Editorial Commentary

Recurrence after neoadjuvant therapy for pancreatic cancer: same challenges, new opportunities

Taylor Neilson^, Jordan M. Cloyd

Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Correspondence to: Jordan M. Cloyd, MD. Associate Professor, Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, 410 W 10th Ave., N-907 Doan Hall, Columbus, OH 43210, USA. Email: jordan.cloyd@osumc.edu.

Comment on: Cass SH, Tzeng CD, Prakash LR, *et al.* Trends over time in recurrence patterns and survival outcomes after neoadjuvant therapy and surgery for pancreatic cancer. Ann Surg 2024. [Epub ahead of print]. doi: 10.1097/SLA.0000000000006269.

Keywords: Neoadjuvant chemotherapy; recurrence patterns; pancreatic ductal adenocarcinoma (PDAC)

Submitted Feb 11, 2025. Accepted for publication Mar 04, 2025. Published online Mar 18, 2025.
doi: 10.21037/hbsn-2025-96
View this article at: https://dx.doi.org/10.21037/hbsn-2025-96

Despite advancements in treating pancreatic ductal adenocarcinoma (PDAC), it remains the third leading cause of cancer-related deaths worldwide and is projected to become the second leading cause within the next decade (1). The 5-year overall survival (OS) rate remains low at just 12% (2), prompting significant efforts to develop new multimodal therapies. While adjuvant therapy has been shown to improve OS after pancreatic cancer resection, many patients are unable to receive it either because of major postoperative complications, poor functional status after surgery, or early cancer recurrence (3,4). Subsequently, the use of chemotherapy and/or chemoradiation therapy prior to surgery, known as neoadjuvant therapy (NT), has significantly increased in the United States and around the world over the past several decades (5). In addition to improving the delivery of multimodality therapy, this approach may also facilitate downstaging of borderline resectable (BR) or locally advanced (LA) cancers and increases the likelihood of a margin-negative resection.

In this context, Cass *et al.* conducted a retrospective, single-institution cohort study involving 727 patients with localized PDAC who received NT and underwent surgical resection between 1998 and 2018 at the University of Texas MD Anderson Cancer Center, largely where NT approaches have been pioneered over the past several decades (6,7). The study analyzed recurrence rates, patterns, and outcomes across three time periods: 1998–2004, 2005–2011, and 2012–2018 (7). Over 80% of patients in the 2012–2018 cohort received FOLFIRINOX or gemcitabine with nab-paclitaxel, marking a significant shift in NT regimens used over time. At the same time, the proportion of patients with BR or LA cancers also increased. Despite these changes, no significant differences were observed in median disease-free survival (DFS), overall recurrence rates, or the location of first recurrence (7). However, the conditional risk of recurrence shifted, decreasing in the first postoperative year and increasing in the second during the most recent period 2012 to 2018. Median OS improved over time from 1998 to 2018 (30.6, 33.6, and 48.7 months for each respected time periods, P<0.005), largely driven by better post-recurrence survival outcomes (7).

A primary rationale for NT is the early prioritization of systemic treatment for a systemic disease (i.e., micro-metastases). Yet, Cass *et al.* found that most recurrences were still distant and that most recurrences occurred within 2 years of surgical resection. Sadly, these findings are not too dissimilar from large studies reporting the outcomes of upfront surgical resection. For example, Groot *et al.* studied the recurrence patterns of a large cohort of patients who underwent upfront surgical resection and found a median recurrence-free survival of only 11.7 months with the majority experiencing distant recurrences (local recurrence

^ ORCID: 0009-0003-5304-2239.

rates of 23.7%) (8). In a large contemporary multicenter Italian series of 1,426 patients undergoing upfront resection of anatomically resectable PDAC with 74% receiving adjuvant therapy, DFS was 16 months (9). These observations highlight that most patients with localized PDAC will develop distant metastatic disease after surgical resection regardless of treatment sequencing. Indeed, a recent meta-analysis found similar distant recurrence rates among patients who received NT versus upfront surgical resection (10). The finding by Cass *et al.* that the conditional risk of recurrence shifted toward the second year in later cohorts suggests that potentially the use of more effective (although arguably more toxic) chemotherapy regimens has been effective at least temporarily controlling micro-metastatic disease. Additional research with longer follow-up will be needed to assess whether this translates to greater cure rates.

The shift in the recurrence patterns and survival curves may also show promise, in light of the study's inclusion of more advanced tumors in the later study periods, that advances in the use of NT, as well as vascular surgery techniques and perioperative medicine have enabled more patients with advanced tumors to successfully undergo resection. On the other hand, it possibly may reflect a greater selection of patients with a locally dominant tumor who have not progressed during systemic treatment. Indeed, a limitation of the study (and most series of NT prior to surgery) is that patients who do not undergo surgical resection after NT are not included (i.e., intention to treat). This is not an uncommon scenario as rates of attrition during NT are high among patients with PDAC (5,11), and failure to undergo surgical resection after NT is associated with worse survival outcomes (12). Patients who develop cancer progression during NT are often opined to have been saved from an unnecessary surgery, but do we know that for sure? What about the patient with initially resectable disease who is unable to undergo surgery because of toxicities from NT? Additional prospective evidence is needed with intention-to-treat outcomes. Fortunately, large multicenter randomized controlled trials, such as Alliance A02180610 and PREOPANC-III (13,14), are currently evaluating the efficacy of NT for potentially resectable PDAC and will provide further clarity on its impact. Until then, recently published consensus best practices for delivering NT offer an opportunity to standardize the multidisciplinary delivery of NT (15).

In summary, the study by Cass *et al.* is one of the largest single institution series on patients with PDAC treated with NT and surgical resection to date. We continue to gain valuable insights from MD Anderson Cancer Center's robust experience for an approach that has become the standard-of-care at most institutions. While their report shows some signals of progress over the past several decades, clearly it also highlights the need for further impactful research to address persistent challenges in optimizing the delivery of NT and minimizing early recurrence after surgery. Hopefully, their work and the work of others will identify new opportunities to surmount these challenges to improve DFS and OS for patients with PDAC.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *HepatoBiliary Surgery and Nutrition*. The article did not undergo external peer review.

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2025-96/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality

Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. NIH. Cancer Stat Facts: Pancreatic Cancer. Accessed September 16, 2024. Available online: https://seer.cancer.gov/statfacts/html/pancreas.html
3. Ahmad SA, Duong M, Sohal DPS, et al. Surgical Outcome Results From SWOG S1505: A Randomized Clinical Trial of mFOLFIRINOX Versus Gemcitabine/Nab-paclitaxel for Perioperative Treatment of Resectable Pancreatic Ductal Adenocarcinoma. Ann Surg 2020;272:481-6.
4. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med 2018;379:2395-406.
5. Brown ZJ, Cloyd JM. Trends in the utilization of neoadjuvant therapy for pancreatic ductal adenocarcinoma. J Surg Oncol 2021;123:1432-40.
6. Cloyd JM, Katz MH, Prakash L, et al. Preoperative Therapy and Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma: a 25-Year Single-Institution Experience. J Gastrointest Surg 2017;21:164-74.
7. Cass SH, Tzeng CD, Prakash LR, et al. Trends over time in recurrence patterns and survival outcomes after neoadjuvant therapy and surgery for pancreatic cancer. Ann Surg 2024. [Epub ahead of print]. doi: 10.1097/SLA.0000000000006269.
8. Groot VP, Rezaee N, Wu W, et al. Patterns, Timing, and Predictors of Recurrence Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma. Ann Surg 2018;267:936-45.
9. Crippa S, Malleo G, Mazzaferro V, et al. Futility of Up-Front Resection for Anatomically Resectable Pancreatic Cancer. JAMA Surg 2024;159:1139-47.
10. Ratnayake B, Savastyuk AY, Nayar M, et al. Recurrence Patterns for Pancreatic Ductal Adenocarcinoma after Upfront Resection Versus Resection Following Neoadjuvant Therapy: A Comprehensive Meta-Analysis. J Clin Med 2020;9:2132.
11. Underwood PW, Leuschner T, Ejaz A, et al. Textbook Neoadjuvant Experience: Defining a Novel Composite Outcomes Measure for Patients with Pancreatic Cancer Undergoing Neoadjuvant Therapy. J Am Coll Surg 2025;240:539-48.
12. Cloyd JM, Colby S, Guthrie KA, et al. Failure to Undergo Resection Following Neoadjuvant Therapy for Resectable Pancreatic Cancer: A Secondary Analysis of SWOG S1505. J Natl Compr Canc Netw 2024;22:e237099.
13. Versteijne E, Suker M, Groothuis K, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol 2020;38:1763-73.
14. Chawla A, Shi Q, Ko AH, et al. Alliance A021806: A phase III trial evaluating perioperative versus adjuvant therapy for resectable pancreatic cancer. J Clin Oncol 2023;41:TPS4204.
15. Cloyd JM, Sarna A, Arango MJ, et al. Best Practices for Delivering Neoadjuvant Therapy in Pancreatic Ductal Adenocarcinoma. JAMA Surg 2025;160:172-80.

Cite this article as: Neilson T, Cloyd JM. Recurrence after neoadjuvant therapy for pancreatic cancer: same challenges, new opportunities. HepatoBiliary Surg Nutr 2025;14(2):308-310. doi: 10.21037/hbsn-2025-96

