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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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.

**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related mortality worldwide with a 5-year overall survival rate of only 9%. 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. However, up to 50% of patients who undergo pancreatectomy fail to initiate adjuvant chemotherapy typically due to postoperative complications or poor performance status and a greater number of patients fail to complete the intended course of adjuvant therapy for similar reasons.

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. Evidence of improved survival with this approach has been supported by results from large cancer databases, meta-analyses of non-randomized trials, Markov decision analysis models, and several small randomized controlled trials (Table 1).

Current guidelines state that either immediate surgical resection or NT followed by surgical resection can be considered but utilization of NT for PDAC in the United States remains low despite the theoretical and empiric advantages of NT. This is in stark contrast to the routine use of NT in other cancers to improve overall survival, margin-negative resection rates, local recurrence, or to facilitate less invasive surgery. 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 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 Sample size | Overall survival | Upfront surgery Sample size | Overall survival | Comments |
|------|---------|------------------|--------------------------------|------------------|----------------------------|------------------|----------|
|      |         |                  | Neoadjuvant therapy % | Overall survival | Upfront surgery % | Overall survival |          |
| Mokdad *et al* [9], 2016 | NCDB | Mixed | 2005 | 26 mo | 6015 | 21 mo | NT: ↓LN, ↓R1/R2 margins |
| Michelakos *et al* [46], 2019 | United States | Chemo | 110 | 38 mo | 155 | 21 mo |        |
| Sugimoto *et al* [47], 2019 | United States | Mixed | 91 | 23 mo | 91 | 19 mo | Resected patients: 29 mo vs 21 mo |
| Versteijne *et al* [10], 2018 | N/A | Mixed | 1738 | 19 mo | 1746 | 15 mo | NT: ↓resected rate, ↑R0 rate, ↓LN |
| Casadei *et al* [44], 2015 | Italy | CRT | 18 | 22 mo | 20 | 19 mo | Did not complete accrual |
| Golcher *et al* [43], 2015 | Germany | CRT | 33 | 17 mo | 33 | 14 mo | Did not complete accrual |
| Jang *et al* [14], 2018 | South Korea | CRT | 27 | 21 mo | 23 | 12 mo | Terminated early (improved survival in NT group) |
| Van Tienhoven *et al* [13], 2018 | Netherlands | CRT | 119 | 17 mo | 127 | 13 mo | Presented in abstract only |
| Unno *et al* [15], 2019 | Japan | Chemo | 182 | 37 mo | 180 | 27 mo | Present 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[21] 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)[22-29].

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 healthcare 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 preferences.

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

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.

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, at least two prior randomized controlled trials evaluating NT were closed early, primarily due to low accrual. Second, a better understanding of patient preferences and priorities will improve the SDM process when making decisions about NT or immediate therapy.
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\[49\]. 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.

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; 68: 7-30 [PMID: 29313949 DOI: 10.3322/caac.21442]
2 Neoptolemos JP, Stocken DD, Friesi H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]
3 Oettle H, Post S, Neubaus P, Gei
tiert K, Langrehr J, Ridwelski K, Schrann M, Fahlke I, Zuelke C, Burkart C, Guteberl K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; 297: 267-277 [PMID: 17227978 DOI: 10.1001/jama.297.3.267]
4 Conroy T, Hammel P, Hebbel M, Ben Abdelghani M, Wei AC, Raoul JL, Choné L, Francois E, Artru P, Biaggi JJ, Leconte T, Assenat E, Faroux R, Ychou M, Saulavet A, Breyacher G, Di Fiore F, Cripps C, Kavan P, Texereau P, Bouvier-Leporrier K, Khemissa-Akouz F, Legoux JL, Zuzyna B, Gourgou S, O'Callaghan CJ, Joubert-Zeller C, Rat P, Malia D, Castan F, Buchet JB; Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med* 2018; 379: 2395-2406 [PMID: 30575490 DOI: 10.1056/NEJMoa1802295]
5 Bilimoria KY, Bentrem DJ, Ko CY, Tomlinson JS, Stewart AK, Winchester DP, Talamonti MS. Multimodality therapy for pancreatic cancer in the U.S.: utilization, outcomes, and the effect of hospital volume. *Cancer* 2007; 110: 1227-1234 [PMID: 17654662 DOI: 10.1002/cncr.22916]
6 Altman AM, Wirth K, Marron S, Lue E, Chang K, Hui JY, Tuttle TM, Jensen EH, Denbo JW. Completion of Adjuvant Chemotherapy After Upfront Surgical Resection for Pancreatic Cancer Is Uncommon Yet Associated With Improved Survival. *Ann Surg Oncol* 2019; 26: 4108-4116 [PMID: 31313044 DOI: 10.1245/s10434-019-07632-6]
7 Cloyd JM, Katz MH, Prakash L, Varadhachary GR, Wolff RA, Shroff RK, Javle M, Fogelman D, Overman M, Crand CH, Koay EJ, Das P, Krishnan S, Minsky BD, Lee JH, Bhutani MS, Weston B, Ross
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W, Bhosale P, Tamm EP, Wang H, Maitra A, Kim MP, Aloia TA, Vauthey NJ, Fleming JB, Abbruzzese JL, Pisters PW, Evans DB, Lee JE. Neoadjuvant Therapy and Pancreatosoduodenectomy for Pancreatic Ductal Adenocarcinoma: a 25-Year Single-Institution Experience. J Gastrointest Surg 2021; 27: 164-174 [PMID: 32778527 DOI: 10.1007/s11605-016-3265-1]

8 Cloyd JM, Wang H, Egger ME, Tzeng CD, Prakash LR, Maitra A, Vardhachary GR, Shroff R, Javel M, Fogelman D, Wolf RA, Overman MJ, Koay EJ, Das P, Herman JM, Kim MP, Vauthey JN, Aloia TA, Fleming JB, Lee JE, Katz MHG. Association of Clinical Factors With a Major Pathologic Response Following Neoadjuvant Therapy for Pancreatic Ductal Adenocarcinoma. JAMA Surg 2017; 152: 1048-1056 [PMID: 28707984 DOI: 10.1001/jamasurg.2017.2227]

9 Mokdad AA, Mintor RM, Zhu H, Augustine MM, Porembka MR, Wang SC, Yopp AC, Lansour JC, Choti MA, Polanco PM. Neoadjuvant Therapy Followed by Resection Versus Upfront Resection for Resectable Pancreatic Cancer: A Propensity Score Matched Analysis. J Clin Oncol 2017; 35: 515-522 [PMID: 27621389 DOI: 10.1200/JCO.2016.68.5081]

10 Versteijne E, Vogel JA, Besseling MG, Busch ORC, Wilming JW, Daams JG, van Eijck CH, Groot Koerkamp B, Rasch CRN, van Tienhoven G; Dutch Pancreatic Cancer Group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg 2018; 105: 946-958 [PMID: 29708892 DOI: 10.1002/bjs.10870]

11 Usno M, Hata T, Motoi F. Long-term outcome following neoadjuvant therapy for resectable and borderline resectable pancreatic cancer compared to upfront surgery: a meta-analysis of comparative studies by intention-to-treat analysis. Surg Today 2019; 49: 295-299 [PMID: 30877550 DOI: 10.1007/s11730-019-01786-w]

12 de Geus SW, Evans DB, Bliss LA, Eskander MF, Smith JK, Wolf RA, Miksad RA, Weinstein MC, Tseng JF. Neoadjuvant therapy versus upfront surgery strategies in resectable pancreatic cancer: A Markov decision analysis. Eur J Surg Oncol 2016; 42: 1525-1560 [PMID: 27570116 DOI: 10.1016/j.ejsco.2016.07.016]

13 Van Tienhoven G, Versteijne E, Sker M, Groothuis KBC, Busch OR, Bonsing BA, de Hingh IHJT, Festen S, Paëtijn GA, de Vos-Geelen J, Zwinderen AH, Punt CJA, van Eijck CH. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial. J Clin Oncol 2018; 36: LBA4002 [DOI: 10.1200/JCO.2018.36.18_suppl.LBA4002]

14 Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, Oh DY, Chie EK, Lee JM, Heo JS, Park JO, Lim DH, Kim SH, Park SJ, Lee WI, Koh YH, Park JS, Yoon DS, Lee JI, Choi SH. 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: 215-222 [PMID: 29462005 DOI: 10.1097/SLA.0000000000002705]

15 Usno M, Motoi F, Matsumoto I, Aosasa S, Shirakawa H, Wada K, Fujii T, Yoshimoto H, Takahashi S, Sho M, Ueno H, Kosuge T. Randomized phase II trial of preoperative gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSP-05). J Clin Oncol 2019; 37: 189-189 [DOI: 10.1200/JCO.2019.37.4_suppl.188]

16 Khorana AA, Mangu PB, Berlin J, Engelsbretson A, Hong TS, Maitra A, Mohile SG, Mutter M, Schiukch R, Shapiro M, Urba S, Zeh HJ, Katz MH. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34: 2541-2556 [PMID: 27247221 DOI: 10.1200/JCO.2016.67.5551]

17 Youngwirth LM, Nussbaum DP, Thomas S, Adam MA, Blazer DG, Roman SA, Sosa JA. Nationwide trends and outcomes associated with neoadjuvant therapy in pancreatic cancer: An analysis of 18 243 patients. J Surg Oncol 2017; 116: 127-132 [PMID: 28407261 DOI: 10.1002/jso.24630]

18 Hashmi A, Kozick Z, Fluck M, Hunsinger M, Wild J, Arora TK, Hossang MM, Blansfield J. Neoadjuvant versus Adjuvant Chemotherapy for Resectable Pancreatic Adenocarcinoma: A National Cancer Database Analysis. Ann Surg 2018; 184: 1439-1445 [PMID: 30268172]

19 Cunningham D, Allium WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scharfe JH, Lofth FJ, Fahl SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chau YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

20 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, Van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Neuenhuijzen GA, Hopsers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers BJ, Punt CJ, Pliukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074-2084 [PMID: 22646320 DOI: 10.1056/NEJMoa1112088]

21 Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten JH, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ, Dutch ColoRectal Cancer Group. Neoadjuvant radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345: 638-646 [PMID: 11547777 DOI: 10.1056/NEJMoa010580]

22 van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vanderveldt C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19: 4224-4227 [PMID: 11795650 DOI: 10.1200/JCO.2001.19.22.4224]

23 Verma V, Li J, Lin C. Neoadjuvant Therapy for Pancreatic Cancer: Systematic Review of Postoperative Morbidity, Mortality, and Complications. Am J Clin Oncol 2016; 39: 302-313 [PMID: 26950460 DOI: 10.1097/SLC.0000000000000278]

24 Abbott DE, Tzeng CW, Merkow RP, Cantor SB, Chang GJ, Kate MH, Bentrem DJ, Biliomina KY, Crane CH, Vardhachary GR, Abbruzzese JL, Wolf RA, Lee JE, Evans DB, Fleming JB. The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. Ann Surg Oncol 2013; 20 Suppl 3: S500-S508 [PMID: 23397153 DOI: 10.1245/s10434-013-2882-0]

25 Légaré F, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. Health Aff (Millwood) 2013; 32: 276-284 [PMID: 23381520 DOI: 10.1377/hlthaff.2012.1078]

26 Tariman JD, Berry DL, Cochrane B, Doorenbos A, Schepp K. Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review. Ann Oncol 2010; 21: 1145-1151 [PMID: 19940010 DOI: 10.1093/annonc/mdp534]
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Neoadjuvant therapy is increasingly being used in the treatment of pancreatic ductal adenocarcinoma. This review discusses the value of neoadjuvant therapy and its impact on patient outcomes.
