Editorial Commentary

Understanding the risk of recurrence after resection of intraductal papillary mucinous neoplasm-associated adenocarcinoma: insights from a large multicenter study

Hong T. Lin[1]^, Somashekar G. Krishna[2]^

[1]Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA; [2]Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Correspondence to: Somashekar G. Krishna, MD, MPH, AGAF, FASGE. Professor of Medicine, Director of Advanced Endoscopy, Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, 395 W. 12th Avenue, Suite 262, Columbus, OH 43210, USA. Email: somashekar.krishna@osumc.edu.

Comment on: Lucocq J, Hawkyard J, Robertson FP, *et al.* Risk of Recurrence After Surgical Resection for Adenocarcinoma Arising From Intraductal Papillary Mucinous Neoplasia (IPMN) With Patterns of Distribution and Treatment: An International, Multicenter, Observational Study (ADENO-IPMN Study). Ann Surg 2024;280:126-35.

Keywords: Pancreatic cancer; adjuvant chemotherapy; tumor recurrence; intraductal papillary mucinous neoplasm (IPMN); pancreatic ductal adenocarcinoma (PDAC)

Submitted Oct 19, 2024. Accepted for publication Oct 30, 2024. Published online Nov 08, 2024.
doi: 10.21037/hbsn-24-583
View this article at: https://dx.doi.org/10.21037/hbsn-24-583

Pancreatic ductal adenocarcinoma (PDAC) accounts for over 90% of pancreatic cancers and is the seventh leading cause of cancer deaths worldwide (1). Considered one of the most aggressive cancers, PDAC is associated with nonspecific symptoms and often presents with widespread metastasis at the time of diagnosis, with an average 5-year survival rate of less than 10% (2). It has both genetic and environmental risk factors and can arise from several precursor lesions, primarily pancreatic intraepithelial neoplasia (PanIN) and, to a lesser extent, intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. As the predominant form of pancreatic cancer, PDAC poses challenges due to its complex pathology, and understanding of its pathogenesis is critical for management.

PanIN lesions are microscopic and progress through a series of genetic and epigenetic alterations. This progression begins with the onset of columnar mucinous epithelium in stage I (PanIN-1) and advances through increasing cellular atypia and mitotic figures in PanIN-2, ultimately leading to high-grade PanIN-3. PanIN-3 can then transform into PDAC, resulting in invasion of the ductal epithelium (3,4).

IPMN is a significant, though less common precursor to PDAC, accounting for approximately 10% of cases (5). Certain variants, such as the pancreatobiliary subtype, are associated with a higher risk of progression to carcinoma. The pathway from IPMN to carcinoma is thought to involve different genetic mutations than those seen in the PanIN pathway. IPMN-derived PDAC generally has a better prognosis compared to conventional PDAC, particularly for the oncocytic and colloid variants. Additionally, IPMN lesions tend to be larger on imaging, making them easier to detect and monitor than PanIN lesions (3,6).

To deepen our understanding of PDAC recurrence and its connection to IPMN, Lucocq *et al.* conducted a pivotal study that addresses these critical gaps. In their study, the authors noted that earlier research had reported a significant

^ ORCID: Hong T. Lin, 0000-0002-1888-2860; Somashekar G. Krishna, 0000-0001-5748-7890.

recurrence rate (32–43%) following pancreatic resection for PDAC in IPMNs (7). However, the patterns of recurrence and associated risk factors for PDAC originating from IPMN remain largely unclear. Additionally, the influence of interventions such as surgery or chemotherapy on recurrence and long-term survival is not well understood. To bridge these knowledge gaps, the investigators set out to identify key predictors of recurrence, explore recurrence patterns, and assess optimal treatment strategies in a large multicenter cohort of patients who had undergone surgical resection for PDAC arising from IPMN. This retrospective multicenter study represents the largest cohort to date for this objective.

A total of 459 patients who underwent surgical resection of IPMN-derived PDAC without neoadjuvant therapy were included. Most patients (57.1%) underwent pancreatoduodenectomy, as most tumors were in the pancreatic head (63.6%). Most PDAC lesions originated from main duct IPMN (57.9%) and mixed duct IPMN (21.6%), with 31.6% of all lesions arising from pancreatobiliary epithelium. Additionally, 59.9% of patients in the cohort received adjuvant chemotherapy.

Detailed recurrence patterns were tracked as part of this study. Overall, 45.5% of patients experienced recurrence, with a median time to recurrence of 32.8 months. Nearly a quarter developed recurrence within the first year. These rates appear to be slightly lower than previously reported values (8,9), although those studies were not limited to PDAC with an IPMN precursor (which tend to have better outcomes) and involved different initial treatment modalities. The most common sites of recurrence were the liver, lungs, and locoregional areas. Increased rates of recurrence were associated with moderate differentiation [hazard ratio (HR) =1.87; P=0.012], poor differentiation (HR =3.29; P<0.001), multi-visceral resection (HR =1.54; P=0.032), perineural invasion (HR =1.63; P=0.016), large carcinoma size (HR =1.49; P=0.021), and lymph node spread (HR =1.90; P<0.001).

After multivariable adjustment, no reduction in recurrence risks was associated with adjuvant chemotherapy for initial lesions. This finding contrasts with prior literature, which suggests a survival benefit when certain adjuvant chemotherapy regimens (e.g., modified FOLFIRNOX) are used in some populations (10). However, Lucocq *et al.* do not provide specific details on the types of adjuvant chemotherapy used in their study population, which adds some challenges to making direct comparisons. Both single- and multi-site recurrences were analyzed. Interestingly, no significant difference in median survival was found between recurrence sites in the liver, lungs, peritoneum, or locoregional areas. Moreover, the presence of single- or multiple-site recurrence did not result in a statistically significant difference in survival duration. These findings highlight the rapid progression of PDAC regardless of the location and extent at which it is found.

Understanding how different treatment modalities affect recurrence is essential for optimizing management strategies, and this study evaluates that aspect. Of the 209 patients who experienced recurrence, 109 received additional treatment (e.g., chemotherapy, surgery, radiation therapy, or a combination thereof). Patients who received treatment for recurrence showed significant improvements in survival duration, with those experiencing local recurrence having a median survival of 31.1 months compared to 18 months for those without treatment. For systemic recurrence, the median survival was 26.9 months for treated patients *vs.* 14.2 months for untreated patients. In the entire cohort, additional treatment of recurrence approximately doubled the length of median survival to 27 months, compared to 14.6 months without further treatment. No statistically significant differences in survival were observed among the various treatment modalities, although chemotherapy appeared to offer the greatest benefit.

The implications of the study extend beyond recurrence patterns, as it also sheds light on overall survival (OS) and disease-free survival (DFS) rates. The OS and DFS rates for the cohort stood at 49.5% and 41.6%, respectively, after a median follow-up period of 63.5 months. The 5-year OS for those who experienced recurrence was 19.2%, compared to 73.0% for those without recurrence, while the 5-year DFS was 40.3%. Factors linked to death or recurrence included larger tumor size, poor cellular differentiation, perineural invasion, lymph node involvement, and R1 resection margins. Poor cellular differentiation was also associated with early recurrence. This study found preoperative carbohydrate antigen 19-9 (CA19-9) to be insignificant for prognosis. These findings largely align with existing knowledge regarding prognostic factors for recurrence (9,11). However, previous studies have also commented on the prognostic value of preoperative diabetes and supported the utility of marked elevated CA19-9 (>175.8 U/mL) (11). This study sets a comparatively lower threshold of 37.0 U/mL for designating CA19-9 elevation; as a result, it is difficult to assess whether a tier-based analysis would have revealed statistically significant CA19-9 predictive value. Treatment

of recurrence, particularly with chemotherapy, was associated with improved OS (67.8 *vs.* 39.3 months).

Twenty patients developed a second tumor recurrence after initial treatment, and among them, 10 received additional treatment, primarily chemotherapy. In this scenario, no significant difference was found between the treatment and control groups. However, this statistical conclusion may be influenced by the small cohort size of patients with a second recurrence, which raises questions about its clinical relevance.

The findings from this comprehensive multicenter study highlight the complexities associated with recurrence patterns, emphasizing the multifactorial nature of PDAC and the necessity for tailored therapeutic strategies. One promising advancement is the increased use of minimally invasive pancreatectomy (MIP), performed using laparoscopic or robotic techniques. Recent studies have indicated that MIP leads to reduced recovery time, shorter hospital stays, and longer DFS compared to open pancreatic resection (12,13). Another innovative technique, endoscopic ultrasound with radiofrequency ablation (EUS-RFA), has been shown to stimulate an anti-tumor immune response within the local microenvironment, promoting tumor regression while maintaining a favorable side effect profile (14,15). This approach could be considered alongside existing chemo- or radiotherapy for the treatment of recurrence, though further studies are needed to establish its efficacy in this context.

The study's limitations include its retrospective nature and the potential for selection bias. Additionally, as mentioned elsewhere, the lack of adjuvant chemotherapy identification and stratified CA19-9 analysis limits comparison with prior studies. However, the large sample size provides robust data on recurrence patterns and treatment outcomes, offering valuable insights for the clinical management of IPMN-derived PDAC.

In summary, this study represents one of the largest investigations into the predictors and recurrence patterns following the resection of invasive IPMN-derived adenocarcinoma. It confirms many established risk factors for recurrence and, notably for the first time, shows that treating recurrence—regardless of the treatment modality—significantly improves survival. This finding underscores the need for a universal protocol for recurrence surveillance after PDAC resection. While the study did not find a clear survival advantage for adjuvant chemotherapy following the initial resection of invasive IPMN, it did reveal a significant survival benefit associated with treating recurrence compared to no treatment, making recurrence management a viable consideration. However, given other studies that suggest potential benefits from adjuvant chemotherapy and the limited comparisons in this research, further investigation is essential to evaluate the advantages of adjuvant chemotherapy and refine strategies for managing recurrent disease.

Acknowledgments

Funding: 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.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-583/coif). S.G.K. reports research grant support (investigator-initiated studies) from Mauna Kea Technologies, Paris, France, and Taewoong Medical, USA (to his institution). The other author has 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. Bengtsson A, Andersson R, Ansari D. The actual 5-year

survivors of pancreatic ductal adenocarcinoma based on real-world data. Sci Rep 2020;10:16425.
3. Patra KC, Bardeesy N, Mizukami Y. Diversity of Precursor Lesions For Pancreatic Cancer: The Genetics and Biology of Intraductal Papillary Mucinous Neoplasm. Clin Transl Gastroenterol 2017;8:e86.
4. Hassid BG, Lucas AL, Salomao M, et al. Absence of pancreatic intraepithelial neoplasia predicts poor survival after resection of pancreatic cancer. Pancreas 2014;43:1073-7.
5. de la Fuente J, Chatterjee A, Lui J, et al. Long-Term Outcomes and Risk of Pancreatic Cancer in Intraductal Papillary Mucinous Neoplasms. JAMA Netw Open 2023;6:e2337799.
6. Distler M, Aust D, Weitz J, et al. Precursor lesions for sporadic pancreatic cancer: PanIN, IPMN, and MCN. Biomed Res Int 2014;2014:474905.
7. Lucocq J, Hawkyard J, Robertson FP, et al. Risk of Recurrence After Surgical Resection for Adenocarcinoma Arising From Intraductal Papillary Mucinous Neoplasia (IPMN) With Patterns of Distribution and Treatment: An International, Multicenter, Observational Study (ADENO-IPMN Study). Ann Surg 2024;280:126-35.
8. Zhang XP, Xu S, Gao YX, et al. Early and late recurrence patterns of pancreatic ductal adenocarcinoma after pancreaticoduodenectomy: a multicenter study. Int J Surg 2023;109:785-93.
9. Murakawa M, Kawahara S, Takahashi D, et al. Risk factors for early recurrence in patients with pancreatic ductal adenocarcinoma who underwent curative resection. World J Surg Oncol 2023;21:263.
10. Biagi JJ, Cosby R, Bahl M, et al. Adjuvant Chemotherapy and Radiotherapy in Resected Pancreatic Ductal Adenocarcinoma: A Systematic Review and Clinical Practice Guideline. Curr Oncol 2023;30:6575-86.
11. Brunner M, Flessa M, Jacobsen A, et al. Recurrence pattern and its risk factors in patients with resected pancreatic ductal adenocarcinoma - A retrospective analysis of 272 patients. Pancreatology 2024;24:930-7.
12. de Rooij T, van Hilst J, van Santvoort H, et al. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. Ann Surg 2019;269:2-9.
13. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Ann Surg 2014;260:633-8; discussion 638-40.
14. Jarosova J, Macinga P, Krupickova L, et al. Impact of Endoluminal Radiofrequency Ablation on Immunity in Pancreatic Cancer and Cholangiocarcinoma. Biomedicines 2022;10:1331.
15. Faraoni EY, O'Brien BJ, Strickland LN, et al. Radiofrequency Ablation Remodels the Tumor Microenvironment and Promotes Neutrophil-Mediated Abscopal Immunomodulation in Pancreatic Cancer. Cancer Immunol Res 2023;11:4-12.

Cite this article as: Lin HT, Krishna SG. Understanding the risk of recurrence after resection of intraductal papillary mucinous neoplasm-associated adenocarcinoma: insights from a large multicenter study. HepatoBiliary Surg Nutr 2024;13(6):1041-1044. doi: 10.21037/hbsn-24-583

