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Review Article

Early Detection of Pancreatic Cancer: Opportunities Provided by Cancer-induced Paraneoplastic Phenomena and Artificial Intelligence

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Abstract

Objective: Pancreatic ductal adenocarcinoma (PDAC) is the most lethal cancer, with a 5-year survival rate of only 11%. Surgery is the only potential cure for PDAC, but approximately 85% of patients present with unresectable tumors at diagnosis. The difficulty in early detection is attributed to the fact that early PDACs cause few or nonspecific symptoms and are frequently obscure or even invisible in imaging studies such as computed tomography (CT). This review aims to briefly summarize the status of screening/surveillance for PDAC and elaborate on the potential windows of opportunity for early detection through PDAC-induced paraneoplastic phenomena and artificial intelligence (AI)-augmented image analysis. **Data Sources:** Relevant studies and review articles were searched in PubMed. **Study Selection:** Studies and articles on human subjects were selected. **Results:** Surveillance for high-risk individuals with imaging-based tools (endoscopic ultrasound and magnetic resonance image) is now advocated, whereas screening for asymptomatic general populations is not warranted at present. Paraneoplastic syndromes, including pancreatic cancer-associated diabetes and cachexia, are prevalent in PDAC patients and may provide windows of opportunity for early detection. S100A9 and galectin-3 are novel PDAC-derived factors mediating pancreatic cancer-associated diabetes and have shown promise in facilitating the early detection of PDAC. Novel computer-aided detection tools based on AI technologies, including deep learning and radiomic analysis with machine learning, have achieved accurate detection and might supplement human interpretation to improve the sensitivity for early PDAC on CT images. **Conclusion:** Novel blood-based biomarkers and AI-augmented image analysis may be complementary and hold promise for the early detection of PDAC.

Keywords: Artificial intelligence, diagnosis, pancreatic cancer, paraneoplastic syndrome

Early Detection: The Best Strategy to Improve the Prognosis of Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is the seventh-leading cause of cancer deaths in Taiwan and is projected to become the second-leading cause of cancer deaths in the US by 2030.[1] Surgery is the only potential cure, but

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approximately 85% of patients present with unresectable tumors at diagnosis; therefore, PDAC is the most lethal cancer, with a 5-year survival rate of only 10%.[2] Early detection may increase the proportion of patients amenable to surgery and represent the best strategy to improve the prognosis.

The difficulty in detecting PDACs early can be attributed to several factors. First, early PDACs are often asymptomatic or present with nonspecific symptoms. Second, early PDACs are frequently obscure or even invisible on computed tomography (CT) and magnetic resonance imaging (MRI), the major tools for detecting PDACs. Search for blood-based biomarkers capable of detecting cancer-derived material in circulation has been undertaken to tackle the first challenge, whereas recent progress in artificial intelligence (AI)-augmented image analysis has shown promise in enhancing the sensitivity of imaging detection/diagnosis. Recently, we have identified S100A9 and galectin-3 as novel PDAC-derived diabetogenic factors mediating pancreatic cancer-associated diabetes mellitus (PCDM) and demonstrated their potential in facilitating early detection of PDAC.[3] We further assessed the potential of cachexia as a clue to early PDAC and investigated its relationship with PCDM and PDAC-derived diabetogenic factors.[4] To improve the sensitivity of CT for PDAC, we developed AI-based computer-aided detection (CAD) tools for PDAC and showed that deep learning (DL)[5] and radiomic analysis with machine learning[6] can accurately detect PDAC on CT. This review aims to summarize the status of screening/surveillance for PDAC and elaborate on the potential windows of opportunity for early detection through unique PDAC-induced paraneoplastic phenomena and AI-augmented image analysis [Table 1].

Surveillance Advocated in High-risk Individuals

Emerging evidence advocates for screening for high-risk individuals (HRIs). The international cancer of the pancreas screening (CAPS) consortium recommends PDAC surveillance in the following HRIs: Peutz–Jeghers syndrome, familial pancreatic cancer (FPC) kindred, familial atypical multiple mole melanoma, hereditary pancreatitis, and family history of PDAC with germline mutations of *BRCA2, BRCA1, ATM, PALB2*, and *MLH1/MSH2/MSH6*.[7] For HRIs, annual screening with MRI and/or endoscopic ultrasound (EUS) has been shown to associate with diagnosis at earlier stages, but whether surveillance improves survival and its cost-effectiveness need further study. In the multicenter CAPS5 study on HRIs, PDACs detected by surveillance (annual EUS and/or MRI/magnetic resonance cholangiopancreatography) were predominantly resectable (88.9%) and stage I (77.8%), with improved overall survival compared with PDACs detected outside of surveillance.[8] On the other hand, the multicenter Dutch FPC surveillance study group did not observe significant survival benefits with annual surveillance by MRI and EUS.[9] That study noted that the cumulative PDAC incidence was significantly higher (9.3%) in carriers of known susceptibility genes mutations compared with FPC kindreds without known susceptibility genes mutations (0%). Notably, four of the 10 PDACs that occurred during a mean follow-up of 63 months were interval cancers, highlighting the insufficiency of imaging-based screening and the need for more sensitive tools.

Screening Not Advocated in Asymptomatic General Population

Given the relatively low incidence of PDAC, it is estimated that screening individuals aged >50 years by a test with even 99% sensitivity and specificity (if available) would only have a positive predictive value of only 3.6%,[10] resulting in many false positives and unnecessary tests and patient anxiety. Therefore, except in individuals at high risk of PDAC because of inherited genetic syndromes or strong family history, US Preventive Service Task Force recommends against screening for PDAC in the general population.[11]

Blood-based Biomarkers and Limitations

CA 19-9 is the most studied biomarker for PDAC. While CA 19-9 is useful for follow-up and prognosis prediction in patients with PDAC, CA 19-9 is not recommended for screening the asymptomatic general population because of inadequate sensitivity and specificity. A recent study discovered that CA19-9 increased exponentially from 2 years before diagnosis, with sensitivities reaching 60% within 0–6 months

Table 1: Potential strategies for enhancing early detection of pancreatic ductal adenocarcinoma

Windows of opportunity	Potential tools	Advantage/pitfalls
High-risk individuals (germline susceptibility genes mutations, familial pancreatic cancer kindred)	EUS, MRI/MRCP	Increased probability of diagnosis at early stages/ some PDACs evade imaging-based surveillance
New-onset diabetes	S100A9, galectin-3	PDACs mostly resectable at onset of diabetes/ moderate sensitivity and specificity
Unexplained weight loss/cachexia	To be identified	-
To be defined	AI-aided image analysis	Noninvasive/for screening, target population and timing need to be defined
	Liquid biopsy (ctDNA, cfDNA/cfRNA, EVs, CTCs, protein biomarkers)	Noninvasive/inadequate sensitivity for early PDAC

EUS: Endoscopic ultrasound, AI: Artificial intelligence, ctDNA: Circulating tumor DNA, cfDNA/cfRNA: Cell-free DNA or RNA, EVs: Extracellular vesicles, CTCs: Circulating tumor cells, PDAC: Pancreatic ductal adenocarcinoma, MRI: Magnetic resonance imaging, MRCP: Magnetic resonance cholangiopancreatography before diagnosis for all cases and 50% for cases diagnosed at the early stage at 99% specificity.[12] Those findings indicate that CA19-9 level may provide an important lead time for the detection of PDAC and be useful for follow-up of individuals at increased risk of PDAC, such as those with chronic pancreatitis and intraductal papillary mucinous neoplasm. Liquid biopsy involves the isolation of tumor-released materials from bodily fluids, including circulating tumor DNA (ctDNA), cell-free DNA or RNA (cfDNA/cfRNA), extracellular vesicles (EVs), and circulating tumor cells (CTCs) to inform disease diagnosis and prognosis. A recent meta-analysis showed that ctDNA achieved a pooled sensitivity of 64% in diagnosing PDAC.[13] Notably, a study showed that *KRAS* mutation could be detected in 30% of resectable PDACs, and combining circulating *KRAS* mutation and CA 19-9 higher than 100 U/ml increased the sensitivity to 60% with nearly perfect specificity.[14] Those studies suggest that combining ctDNA with protein biomarkers may be a viable strategy and warrants further validation. Alternatively, analysis of methylome in cfDNA has also shown promise in the detection of PDAC. In a prospective case–control study, cfDNA methylome achieved a sensitivity of 0.63, 0.83, 0.75, and 1.0 for Stage I, II, III, and IV PDAC, respectively.[15] Studies have also been conducted to evaluate the usefulness of EVs, CTCs, and cfRNAs.[16] Collectively, liquid biopsy has shown promise as a potential noninvasive tool that may facilitate early detection. However, the sensitivity for early PDACs needs further improvement, and the optimal combination of markers remains to be defined before wide clinical implementation.

Pancreatic Cancer-associated Diabetes Mellitus: A Window of Opportunity for Early Detection

Approximately 50% of PDAC patients develop diabetes mellitus (DM) within 2 years preceding the diagnosis of PDAC (i.e., PCDM).[17] At the onset of PCDM, tumor is generally early or even radiologically undetectable,[18] and resection of the PDAC results in improved insulin resistance and resolution of DM.[19] Therefore, PCDM provides a unique window of opportunity to detect PDAC 18–24 months before symptoms appear, when tumor remains resectable. However, subjecting all individuals with new-onset DM to CT or MRI for screening of PDAC is not feasible because only approximately 1% of patients with new-onset diabetes older than 50 years are diagnosed with PDAC.[20] PCDM is a paraneoplastic syndrome mediated by obscure tumor-secreted factors.[21] Identifying PDAC-produced diabetogenic factors may help identify patients with PCDM among patients with new-onset DM.

S100A9 and Galectin-3: Potential Novel Pancreatic Cancer-derived Diabetogenic Factors

Using proteomic and bioinformatic approaches, we have identified two proinflammatory factors, S100A9 and galectin-3, as novel PDAC-produced mediators of PCDM.[21] In that study, secreted proteins of MIA PaCa-2 cells were analyzed by proteomics, and those with ≥10-fold overexpression in transcriptome analysis were assessed by bioinformatics and glucose uptake assay to identify candidate factors that can mediate insulin resistance in muscle cells. The expression of candidate factors was compared between surgically resected tumors from PDAC patients with and without PCDM. Serum levels of candidate factors in PDAC patients with PCDM were compared with those in PC patients without PCDM, patients with type 2 diabetes, pancreatitis, other pancreatic/peripancreatic tumors, and controls. The results showed that S100A9 and galectin-3 can induce insulin resistance by inhibiting insulin-induced glucose uptake in muscle cells and are overexpressed in tumors of patients with PCDM compared with those of PDAC patients without PCDM. Furthermore, serum levels of galectin-3 and S100A9 are differentially increased in PCDM patients and distinguish PCDM from type 2 DM in patients with new-onset DM, with a sensitivity/specificity of 72.1%/86.1% for galectin-3 and 69.8%/58.1% for S100A9. Notably, serum levels of galectin-3 and S100A9 achieved approximately 70% sensitivity in patients with resectable stage I and II PDACs, which are difficult to detect by biomarkers. Collectively, this study showed that galectin-3 and S100A9 are PDAC-derived factors mediating PCDM and may help identify patients at high risk of PCDM for further confirmatory examinations.

Pancreatic Cancer-induced Cachexia: A Common Paraneoplastic Phenomenon with Diagnostic and Therapeutic Implications

Although PCDM provides a window opportunity for detecting PDACs at early stage, only approximately 50% of PDAC patients develop PCDM. PDAC-induced cachexia represents another window of opportunity for early detection. Cancer cachexia is a paraneoplastic syndrome triggered by cancer-induced systemic inflammation and characterized by pronounced weight loss and muscle wasting.[22] Cachexia negatively impacts the survival of PDAC patients, with one-third of PDAC patients dying from cachexia-associated complications, including impaired immunity and cardiopulmonary dysfunction.[23] Significant weight loss may emerge from 1 year before the diagnosis of PDAC,[17] with approximately 40% of patients reaching the degree of cachexia at the time of PDAC diagnosis.[23] In our previous study, the prevalence of cachexia/sarcopenia at the time of PDAC diagnosis reached even 40%/60% in patients with stage I PDAC and 50%/78.6% in those with tumors <= 2 cm, respectively.[4] Interestingly, the tumor stage was not associated with the risk of cachexia. Our results further support the notion that PDAC-induced cachexia is a paraneoplastic phenomenon mainly attributed to the metabolic phenotype of the cancer cells and begins before the tumor is clinically apparent.

Pancreatic Cancer-associated Diabetes Mellitus and Pancreatic Ductal Adenocarcinoma-induced Cachexia Often Coexist but May be Mediated by Disparate Mechanisms

Significant weight loss often occurs with rising blood glucose levels in patients with PCDM. Mechanistically, PCDM might mediate cachexia through multiple mechanisms. First, poorly controlled diabetes induces muscle wasting and unintentional weight loss.[24] Furthermore, insulin resistance, the hallmark of PCDM, plays an important role in cancer cachexia-associated muscle wasting.[25] However, our previous study showed that no significant differences existed between PDAC patients with and without PCDM in the prevalence of cachexia at diagnosis (64.8% vs. 51.1%, $P = 0.093$), percentage of weight loss (median 6.8 vs. 4.0, $P = 0.085$), and lumbar skeletal muscle index (SMI) measured on CT images (median 45.8 cm^2/m^2 vs. 45.3 cm^2/m^2 in men, $P = 0.119$; 34.9 cm^2/m^2 vs. 36.3 cm^2/m^2 in women, $P = 0.418$).[4] In patients with cachexia, the percentage of weight loss and SMI were also similar between patients with and without PCDM. In patients with PCDM, fasting blood glucose was comparable between patients with and without cachexia and did not correlate with the percentage of weight loss or SMI. Neither serum S100A9 level nor galectin-3 level correlated with the percentage of weight loss or SMI. Collectively, our results supported that neither fasting blood glucose nor mediators of PCDM were associated with cachexia-related parameters, supporting that PCDM and hyperglycemia do not directly mediate PDAC-induced cachexia. Those results indicate that the factors mediating PDAC-induced cachexia remain to be identified.

Artificial Intelligence May Supplement Human Imaging Interpretation

CT is the major imaging modality for the detection of PDAC,[26] but its sensitivity for small PDACs is modest. Notably, approximately 40% of tumors smaller than 2 cm are missed on CT,[27] underscoring an urgent need for novel tools to improve the sensitivity for PDAC. Moreover, the diagnostic performance of CT varies depending on radiologists' experience/expertise.

Recent advances in AI have shown great promise in medical image analysis.[28] Two main classes of AI methods are used in medical image analysis. Machine learning algorithms calculate human-crafted features based on domain knowledge and then identify the best combinations of features to classify lesions or support clinical decision-making. Radiomics extracts features representing quantitative information on density, shape, and texture from the image,[29] often subsequently analyzed with machine learning algorithms. On the other hand, DL algorithms such as convolutional neural networks (CNNs) identify the significant features without requiring human-crafted features (i.e., learning from examples) and show promise to detect subtle imaging characteristics which are imperceptible to the naked eye.[30]

To investigate whether DL can capture the imaging characteristics of PDAC to supplement human interpretation, we trained and tested a CNN to distinguish PDAC and normal pancreas in CT images.[5] In the Taiwanese test sets, the CNN-based analysis achieved 98.8% accuracy and achieved a higher sensitivity for PDAC compared with radiologist interpretation (98.3% vs. 92.9%, difference 5.4% [95% confidence interval 1.1%–9.8%]; $P = 0{\cdot}014$). Notably, CNN-based analysis achieved 92.1% sensitivity for PDACs smaller than 2 cm and correctly classified 92% of PDACs missed by radiologists. Testing the CNN trained using images from Taiwanese patients with images from the US yielded acceptable generalizability with an accuracy of 83.2%. By developing the first CNN that can detect PDAC on CT, this study provided the first proof of the concept that AI may supplement radiologist interpretation to facilitate the early detection of PDACs.

We also conducted a study[30] to identify the distinguishing CT radiomic features of PDAC, assess whether radiomic analysis with machine learning could differentiate between PDAC and noncancerous pancreas, and assess the generalizability across institutions and populations. We found that certain features representing image intensity (first order: mean, first order: median, and first order: 90 percentile) were consistently lower across populations in PDAC compared with noncancerous pancreas, whereas certain features representing heterogeneity (neighborhood gray-tone difference matrix busyness, gray-level dependence matrix [GLDM], gray-level nonuniformity, and GLDM dependence nonuniformity) were consistently higher in PDAC, corresponding with the typical CT findings of PDACs as hypodense heterogeneous masses. Radiomic analysis with a machine learning model trained with predominantly Taiwanese images could differentiate between PDAC patients and controls in test images from Taiwan (accuracy 95.0%) and US (accuracy 86.5%), with 96.9% and 90.9% sensitivity for PDACs <2 cm, respectively. Notably, radiomics-based analysis achieved comparable sensitivity to radiologists of a referral center and correctly detected all PDACs missed by radiologists, supporting the potential of supplementing radiologist interpretation.

Recently, we conducted a nationwide population-based study to test the performance of an automatic end-to-end DL-based CAD tool using real-world images obtained from institutions throughout Taiwan.[31] The CAD tool achieved 89.7% sensitivity and 92.8% specificity in distinguishing between patients with and without PDAC, with 74.7% sensitivity for tumors smaller than 2 cm. Those results provide support for the robustness and generalizability of the CAD tool, which might be used to assist clinicians in enhancing the early detection of PDAC.

Concluding Remarks

Early detection of PDAC is the most effective strategy to improve the prognosis of PDAC, but it remains an unmet clinical need. Surveillance for HRIs with imaging-based tools is advocated, whereas screening for asymptomatic general populations is not warranted at present. Novel blood-based biomarkers have shown promising results, but further research is needed to identify novel markers with further improved sensitivity and specificity. PDAC-induced paraneoplastic syndromes, including PCDM and cachexia, are potential windows of opportunity for early detection. Novel DL-based and radiomics-based CAD tools for PDAC hold promise for supplementing human interpretation to reduce miss rate and enhance early detection. Those different approaches can be complementary, and the potential usefulness and clinical impact need to be further investigated. Once more effective biomarkers and image analytic tools for general or high-risk populations such as new-onset diabetics are developed and further validated, future guidelines should be prioritized to incorporate those novel modalities to enhance the early detection of PDAC.

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Conflicts of interest

There are no conflicts of interest.

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