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Role of artificial intelligence in pancreatic cystic neoplasms: modernizing the identification and longitudinal management of pancreatic cysts

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Abstract

Mucinous cysts of the pancreas represent the most common identifiable precursor to pancreatic cancer. Evidence-based guidelines for screening and surveillance exist, but many patients are either not properly identified or lost to follow-up. Artificial Intelligence, specifically computational linguistics models, can dramatically improve patient identification and mitigate risk through modernizing pancreatic cyst longitudinal surveillance. Herein we discuss the risk associated with mucinous cysts of the pancreas and modern approaches to patient identification and follow-up.

Keywords: Pancreatic cyst, mucinous cysts, intraductal papillary mucinous cystic neoplasm (IPMN), mucinous cystic neoplasm (MCN), pancreatic duct adenocarcinoma, computational linguistics

INTRODUCTION

Mucinous cysts of the pancreas represent the most common identifiable precursor to pancreatic cancer. In 2021, pancreas cancer represented the tenth and eighth most commonly diagnosed cancer in men and women, respectively. However, pancreatic cancer was the fourth leading cause of cancer-related mortality[1]. Currently, over 60,000 Americans are expected to be diagnosed with pancreatic ductal adenocarcinoma (PDAC) in 2022, with over 48,000 estimated deaths[1]. Moreover, the median survival for a resected and multimodal treated PDAC remains 48 months with a 5-year survival rate of 11% for all-comers[2,3]. Due to these statistics, efforts have been placed on early identification and intervention. One particular risk factor which has seen recent increased research and attention is a mucinous pancreatic cyst. This review will document the risk of mucinous cysts of the pancreas and address an Artificial Intelligence platform that has been implemented to identify and follow pancreatic cyst patients with the goal of reliably identifying pancreatic cancer as early as possible.

When assessing the risk for the development of pancreatic cancer, non-modifiable and modifiable risk factors have been identified. Factors that cannot be mitigated include age (median age at diagnosis is 70 years), male gender, race, family history of pancreatic cancer and inherited genetic alterations such as BRCA1, BRCA2, PALB2, FAMMM (p16/CDKN2A), familial pancreatitis (PRSS1), HNPCC and Peutz-Jeghers syndrome (STK11)[4]. However, factors that may be altered, leading to decreased risk, include tobacco use, obesity, pancreatitis, diabetes and active management of pancreatic cysts. Although the propensity to develop a mucinous pancreatic cyst cannot be altered, the identification and appropriate management certainly can. Due to improvements in modern imaging quality, currently, 2.3% of abdominal computed tomography (CT) scans and 19.6% of abdominal magnetic resonance imaging (MRI) exams will incidentally identify a pancreatic cyst[5,6]. These data are in concordance with the American Gastroenterological Association which has stated that upwards of 15% of Americans harbor a pancreatic cyst. Although certain pancreatic cysts can be benign, such as serous cysts or pseudocysts, intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms represent pre-malignant tissue and will be the focus of this review.

Mucinous pancreatic cysts

Numerous challenges are encountered when assessing patients with mucinous pancreatic cysts. First, mucinous cysts are pre-malignant mucin-producing epithelial tumors that arise from the pancreatic ductal system[7,8]. Second, progression from low-grade dysplasia to high-grade dysplasia to invasive cancer is the course followed by up to 30% of PDACs[9]. Moreover, most experts believe that IPMN represents a field defect of the pancreas and that the risk is not only in the area of radiographic IPMN. Pulling this information together, the crux for pancreatic care teams is the fact that they are faced with the dilemma between recommending complex surgery which carries morbidity and mortality risk for low-risk IPMN or recommending observation for those who could possibly be harboring a radiologically occult malignancy. Extensive uncertainty exists on the true risk of mucinous pancreatic cysts, and as a result, guidelines vary considerably. Therefore, pancreatic cyst patients need modern identification and surveillance strategies.

Pancreatic cyst guidelines

Currently, there are at least six separate consensus-based guidelines (The European Study Group, The American Gastroenterological Association, The American College of Radiology, The American College of Gastroenterology, The International Association of Pancreatology and the Sendai/Fukoaka Consensus Criteria)[10]. Although all of these guidelines were designed to assist in the risk stratification of pancreatic cysts, they are all varied in their recommendations and their target populations[10]. In essence, a lack of uniform consensus remains on the true risk of mucinous cysts of the pancreas as well as how to longitudinally follow these patients. This topic was explored by Heckler *et al*. in Pancreatology in 2017, which published a meta-analysis on the accuracy of the Sendai and Fukuoka Consensus Criteria since the risk of malignancy in branch duct IPMN is controversial[11]. The analysis included 2,710 patients with a median age of 63 years. Results found the Sendai criteria had a sensitivity of 56% and specificity of 74% in accurately identifying high-risk cysts. The Fukuoka Consensus was found to have 83% sensitivity and 53% specificity, which was improved over Sendai but still lacked adequate specificity. Moreover, Lee *et al*. evaluated the revised guidelines for predicting malignant potential and compared the diagnostic performance and concordance between contrasted CT and MRI[12]. This group found that both CT and MRI were comparable and high-risk stigmata included enhancing mural nodule > 5 mm, abrupt main pancreatic duct caliber change, lymphadenopathy, larger main pancreatic duct size, and faster cyst growth rates; and this is in line with what was identified as high risk in the European Guidelines[12]. In summary, considering the relatively high rate of malignancy in initially Sendai-negative lesions as well as the rate of concomitant malignant lesions, more accurate criteria for clinical decision-making were warranted. In brief, this analysis was clear that pancreatic cyst patients still needed ways of distinguishing between patients who would benefit from an aggressive surgical approach and those who qualify for observation without the risk of missing malignant transformation.

The European Study Group on Cystic Tumours of the Pancreas then published consensus guidelines in 2018 in Gut, which aimed to improve the diagnosis and management of pancreatic cysts[13]. Details that were quoted from this analysis included: (1) cyst size greater than 30 mm had a 5% risk of malignancy and subsequent death within 3 years; (2) cyst size less than 30 mm had a 5-year risk for developing malignancy of 45% if the cyst increases more than 2 mm per year; and (3) a cyst size increase over 5 mm per year or total growth of 10 mm had a 20-fold higher risk of malignant progression[13]. Additionally, absolute indications for surgery were recommended, including positive cytology for malignancy or high-grade dysplasia, solid mass, jaundice related to tumor, an enhancing mural nodule greater than 5 mm, or main pancreatic duct dilation greater than 10 mm. Finally, relative surgical indications were created, including growth rate greater than 5 mm per year, increased levels of serum CA 19-9, main pancreatic duct dilation between 5 and 9.9 mm, cyst diameter greater than 40 mm, new onset of diabetes, acute pancreatitis caused by the cyst, and an enhancing mural nodule less than 5 mm[13].

Challenges of identification and surveillance

However, extraordinarily pertinent clinical questions remained. For instance, in terms of diagnostic investigation, which modality most reliably distinguishes neoplastic from non-neoplastic cysts, and which modality can most reliably detect high-grade dysplasia or early cancer? With respect to surveillance, what is cost-effective surveillance of cysts, which risk factors for progression need to be considered, and what is the optimal modality and follow-up scheme for patients after partial pancreatectomy for resection of IPMN? In other words, how can the pancreatic cyst community better identify and risk stratify mucinous cysts?

Attiyeh *et al*. in 2018 explored this topic of risk stratification. Using prospectively maintained data from three high-volume institutions, Memorial Sloan Kettering Cancer Center, Johns Hopkins and the Mayo Clinic, the authors sought to identify more accurate markers of high-grade dysplasia or carcinoma to help avoid unnecessary surgery or support potentially curative intervention[14]. Most patients (69%-77%) who met high imaging risk criteria for branch duct IPMN and underwent surgical resection were found to have low-risk disease on pathology (1,028 resected IPMN specimens). The authors concluded that the consequences of overestimating the risk of malignancy based on imaging criteria should not be understated as pancreaticoduodenectomy continues to be associated with a 2%-4% risk of mortality and a 20%-25% risk of major morbidity at high-volume institutions[14]. Therefore, improving our ability to predict high-risk mucinous pancreatic cysts would no doubt improve clinical care.

Another topic of controversy in the mucinous pancreas cyst population is the length of follow-up needed after surgical resection / partial pancreatectomy. Efishat *et al*. assessed the rates, patterns and predictors of progression in the pancreatic remnant following segmental resection of noninvasive or microinvasive IPMN[15]. Progression was defined as the development of cancer, a new IPMN cystic lesion over 10 mm or more than a 50% increase in the diameter of residual IPMN lesions. Out of 319 patients analyzed, there was a 22% progression over time which included the formation of invasive cancer in 16%. The cumulative incidence of progression was 10% at two years and 26% at five years. IPMN patients, therefore, represent a high-risk group and should undergo long-term radiologic surveillance[15].

Due to the data presented above, mucinous cysts of the pancreas are pre-malignant and require appropriate identification and longitudinal surveillance. However, this disease remains one with a paucity of knowledge within the medical community. Nationally, innumerable patients each year develop PDAC in the setting of pancreatic cystic disease due to a lack of identification and evidence-based follow-up. The challenges with caring for pancreatic cyst patients start at the initial scan. Given that the majority of pancreatic cysts are incidentally identified, most patients are never referred for further surveillance. Moreover, even in the select patients who are referred, demographic and clinical data is manually entered into Excel spreadsheets which lack patient demographics and clinical correlates; patient compliance for the return for screening can be low; the clinical data are fragmented and an individual office lacks the ability to submit this data to a national registry. Despite 2.2% of upper abdominal CTs and 19.6% of MRI exams reporting pancreatic cysts, only 30% of these incidental patients receive follow-up care. In summary, patients with incidental pancreatic cysts are not identified, identified patients are not referred, referred patients are manually tracked, and patient data are not entered into a database repository to ask quality and research questions on a population level.

Artificial intelligence and computational linguistics models

Artificial intelligence has entered many arenas of healthcare, and more recently, its role has become more formalized in the pancreas space[16]. Currently, AI has the ability to aid in the detection and diagnosis of pre-malignant or malignant processes within the pancreas. Due to the anatomic location of the pancreas and the stomach, Endoscopic Ultrasound (EUS) has become paramount in pancreatic cyst risk stratification. Not only are the images clinically relevant for the care team, but pancreatic cyst fluid can also be aspirated and diagnostically evaluated. To date, numerous studies have found that deep learning and convoluted neural network AI models can differentiate normal pancreas from autoimmune pancreatitis, chronic pancreatitis, and pancreatic ductal cancer[16-20].

With respect to imaging detection, Vilas-Boas *et al.* recently published a pilot study assessing deep learning for automatic differentiation between mucinous versus non-mucinous pancreatic cysts[21]. Utilizing EUS videos from 28 patients, this group assess 5,505 images (3,725 from mucinous lesions and 1780 from non-mucinous lesions). Utilizing a convoluted neural network of deep learning, they found an overall accuracy of 98.5%, sensitivity of 98.3%, and specificity of 98.9%[21]. Although this was only a pilot study and hypothesis-generating, AI may play a significant role in future risk stratifying pre-malignancy.

Regarding AI in imaging, Eon (https://eonhealth.com-Denver CO) has designed a highly flexible software system called Eon Patient Management or EPM, utilizing computational linguistics models and a codebook specific to pancreatic imaging. The EPM system integrates with the electronic health record and facilitates patient identification, risk assessment, care plan setting, care plan tracking, patient and provider communication, outcome recording, and registry functionality. The EPM system covers incidentally and screening-detected findings across a broad array of organ systems. Using computational linguistics (CL) data models, the EPM pancreas solution can accurately identify and capture pancreatic abnormalities from radiology reports with 93.9% accuracy on multiple radiology modalities including CT, MRI and US. Also, the EPM software uses Robotic Process Automation (RPA) to automate mundane and repetitive tasks such as sending letters and tracking if appointments have been made. The advantages of using this Artificial Intelligence software will be discussed in two categories: the first is identification and the second is surveillance.

With respect to identification, patients with pancreatic cysts and their respective demographics are electronically populated from the Electronic Medical Record (EMR) into the EPM dashboard for the end user. To accomplish this task, radiology reports are analyzed through the CL model, and patients identified with pancreatic cysts are added to the EPM worklist so they can be tracked and management decisions are captured. Following identification, at our institution, patients are contacted by letter and phone call by a nurse navigator and offered a consultation with one of our pancreatic surgeons. The ordering provider is also sent a letter explaining the identification and program. If the patient elects to be seen, consultation is scheduled at that time. The use of the AI computational linguistics model, therefore, mitigates patient loss and prevents the lack of follow-up options for a possible pre-malignant lesion of the pancreas. Moreover, in our own practice, this software has identified ampullary adenoma, ampullary cancer, metastatic cancer, and pancreatic neuroendocrine tumors. Therefore, the identification of "at risk" patients goes far beyond pancreatic cysts.

Similarly, Kooragayala *et al.* utilized natural language processing to identify pancreatic cystic lesions[22]. Overall, from 18,769 subjects, the algorithm could correctly classify CT scan reports and maintain a diagnostic accuracy of 98.7% (393 reports correctly identified out of 398). IPMNs were the lesions of the pancreas that were identified most frequently when the Natural Language Processing program was utilized, 20.7% (48 patients). Nineteen percent (44 patients) were found to be due to trauma, 17.7% (41 patients) due to pancreatitis, 15.5% (36 patients) were pancreatic cysts, 12.9% (30 patients), and 8.2 % (19 patients) were ductal abnormalities. A negative exam was identified in 2.2% of cases (5 patients), 1.7% (4 patients) had previous surgery of the pancreas and 2.2% (5 patients) were found to have findings that were unrelated. Natural Language Processing can improve screening and automate referral for patients with precancerous pancreatic lesions[22].

For longitudinal surveillance, the cloud-based EPM dashboard takes the place of the traditional and antiquated Excel spreadsheet. The dashboard electronically monitors orders and appointments for the patients on the worklist. Thus, EPM is able to not only show patients identified and patients seen, but also to highlight upcoming events, patients who are missing follow-up, and document the follow-up advised by the pancreatic surgeon. Phone call reminders or reminder letters to patients can be set and reminders for surveillance imaging and time points can be set to ensure that exams and procedures are scheduled and performed. The automation rules and electronic monitoring makes it easy for the care team to identify patients who have missed their interval imaging, endoscopy or surveillance appointment since the EPM software is organized into work lists to make sure patients are not lost to follow-up. Moreover, on a patient level, the dashboard allows the care team to see the cyst details longitudinally to assess for concerning change and can therefore perform real-time risk stratification. Overall, the Eon Patient Management (EPM) software automates repetitive tasks allowing patient coordinators to spend more time on patient care and less time on administrative duties. The software ensures patients are tracked and followed according to the published evidence-based guidelines.

An additional major advantage of this software is the ability to automatically populate a national registry. Currently, in the Lung Cancer Screening space, Eon is automatically uploading data to the American College of Radiology Lung Cancer Screening Registry (LCSR). In addition, Eon has created a national bronchoscopy (pulmonary nodule) registry in coordination with the American Association for Bronchoscopy and Interventional Pulmonology (AABIP). This registry seeks to improve clinical outcomes, create benchmarks, share qualitative data, and improve the quality of care overall. Using the LCSR as a model, we are now working towards creating a national pancreatic cyst registry to not only improve current patient outcomes, but also to perform predictive analytics on a national population to improve the future care of pancreatic cyst patients.

CONCLUSION

Mucinous pancreatic cysts represent the most common identifiable precursor to pancreatic cancer. These patients require lifelong surveillance, but many are not accurately identified at diagnosis or lost to follow-up. In summary, Artificial Intelligence software has modernized the identification, capture and longitudinal management of patients with pancreatic cysts. This software will therefore allow more patients to receive the evidence-based, high-quality management they deserve and not be lost to follow-up.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Langan RC, Pitt HA, Schneider E

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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