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Neoadjuvant therapy for resectable pancreatic ductal adenocarcinoma: The need for patient-centered research

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Abstract

Pancreatic ductal adenocarcinoma is an aggressive cancer with high recurrence rates following surgical resection. While adjuvant chemotherapy improves survival, a significant proportion of patients are unable to initiate or complete all intended therapy following pancreatectomy due to postoperative complications or poor performance status. The administration of chemotherapy prior to surgical resection is an alternative strategy that ensures its early and near universal delivery as well as improves margin-negative resection rates and potentially improves long-term survival outcomes. Neoadjuvant therapy is increasingly being recommended to patients with pancreatic ductal adenocarcinoma, however, patient-centered research on its use is lacking. In this review, we highlight opportunities to focus research efforts in the domains of patient preferences, patient-reported outcomes, patient experience, and survivorship. Novel research in these areas may identify relevant barriers and facilitators to the use of neoadjuvant therapy thereby increasing its utilization, improve shared-decision making for patients and providers, and optimize the experience of those undergoing neoadjuvant therapy.

Key words: Preoperative therapy; Pancreatic ductal adenocarcinoma; Quality of life; Shared decision making; Patient preferences

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Core tip: Neoadjuvant therapy is increasingly being recommended to patients with

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pancreatic ductal adenocarcinoma, however, patient-centered research on its use is lacking. In this review, we highlight opportunities to focus research efforts in the domains of patient preferences, patient-reported outcomes, patient experience, and survivorship. Novel research in these areas may identify relevant barriers and facilitators to the use of neoadjuvant therapy thereby increasing its utilization, improving shared-decision making for patients and providers, and optimizing the experience of those undergoing neoadjuvant therapy.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related mortality worldwide with a 5-year overall survival rate of only 9%^[1]. Although the majority of patients with PDAC present with locally advanced or metastatic disease, even those with resectable cancers who undergo potentially curative surgery are likely to experience cancer recurrence. For all patients with resectable cancers, adjuvant chemotherapy after surgery improves overall survival^[2-4]. However, up to 50% of patients who undergo pancreatectomy fail to initiate adjuvant chemotherapy typically due to postoperative complications or poor performance status^[5] and a greater number of patients fail to complete the intended course of adjuvant therapy for similar reasons^[6].

The administration of chemotherapy prior to surgical resection is an alternative strategy that ensures its early and near universal delivery. Neoadjuvant therapy (NT) offers several other theoretical benefits including improved margin-negative resection rates, decreased lymph node positivity, early treatment of presumed micro-metastatic disease, and the ability to measure *in vivo* response to therapy histologically after resection^[7,8]. Evidence of improved survival with this approach has been supported by results from large cancer databases^[9], meta-analyses of non-randomized trials^[10,11], Markov decision analysis models^[12], and several small randomized controlled trials^[13-15] (Table 1).

Current guidelines state that either immediate surgical resection or NT followed by surgical resection can be considered^[6] but utilization of NT for PDAC in the United States remains low despite the theoretical and empiric advantages of NT^[7,18]. This is in stark contrast to the routine use of NT in other cancers to improve overall survival^[9], margin-negative resection rates^[20], local recurrence^[21], or to facilitate less invasive surgery^[22]. The reasons for this discrepancy are unclear but we hypothesize, in part, that it is related to a lack of patient-centered research on the use of NT for PDAC. In this article, we describe specific evidence gaps in patient-centered research that should be addressed and the significance these findings could have on improving the outcomes of patients with PDAC.

DECISION MAKING

Scant research is available on how decisions are made with regards to treatment sequencing for PDAC. The relative importance of institutional-, patient-, and physician-related factors to decision making is unknown. A novel conceptual model (Figure 1) can define the probable determinants and outcomes of treatment sequence decision making for PDAC. Since the optimal treatment sequencing for PDAC has not been established, decisions are typically made on an individual basis. Decision making may be influenced not only by patient demographic or tumor-related factors and physician preferences, but also patient perceptions, preferences, values, or expectations. The sequencing of treatment for PDAC directly impacts, and conversely is impacted by, the patient experience and survivorship.

Table 1 Selected comparative effectiveness studies of neoadjuvant therapy vs upfront surgery for pancreatic ductal adenocarcinoma

Ref.	Setting	Neoadjuvant type	Neoadjuvant therapy		Upfront surgery		Comments
			Sample size	Overall survival	Sample size	Overall survival	
Population-based analyses							
Mokdad <i>et al</i> ^[9] , 2016	NCDB	Mixed	2005	26 mo	6015	21 mo	NT: ↓LN, ↓R1/R2 margins
Retrospective institutional analyses							
Michelakos <i>et al</i> ^[46] , 2019	United States	Chemo	110	38 mo	155	21 mo	
Sugimoto <i>et al</i> ^[47] , 2019	United States	Mixed	91 ¹	23 mo ¹	91 ¹	19 mo ¹	Resected patients: 29 mo <i>vs</i> 21 mo
Meta-analyses of retrospective studies							
Versteijne <i>et al</i> ^[10] , 2018	N/A	Mixed	1738 ¹	19 mo ¹	1746 ¹	15 mo ¹	NT: ↓resected rate, ↑R0 rate, ↓LN
Prospective randomized trials							
Casadei <i>et al</i> ^[44] , 2015	Italy	CRT	18 ¹	22 mo ¹	20 ¹	19 mo ¹	Did not complete accrual
Golcher <i>et al</i> ^[43] , 2015	Germany	CRT	33 ¹	17 mo ¹	33 ¹	14 mo ¹	Did not complete accrual
Jang <i>et al</i> ^[14] , 2018	South Korea	CRT	27 ¹	21 mo ¹	23 ¹	12 mo ¹	Terminated early (improved survival in NT group)
Van Tienhoven <i>et al</i> ^[13] , 2018	Netherlands	CRT	119 ¹	17 mo ¹	127 ¹	13 mo ¹	Presented in abstract only Resected patients: 30 mo <i>vs</i> 17 mo
Unno <i>et al</i> ^[15] , 2019	Japan	Chemo	182 ¹	37 mo ¹	180	27 mo ¹	Presented in abstract only

¹Intention-to-treat. NCDB: National Cancer Database; LN: Lymph node positivity; NT: Neoadjuvant therapy; CRT: Chemoradiation therapy.

PATIENT PREFERENCES

Previous research on NT for PDAC has focused on its safety^[23] efficacy^[7], and cost-effectiveness^[24]; missing from prior studies has been an evaluation of patient preferences regarding its use. Cancer-related treatment decisions are complex and require consideration of multiple competing factors such as efficacy, toxicity, costs, and psychosocial well-being, each of which may be valued differently by patients. Such preference sensitive decisions are often made in the context of shared decision making (SDM), a model in which informed and engaged patients make health-care decisions in conjunction with their providers^[25]. The degree to which patients are involved in the SDM process of choosing NT or immediate surgery is unclear. Moreover, whether patients have strong preferences for their cancer treatment sequencing is unknown. However, most patients with cancer desire an active role in making decisions about their care^[26] and such patient-centered decision making has been shown to improve patients' understanding of their treatment options, satisfaction with their health care, and overall quality of life (QOL)^[27-29].

Previous research in breast and rectal cancer suggest patient-centered approaches to SDM regarding NT are lacking in clinical practice^[30-32]. Indeed, SDM is underutilized by surgeons in general^[33]. Other qualitative research among patients with PDAC has highlighted that patient expectations often differ from that of their health-care providers and that SDM is infrequently used^[34]. Eliciting and understanding patient opinions, values, and preferences regarding NT will help facilitate SDM which will not only improve patient-centered care but also may increase NT utilization.

Little research has been conducted on patient opinions regarding neoadjuvant approaches to solid tumor malignancies or their preferences towards treatment sequencing. In practice, multiple barriers to the receipt of NT are often expressed by patients. Some patients may have financial concerns secondary to missing work by "delaying" surgery. Others worry about arranging and/or affording transportation for NT due to long travel distances. Frequently, patients state their desire to "just get the cancer out" even if this emotional response does not align with one's values and

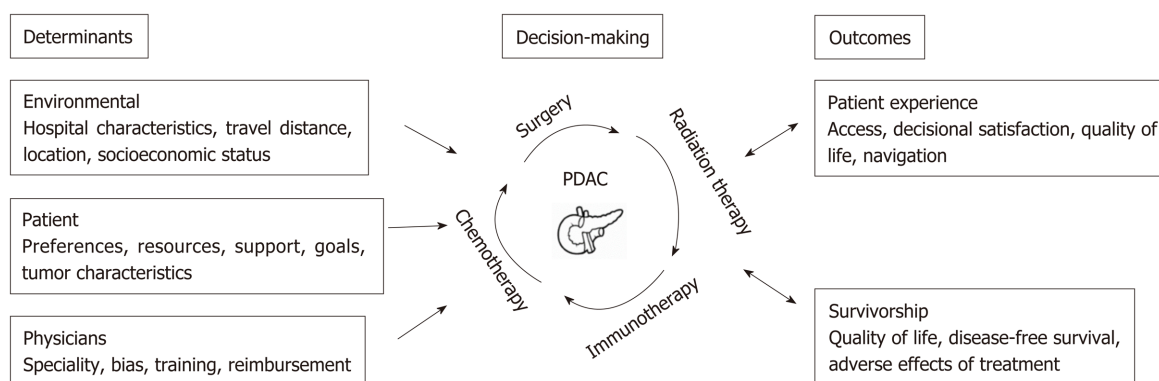


Figure 1 Conceptual model for determinants and outcomes of treatment sequencing for pancreatic cancer. PDAC: Pancreatic ductal adenocarcinoma.

priorities (*e.g.*, maximizing survival, avoiding unnecessary treatment, not becoming a burden on caregivers).

PATIENT EXPERIENCE

While clinical trials have traditionally focused on efficacy, the importance of patient-reported outcomes (PRO) is increasingly recognized^[35,36]. Still, little research has been performed on PROs in PDAC despite its relative importance given the short survival durations experienced by most patients. Recently, an international collaboration of both health care providers and patients identified 8 key PROs for PDAC utilizing a Delphi method^[37]. Interestingly, the authors found similarity in the core PROs identified among patients treated with curative- and palliative-intent. Whether patients who are receiving NT prioritize the same PROs, due to uncertainty about the prospects of curative surgery, symptoms of the primary tumor, or effects of treatment, is unknown. Interestingly, a recent randomized controlled trial of patients with advanced ovarian cancer actually found improved QOL among patients who received NT compared to those who underwent immediate surgery followed by adjuvant chemotherapy^[38].

Equally important, and even less well studied, is the experience of patients undergoing NT for PDAC. The neoadjuvant period is particularly complex and potentially distressing to patients given the need for numerous tests, consultations, and care from multiple providers. Patient assessment of the coordination and communication among their care providers during this time is also unknown. Furthermore, patient perception of provider attentiveness to their physical and psychosocial symptoms as well as their awareness of resources to address them has not been studied. As patient experience is a key domain of health care delivery, further research in this area is needed.

SIGNIFICANCE

While interest in NT for PDAC has increased considerably over the past decade, significant gaps exist in patient-centered outcomes research. Therefore, resources and efforts should be directed towards addressing unanswered questions in several domains: Patient preferences, SDM, the patient experience, PROs, and survivorship, among others (Table 2).

Changing decision-making paradigms in PDAC could have profound significance. First, an understanding of patient opinions and preferences may help explain why utilization rates of NT are especially low. Indeed, a clearer understanding of the relevant barriers and facilitators to the use of NT may identify opportunities to increase its utilization. Since completion of multimodality therapy is one of the strongest determinants of long-term survival, increasing utilization of NT represents an immediate opportunity to improve the outcomes of patients with PDAC while novel systemic therapies are being developed. Furthermore, participation in clinical trials is low. While multiple trials are currently under investigation^[39-42], at least two prior randomized controlled trials evaluating NT were closed early, primarily due to low accrual^[43,44]. Second, a better understanding of patient preferences and priorities will improve the SDM process when making decisions about NT or immediate

Table 2 Proposed goals of future patient-centered research on neoadjuvant therapy for pancreatic ductal adenocarcinoma**Patient preferences**

What are patient perceptions and opinions regarding NT?

What are the barriers and facilitators to NT?

What sources of information inform decision making for NT?

The patient experience

How does shared decision making occur regarding NT?

How do patients perceive communication, coordination, and the health care experience during NT?

What resources are needed by patients undergoing NT?

Patient-reported outcomes (PROs)

Are PROs for pancreatic cancer similar or unique during NT?

How is patient quality of life affected by NT?

Survivorship

Does receipt of NT influence survivorship during and following treatment?

Do patients experience decisional regret/satisfaction?

NT: Neoadjuvant therapy.

surgery. Such information could enable the creation of educational tools or decision aids. Similar decision aids have been shown to be helpful in the decision making process regarding NT for breast cancer^[45]. Finally, an enhanced focus on the patient experience, PROs, and survivorship should improve patient QOL both during and following treatment.

CONCLUSION

PDAC is an aggressive malignancy with a high rate of recurrence even among patients who undergo curative-intent surgery. While NT is a novel and increasingly utilized approach to treatment, patient-centered research, particularly within the domains of patient preferences, patient experience, PROs, and survivorship, are lacking. Studies that address these evidence gaps are expected to improve the delivery of patient-centered care and ultimately outcomes of patients with PDAC.

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