Neoadjuvant therapy for pancreatic ductal adenocarcinoma: Opportunities for personalized cancer care

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy that is best treated in a multidisciplinary fashion using surgery, chemotherapy, and radiation. Adjuvant chemotherapy has shown to have a significant survival benefit in patients with resected PDAC. However, up to 50% of patients fail to receive adjuvant chemotherapy due to postoperative complications, poor patient performance status or early disease progression. In order to ensure the delivery of chemotherapy, an alternative strategy is to administer systemic treatment prior to surgery. Precision oncology refers to the application of diverse strategies to target therapies specific to characteristics of a patient’s cancer. While traditionally emphasized in selecting targeted therapies based on molecular, genetic, and radiographic biomarkers for patients with metastatic disease, the neoadjuvant setting is a prime opportunity to utilize personalized approaches. In this article, we describe the current evidence for the use of neoadjuvant therapy (NT) and highlight unique opportunities for personalized care in patients with PDAC undergoing NT.

Key Words: Pancreatic cancer; Preoperative therapy; FOLFIRINOX; Precision oncology; Patient-reported outcomes; Personalized medicine; Targeted therapy; Whipple; Pancreatectomy

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Core Tip: Neoadjuvant therapy (NT) is an increasingly utilized approach that maximizes the receipt of multimodality therapy, improves margin-negative resection rates, and potentially increases survival durations. In the era of personalized medicine, the neoadjuvant period can also be used to emphasize precision oncology. Already,
current methods of anatomically staging, molecularly profiling, and monitoring response to therapy can be used to personalize neoadjuvant treatment for localized pancreatic ductal adenocarcinoma (PDAC). In this article, we describe the current evidence for the use of NT and highlight unique opportunities for personalized care in patients with PDAC undergoing NT.

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INTRODUCTION
Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related deaths worldwide with a 5-year overall survival (OS) rate of only 10%[1]. Despite surgical resection being the only hope for cure, only a small proportion of patients present with resectable disease and the majority of patients will develop locoregional or metastatic recurrence after surgery[2,3]. Adjuvant chemotherapy has shown to have a significant survival benefit in patients with resected PDAC[3]. However, up to 50% of patients fail to receive adjuvant chemotherapy due to postoperative complications, poor patient performance status or early disease progression[4-6].

In order to ensure the delivery of chemotherapy, an alternative strategy is to administer systemic treatment prior to surgery. Neoadjuvant therapy (NT) has been shown to confer several clinical benefits such as improved margin-negative resection rates, decreased lymph node positivity, early treatment of presumed micro-metastatic disease, an optimal window of time to provide prehabilitation before surgery, and the ability to measure in vivo response to therapy histologically after resection[7-9]. Moreover, increasing evidence from randomized controlled trials (RCT) suggests NT may improve OS in patients with non-metastatic PDAC compared with upfront resection[10,11]. Despite the advantages of NT, its use in the United States has remained relatively low[12,13]. While NT is now the recommended treatment strategy for borderline resectable (BR) or locally advanced cancer, current NCCN guidelines support either upfront surgical resection or NT for patients with resectable disease[4].

There is growing interest in emphasizing personalized approaches to multidisciplinary cancer care that reflects not only unique differences in cancer biology but also individual circumstances and treatment goals. Precision oncology refers to the application of diverse strategies to target therapies specific to characteristics of a patient’s cancer. While traditionally emphasized in selecting targeted therapies based on molecular, genetic, and radiographic biomarkers for patients with metastatic disease, the neoadjuvant setting is a prime opportunity to utilize personalized approaches. In this article, we describe the current evidence for the use of NT and highlight unique opportunities for personalized care in patients with PDAC undergoing NT.

RATIONAL FOR NT
Large cohort and population-based studies have shown that as many as 50% of patients who undergo surgical resection for PDAC are unable to receive adjuvant therapy due to postoperative complications, poor performance status, or early disease progression[4-6,15,16]. Even among healthy patients enrolled in clinical trials, a substantial proportion of patients are unable to initiate adjuvant therapy due to the morbidity of pancreatic surgery[4]. An even greater proportion of patients fail to complete all intended cycles of adjuvant therapy[5]. Thus, the ability to ensure receipt of systemic therapy and facilitate multimodality therapy is one of the strongest reasons to recommend NT. Other advantages that support the use of NT include the early treatment of presumed micrometastatic disease, the ability to potentially downstage BR disease improving the chances of R0 resection, and improved patient selection by...
avoiding surgery in those patients with rapid disease progression during preoperative treatment. Additionally, well-oxygenated, non-devascularized tissue is more susceptible to the effects of chemoradiation, which theoretically increases the efficacy of chemoradiation if given prior to surgery[17,18].

These advantages must be carefully weighed against the potential disadvantages of pursuing NT. First, unlike in a surgery-first approach, tissue diagnosis and biliary decompression are uniformly required. These procedures may delay the initiation of treatment and are associated with small, but non-zero, risks. Second, NT is inherently multi-disciplinary and require careful coordination among providers. Third, and most importantly, delivering aggressive chemotherapy and/or radiation prior to surgery can lead to severe toxicity that, in extreme cases, can preclude subsequent surgical resection. Indeed, a systematic review by the Dutch Pancreatic Cancer Group calculated a Grade III or higher toxicity rate of 64% among patients undergoing NT [19]. The recent SWOG S1505 trial of NT for resectable PDAC found that nearly 13% that started NT were unable to undergo surgery because of performance status decline [20]. Finally, while distant progression while on NT is far more common, a small risk of local progression that leads to unresectability exists. These challenges highlight the importance not only of personalizing treatment decisions regarding NT, but also of emphasizing research that improves the delivery of NT for patients with localized PDAC.

**CURRENT EVIDENCE FOR NT**

Support for the use of NT for localized PDAC has largely come from small prospective trials, single-institutional series, and cancer registries[21]. These studies largely demonstrated its feasibility and proposed NT as an acceptable approach for PDAC. Suggestions of improved outcomes compared to upfront surgery have been limited by study design. However, the completion of several RCT in recent years comparing NT to upfront surgery have generated increased support for NT. For example, two RCTs found improved margin-negative resection rates and OS among patients with BR PDAC[22] who received neoadjuvant CRT compared to immediate surgery. Furthermore, the PACT-15 and Prep-02/JSAP-05 RCTs found improved OS among patients with resectable PDAC treated with neoadjuvant chemotherapy compared to those who underwent immediate surgery[16,23].

In a recent meta-analysis of only prospective RCTs, Cloyd et al[13] showed that the OS of patients with resectable or BR PDAC who received NT was nearly 30% better than that of patients who underwent surgery upfront using an intention-to-treat design. Furthermore, the meta-analysis found that NT improved R0 resection rate and decreased lymph node positivity rate. Since then, preliminary results from the ESPAC-5 trial, a four-arm RCT comparing patients undergoing surgery upfront, neoadjuvant gemcitabine/capecitabine (GEMCAP), neoadjuvant FOLFIRINOX, and neoadjuvant capecitabine-based radiation, showed improved one-year OS among patients receiving NT[24]. As a limitation of previous RCTs is the use of non-traditional neoadjuvant regimens (e.g., folfitinex or gemcitabine-abraxane), the long-term results of this trial and other contemporary studies comparing NT to immediate surgery are anxiously awaited.

**OPPORTUNITIES FOR PERSONALIZED CANCER CARE**

Several factors make the neoadjuvant period an optimal scenario to emphasize precision oncology (Table 1). First, PDAC is anatomically and genetically heterogeneous as is the clinical presentation of patients with localized disease. Second, patient and tumor response to NT differs significantly. Evaluating and responding to this dynamic staging offers an opportunity to personalize subsequent treatment.

**Anatomic staging**

Using high-quality cross-sectional imaging, localized PDAC is classified as resectable, BR or locally advanced (LA; also termed unresectable) according to its relationship with major vascular structures. While several organizations have published staging criteria with only slight differences, the SSO/SSAT/AHPBA consensus definitions are commonly employed. As these criteria reflect the likelihood of achieving a margin-negative resection with upfront surgery, the development of a uniform anatomic staging...
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| Concept               | Description                                                                 | Examples                                                                                                                                  | Outcome                                                                                                           |
|-----------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Anatomic staging      | Characterization of local extent and vascular involvement of tumor          | Locally advanced/unresectable; Borderline resectable; Potentially resectable                                                             | Anatomic staging can influence the recommended duration and components (e.g., preoperative radiation) of neoadjuvant therapy |
| Molecular staging     | Identification of tumor/germline genetic and molecular markers              | BRCA mutations; Mismatch repair-deficiency; Molecular markers                                                                             | Specific tumor/germline mutations may identify opportunity for targeted therapies (e.g., immunotherapy, PARP inhibitors) |
| Dynamic staging       | Measuring biochemical, radiographic, and histologic response of the tumor to neoadjuvant therapy | Carbohydrate antigen 19-9; Response evaluation criteria in solid tumors response; Pathologic response                                      | Measuring response to neoadjuvant therapy can influence treatment strategies (e.g., changing neoadjuvant regimen, use of radiation, recommendations for adjuvant therapy) |

staging system has been pivotal for improved clinical protocol standardization specifically concerning the use of NT [25] (Table 2).

LA PDAC truly represents unresectable disease, typically because of arterial encasement or non-reconstructable venous involvement. Still, recent studies have found that a small but significant proportion of patients can be converted to resectable disease after aggressive NT [26]. For example, a large retrospective study by Hackert et al [27] showed that 61% of patients with LA PDAC receiving FOLFIRINOX as NT underwent successful surgical resection with a 40.8% R0 resection rate. Another study by Gememtizis et al [28] showed that FOLFIRINOX-based therapy and stereotactic body radiation therapy correlated with increased probability of resection ($P = 0.006$); patients who eventually underwent surgical resection had higher median OS compared with those who did not (35.3 mo vs 16.3 mo; $P < 0.0001$). Given the vascular involvement and low likelihood of achieving negative microscopic margins, preoperative radiation therapy is commonly employed after induction systemic chemotherapy prior to attempts at surgical resection. This approach is logical since consolidative radiation is frequently administered for patients with LA disease who are not surgical candidates to enhance locoregional control [29].

A similar approach should be considered for patients with BR PDAC yet with higher likelihood of undergoing surgical resection. Current practice is to typically begin with induction systemic chemotherapy. For example, the Alliance for Clinical Trials in Oncology group A021101, demonstrated a 93% R0 resection rate for patients with BR PDAC after receiving FOLFIRINOX followed by capecitabine-based chemoradiation as NT [30]. Similarly, a single-arm prospective trial of neoadjuvant FOLFIRINOX followed by radiation resulted in a high degree of R0 resection in those who underwent surgery with impressive progression-free survival (PFS) and OS durations [31]. Despite these results, the role of radiation following induction chemotherapy remains controversial for BR PDAC. The Alliance A021501 trial, randomized patients with BR PDAC to either 8 cycles of FOLFIRINOX or 7 cycles of FOLFIRINOX followed by hypofractionated radiation before surgery. Patients who received radiation therapy were less likely to undergo surgical resection and experienced shorter OS [32]. In summary, NT with systemic chemotherapy with selective use of preoperative radiation is currently the preferred approach for BR PDAC.

The use of NT remains the most controversial in patients with resectable PDAC and wide variation in practices exist [21]. Nevertheless, the use of NT continues to increase given the previously described rationale and increasing evidence that highlights improved outcomes. However, given the lesser need for downsizing and higher likelihood of achieving an R0 resection, current neoadjuvant approaches tend to utilize systemic chemotherapy alone. For example, the SWOG S1505 trial was a recent RCT of either neoadjuvant mFOLFIRINOX or gemcitabine/nab-paclitaxel prior to surgical resection for resectable PDAC as NT [33]. In addition, the recently opened Alliance A021806 will randomize patients with resectable PDAC to either perioperative mFOLFIRINOX or surgery upfront followed by adjuvant mFOLFIRINOX [34].

**Molecular staging**

The last decade has seen dramatic advances in our understanding of the genetic underpinnings of PDAC pathogenesis. With advanced tumor profiling and next-generation sequencing, recent studies have characterized the frequency of genetic and molecular alterations in PDAC tumors [35]. This information, if obtained routinely via tissue biopsy or surgical specimen, can contribute to a more personalized approach to
Table 2 Anatomic staging of localized pancreatic ductal adenocarcinoma as defined by the 2008 AHPBA/SSO/SSAT consensus guidelines

| SMV-PV | SMA | Celiac axis |
|-------|-----|------------|
| Resectable | Borderline | Locally advanced |
| Uninvolved with tumor with clear fat planes around vessels | Abutment, encasement, or occlusion of short segment of vein | Occlusion, thrombosis, or encasement extending several centimeters |
| Uninvolved | Tumor abutment < 180° | Tumor abutment > 180° (encasement) or thrombosis of artery |
| Uninvolved | Uninvolved celiac axis; short segment encasement or abutment of common hepatic artery may be amenable to resection and reconstruction | Abutment or encasement of celiac axis indicates unresectability |

SMV: Superior mesenteric vein; PV: Portal vein; SMA: Superior mesenteric artery.

In a study by Krepline et al [37], 73 out of 78 resected PDAC specimens were found to have a pathogenic variant on NGS of which 18% were potentially actionable. For example, patients with BRCA1/BRCA2 mutations are known to benefit from platinum-based chemotherapy and PARP inhibitors [38,39]. Pancreatic cancer that is mismatch repair-deficient (dMMR), a small but clinically relevant proportion, are known to respond to immunotherapy [40,41]. Finally, the efficacy of standard chemotherapy regimens can be modified depending on thymidylate synthase (TYMS), excision repair cross-complementing (ERCC1) protein, ribonucleotide reductase M1 (RMM1), secreted protein acid and rich in cysteine (SPARC), topoisomerase I (TOP1), and human equilibrative nucleoside transported 1 (hENT1) levels. Low TYMS, ERCC1 protein, and RRM1 Levels predict efficacy of 5-FU based therapies and capecitabine, cisplatin, and gemcitabine respectively [42-44]. Elevated SPARC level predicted sensitivity to nab-paclitaxel while low levels of hENT1 have been associated with gemcitabine resistance [43,45].

These molecular biomarkers, if obtained from preoperative endoscopic ultrasound biopsies, can thus be used to tailor NT. In a recent prospective trial, Tsi et al [46] delivered neoadjuvant systemic therapy to 130 patients based on the molecular profile results. In this trial, 6 molecular targets were utilized to predict chemosensitivity: TYMS, ERCC1, RMM1, SPARC, TOP1, and hENT1. Of the 92 patients with predictive molecular profiling, 74 (80%) received fluoropyrimidine-based systemic therapy and 18 (20%) received gemcitabine-based systemic therapy [46]. Of the 130 overall patients enrolled, 107 (82%) completed all intended NT followed by surgical resection including 56 (92%) with resectable PDAC and 51 (74%) with BR PDAC. The importance of this trial was to demonstrate the increased rate of resectability, which suggests that molecular profiling potentially improved the efficacy of NT [46]. Furthermore, the Individualized Molecular Pancreatic Cancer Therapy (iMPaCT) trial documented the feasibility of acquiring and screening pancreatic tumor tissue for HER2 amplification, KRAS mutation, and mutations in BRCA1, BRCA2, PALB2, and ATM [47]. A pilot study using molecular profiling in a wide variety of metastatic cancers demonstrated a longer PFS in 27% of patients receiving molecular profiling-based systemic therapy [36]. The scarcity of studies in this field suggest that this method of personalized care is under-utilized and warrants further investigation.

**Dynamic staging**

In contrast to standard adjuvant therapy, administering nonoperative therapies prior to surgery provides a unique opportunity to measure the tumor response to treatment *in vivo*. Traditional measures of tumor response to NT include biochemical, radiographic, and histologic. There is abundant data supporting the use of carbohydrate antigen 19-9 (CA 19-9) in the clinical management of patients with PDAC. While baseline CA 19-9 is an important measure of disease burden, numerous studies have highlighted the prognostic significance of CA 19-9 response to NT [48-52]. For example, Boone et al [49] found that CA 19-9 response to NT was associated with R0 resection rate, histopathological response, and OS.

Restaging with cross-sectional imaging is routinely performed during and following NT, mostly to rule out disease progression but also to assess the response of the primary tumor to treatment. While the Response Evaluation Criteria in Solid Tumors (RECIST) grading system has historically felt to under-represent treatment response [53], Perri et al [54] recently found in a large retrospective study that RECIST partial response and a reduction in tumor volume after NT were independently associated
with pathologic response in patients with localized PDAC. In addition to serologic and radiographic measures, the response to NT can be measured histologically in surgical specimens as the proportion of active cancer cells. Unfortunately, previous studies have found that only a major pathologic response (defined as < 5% active cancer cells) is associated with improved prognosis[8] and that pathologic complete responses are rare[55].

A dynamic assessment of tumor response to treatment may help personalize treatment in several ways. First, non-responders to induction systemic chemotherapy can be switched to alternative regimens. In a study by Vreeland et al[36], of 25 BR or LA PDAC patients who did not respond to FOLFIRINOX after 4 mo of treatment as NT, 21 (84%) showed a serologic or radiographic response after switching to gemcitabine/nab-paclitaxel and 11 of them underwent surgical resection (Figure 1). In contrast, responders who are tolerating therapy may be selected to continue this regimen particularly if CA 19-9 has not normalized yet or additional downstaging is required. Second, reassessment of anatomic location may assist decision making regarding the role of preoperative radiation. Third, information on response to NT may guide the use of adjuvant therapy. For example, Liu et al[50] showed that in a cohort of patients in whom CA 19-9 normalized with a decrease > 50% after NT, adjuvant therapy was not associated with additional survival benefit whereas in patients with no normalization of CA 19-9 or decrease of > 50%, receipt of adjuvant therapy was in fact associated with a survival benefit[50]. Additional research is needed to determine whether alternative adjuvant regimens (e.g., gemcitabine-based chemotherapy) should be utilized in patients who do not respond to first-line neoadjuvant chemotherapy (e.g., FOLFIRINOX).

FUTURE DIRECTIONS

Novel biomarkers
With an improved understanding of tumor biology, cancer care is becoming increasingly personalized. Integrated genomic analysis has revealed several molecular tumor subtypes of PDAC as well as subsets of the tumor microenvironment (TME)[57, 58]. The clinical applications of such classification systems are still in development but perhaps this data can be used to inform about prognosis or aid in treatment decisions [59]. A shift toward personalized NT will depend greatly on the development and validation of novel biomarkers. As an example, SPARC is a protein that is overly expressed in the TME of PDAC tumors. SPARC expression was associated with an inferior survival in patients receiving gemcitabine-based chemotherapy while no association was detected for patients receiving fluoropyrimidine-based chemotherapy suggesting SPARC expression might act as a negative predictive biomarker in patients treated with gemcitabine-based chemotherapy[60]. However, SPARC expression was not associated with survival or response to gemcitabine-based chemotherapy in patients with metastatic PDAC[61]. Similarly, hENT1 is a receptor that is upregulated on the surface of PDAC cells. Gemcitabine exerts its cytotoxic effects after its cellular uptake by hENT1. Therefore, hENT1 expression could potentially predict therapeutic activity of gemcitabine while its under-expression would be a mechanism for resistance[62,63]. hENT1 was studied as a predictor of response to gemcitabine in the adjuvant setting[64,65], but again could not be validated in the metastatic setting[66]. Additionally, microRNA, serum metabolism profiling, or methylation patterns may prove to be useful biomarkers for diagnosis and potential response to therapy in PDAC[67-69].

Improved methods of measuring response
As systemic therapies for PDAC improves, more novel and sophisticated methods of monitoring tumor response are needed. Response to therapy is routinely based on imaging obtained during the course of treatment. Changes in the tumor-parenchyma interface may serve as an early predictor of response to therapy based on computed tomography imaging[70]. Other novel methods such as detection of circulating tumor cells and circulating tumor DNA (ctDNA) are on the horizon for both diagnosis and markers of response to therapy[71,72]. In patients with PDAC, ctDNA levels have been found to correlate with tumor burden and serial monitoring of ctDNA may provide a method to monitor early response to chemotherapy[73]. Patients who received NT had significantly lower circulating tumor cells compared to patients who were eligible for upfront resection who did not receive NT. Interestingly, alterations in circulating tumor cells were not only observed in response to treatment but also seen before...
disease recurrence[74]. Future studies will be needed to apply and validate them in the neoadjuvant setting.

**Patient-centered outcomes**

As the use of NT increases for all stages of PDAC, a greater emphasis on optimizing patient-centered outcomes is necessary and likely to be best achieved through a personalized approach[75]. Despite the advantages of NT, recent evidence has highlighted that some patients will be unable to complete NT and undergo surgery, most commonly because of disease progression or a decrease in their performance status. Recent interest in prehabilitation and advanced nutritional strategies prior to pancreatectomy could be applied to this patient population to improve readiness for surgery[76,77]. Furthermore, although health-related quality of life appears to be preserved during NT, patient symptoms are common during treatment[78]. Prior literature has highlighted the value of monitoring and responding to changes in patient-reported outcomes which could be used to improve and personalize NT[79].

**CONCLUSION**

PDAC is an aggressive malignancy that is best treated in a multidisciplinary fashion using surgery, chemotherapy, and radiation. NT is an increasingly utilized approach that maximizes the receipt of multimodality therapy, improves margin-negative resection rates, and potentially increases survival durations. In the era of personalized medicine, the neoadjuvant period can also be used to emphasize precision oncology. Already, current methods of anatomically staging, molecularly profiling, and monitoring response to therapy can be used to personalize neoadjuvant treatment for localized PDAC. Ongoing efforts in developing novel biomarkers, innovative methods of measuring response, and patient-reported outcome measurements will expand opportunities for precision oncology during NT. These efforts, along with the development of novel treatment options for this aggressive disease, offer hope for improved multidisciplinary, patient-centered, cancer care.

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