HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Am J Gastroenterol. 2019 April ; 114(4): 560–561. doi:10.14309/ajg.0000000000000192.

Early Detection of Pancreatic Cancer in High-Risk Individuals: Where Do We Go From Here?

Phil A. Hart, MD[1]

[1]Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH

Abstract

Pancreatic cancer is a lethal disease that is commonly diagnosed at a late stage. Screening asymptomatic patients is necessary for early detection, but this is not currently recommended in the general population. As demonstrated in the current study, an important number of patients at increased risk can be diagnosed using either MRI/MRCP or EUS. Further collaborative efforts are needed to refine the ideal population for testing, and refine the current approach to pancreatic cancer surveillance.

Keywords

screening; surveillance; BRCA2; ATM; CDKN2A; PRSS1

Pancreatic cancer (i.e., pancreatic ductal adenocarcinoma (PDAC)) now represents the third most common cause of cancer-related deaths in the United States accounting for approximately 45,000 deaths per year, even though the incidence rate is low[1]. Despite recent improvements in the efficacy of systemic chemotherapy and ongoing refinement of surgical techniques the five-year mortality rate remains <10%[1]. One of the major contributors to the poor mortality rate is the unfavorable distribution of cancer stage at the time of diagnosis, which can be attributabled to the late onset of symptoms. Thus, to improve survival with early detection, it is necessary to perform screening in asymptomatic individuals. As recently discussed, it is futile to attempt screening the general population with a single test (as employed for colon and breast cancer) since the low disease prevalence would produce an unacceptably high number of false positive test results[2]. Conversely, screening (or more precisely “surveillance”) may be beneficial in patients with an increased risk for PDAC, but many uncertainties exist.

In the current issue of *Amercian Journal of Gastroenterology*, Spaiella and colleagues describe the diagnostic yield from a multicenter surveillance program in Italy of high risk

Address for reprints and correspondence: Phil A. Hart, Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, 410 West Tenth Avenue, Columbus, OH 43210, philip.hart@osumc.edu,Phone: 614-366-6213, Fax: 614-293-8518.

Specific author contribution: study conception and manuscript writing/approval

Potential competing interests: none

Guarantor of the Article: Phil Hart

individuals (HRI) for PDAC[3]. The phrase HRI is used to denote patients with an increased risk for PDAC based on a family history consistent with familial pancreatic cancer syndrome (i.e., there are at least two affected relatives in the family, with at least one having a first degree relationship to the patient) or a germline genetic mutation associated with increased risk of PDAC (including APC, ATM, BRCA1, BRCA2, PALB2, CDKN2A, PRSS1, STK11, TP53, and mismatch repair genes (MLH1, MSH2, MSH6, PMS2, and EPCAM)) [4, 5]. For mutations associated with lower penetrance of PDAC (such as ATM and BRCA2) an associated family history is required to be classified as HRI[5]. In the current study, a total of 187 subjects were enrolled during the three year study period and completed baseline imaging. A minority of subjects (11.8%) had an identified gene mutation associated with PDAC; the balance were classified as familial pancreatic cancer syndrome. Most subjects (93.1%) underwent baseline imaging with an MRI/MRCP, and the remainder underwent endoscopic ultrasound (EUS). EUS was also performed in a subset of subjects for diagnostic follow-up of abnormalities detected on MR imaging. In the final analysis, pooling all subjects irrespective of genetic mutation profile and testing method, the PDAC detection rate was 2.6% at baseline evaluation. Importantly, only two of the five subjects with cancer were able to undergo pancreatic resection, while the others had either locally advanced (n=1) or metastatic (n=2) PDAC at the time of diagnosis.

Although the study investigators collected similar data from subjects and generally used a similar approach to PDAC surveillance, decisions regarding age to begin surveillance, testing modality (MRI/MRCP vs. EUS), and germline testing were left to the discretion of the individual study sites and study participants. This pragmatic design was necessary for study execution in the absence of funding, and likely increased acceptance by study sites, participant uptake into the registry, and perhaps generalizability of the results. The unintended consequences are the introduction of heterogeneity in the intervention (i.e., baseline imaging) and reduced the ability to control for differences in predicted risk. Although the majority of subjects underwent baseline imaging with MRI/MRCP only, there was a subset (6.9%) that underwent EUS due to “personal preference”. There are circumstances in which a high quality MRI scanning is contraindicated (e.g., metallic implant, contraindication to gadolinium based contrast), so this is not unexpected. Notably, four of the five cancers identified in the study were detected in the small group undergoing a baseline EUS. Combined with recent data suggesting a higher diagnostic yield with EUS compared to cross-sectional imaging, one must question whether it might be more appropriate to use EUS for all subjects at baseline[6]. Alternatively, it remains possible these cases were clinical outliers (e.g., subjects who had additional symptoms or excessive predicted risk that ultimately led to the decision to perform EUS rather than MRI). Longitudinal surveillance results are awaited and will provide more complete information regarding missed lesions on baseline MRI scans (i.e., the false negative rate).

The authors acknowledge that germline mutation testing was not universally performed in in the FPC group, so the proportion that truly lack a germline mutation is unknown. Secondary analyses showed no difference in detection rates depending on the number of affected family members, but this is likely inadequate to control for the effects of genetic susceptibility. Recent changes in genetic testing for susceptibility for PDAC have occurred since the initiation of this study that have increased accessibility, increases in the number of genes

covered on multigene panels and significant reductions in cost. Combined with data demonstrating that only half of patients with PDAC associated with a germline mutation have a positive family history, it has recently been suggested to consider germline mutation testing for all patients with newly diagnosed PDAC[4]. Thus, over time it is anticipated that many FPC kindreds will be reclassified as having an underlying genetic basis, which will further improve the accuracy of risk estimates.

This study contributes to ongoing work being performed internationally to demonstrate the effectiveness of surveillance in HRI for PDAC. The observation of 2.6% of subjects with PDAC detected with baseline imaging is striking, and may be questioned since this is similar to the cumulative rate of PDAC (including both baseline and follow-up imaging) reported in a recent meta-analysis[6]. The discrepancy may be explained by an overestimated risk in the current study (e.g., absence of subjects with mutations associated with lower risk of PDAC, including ATM, PALB2, and mismatch repair genes) and/or an underestimated risk in the meta-analysis (which included many studies with less stringent definitions of HRI). The diagnostic yield of longitudinal surveillance imaging is not within the scope of the current study, so additional follow-up is awaited to compare rates of incident PDAC detected during surveillance with other recent studies[7].

In addition to the diagnostic yield of pancreatic neoplasms, it is important to consider incidental findings and false positive test results resultant from PDAC surveillance. The authors have done an excellent job reporting the prevalence of detecting other pancreatic abnormalities (e.g., pancreatic cysts, solid pseudopapillary tumor), including false positives (e.g., two cases with non-malignant solid lesions seen on MRI). The most common pancreatic abnormalities on testing included, presumed branch duct IPMNs (n=27, 14.4%), unclassified pancreatic cystic lesions (n=8, 4.6%), and sonographic features of chronic pancreatitis (n=7, 3.7%). In addition to the immediate test results, one must also consider potential harms of surveillance including the psychologic impact and potential complications from treatment, particularly an inappropriate surgery. Considering these factors, the U.S. Preventive Services Task Force (USPTF) has proposed a comprehensive list of research questions that must be simultaneously considered when evaluating the overall effectiveness of surveillance for PDAC in HRI (Box)[8].

While the questions to guide the next steps are easily articulated, it will be challenging to address them definitively due low number of patients fulfilling study definitions of HRI as well as the statistically low rate of incident PDAC during surveillance. Ongoing efforts are needed to further refine classification of subjects with HRI, identify common data elements, and standardize reporting of clinical outcomes to permit accurate pooling of individual patient level data. Similarly, the development of rigorous biorepository platforms for biomarker discovery and validation are needed. While there are many challenges to overcome, collaborative multicenter efforts, such as in the current study, produce hope that meaningful progress for these patients is possible.

Abbreviations:

EUS	endoscopic ultrasound

HRI	high risk individual
MRI/MRCP	magnetic resonance imaging/cholangiopancreatography
PDAC	pancreatic ductal adenocarcinoma

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34. [PubMed: 30620402]
2. Hart PA, Chari ST. Is Screening for Pancreatic Cancer in High-Risk Individuals One Step Closer or a Fool's Errand? Clin Gastroenterol Hepatol 2019;17:36–38. [PubMed: 30268560]
3. Spaiella S, Capurso G, Cavestro G. Results of first-round of surveillance in individuals at high-risk of pancreatic cancer from the AISP (Italian Association for the Study of the Pancreas) Registry. Am J Gastroenterol 2019.
4. Stoffel EM, McKernin SE, Brand R, et al. Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol 2019;37:153–164. [PubMed: 30457921]
5. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62:339–47. [PubMed: 23135763]
6. Corral JE, Mareth KF, Riegert-Johnson DL, et al. Diagnostic Yield From Screening Asymptomatic Individuals at High Risk for Pancreatic Cancer: A Meta-analysis of Cohort Studies. Clin Gastroenterol Hepatol 2019;17:41–53. [PubMed: 29775792]
7. Canto MI, Almario JA, Schulick RD, et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. Gastroenterology 2018;155:740–751 e2. [PubMed: 29803839]
8. U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan/pancreatic-cancer-screening1. Last accessed January 28, 2019, 2019.

Box

Proposed research questions to address regarding pancreatic cancer screening by the U.S. Preventive Services Task Force (USPTF).

1. Does screening effectiveness vary by clinically relevant subpopulations (e.g., number of affected first degree relatives, specific genetic mutations, new onset diabetes mellitus)?
2. What is the diagnostic accuracy of screening tests for PDAC?
3. What are the harms of screening for PDAC?
4. Does treatment of screen-detected PDAC improve cancer mortality, all-cause mortality, or quality of life?
5. What are the harms of treatment of screen-detected PDAC?