (77%)</td>
<td>21.2</td>
</tr>
<tr>
<td>Mellon 2015 (55)</td>
<td>Single institution retrospective review, 2009–2014</td>
<td>NCCN 2009</td>
<td>110‡</td>
<td>Variable 89 (81%) GTX</td>
<td>SBRT; 40 Gy/5 fr</td>
<td>56 (51%)</td>
<td>54 (96%)</td>
<td>19 (34%)</td>
<td>NR</td>
<td>19.2</td>
</tr>
<tr>
<td>Okada 2017 (56)</td>
<td>Single institution phase 1 trial, Jul 2015–Nov 2015</td>
<td>NCCN 2014</td>
<td>10</td>
<td>Gem + nab-paclitaxel</td>
<td>NR</td>
<td>8 (80%)</td>
<td>7 (87.5%)</td>
<td>5 (50%)</td>
<td>Chemotherapy with S-1</td>
<td>NR</td>
</tr>
</tbody>
</table>

‡, study also included patients with locally advanced unresectable pancreatic cancer but these numbers are reflective of only BRPC; *, including within 1 mm of inked margin. Abbreviations: m, modified; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, oxaliplatin; gem, gemcitabine; EBRT, external beam radiation therapy; RT, radiotherapy; Gy, Gray; fr, fractions; cape, capecitabine; OS, overall survival; MCW, Medical College of Wisconsin; NR, not reported; AHPBA, Americas Hepato-Pancreato-Biliary Association; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology; ox, oxaliplatin; NCCN, National Comprehensive Cancer Network; GTX, gemcitabine, docetaxel, capecitabine; SBRT, stereotactic body radiation therapy.
47 patients with BRPC concluded the safety of resection after induction FOLFIRINOX with 30-day-mortality, major complications and symptomatic pancreatic fistula rates of 2.5%, 22.5% and 4% respectively, comparable to patients undergoing surgery de novo (69).

In addition to FOLFIRINOX, gemcitabine based regimens have also been shown to be effective in a preoperative setting (63). Mellon et al. reported resection and R0 rate of 51% and 96% respectively with estimated median OS of 19.2 months in 110 BRPC patients who received variable regimens, primarily gemcitabine in combination with docetaxel and capecitabine (GTX) followed by stereotactic body RT (SBRT) 40 Gy in 5 fractions (55). Addition of nab-paclitaxel to gemcitabine has shown promising results in metastatic patients (70) and prompted further exploration of the role of this combination in induction therapy, a recently concluded phase 1 study of 10 patients with BRPC reported resection rate of 80% and pathologic response of 30% comparable to previously published data with FOLFIRINOX. However the rate of ≥ grade 3 toxicity (the majority being neutropenia) was much higher at 90%. Additionally, radiographic response was not observed in any of the ten cases (56).

A phase II intergroup study Southwest Oncology Group (SWOG) Trial 1505 is currently recruiting participants and randomizing patients with resectable pancreatic cancer to three cycles of systemic FOLFIRINOX or three cycles of gemcitabine plus nab-paclitaxel. Patients without progression then undergo surgical resection followed by three cycles of the same regimen following surgery. The primary objective of this study is to pick the superior regimen with respect to OS (71). The results of this trial may inform future studies of borderline resectable disease.

**Radiation therapy (RT)**

The rationale for the use of RT in a preoperative setting is potential treatment of microscopic disease in regional lymph nodes and sterilization of the periphery of tumor to enhance the probability of negative margins at pancreatectomy (72-74). The standard approach at MD Anderson Cancer Center has historically been to use 50.4 Gy doses of RT in 28 fractions or 30 Gy in 10 fractions with conventional external beam RT (EBRT) and concurrent gemcitabine or 5-FU or capecitabine (75,76). In addition to the primary tumor, SMA and celiac axis should always be contoured and included within the margin (16). Recently, we have moved toward the use of SBRT, which is a modality designed to deliver high doses of RT precisely to small tumors, usually in five or fewer treatments. Intensity-modulated RT (IMRT) uses higher dose of radiation with the goal of varying intensities across the treatment field, and represents another option.

Retrospective single institution data suggests that SBRT is well tolerated and does not compromise potential surgery option or increase post-operative complications (55,77-79). Additionally, results of a single-institution phase 1 clinical trial with 13 patients suggests that SBRT after mFOLFIRINOX allows for higher radiation dose safely and may potentially aid in negative margin resections (80). Similarly, retrospective single institution studies suggest IMRT following induction chemotherapy may improve likelihood of R0 resection rate without compromising the organs at risk for toxicity (81,82). Though there is a theoretical advantage in using IMRT and SBRT, they have not proven to be more effective or to result in fewer side effects than standard RT (16).

**Pancreatectomy and histopathologic assessment**

Radical resection of the primary tumor and regional lymphadenectomy offers the only viable option for cure (83). Even following the administration of preoperative therapy, surgeons must anticipate the need for vascular resection and reconstruction during pancreatectomy for all patients with advanced cancers (21). Venous resection and reconstruction should be performed for borderline resectable tumors involving the SMV/PV as long as reasonable venous inflow and outflow is present and the surgeon feels that an R0 or R1 resection likely can be accomplished (84). When adequately planned for and performed by an experienced surgeon, vascular resection itself been shown to have no adverse impact on survival with postoperative morbidity, mortality rates and median survival of approximately 2 years, comparable with standard pancreatectomy procedures and superior to historical patients believed to have locally advanced disease treated palliatively (60,85,86). Nevertheless, arterial resection is associated with poor short and long-term outcome and may be justified but not recommended outside of clinical trials (7,87). Two primary surgical objectives in patients with borderline resectable PDAC include meticulous dissection along the peri-adventitial plane of the vessel to skeletonize SMA to
maximize the potential for a margin-negative resection as cancer cells frequently infiltrate outward from the primary tumor toward the SMA through the perineural tissues in the retroperitoneum (76,88) and re-establishment of portal venous blood flow from the stomach and spleen, if necessary, to minimize the risk of postoperative sinistral portal hypertension (89). Since non-resectability is determined by involvement of the SMA, a need for early determination of resectability before an irreversible step, has promoted the development of an ‘artery-first’ approach (90) and although the operative technique and approach used vary, it has been shown to be safe and feasible in pancreatic resections and should be considered whenever tumor is thought to involve the SMV and/or PVs as a means to facilitate safe venous resection and reconstruction while preserving sound oncologic principles (91-93).

Margin status should be assessed intra-operatively by the surgeon and thoroughly evaluated by the pathologist. Each surgical specimen should be analyzed following standardized guidelines set by College of American Pathologist (CAP) guidelines and the American Joint Committee on Cancer (94-96). Specifically, the pancreatic and bile duct margins should be inked en face and are considered positive if tumor cells are present at the ink, whereas the entire inked SMA margin should be sectioned perpendicularly for microscopic evaluation and due to impact on outcome, the presence of tumor cells at or within 1 mm of the ink should also be considered a R1 resection (97). The treatment effect is measured histologically as the percentage of residual viable cancer cells and although varying staging scores are currently used, we use the modified CAP grading scheme as CR or minimal residual tumor (<5%) is an independent prognostic factor for patients receiving neoadjuvant therapy (98).

**Postoperative therapy**

Although survival benefits of adjuvant therapy after pancreatectomy in surgery de novo patients are widely accepted (99-101), the significance of postoperative therapy for patients who have already received preoperative therapy is unknown. Our group has previously shown that administration of postoperative therapy in these patients was associated with improved median OS (72 vs. 33 months; P=0.008) in absence of extensive metastatic disease in the regional lymph nodes (LNR <0.15). There was no association between postoperative chemotherapy and OS for patients with LNR ≥0.15, notably only 36 (14%) of the 263 patients identified received additional postoperative therapy (48).

**Supportive therapy**

In addition to a team of diagnostic radiologist, surgical oncologists, medical oncologists and radiation oncologists specializing in PDAC for accurate diagnosis and treatment; nutritionists, physical therapist and internist are integral in the management and optimization of functional status of BRPC patients.

**Recent national studies**

Currently available data consists of largely single-institutional retrospective reports that are limited by variability in patient cohort, definitions used, treatment regimens and absence of quality controls (12). Conducted by Alliance for Clinical Trials in Oncology, the recently concluded A021101 and currently enrolling A021501 have been designed with rigorous quality control of radiographic review, treatment modalities, the performance of surgery and histopathologic analysis providing a new standard for multi-institutional trials of preoperative therapy (9). In A021101, 22 patients with BRPC received neoadjuvant FOLFIRINOX followed by 5.5 weeks of EBRT, 50.4 Gy delivered in 28 daily fractions under A021101. Although 14 (64%) had a grade 3 or higher adverse event and only 27% showed RECIST response, 68% underwent pancreatectomy and negative resection margin was achieved in 93%. Pathologic response, defined as presence <5% viable tumor cells was reported in 33% of patients. Notably, one third of the resected patients did not start post-operative therapy further emphasising the importance of neoadjuvant therapy. The median OS of all patients from registration was 21.7 months (95% CI, 15.7 to not reached) and was comparable to previously reported OS of 21.2 months.

The currently enrolling A021501 trial is a randomized phase II study for BRPC of the head of the pancreas that compares two intensive preoperative therapy regimens. Patients receive either a systemic regimen of mFOLFIRINOX for eight cycles, or a combination regimen of seven cycles of mFOLFIRINOX followed by a 5-day radiation regimen using either SBRT or hypofractionated image-guided RT (102). The estimated enrollment is...
134 patients and the purpose of this trial is to compare OS rates at 18 months, in addition to rate of pathologic response, toxicity and resection rate between a group receiving chemotherapy vs. chemotherapy and RT.

Conclusions
Although there is general consensus that preoperative therapy in patients with BRPC is beneficial, the optimal treatment regimen is unknown. Quality controlled prospective trials designed to overcome these limitations are paving the way for a more evidence-based management. The recently concluded intergroup study has shown the feasibility of such multicentric efforts as well as favorable resection rate and survival with use of multimodality therapy. Similar trials may aid in establishing an optimal strategy to achieve maximal outcomes in this high-risk group by further determining the most efficacious first line regimen and the roles of radiation and postoperative therapy.

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Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.

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