Advances in Borderline Resectable Pancreatic Adenocarcinoma

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Abstract: Pancreatic adenocarcinoma is one of the most lethal cancers in oncology. Pancreatic cancer is the third most common cause of cancer-related mortality in the United States. As the years have progressed, the importance of a multidisciplinary and multimodal approach to pancreatic cancer care has been recognized and is now recommended in all major society guidelines. A subset of pancreatic cancer, borderline resectable pancreatic cancer (BRPC), has emerged as a distinct clinical entity for which specialized treatment plans are now being developed. The medical oncologist, surgical oncologist, and radiation oncologist must work jointly to help deliver the best clinical outcome for the patient with pancreatic cancer. In this discussion, we describe the current state of surgical, locoregional therapies and systemic therapy in BRPC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, representing the third most common cause of cancer-related mortality in the United States.[1] Approximately 441,000 people worldwide died of PDAC in 2017.[2]

Complete surgical extirpation is necessary to achieve a cure. However, only a minority of patients have cancers that are amenable to such therapy. Thus, an urgent avenue of investigation is increasing the number of patients who are able to undergo resection. Certainly, early detection of cancer is a key factor in these attempts. Nonsurgical therapies, such as radiation and/or systemic chemotherapy, are increasingly being used in combination with surgery. Neoadjuvant and preoperative therapies are also being used in an effort to increase survival, reduce the number of PDAC patients requiring vascular resection, improve the rate of negative margins, and perhaps decrease operative morbidity.

The treatment approach to borderline resectable pancreatic cancer (BRPC) differs from that used in locally advanced pancreatic cancer (LAPC), which is a similar but distinct entity. As defined by guidelines from the National Comprehensive Cancer Network (NCCN), LAPC has greater tumor involvement than BRPC and is unsuitable for reconstruction of the superior mesenteric vein (SMV)

or portal vein (PV) owing to occlusion by a tumor or thrombus, or to more extensive tumor involvement.[3] However, as with borderline resectable disease, the treatment of LAPC has become more nuanced in the setting of improved chemotherapeutic and radiation therapies.[4] Evans and others have attempted to distinguish between patients with LAPC who may ultimately be treated in a fashion similar to BRPC from those who will never benefit from resection.[4,5] Key factors may include the extent of involvement of the superior mesenteric artery, the celiac artery, and/or the hepatic artery. Additional work by Truty and colleagues has further delineated factors for predicting outcomes in advanced disease.[6] The current NCCN guidelines advocate treatment based on performance status (PS), wherein patients with good PS receive more aggressive chemotherapy or chemoradiotherapy, and those with poor PS receive best supportive care using either single-agent chemotherapy or palliative radiation.[3] Surgical resection with an R0 margin (microscopically negative) in the borderline resectable population is still possible in the up-front setting, especially if neoadjuvant therapy is used.

The concept of BRPC has evolved since its first description in the early 1990s. In 1992, Ishikawa and colleagues proposed and published a classification system to predict pancreatic tumor involvement of the SMV/PV based on radiographic findings regarding the caliber of the SMV and/or PV.[7] In 2006, a surgical group from the MD Anderson Cancer Center proposed criteria for BRPC that included: (1) tumor abutment of less than or equal to 180° of the circumference of the superior mesenteric artery; (2) short-segment encasement or abutment of the common hepatic artery/celiac axis; or (3) short-segment occlusion with suitable vessel above and below the SMV/PV confluence.[8]

Given the variance of expertise and definitions among clinicians, a more standardized approach has been sought for radiographic evaluation of pancreatic adenocarcinoma. Al-Hawary and colleagues proposed a standardized framework for reporting on pancreatic adenocarcinoma. They proposed multiple categories of evaluation, including multidetector computed tomography (CT)–dedicated pancreatic protocol parameters, morphologic evaluation, arterial evaluation, extrapancreatic evaluation, and venous evaluation.[9] The NCCN guidelines define BRPC based on arterial and venous criteria, as largely recommended by Al-Hawary and colleagues, and represent as close to a standard definition as exists at this time (Table).[3,9,10]

Accurately classifying a patient's pancreatic cancer as borderline resectable is often the initial hurdle in the care of such patients. Unfortunately, even with highly sensitive multidetector CT scanners, preoperative evaluation for resectability has high intra-user variability. Two previous studies demonstrated relative concordance for intra-user decision-making regarding unresectable arterial involvement and resectable venous involvement of pancreatic masses. When preoperative imaging reveals partial arterial involvement, it is difficult to decide if the patient has borderline resectable cancer.[11,12] Contrast-enhanced CT remains the diagnostic modality of choice, with sensitivity and specificity ranging from 63% to 82% and from 92% to 100%, respectively.[13] Magnetic resonance imaging (MRI) may be used when contrast-enhanced CT is contraindicated, but has been demonstrated to be inferior for evaluation of resectability in borderline resectable PDAC.[14] In an attempt to better define these cases and help radiologists assess response, some have turned to computer-based analytics with deep learning computer models and CT texture analysis.[15] Functional imaging using ^{18}F-fluorodeoxyglucose–positron emission tomography coupled with CT scanning (^{18}F-FDG PET/CT) has been advocated by some groups as an additional tool to assess remaining viable tumor following neoadjuvant therapy.[6,16] These results have been promising, but PET/CT has yet to become a standard part of post-treatment restaging.

Issues with imaging in borderline resectable PDAC are further confounded in the era of neoadjuvant chemotherapy because radiographic changes are often subtle and difficult to interpret. Standardized methods, such as the Response Evaluation Criteria in Solid Tumors (RECIST), often fail to detect radiographic changes following neoadjuvant therapy even in tumors that are later found to have a pathologic response. Of particular importance in borderline resectable PDAC is the rare incidence of radiographic regression from vessels despite an identifiable treatment effect at the time of resection.[6,17] Ferrone and colleagues further highlighted the challenges in interpreting imaging obtained after neoadjuvant treatment in a retrospective study of 188 patients undergoing resection for PDAC. Of these, 40 patients who were classified with borderline resectable or locally advanced pancreatic cancer received neoadjuvant leucovorin/5-fluorouracil (5-FU)/irinotecan/oxaliplatin (FOLFIRINOX) with or without chemoradiotherapy, 87 patients had up-front surgery, and 61 patients received other neoadjuvant therapy. A total of 7 patients did not undergo surgery owing to persistent locally advanced disease or progression to metastatic disease. After neoadjuvant therapy, imaging review of the 40 FOLFIRINOX patients found that prior to their surgeries, 19 patients were classified as locally advanced but resectable, 9 were borderline resectable, and 12 were resectable.[18] Pathology from surgery showed an R0 resection rate of 92% in the FOLFIRINOX group vs 86% in the group who did not receive neoadjuvant treatment. The percentage of patients with positive lymph

Table. NCCN Definition of Borderline Resectable Pancreatic Cancer

Arterial	Venous
Pancreatic head/uncinate process tumors: • Solid-tumor contact with the common hepatic artery without extension into the celiac artery or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction • Solid-tumor contact with the superior mesenteric artery of ≤180° • The guidelines state that tumor contact with any potential variant arterial anatomy and the presence and degree of any tumor contact are important to note, as these impact surgical management *Pancreatic tail/body tumors:* • Solid-tumor contact with the celiac artery of ≤180° • Solid-tumor contact with the celiac artery of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery, thereby permitting a modified Appleby procedure. Within the guidelines, there is a note that some members of the panel prefer these particular criteria to be in the unresectable category	• Solid-tumor contact with the superior mesenteric vein or portal vein of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction • Solid-tumor contact with the inferior vena cava
Notes: • Per the NCCN guidelines, solid-tumor contact may be substituted with increased hazy density/stranding of the fat surrounding the peripancreatic vessels, which can be seen with neoadjuvant treatment. NCCN guidelines recommend this finding be reported and monitored via staging and follow-up scans. • Distant disease, including nonregional lymph node disease, indicates that the patient should not be treated with up-front surgery.	

NCCN, National Comprehensive Cancer Network.

Source: National Comprehensive Cancer Network. Pancreatic Adenocarcinoma. v.1.2020.[3]

nodes was lower in the FOLFIRINOX group than in those who received no neoadjuvant therapy, at 38% vs 49%, respectively.[18]

Given the varied or absent radiographic changes following neoadjuvant therapy, circulating biomarkers can provide additional information in assessing which patients should be offered surgical resection. The tumor marker CA 19-9 has been the most studied to date. A decrease or normalization of a previously elevated CA 19-9 can be a good predictor of response, particularly in the setting of stable radiographic disease.[19] It has been suggested, however, that CA 19-9 response likely reflects the systemic response, and should be used with caution to predict local response.[6]

Surgical Considerations

Proper staging and application of neoadjuvant modalities are important in order to select the patients who will benefit from surgical resection. The surgical approach for pancreatic cancer is dependent upon the anatomic location of the mass, and may consist of pancreaticoduodenectomy, extended pancreatectomy, distal pancreatosplenectomy, or even total pancreatectomy. These surgical approaches have long been described, and with time have become safe and efficacious in the treatment of resectable pancreatic malignancies.[20,21] It was once thought that any vascular involvement of the pancreatic mass reflected a more aggressive biology, and therefore portended a poor prognosis. It has since been established that surgical procedures that involve resection of the superior mesenteric vein or portal vein with reconstruction have survival outcomes comparable to those reported with resections that do not involve venous resection. This was demonstrated in a study by Furhman and colleagues, who compared patients who underwent pancreaticoduodenectomy with or without venous resection and noted no differences in length of hospital stay, morbidity, mortality, or pathologic

outcomes between the 2 groups.[22] Additional studies have expanded on these findings, and have evaluated more aggressive surgical approaches following total neoadjuvant therapy. Specialized surgical centers have achieved ever-improving long-term overall survival (OS), with median survival reaching 38.9 months.[4,6,23]

Despite these encouraging findings, it is critical to remember that venous resection adds an additional component to an already-complicated pancreatic surgical procedure. Techniques employed range from a small side-bite that can be repaired immediately, to cases with long segment involvement requiring resection and reconstruction with grafts. The impact of the addition of a vascular resection can be as varied as the techniques noted above. Vein resection has consistently been associated with longer operating room times and higher blood loss. Rates of significant morbidity are similar to those reported for resections without venous resection in high-volume centers.[24-26] Meta-analyses and larger population-based studies have reported mixed results regarding outcomes, which likely reflect early experiences with vascular resection and reconstruction and do not capture the improved outcomes achieved as techniques have evolved.

Whereas venous resection has become standard practice at high-volume centers and is a key component in the treatment of borderline resectable PDAC, arterial resection remains a highly demanding procedure that is practiced only at selected centers. Arterial resection has a higher morbidity and mortality than venous resection. Recent case studies and single-institution series demonstrate the risks involved, and underscore that this procedure should be considered in a highly selective manner.[23,27] In the largest case series of arterial resection with pancreatectomy, with a total of 111 patients, the rate of major morbidity (grade ≥3) was 54% and the mortality rate was 13%. These studies underscore the need to identify patients who will benefit from these types of aggressive surgical approaches. Before arterial resection can be considered a standard approach, improvements are needed in preoperative, operative, and postoperative strategies. At the current time, these techniques are best employed at high-volume specialty centers and as part of structured clinical trials.

From a technical surgical standpoint, a neoadjuvant approach has been associated with a significantly improved negative or R0 resection margin in patients who have received neoadjuvant therapy.[28-30] Likewise, these studies have reported lower rates of required vascular resection and reconstruction following administration of neoadjuvant therapy.

Thus, the relationship of the tumor to the vasculature in borderline resectable PDAC does not in and of itself preclude resection or indicate a worse prognosis if an oncologically sound resection can be performed. These advances continue to expand the number of patients who may benefit from local therapy in the form of surgical resection as part of a multimodality treatment protocol.[4-6,22]

Systemic Chemotherapy

Even with mounting evidence supporting the investigation and use of neoadjuvant therapy for borderline resectable PDAC, it must be recognized that most available data are limited. Varying definitions exist for what constitutes borderline resectable, heterogeneous neoadjuvant therapy, and most studies are retrospective and/or single-institution. Very few prospective randomized studies exist, and even those are often underpowered. With the development of more effective combination chemotherapies, administered with or without radiation, the enthusiasm for neoadjuvant therapy has grown.

The primary rationale for the use of perioperative chemotherapy in patients undergoing surgical resection of PDAC—initially as adjuvant therapy and increasingly as neoadjuvant therapy—is the recognition that distant metastatic disease is the leading reason that surgery (with or without radiation) fails.

Versteijne and colleagues completed a meta-analysis of 12 studies that compared up-front surgery with neoadjuvant therapy in patients with resectable or borderline resectable pancreatic cancer. Across all 1746 patients from these 12 studies, the median OS was 14.8 months. Among 927 patients with BRPC who underwent up-front surgery, the weighted median OS was 12.8 months (range, 11.6-16.3 months). Within the same meta-analysis, 21 studies were analyzed that evaluated up-front neoadjuvant therapy with BRPC. The weighted median OS for patients with BRPC who were undergoing neoadjuvant therapy was 19.2 months (range, 11-32 months).[31] The neoadjuvant therapy received in these studies was chemotherapy alone, chemoradiotherapy, or mixed, with inadequate information to conclude if there was a preferred approach. Versteijne and colleagues also evaluated the R0 resection rate in those undergoing up-front resection compared to those who received neoadjuvant therapy. The R0 resection rate in BRPC patients who received neoadjuvant therapy was 88.6%. Those patients with borderline resectable disease who ended up having up-front surgery had an R0 rate of 63.9%.[31]

There is no clear first choice of a neoadjuvant chemotherapy regimen for BRPC, and no consensus among society guidelines. Today, 2 predominant options are currently used in the neoadjuvant setting, reflecting the most active regimens in metastatic PDAC: gemcitabine/nab-paclitaxel (Abraxane, Celgene) and the combination

of 5-FU/oxaliplatin/irinotecan or FOLFIRINOX. FOLFIRINOX has been well studied in the metastatic setting, and its benefit vs gemcitabine monotherapy was detailed in the PRODIGE 4/ACCORD 11 trial (Combination Chemotherapy as First-Line Therapy in Treating Patients With Metastatic Pancreatic Cancer). In that study, the median OS was 11.1 months in the FOLFIRINOX group vs 6.8 months in the gemcitabine group. However, FOLFIRINOX was associated with a higher burden of toxicity. Similarly relevant in a setting where shrinkage of the disease may be important, FOLFIRINOX also resulted in a significantly higher response rate, at 31.6% compared with 9.4% for gemcitabine.32 The combination of nab-paclitaxel and gemcitabine is also beneficial in metastatic pancreatic cancer, as demonstrated in the MPACT study (Phase III Study of ABI-007 Plus Gemcitabine Versus Gemcitabine in Metastatic Adenocarcinoma of the Pancreas). This study compared gemcitabine alone vs a combination of nab-paclitaxel and gemcitabine. The nab-paclitaxel/gemcitabine group had improved median OS vs the gemcitabine-alone group, at 8.5 months vs 6.7 months, respectively, and a higher response rate, at 23% vs 7%, respectively.[33]

In addition, a meta-analysis analyzed the use of FOLFIRINOX in the neoadjuvant setting in borderline resectable or unresectable pancreatic cancer. A total of 13 studies were reviewed in the meta-analysis. Of these, 9 included a component of radiotherapy and chemotherapy given as gemcitabine or gemcitabine in combination with other chemotherapy after neoadjuvant FOLFIRINOX, and 4 studies had no radiotherapy group. Three of the studies were limited to BRPC, whereas 6 studies looked at a mixed population of borderline resectable and unresectable cancer. Of the identified borderline resectable patients, the overall rate of resection was 68.5% and the rate of R0 resection was 63.5%.[34] OS was not reported by every study. Among the 3 studies that reported overall survival, the median duration ranged from 13.7 to 24.2 months.[34]

A small retrospective review compared FOLFIRINOX vs gemcitabine/nab-paclitaxel in the neoadjuvant setting for resectable and borderline resectable pancreatic cancer. Although this review did not look only at BRPC, it showed that the median OS was 38.7 months in the 73 patients receiving FOLFIRINOX vs 28.6 months in the 120 patients receiving gemcitabine/nab-paclitaxel.[35] The rate of R0 resection was 84.9% in the FOLFIRINOX group and 80.8% in the gemcitabine/nab-paclitaxel group. The patients who had N1 status at the time of resection were also reviewed. N1 status occurred in 56.2% of the FOLFIRINOX group vs 71.7% of the gemcitabine/nab-paclitaxel group. The authors concluded that either regimen is reasonable for neoadjuvant chemotherapy.[35] Based on extrapolation from the landmark metastatic trials and available data in retrospective settings, our institution recommends either FOLFIRINOX (standard or modified) or the combination of gemcitabine/nab-paclitaxel for up-front neoadjuvant chemotherapy, with a preference for the former in patients with good functional status.

Radiation/Chemoradiation

Although the use of neoadjuvant chemotherapy has become relatively established, the role of preoperative radiation therapy has remained less clear. In the neoadjuvant setting, the goal of radiation therapy is to further neutralize the tumor along critical structures to improve R0 resection rates as well as to treat lymph nodes within the treatment zone. Studies in BRPC have been mixed, however. Some have reported higher rates of R0 resection, lower positive lymph node rates, and decreased perineural and lymphovascular invasion, whereas others have failed to show benefits.[6,36-38]

In the meta-analysis reported by Versteijne and colleagues, chemoradiation was used as a component of treatment for 29 of 35 included studies. Chemoradiation has historically been the most commonly investigated neoadjuvant approach for BRPC.[31] The reported resection rates following neoadjuvant chemoradiation have varied broadly, from less than 30% to greater than 90%.[39] The majority of trials and single-institution experiences, including those in the meta-analysis, used a dose of 45.0 to 50.4 Gy with conventional fractionation of 1.8 to 2.0 Gy per fraction accompanied by concurrent radiosensitizing chemotherapy, most commonly gemcitabine, capecitabine, or infusional 5-FU with or without cisplatin.

Although the majority of initial reports used 3-dimensional conformal radiation therapy (3D CRT), the recent focus in gastrointestinal radiation oncology has been on leveraging newer technologies to improve patient tolerance and local control. The current standard is intensity-modulated radiation therapy (IMRT), which allows improved dose conformality to irregular target volumes and reduces exposure to adjacent organs. Improvements in radiation delivery via daily image guidance (IGRT) and motion management through the use of 4-dimensional CT simulation have facilitated a reduction in treatment margins. A recent report from the Memorial Sloan Kettering Cancer Center showed that, despite a higher median radiation dose (56.0 vs 50.4 Gy), the use of IMRT significantly reduced gastrointestinal toxicity vs 3D CRT.[40] The rate of gastrointestinal toxicities of at least grade 2 was 34% with 3D CRT, compared with 16% for IMRT.

Other investigators have been interested in using IMRT to offer dose escalation to the primary tumor. The

ability to "dose paint" via a simultaneous integrated boost to a region of greatest risk allows for focal dose escalation to internal sub-volumes without increasing marginal doses to adjacent organs. Investigators at the MD Anderson Cancer Center retrospectively reported a series of 200 locally advanced patients treated with induction chemotherapy followed by concurrent chemoradiation. Using simultaneous integrated boost via IMRT, dose escalation to a biologically effective dose greater than 70 Gy was possible in 47 patients, which translated to improved locoregional control and improved estimated 3-year OS (31% vs 9%). More important, given the limitations of the retrospective study design, was the observation of no additional toxicity in the high-dose group.[41] Dose escalation via a simultaneous integrated boost can also be delivered to sites of tumor-vessel abutment in potentially resectable patients. In a series of 104 borderline resectable patients, the use of a vessel boost (n=23) showed a trend toward improved surgical resection (odds ratio, 2.77; 95% CI, 0.89-8.57; *P*=.077).[42]

The value of chemoradiation for treatment of LAPC is controversial, and this controversy only increased following the publication of the LAP07 trial (Gemcitabine With or Without Capecitabine and/or Radiation Therapy or Gemcitabine With or Without Erlotinib in Treating Patients With Locally Advanced Pancreatic Cancer That Cannot Be Removed by Surgery).[43] This was an international, phase 3 randomized trial that included 449 patients who underwent initial induction chemotherapy with gemcitabine alone or gemcitabine plus erlotinib (Tarceva, Genentech/Astellas) for 4 cycles. Those without progression were randomly assigned to chemoradiation (54 Gy plus capecitabine) or 2 additional cycles of gemcitabine. Chemoradiation was associated with improvements in local control and progression-free survival, but there was no difference in OS between the 2 arms, with a median survival of 16.5 months in the chemotherapy arm vs 15.2 months in the chemoradiation arm.[43] Although the eligibility criteria (stage III, T4 N0/1 M0) potentially allowed for some inclusion of borderline resectable disease, only 4% of patients underwent definitive resection, indicating that this trial largely enrolled unresectable patients. The improvements in local control and progression-free survival suggest that when there is potential for definitive resection, the ability of chemoradiation to sterilize the tumor margin and facilitate R0 resection may have value in the neoadjuvant setting.

The PREOPANC trial (Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer) recently published its results of their randomized control trial. This phase 3 trial included 246 patients with resectable or borderline resectable pancreatic cancer, and randomly assigned patients to up-front surgery followed by adjuvant chemotherapy, or preoperative chemoradiation followed by adjuvant chemotherapy. The preoperative chemoradiotherapy consisted of 36 Gy in 15 fractions combined with gemcitabine at 1000 mg/m^2 on days 1, 8, and 15, preceded and followed by 1 cycle of gemcitabine administered at 1000 mg/m^2 on days 1 and 8 every 3 weeks, and an additional 4 cycles of standard gemcitabine at 1000 mg/m^2 on days 1, 8, and 15 on an every-4-week cycle. The control group underwent up-front surgery and 6 cycles of standard postoperative adjuvant gemcitabine. The recently published results showed a higher rate of resection in the up-front group vs the neoadjuvant group (72% vs 61%, respectively; *P*=.058), a difference that did not reach statistical significance. However, the R0 resection percentage was higher in the neoadjuvant group (72% vs 40%; *P*<.001). The reported incidence of perineural invasion was also less in the neoadjuvant group (39% vs 73%; *P*<.001), and the percentage of patients with positive lymph nodes also was less in the neoadjuvant group (33% vs 78%; *P*<.001). The median OS was 16 months in patients who underwent neoadjuvant treatment vs 14.3 months in the immediate-surgery group, which was not a statistically significant difference (HR, 0.78; 95% CI, 0.58-1.05; *P*=.096).[44]

In analyzing the 113 patients determined to have BRPC, the median OS was 17.6 months in the neoadjuvant group compared with 13.2 months in the up-front surgery group (HR, 0.62; 95% CI, 0.40-0.95; *P*=.029). Within the BRPC group, both the locoregional failure-free interval (LFFI) and the distant metastasis–free interval (DMFI) were considerably higher in the neoadjuvant group. LFFI was 27.7 months in the neoadjuvant group vs 11.8 months in the up-front surgery group (HR, 0.54; 95% CI, 0.32-0.91; *P*=.022), and the DMFI was 21.5 months in the neoadjuvant group compared with 12.2 months in the up-front surgery group; this difference did not reach statistical significance (HR, 0.69; 95% CI, 0.42-1.15; *P*=.150). Although the overall intention-to-treat population did not show a statistically significant improvement in median OS, the reported data in BRPC did identify a statistically significant improvement with neoadjuvant therapy in terms of median OS.[44]

Alliance A021101 (Chemotherapy and Radiation Therapy Before Surgery Followed by Gemcitabine in Treating Patients With Pancreatic Cancer) was a single-arm trial that included 22 borderline resectable patients who received modified FOLFIRINOX for 4 cycles followed by chemoradiation (50.4 Gy in 28 fractions plus capecitabine).[45] Overall, 15 of 22 patients (68%) underwent pancreaticoduodenectomy. An R0 resection was achieved in 14 patients (93%). A pathologic complete response was observed in 2 patients (13%). The

median OS for all patients was 21.7 months (95% CI, 15.7 to not reached).[45]

A recently reported, single-institution, phase 2 trial evaluated total neoadjuvant therapy with FOLFIRINOX for up to 8 cycles followed by individualized chemoradiation in patients with BRPC. After completion of induction chemotherapy, a pancreas-protocol CT scan was used to re-evaluate resectability. If the tumor was clearly resectable without vascular involvement, short-course chemoradiation (25 Gy in 5 fractions plus capecitabine) was delivered, followed by prompt surgery. If persistent vascular involvement was observed, long-course chemoradiation (50.4 Gy in 28 fractions plus capecitabine) was given. Overall, 44 patients were treated, with 27 receiving short-course radiation and 17 receiving long-course radiation. Among 32 patients who underwent resection, 31 had an R0 resection. The median OS among all 48 eligible patients was 37.7 months, with a locoregional recurrence rate of 6%, which the authors noted was favorable compared with historical controls.[46]

The proof of principle that optimizing the sequence of therapy can significantly impact patient outcomes should solidify the neoadjuvant space as the avenue for future investigation in resectable pancreatic cancer. Despite positive results, the limitations of the PREOPANC-1 trial include the absence of the most active systemic regimens, such as gemcitabine and nab-paclitaxel or FOLFIRINOX, as a component of preoperative treatment. The incorporation of induction chemotherapy and chemoradiation as total neoadjuvant therapy could further expand resectability and reduce the presence of adverse pathologic results.

Stereotactic body radiation therapy (SBRT) offers an attractive modality, given its ability to limit the potential collateral damage to surrounding structures that can occur with external beam radiation. SBRT is able to deliver more ablative doses of radiation through a reduction in the planning target volumes, which is facilitated by advanced motion management and precise, image-guided delivery. This new technology warrants additional study as neoadjuvant therapy for borderline resectable PDAC, but might be limited by the lack of treatment to the surrounding lymph node basin. This may be countered by the potential benefits of a shorter course of SBRT. Comparative effectiveness data for long-course chemoradiation vs SBRT are scarce. Although most of the experience with SBRT has been reported in locally advanced and unresectable disease, trials for potentially resectable patients have been published.

A single-institution report of 101 borderline-resectable patients incorporated SBRT (30 Gy in 5 fractions) with simultaneous integrated boost to the tumor-vessel interface (median dose, 35 Gy) following induction chemotherapy. Fifty-five patients (54.5%) were able to undergo resection, and R0 was achieved in 95.5%. The pathologic complete response rate was 14.5%.[47] The Alliance A021501 trial (Combination Chemotherapy With or Without Hypofractionated Radiation Therapy Before Surgery in Treating Patients With Pancreatic Cancer) is currently ongoing. This phase 2 trial for patients with borderline resectable cancer of the head of the pancreas is randomly assigning patients to modified FOLFIRINOX before and after surgery, with or without preoperative SBRT. Although results have not been published, investigators have decided that the successor phase 3 trial will not be pursued owing to the difference between the 2 arms of the phase 2 portion of the study crossing the futility boundary.[48]

Although not broadly available, intraoperative radiation therapy (IORT) is a potentially useful strategy in managing patients with borderline resectable disease. IORT using a superficially penetrating electron beam permits targeting of the regions at highest risk of harboring microscopic disease, such as the tumor-vessel interface. IORT delivered in a single large fraction permits complete sparing of adjacent viscera, which are the dose-limiting structures for IMRT and 3D CRT. It is typically delivered as a boost following a conventional course of the neoadjuvant therapy when intraoperative frozen tissue assessment uncovers close or positive margins.

The largest series included 210 resected patients from a multicenter experience in Japan. Although reported before the era of multiagent chemotherapy, the incorporation of IORT (median dose, 25 Gy) yielded a 2-year local control rate of 83.7%.[49] A more contemporary series that included only patients receiving FOLFIRINOX or gemcitabine with nab-paclitaxel as induction followed by chemoradiation was recently reported (N=68). Forty-one patients (60.3%) had resectable cancer. Of these, 22 received IORT (10 Gy) for close or positive margins, without an increase in operative morbidity. Median OS was 26.6 months for all resectable patients, 35.1 months for patients who underwent resection and IORT, and 24.5 months for patients who underwent resection alone; these differences were not statistically significant.[50]

Conclusions and Future Directions

Borderline resectable PDAC has increasingly been recognized as a distinct clinical entity that should be approached differently than locally advanced PDAC and resectable PDAC. A growing body of data suggest that initial or neoadjuvant therapy with chemotherapy (with or without radiation) improves all key outcomes, including resectability, R0 resection, and survival in particular. However, a key issue with the data that are

used to support neoadjuvant therapy is the problem of patient selection, in particular the comparison of outcomes among similar patients who undergo chemotherapy or chemoradiation, but not surgery. In addition, the generalizability of results remains in question, as reports to date generally have come from specialized institutions rather than from community practice.

The optimal neoadjuvant regimen remains to be defined, but with greater agreement about the definition of borderline resectable PDAC (Table), prospective trials—including Alliance A021501—are underway that are investigating a variety of neoadjuvant approaches and different treatment modalities. New chemotherapy combinations are also being explored. The PRIMUS 002 study (Looking at 2 Neo-adjuvant Treatment Regimens for Resectable and Borderline Resectable Pancreatic Cancer) is currently enrolling patients, who are then randomly assigned to FOLFOX with nab-paclitaxel alone vs nab-paclitaxel plus gemcitabine.[51]

As with metastatic PDAC, the development and assessment of neoadjuvant or induction therapies focuses on cytotoxic chemotherapy, given that the role of novel targeted therapies and immunotherapy at this time is largely uncertain. However, with the recognition that poly(ADP-ribose) polymerase (PARP) inhibitors have activity as maintenance therapy in metastatic PDAC, further investigation of their role in borderline resectable PDAC—with chemotherapy and/or radiation—should be contemplated.[52] The results of these avenues of investigation should help obtain important data to help advance the management of BRPC.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
2. GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol.* 2019;4(12):934-947.
3. National Comprehensive Cancer Network. Pancreatic Adenocarcinoma. v.1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf Accessed December 5, 2019.
4. Chatzizacharias NA, Tsai S, Griffin M, et al. Locally advanced pancreas cancer: staging and goals of therapy. *Surgery.* 2018;163(5):1053-1062.
5. Evans DB. What makes a pancreatic cancer resectable? *Am Soc Clin Oncol Educ Book.* 2018;38:300-305.
6. Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer [published online April 5, 2019]. *Ann Surg.* doi:10.1097/SLA.0000000000003284.
7. Ishikawa O, Ohigashi H, Imaoka S, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. *Ann Surg.* 1992;215(3):231-236.
8. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol.* 2006;13(8):1035-1046.
9. Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. *Radiology.* 2014;270(1):248-260.
10. Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic adenocarcinoma, version 1.2019. *J Natl Compr Canc Netw.* 2019;17(3):202-210.
11. Morgan DE, Waggoner CN, Canon CL, et al. Resectability of pancreatic adenocarcinoma in patients with locally advanced disease downstaged by preoperative therapy: a challenge for MDCT. *AJR Am J Roentgenol.* 2010;194(3):615-622.
12. Wittel UA, Lubgan D, Ghadimi M, et al. Consensus in determining the resectability of locally progressed pancreatic ductal adenocarcinoma - results of the Conko-007 multicenter trial. *BMC Cancer.* 2019;19(1):979.
13. Tamburrino D, Riviere D, Yaghoobi M, Davidson BR, Gurusamy KS. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer [published online September 15, 2016]. *Cochrane Database Syst Rev.* doi:10.1002/14651858.CD011515.pub2.
14. Shrikhande SV, Barreto SG, Goel M, Arya S. Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature. *HPB (Oxford).* 2012;14(10):658-668.
15. Borhani AA, Dewan R, Furlan A, et al. Assessment of response to neoadjuvant therapy using CT texture analysis in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma. *AJR Am J Roentgenol.* 2020;214(2):362-369.
16. Akita H, Takahashi H, Ohigashi H, et al. FDG-PET predicts treatment efficacy and surgical outcome of pre-operative chemoradiation therapy for resectable and borderline resectable pancreatic cancer. *Eur J Surg Oncol.* 2017;43(6):1061-1067.
17. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer.* 2012;118(23):5749-5756.
18. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg.* 2015;261(1):12-17.
19. van Veldhuisen E, Vogel JA, Klompmaker S, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. *HPB (Oxford).* 2018;20(7):605-611.
20. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. *HPB (Oxford).* 2011;13(6):377-384.
21. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol.* 2018;24(43):4846-4861.
22. Fuhrman GM, Leach SD, Staley CA, et al; Pancreatic Tumor Study Group. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. *Ann Surg.* 1996;223(2):154-162.
23. Tee MC, Krajewski AC, Groeschl RT, et al. Indications and perioperative outcomes for pancreatectomy with arterial resection. *J Am Coll Surg.* 2018;227(2):255-269.
24. Ouaissi M, Hubert C, Verhelst R, et al; Multidisciplary HPB Group of Center of Cancer. Vascular reconstruction during pancreatoduodenectomy for ductal adenocarcinoma of the pancreas improves resectability but does not achieve cure. *World J Surg.* 2010;34(11):2648-2661.
25. Ouaïssi M, Turrini O, Hubert C, Louis G, Gigot JF, Mabrut JY. Vascular resection during radical resection of pancreatic adenocarcinomas: evolution over the past 15 years. *J Hepatobiliary Pancreat Sci.* 2014;21(9):623-638.
26. Worni M, Castleberry AW, Clary BM, et al. Concomitant vascular reconstruction during pancreatectomy for malignant disease: a propensity score-adjusted, population-based trend analysis involving 10,206 patients. *JAMA Surg.* 2013;148(4):331-338.
27. Bacalbasa N, Balescu I, Dima S, et al. Pancreatoduodenectomy en bloc with vascular resections in borderline resectable pancreatic cancer. *In Vivo.* 2019;33(6):2303-2308.
28. Jang JY, Han Y, Lee H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. *Ann Surg.* 2018;268(2):215-222.

29. Murakami Y, Uemura K, Sudo T, et al. Survival impact of neoadjuvant gemcitabine plus S-1 chemotherapy for patients with borderline resectable pancreatic carcinoma with arterial contact. *Cancer Chemother Pharmacol.* 2017;79(1):37-47.
30. Torgeson A, Lloyd S, Boothe D, et al. Multiagent induction chemotherapy followed by chemoradiation is associated with improved survival in locally advanced pancreatic cancer. *Cancer.* 2017;123(19):3816-3824.
31. Versteijne E, Vogel JA, Besselink MG, et al; Dutch Pancreatic Cancer Group. Meta-analysis comparing up-front surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg.* 2018;105(8):946-958.
32. Vaccaro V, Sperduti I, Milella M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;365(8):768-769.
33. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.
34. Petrelli F, Coinu A, Borgonovo K, et al; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD). FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. *Pancreas.* 2015;44(4):515-521.
35. Dhir M, Zenati MS, Hamad A, et al. FOLFIRINOX versus gemcitabine/nab-paclitaxel for neoadjuvant treatment of resectable and borderline resectable pancreatic head adenocarcinoma. *Ann Surg Oncol.* 2018;25(7):1896-1903.
36. Franko J, Hsu HW, Thirunavukarasu P, Frankova D, Goldman CD. Chemotherapy and radiation components of neoadjuvant treatment of pancreatic head adenocarcinoma: impact on perioperative mortality and long-term survival. *Eur J Surg Oncol.* 2017;43(2):351-357.
37. Lutfi W, Talamonti MS, Kantor O, et al. Neoadjuvant external beam radiation is associated with No benefit in overall survival for early stage pancreatic cancer. *Am J Surg.* 2017;213(3):521-525.
38. Cloyd JM, Chen HC, Wang X, et al. Chemotherapy versus chemoradiation as preoperative therapy for resectable pancreatic ductal adenocarcinoma: a propensity score adjusted analysis. *Pancreas.* 2019;48(2):216-222.
39. Toesca DAS, Koong AJ, Poultsides GA, et al. Management of borderline resectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2018;100(5):1155-1174.
40. Prasad S, Cambridge L, Huguet F, et al. Intensity modulated radiation therapy reduces gastrointestinal toxicity in locally advanced pancreas cancer. *Pract Radiat Oncol.* 2016;6(2):78-85.
41. Krishnan S, Chadha AS, Suh Y, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. *Int J Radiat Oncol Biol Phys.* 2016;94(4):755-765.
42. Wang LS, Shaikh T, Handorf EA, Hoffman JP, Cohen SJ, Meyer JE. Dose escalation with a vessel boost in pancreatic adenocarcinoma treated with neoadjuvant chemoradiation. *Pract Radiat Oncol.* 2015;5(5):e457-e463.
43. Hammel P, Huguet F, van Laethem JL, et al; LAP07 Trial Group. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA.* 2016;315(17):1844-1853.
44. Versteijne E, Suker M, Groothuis K, et al; Dutch Pancreatic Cancer Group. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial [published online February 27, 2020]. *J Clin Oncol.* doi:10.1200/JCO.19.02274.
45. Katz MHG, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg.* 2016;151(8):e161137-e161137.
46. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. *JAMA Oncol.* 2018;4(7):963-969.
47. Rashid OM, Pimiento JM, Gamenthaler AW, et al. Outcomes of a clinical pathway for borderline resectable pancreatic cancer. *Ann Surg Oncol.* 2016;23(4):1371-1379.
48. Katz MHG, Ou FS, Herman JM, et al; Alliance for Clinical Trials on Oncology. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *BMC Cancer.* 2017;17(1):505.
49. Ogawa K, Karasawa K, Ito Y, et al. Intraoperative radiotherapy for resected pancreatic cancer: a multi-institutional retrospective analysis of 210 patients. *Int J Radiat Oncol Biol Phys.* 2010;77(3):734-742.
50. Keane FK, Wo JY, Ferrone CR, et al. Intraoperative radiotherapy in the era of intensive neoadjuvant chemotherapy and chemoradiotherapy for pancreatic adenocarcinoma. *Am J Clin Oncol.* 2018;41(6):607-612.
51. Grose DB, McKay CJ, Cooke S, et al. PRIMUS-002: A multicentre, open-label, phase II study examining FOLFOX and nab-paclitaxel (FA) and nab-paclitaxel and gemcitabine (AG) as neoadjuvant therapy for (borderline) resectable pancreatic cancer (PC), focusing on biomarker and liquid biopsy development [JCO abstract TPS4166]. *J Clin Oncol.* 2019;37(15)(suppl).
52. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med.* 2019;381(4):317-327.