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Advancements in early detection of pancreatic cancer: the role of artificial intelligence and novel imaging techniques

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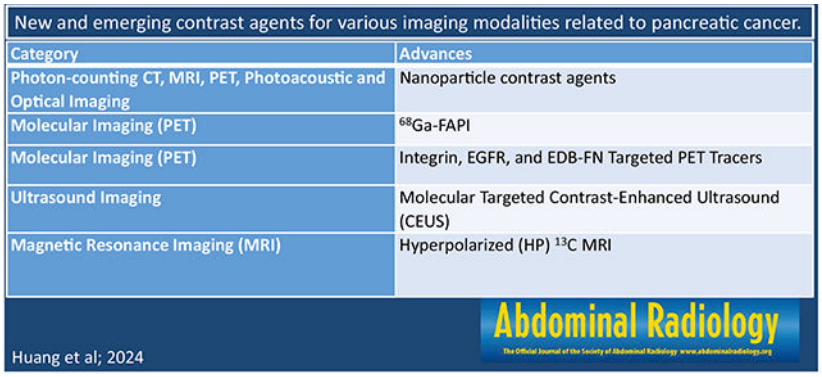
Abstract

Early detection is crucial for improving survival rates of pancreatic ductal adenocarcinoma (PDA), yet current diagnostic methods can often fail at this stage. Recently, there has been significant interest in improving risk stratification and developing imaging biomarkers, through novel imaging techniques, and most notably, artificial intelligence (AI) technology. This review provides an overview of these advancements, with a focus on deep learning methods for early detection of PDA.

Graphical abstract



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Conflict of interest The authors declare no competing interests.

Keywords

Early detection; Pancreatic cancer; Artificial intelligence; Nanoparticle contrast agent; Photon-counting CT

Introduction

Despite advances in the detection of pancreatic ductal adenocarcinoma (PDA), it continues to have a poor prognosis due to late stage diagnosis and limited treatment options for advanced stage cancers. The difficulty of early detection, combined with the expected rise in incidence driven by risk factors like obesity and diabetes in individuals over 50, sets the stage for pancreatic ductal adenocarcinoma (PDA) to become the second leading cause of cancer-related deaths in the United States by 2030, superseding breast, colorectal and prostate cancers [1–3].

The United States Preventive Services Task Force (USPSTF) currently does not recommend screening asymptomatic adults for PDA because of its low incidence in the general population and insufficient evidence that screening in this population can improve morbidity or mortality [4]. There are guidelines however, recommending imaging screening (MR and EUS) and surveillance strategies for high-risk populations, defined as those with a lifetime risk exceeding 5% and other and meeting predefined inclusion criteria [5, 6]. Additionally, there is an ongoing randomized controlled trial of algorithm-based screening in patients with new-onset diabetes using CT imaging (NCT04662879) [7]. Nonetheless, due to the lack of specific biomarkers and current limitations of CT and MRI for detecting PDA smaller than 2 cm [8], early detection remains challenging even in individuals with elevated risk.

Fortunately, recent advancements in imaging technology and analysis show promise for improving the sensitivity and specificity of early detection of PDA. These advances include cancer-specific positron emission tomography (PET) tracers, ultrasound contrast agents, and imaging data analysis methods such as radiomics and artificial intelligence algorithms. This review provides an update on imaging advancements for early detection of PDA with emphasis on deep learning methods.

Advances in imaging technology and tracers

Photon counting CT

Photon-counting CT scanners represent the latest advancements in CT technology offering enhanced imaging capabilities and improved diagnostic potential. A detailed discussion of the physical principles of photon-counting CT scanners is outside the scope of this review but in brief, unlike conventional energy with its energy-integrating detectors (EID), photon-counting detector (PCD) CT utilizes energy-resolving X-ray detectors that precisely count the number of incoming photons and measure their individual energy levels [9]. This innovative approach results in several key advantages including a higher contrast-to-noise ratio, improved spatial resolution, and increased lesion conspicuity at lower kiloelectron volt (keV) monoenergies (e.g., 50 keV) due to improved iodine signal. Similar to dual-energy CT (DECT), this additional capability permits the reconstruction of virtual monoenergetic

(VMI) imaging data sets at a lower keV accentuating the imaging contrast between normal pancreatic parenchyma and PDA which is more commonly relatively hypodense. Prior investigations of DECT have shown that low keV VMI (e.g., 40 keV) increases the conspicuity of PDA [10], including smaller lesions ≤ 3 cm [11]. Similarly, PCD-CT has been shown to leverage low keV to increase the conspicuity of PDA [12, 13] (Fig. 1). On the other hand, it has been reported that up to 44% of the tumors missed on conventional CT are isodense to pancreatic parenchyma, particularly those smaller than 2 cm [8]. Further studies are required to determine whether PCD-CT can enhance the detection of small isodense PDA.

Another area of advancement is in development of molecular CT contrast agents other than iodine. Table 1 presents a summary of new and emerging contrast agents for various imaging modalities related to PDA. For example, nanoparticle can be utilized across different imaging modalities by incorporating materials or functional groups tailored to the physical principles underlying each technique. This versatility allows their use in CT, MRI, and ultrasound [14]. At present, the most extensively studied nanoparticle incorporates gold labeling, albeit with concentrations too low for conventional CT scans to detect. However, PCD-CT, because of its K-edge imaging potential is capable of detecting these nanoparticles even at very low concentrations [9]. This feature is particularly advantageous because it may improve the conspicuity of primary tumors as well as metastases and ultimately, permit earlier and more accurate diagnosis and staging. Additionally, nanoparticles can be engineered to interact with specific molecular targets on PDA cells, offering promise for more efficient and precise treatment delivery (theranostics) [15]. While they also hold potential for the early detection of PDA, nanoparticles have primarily been investigated as blood-based markers rather than imaging agents specific for PDA to date [16, 17].

New tracers for positron emission tomography (PET)

Molecular imaging with PET radiotracers continues to be an area of great interest for diagnosis and staging of PDA with multiple tracers in various stages of investigation. Currently, the most commonly utilized PET radiotracer in clinical practice, ^{18}F-fluorodeoxyglucose (FDG), is not routinely recommended by the National Comprehensive Cancer Network for use in the detection and staging of PDA [18]. As with other cancers, detection of small lesions with FDG-PET/CT is challenging because of the relatively low signal-to-noise ratio generated by small tumors as compared to background pancreatic parenchymal activity which can be quite heterogeneous, especially in the setting of concomitant inflammation. As a result, other molecularly targeted PET imaging agents are being explored to improve early detection of PDA.

On histopathology, PDAs are typically hypovascular tumors composed of small tubular (ductal) structures embedded within dense fibrovascular stroma and have a more infiltrative pattern of growth rather than mass forming. Targeting that fibro-inflammatory or desmoplastic stroma is an area of great interest. Fibroblast activation protein (FAP) is overexpressed by cancer-associated fibroblasts in many malignancies including PDA [19]. Several radiotracers targeting FAP have been developed, most notably ^{68}Ga-FAPI which acts as an inhibitor of FAP and demonstrates uptake in multiple different cancers [20].

Multiple studies have shown the potential application of FAPI-PET/CT in PDA and its advantages over FDG-PET/CT [21–24]. However, FAPI-PET/CT suffers from the same potential limitation of FDG and that is the difficulty in distinguishing between inflammation and tumor [25] (Fig. 2). However, trials exploring the use of FAPI-PET/CT in mouse models of PDA have demonstrated promising results with early detection of tumors when compared to FDG-PET/CT [26]. Preliminary trials in humans also show its potential applications in early tumor detection and malignant transformation of mucinous pancreatic lesions [27, 28]. While additional research is needed to determine its accuracy and cost-effectiveness, FAPI-PET/CT may play a future role in selecting patients for early detection of PDA.

Additional PET-tracers under investigation include those targeting Integrin, epidermal growth factor receptor (EGFR) and extradomain-B fibronectin (EDB-FN). Integrin is a cell surface molecule that serves as a fibronectin receptor and is upregulated in many cancers, serving roles in mediating cell–cell interactions and contributing to proliferation and angiogenesis [29–32]. EGFR is a transmembrane glycoprotein upregulated in multiple malignancies and plays a key role in neoangiogenesis and proliferation in tumor cells [33, 34]. EDB-FN is a glycoprotein found in the extracellular matrix of many cancers, including PDA [35]. However, work on these tracers is mostly in its early stages and additional research is needed to establish if any of these PET radiotracers play a role in the early detection of PDA.

New targeted microbubble agents for contrast-enhanced ultrasound

Molecularly targeted ultrasound has shown promise in improving early detection of PDA. Several groups have focused on developing microbubbles targeting specific vascular endothelial biomarkers in PDA [36–38]. In transgenic mouse models of PDA, vascular endothelial growth factor receptor type 2 (VEGFR2)-targeted ultrasound has been shown to detect small foci of tumors < 3 mm in diameter [38]. Thymocyte differentiation antigen 1 (Thy 1) is a molecular marker differentially upregulated on the neovasculature of PDA, and in vivo molecular ultrasound with a Thy 1-binding single chain-antibody ligand has been shown to detect PDA in both orthotopic and transgenic mouse models [36, 37]. BR55 (Bracco, Geneva, Switzerland), a clinical grade molecularly targeted ultrasound contrast agent, has been evaluated in multiple clinical trials including in a phase 2 trial for the characterization of pancreatic lesions in patients with suspected PDA after transabdominal ultrasound (ClinicalTrials.gov identifier NCT03486327). This contrast agent targets against the kinase insert domain receptor (KDR), the human analog of VEGFR2. The study has completed recruitment as of March of 2022, and the results are pending.

Hyperpolarization technique in MR molecular imaging

Increasing evidence points to the vital role of metabolic reprogramming in PDA pathogenesis and growth. Mutations in the *KRAS* oncogene occur in 90% of PDA cases, drive glycolysis in PDA, with increased expression of multiple glycolytic enzymes including lactate dehydrogenase A, and enhanced aerobic glycolysis and flux to lactate to promote tumor growth [39]. Conversely, genes encoding alanine aminotransferase, which mediate pyruvate to alanine conversion, are downregulated in PDA cells [40, 41]. This metabolic reprogramming can be noninvasively interrogated using hyperpolarized (HP) ^{13}C MRI,

an emerging molecular imaging method that has the sensitivity and chemical specificity for rapid and pathway-specific investigation of dynamic metabolic processes that were previously inaccessible by imaging.

Hyperpolarization, achieved through the dynamic nuclear polarization (DNP) technique provides unprecedented gains in sensitivity (> 10,000-fold signal increase) for imaging ^{13}C-labeled bio-molecules that are *endogenous, nontoxic, and nonradioactive* [42]. In the context of PDA, HP ^{13}C pyruvate MRI has been shown to detect and monitor the progression of PDA precursor lesions in transgenic mouse models [40, 43]. Specifically a progressive decrease in the ^{13}C alanine/^{13}C lactate signal ratio was observed in the pancreas during disease progression from pancreatic intraepithelial neoplasia (PanIN) precursor lesions to PDA. A recent clinical study has shown the feasibility of HP ^{13}C pyruvate MRI to quantify metabolism in normal pancreas and PDA in patients and to detect early changes in PDA metabolism following systemic therapy [44]. These studies highlight the potential of this MRI technique to improve the management of patients at high risk of developing PDA. Notably, HP ^{13}C pyruvate MRI has already been shown to be safe in initial human studies, and there are currently 15 sites performing these studies investigating cancer, cardiac, and brain metabolism [45–48].

Artificial intelligence

Artificial intelligence is an overarching term used to classify machines that mimic human intelligence and cognitive functions such as problem-solving and learning. Machine learning (ML) is a subset of AI and deep learning (DL) is a specialized approach within the realm of ML. DL represents a significant advancement over machine learning ML techniques, particularly in the field of medical imaging. Unlike ML, which often requires manual feature extraction, DL utilizes neural networks, specifically convolutional neural networks (CNNs) and transformers [49] to automatically identify and learn features from vast amounts of data. This is in contradistinction to ML models which require that medical images be converted into numerical features, such as radiomic features through a manual process that often requires domain knowledge (i.e., oversight by a human expert), whereas DL models can directly process raw images.

Key components of a DL project include data collection and preprocessing, model selection and architecture design, training and validation, and performance evaluation. Recent progress has shown encouraging results in the (a) detection and segmentation of the pancreas and pancreatic lesions, (b) classification of lesions as benign or malignant, and (c) development of predictive models for early detection. The focus here is to provide an update on the current status of DL models for detection and diagnosis of early stage pancreatic cancer and the potential impact of these algorithms on clinical practice.

Non-imaging based AI algorithmic risk stratification

Assessing pre-test probability: The general population has a low incidence of PDA, at approximately 1.7% over a lifetime in the US, for example [50]. Therefore, even a highly specific biomarker—whether imaging-based or blood-based—would still result in a significant number of false positives. Risk stratification of the population before any serum,

bodily fluid sampling, or imaging is critical to the success of any screening program and decreases the downstream physical, psychological, and socioeconomic harms that could occur from unnecessary testing.

Current models for identifying patients at risk: Placido et al. utilized DL methods to analyze clinical data from 6 million patients [including 24,000 with pancreatic ductal adenocarcinoma (PDA)] in the Danish National Patient Registry (DNPR) and 3 million patients (with 3900 cases of PDA) in the United States Veterans Affairs (US-VA) databases. Their objective was to determine if they could predict the occurrence of pancreatic cancer within 36 months of initial diagnosis based on data extracted from electronic health records such as diagnostic codes and clinical history [51, 52]. The model with the best performance had an area under the receiver operating characteristic (AUROC) curve of 0.879 (0.877–0.880) but performance did drop to 0.710 (0.708–0.712) when applying the algorithm to data from the US VA healthcare system. This difference in performance is thought most likely due to differences in clinical charting practices and diagnosis coding systems as well as varying thresholds for seeking medical care.

Yet, there were overlapping characteristics between populations with some of the top symptoms and disease codes 0–6 months before PDA diagnosis including unspecified jaundice, diseases of the biliary tract and pancreas, abdominal and pelvic pain, weight loss, diabetes and neoplasms of digestive organs. This study is promising because it demonstrates how using electronic medical data may help inform clinicians. It may reveal subtle trends over time or identify risk factors early that may be hard for a clinician to recognize on a per-visit basis, especially if patients do not have consistent care providers. Perhaps future algorithms incorporating laboratory data such as glucose levels and weight trends extracted from medical chart data would improve future results for early detection of PDA and might more easily identify patients who need to address potentially modifiable risk factors.

Challenges of AI algorithm for pre-test risk stratification: The current overarching hurdle to developing robust AI algorithms in the United States is that while there are vast amounts of medical data within electronic health records systems, the quality is variable and access to large amounts of patient data especially disparate data from different institutions remains difficult and is not without security concerns. Much of our medical data is unstructured, inaccurate, and noisy, precluding efficient and accurate data mining necessary for large-scale DL model development.

Imaging-based AI models

Rationale: Imaging is essential for the diagnosis, staging and treatment planning of PDA. Conventional CT and MRI have limited diagnostic accuracy for detecting tumors smaller than 2 cm (69% and 82% respectively) [53], prompting the exploration of radiomics and DL to enhance diagnostic performance for early-stage PDA.

Mechanism: Most existing DL models for PDA detection follow a two-step workflow. First, they use a segmentation model, like U-Net [54] and its variants, to demarcate and isolate the pancreas from other structures on relevant CT slices. The inputs are volumetric

CT data, and the outputs are either bounding boxes (regions of interest) around the pancreas or pixel-wise segmentation maps. Second, a classification model determines the presence or absence of a malignant lesions within the pancreas. The input to these classifiers is the focused regions of the pancreas on the CT data produced by the segmentation model, and the output is a numerical score indicating the *probability of a malignant lesion*.

The success of this approach relies on two key factors: the quality of the pancreas segmentation and performance of classifiers. The quality of segmentation is crucial for accurate detection. Recent advances in DL, particularly the introduction of foundational segmentation models for medical images such as MedSAM [55] have shown that DL models can reliably segment the pancreas from CT images. The performance of the classifiers depends on the size and diversity of the training data. The classifier needs to encounter various PDA characteristics (size, shape, stages) in images acquired from different devices and a diverse patient population (age, gender and race).

Several landmark imaging-based ML and DL studies have shown promise in the early detection of PDA. The criteria for selecting the studies included in this review are based on their innovative approaches, significant findings, and potential impact on clinical practice as subjectively assessed by the authors.

United States data

Mayo Clinic: Mayo investigators demonstrated that radiomics-based machine learning models [Radiomics Early Detection Model (RED-MOD)] could detect and quantify the imaging signature of early PDA from volumetrically segmented normal-appearing pancreas on standard-of-care CTs [56]. Specifically, a support vector machine (SVM)-based ML model could detect visually occult PDA on pre-diagnostic single portal venous phase CT scans performed for unrelated indications between 3 and 36 months before its eventual clinical PDA diagnosis [57], with a median of 12.6 months (97–1092 days) prior to clinical diagnosis. Importantly, these CTs had been interpreted to be negative for PDA during routine clinical interpretation.

The model's high specificity was generalizable to both an independent internal dataset and publicly available datasets from the National Institutes of Health-Pancreas CT (NIH-PCT) dataset [58]. The model outperformed radiologists by a substantial margin in identifying PDA on the pre-diagnostic CTs. The model's high performance for detection of visually occult PDA was robust within a broad range of clinically relevant variations in image acquisition and radiomics workflow [59].

Furthermore, this research group has developed a fully automated DL based-AI model (AutoCNN) for early PDA detection [60], which allowed an automated approach using AI-derived segmentations instead of relying on the less scalable approach of radiologist-provided segmentations [61, 62]. They trained the AI model on an extensive dataset (~ 3000) of standard-of-care portal venous phase CTs, making it one of the largest datasets to date. Of note, they excluded CTs with biliary stents because devices such as stents are a known source of bias as the model learns to associate such a device with the tumor [63]. Their automated model accurately detected PDA on diagnostic CTs, including small

and isodense tumors, and the performance was generalizable on multi-institutional public datasets. Interestingly, even though the model was trained on CTs with larger tumors, the model detected PDA in prediagnostic CTs at a median of 475 days (15–16 months) before the clinical diagnosis. The model also showed potential in a bootstrapped population with a case–control distribution that matched high-risk groups such as glycemically-defined new-onset diabetes [64]. Furthermore, the model demonstrated reliability and consistent accuracy across diverse patient demographics, scanner technology, and imaging protocols. Prospective evaluation in combination with emerging blood-based biomarkers is warranted to assess the potential for these AI-based approaches for early detection of sporadic PDA in high-risk cohorts.

Selected data from Asia

Taiwan: Chen et al. developed a DL algorithm from 546 patients with PDA and 733 control subjects, which achieved 89.9% sensitivity, 95.9% specificity, and AUC of 0.96 for detection of PDA on contrast-enhanced portal venous phase CT [65]. There was no significant difference between the sensitivity of the DL algorithm and the radiologist report in an internal test set (DL 90.2%, radiologist report 96.1%, $p = 0.11$). More importantly, the algorithm performance was maintained on an external validation dataset of 1473 CT scans (669 patients with PDA, 804 control subjects) from institutions throughout Taiwan, with 89.7% sensitivity, 92.8% specificity, and an AUC of 0.95. In the subset of tumors smaller than 2 cm, which can be easily missed in clinical practice, the DL algorithm achieved a reasonable sensitivity of 74.7%.

South Korea: Other investigators have sought to use DL to detect other types of pancreatic neoplasms in addition to PDA. Park et al. developed DL algorithms that could detect seven different types of solid and cystic pancreatic neoplasms including PDA, neuroendocrine tumor (NET) and intraductal papillary mucinous neoplasm, IPMN [66]. The study included 852 patients with various solid and cystic pancreatic neoplasms in the training set, 603 patients in the internal test set, and 589 patients in the external test set, and the DL performance was compared to two board-certified radiologists. In the internal test set, DL achieved an AUC of 0.91, which was not significantly different from the AUC of the radiologists at 0.92–0.95. Although the performance of the DL approach was lower than that of the radiologists in the external test set (AUC of 0.87 vs. 0.95–0.96, $p < 0.001$), this approach still represented a significant step forward in automatic pancreatic tumor detection for lesion as small as 1 cm (not in lesion classification), with inclusion of wider range of pathologies seen in clinical practice.

China: Researchers developed a DL model named PANDA (pancreatic cancer detection with artificial intelligence), which aimed to detect and diagnose various pancreatic lesions with high accuracy using *non-contrast CT scans* [67]. PANDA is a DL model that not only detects the presence of a lesion, but also segments and classifies lesion subtypes. It was first trained on a dataset of 3208 patients from a single center, and validated in a multi-center cohort of 6239 patients across 10 centers. PANDA achieved an excellent area under the receiver operating characteristic curve (AUROC) of 0.986–0.996 for detecting lesions. Two reader studies were conducted. Firstly, 33 radiologists of varying levels

of experience (ranging from residents to pancreatic imaging specialists) interpreted 291 patients' non-contrast phase CTs. PANDA outperformed radiologist performance in PDA diagnosis by 34.1% in sensitivity and 6.3% in specificity. Secondly, another 15 pancreatic imaging specialists interpreted multi-phase contrast-enhanced CT scans of the same 291 patients (non-contrast, arterial and portal venous phase). PANDA (again using only non-contrast CT) outperformed the specialists in PDA diagnosis by 13.0% in sensitivity and 0.5% in specificity. Upon external validation of datasets from China, Taiwan and Czech Republic, PANDA maintained high AUC. A subanalysis for small PDA (< 2 cm) revealed high sensitivity of 92.2%.

The researchers took it a step further in testing it in a real-world dataset, where there is concern that the model's performance may drop due to reasons such as the greater number of low-risk lesions and normal pancreas in the training set and variations in imaging protocols and clinical presentation. In the real-world clinical evaluation of 20,530 consecutive patients, PANDA achieved high sensitivity (> 96%) and specificity of 99.9% for detecting early-stage PDA. The researchers proposed that PANDA could potentially be utilized as a novel tool for large-scale opportunistic screening for PDA, leveraging the widespread use of non-contrast CT scans that are routinely conducted for various other clinical indications.

Challenges of AI in PDA early detection

The findings from these studies represent a significant step forward in AI-facilitated early PDA detection. However, their translation into clinical practice necessitates rigorous prospective multi-institutional validation. This validation process should encompass diverse patient populations and healthcare settings to ensure the generalizability and reliability of the AI models.

AI research in pancreatic imaging encounters several key challenges. A primary issue is the scarcity of large, open-source datasets (> 10,000 patients) which are essential for training and validating AI models effectively. Most published models are not open-source, lacking transparency in the training processes, datasets used, model parameters, and hyperparameters. This opacity compromises reproducibility, leading many institutions to develop their own models on smaller datasets that often fail to generalize well across different imaging sets. Ideally, a large-scale open-source dataset would allow for benchmarking all models, making it possible for objective performance assessments and improving reproducibility. Another challenge is the quality variability in existing open-source datasets for pancreas imaging, which compromises their utility in developing robust and reliable AI models. Moreover, the explainability of AI models, the ability to interpret and understand the decision-making process of AI models, remains elusive. Most deep learning models function as black boxes without mechanisms for users to examine their reasoning, yet transparency and trust are critical in medical applications. Additionally, challenges related to reimbursement policies, integration of AI into clinical workflows, and the need for comprehensive training and education of end-users, including radiologists and clinicians, are significant barriers to the widespread adoption of AI technologies in pancreatic imaging.

Future directions

AI: Most existing DL approaches lack explainability. Although some DL models use saliency maps to highlight crucial regions on CT images that influence predictions, these maps offer subjective interpretations and do not explicitly reveal the model's rationale. A promising direction is incorporating interpretable AI techniques which categorize salient visual features into concepts with textual explanations. Another approach to enhance explainability is enabling AI models to quantify and output diagnostic uncertainty. Methods such as Bayesian Neural Networks [68], Monte Carlo Dropout [69], and Deep Ensembles [70] estimate how uncertain the AI is when making predictions. Accurate uncertainty quantification assists clinicians in interpreting the AI's predictions and focusing on ambiguous cases where the model is less confident, potentially due to atypical presentations or low-quality images. Second, most current approaches depend solely on CT images and overlook other informative clinical variables such as gender, age, disease history, and BMI. Moreover, the integration of AI algorithms with emerging fluid-based biomarkers presents an exciting opportunity to enhance the accuracy and efficiency of early PDA detection. Future research should aim to design DL models that integrate these variables with images for more comprehensive PDA detection. Lastly, the evaluation of existing work is primarily based on retrospectively collected data. To ascertain their true clinical value, these DL models must be tested in prospective studies within a clinically realistic setting.

Support for research and patient awareness/education: To enable early detection of pancreatic cancer given its low incidence and high severity, more research in large cohorts of populations is needed. Multi-institutional efforts across organizations provide the most effective opportunity to generate data and evidence on the benefits or harms of early detection and its outcome on the health of the general population. Several national organizations such as the Pancreatic Cancer Action Network (PanCAN) and Pancreatic Cancer Detection Consortium (PCDC) are leading such efforts to identify imaging-based biomarkers in early-stage pancreatic cancer [7]. Such efforts would need standardized procedures and collaborative undertakings between important stakeholders to ensure that any screening biomarker can be widely applied across different sections of the general population leading to equitable care. Community outreach paralleling research efforts is an integral part of such screening mechanisms and needs inclusion of public health organizations.

Standardization of patient data collection, interpretation and reporting: Standardization of data collection and reporting are needed to reduce interobserver variability and promote reproducible exams that facilitate comparison over time and across providers. Recent publications have advocated for standardization of clinical and imaging data collection in early PDA detection [71–73]. Clinical data should include the gold standard of a 3-generation family history pedigree including primary cancer sites and age of diagnosis. Important risk factors to document include diabetes history, onset, and course, fasting blood glucose or hemoglobin A1C, body mass index, smoking history, and alcohol use. Results of genetic testing should be reported, noting there is variation in the types of genetic testing offered given its evolving state [73]. EUS and MRI/MRCP are the preferred

imaging modalities for PDA early detection, but there is no consensus on the order to use them.

Annual surveillance is recommended in the absence of concerning lesions, to start in those with familial risk at age 50 or 10 years earlier than the youngest affected relative [5]. MRI images are saved and readily accessible for comparison, with a recently proposed MRI protocol and reporting template for high-risk individuals [72]. EUS is more difficult to compare across institutions due to lack of standardized image capture and less frequent use of reporting templates. A standardized EUS technique, identifiable landmarks for imaging collection, and a reporting template has also been recently proposed for use with high-risk individuals [74]. Increasing adoption of standardized procedures promises to not only improve the consistency of care for individual patients but also facilitate the comparison of data across different research centers.

Conclusion

There has been significant enthusiasm and progress in the early detection of PDA using AI. Current approaches encompass pre-imaging risk stratification and population enrichment through electronic health record (EHR)-based analysis, as well as imaging-based AI, predominantly utilizing computed tomography (CT) for opportunistic screening. These methods frequently employ deep learning techniques nowadays. Despite notable successes, numerous challenges in the application of AI persist before clinical adoption. Simultaneously, advancements in imaging tracers, imaging technologies, and biomarkers have emerged. However, their roles in early pancreatic cancer diagnosis necessitate further investigation through clinical research studies. Future multi-institutional collaborations with high-quality and diverse data are essential for meaningful advancements in early pancreatic cancer detection, particularly in the realm of AI. Additionally, integrating AI with these new innovations, such as biomarkers, presents a promising direction for further exploration.

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Data availability

No datasets were generated or analysed during the current study.

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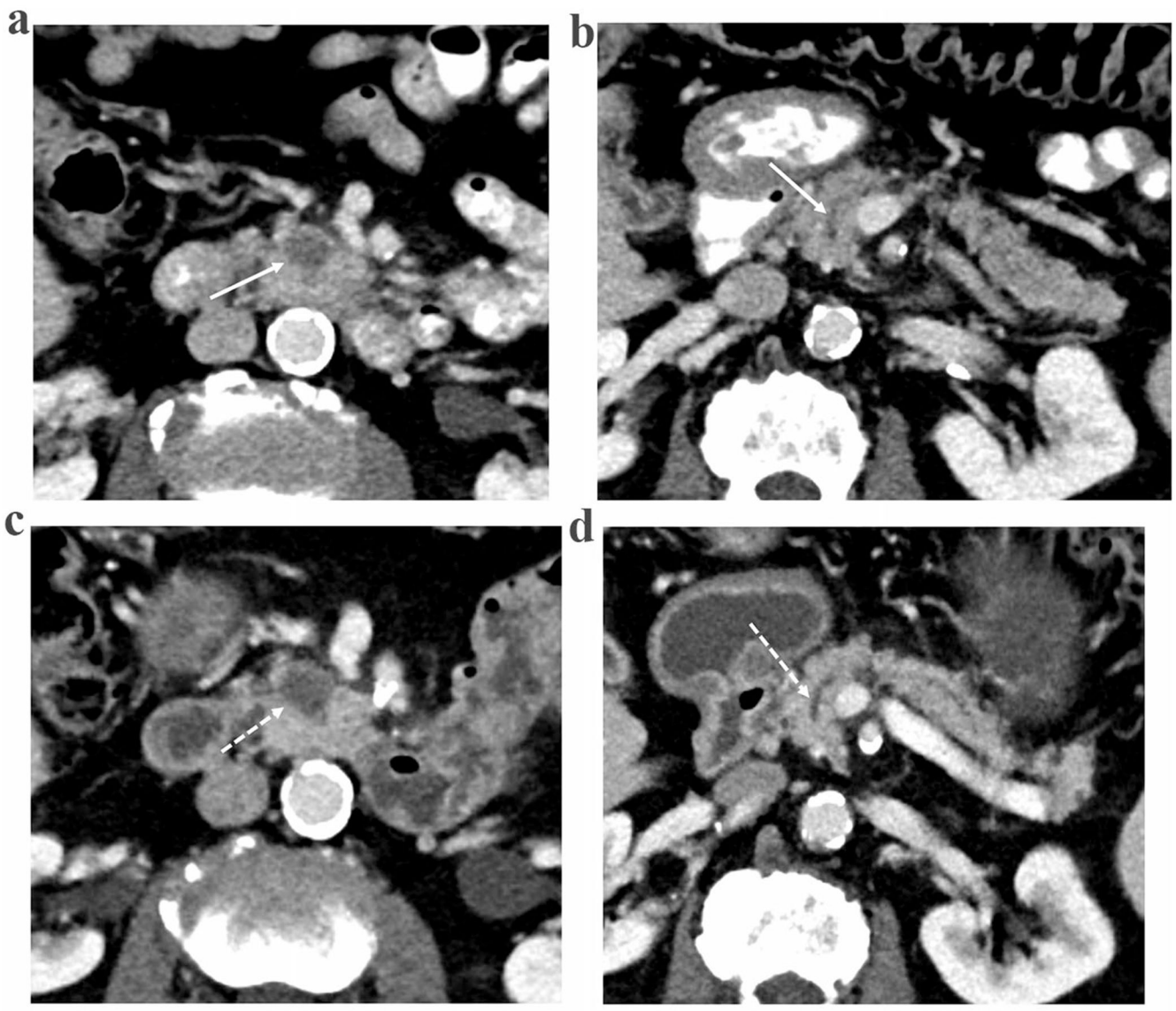

Fig. 1.

80-Year-old man presented for inguinal hernia assessment. **A** and **C** Axial post-contrast portal venous phase images performed on a Siemens 64-slice CT scanner. **A** Image at the level of the uncinate process demonstrates a 1.3 cm hypodense mass (solid arrows). **C** The upstream main pancreatic duct is not dilated and is barely seen (dashed arrows). **B** and **D** Following biopsy confirming pancreatic ductal adenocarcinoma (PDA), and 13 days after the first CT, a staging pancreatic protocol CT was performed on a photon counting CT (Naeotom Alpha). Axial post-contrast portal venous phase images **B** at the level of the uncinate process demonstrate a more conspicuous hypodense mass with a sharper demarcation (solid arrows) between the tumor and normal parenchyma. **D** The upstream normal caliber main pancreatic duct also demonstrates a sharp border and can be well visualized in the head and body (dashed arrows)

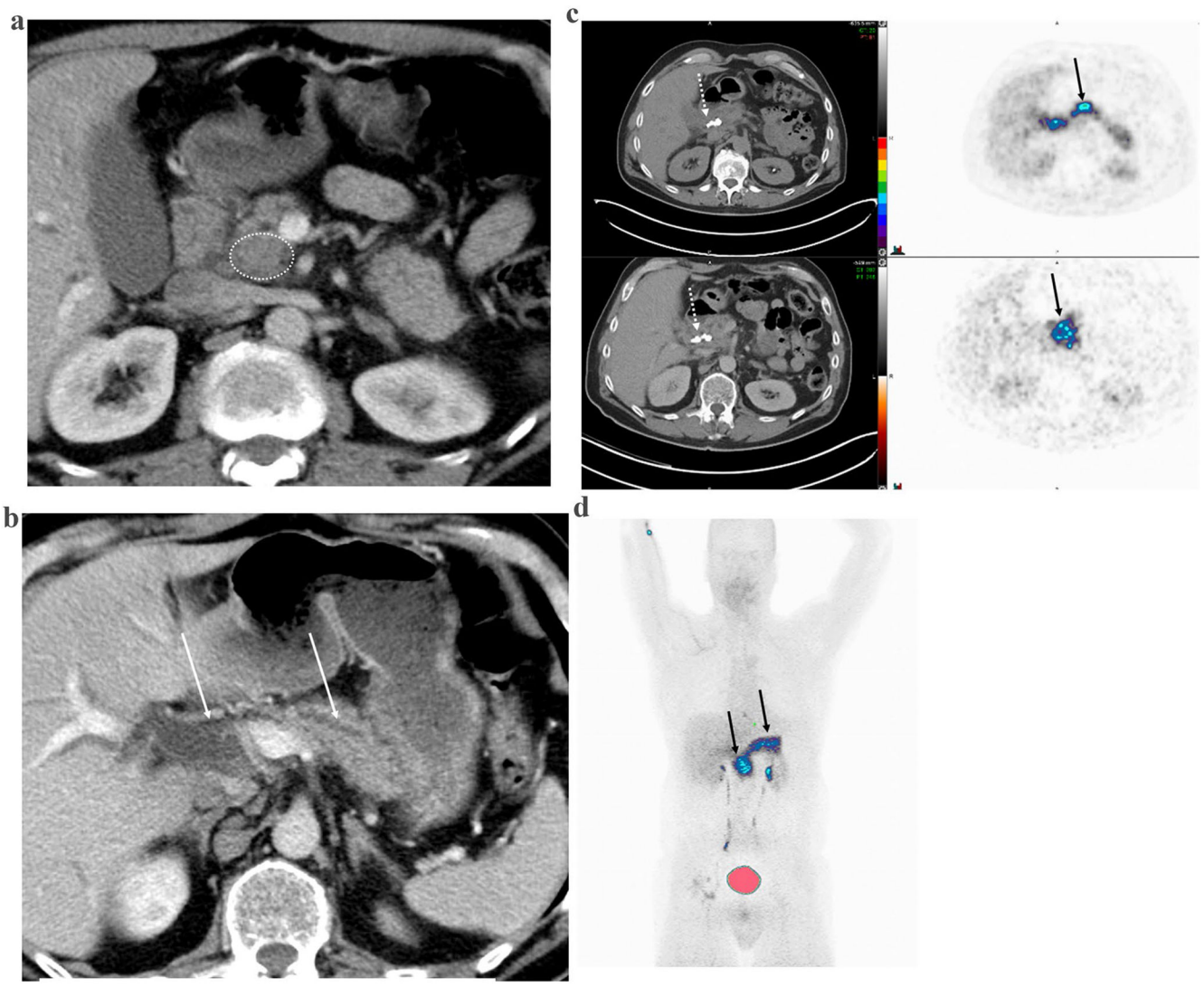

Fig. 2.

63-Year-old man with an isodense pancreatic head PDA. (A and B) Axial post-contrast portal venous phase images show **A** a 2.5 cm isodense mass in the pancreatic head (white dashed circle) and **B** upstream biliary and main pancreatic duct dilation (white solid arrows). **C** and **D** Eighteen days after the initial CT and following biliary stent placement (white dashed arrows), the patient underwent a ^{68}Ga-FAPI46 PET/CT as a clinical trial participant. Increased ^{68}Ga-FAPI46 uptake is noted in the pancreatic head mass (SUV 19 and 17 at 15 and 60 min after injection, respectively) and diffusely within the pancreas where there is subclinical post-obstructive pancreatitis (SUV 18 and 16 at 15 and 60 min after injection, respectively) (black solid arrows)

Table 1

Summary of new and emerging contrast agents and tracers

Category	Advances	Description
Photon-counting CT, MRI, PET, Photoacoustic and Optical Imaging	Nanoparticle contrast agents	• Nanomaterials have unique properties such as ultra small size, stability, biocompatibility, scalability for manufacturing and can be used for targeted treatment delivery (theranostics) • Gold nanoparticles are the most well-studied at present
Molecular Imaging (PET)	^{68}Ga-FAPI	• FAPI targets fibroblast activation protein (FAP) overexpressed in cancer-associated fibroblasts • Early studies show it may improve detection of PDA, especially compared to FDG-PET/CT
Molecular Imaging (PET)	Integrin, EGFR, and EDB-FN targeted PET tracers	• PET tracers targeting Integrin, EGFR, and EDB-FN are in the early stages of investigation • These molecules are involved in cell–cell interactions, tumor proliferation, and neovascularization, all of which are relevant to PDA
Ultrasound Imaging	Molecular targeted contrast-enhanced ultrasound (CEUS)	• Microbubbles targeting biomarkers like VEGFR2 and Thy1 have shown promise in detecting small PDA tumors (< 3 mm) in preclinical models • The contrast agent BR55 targets VEGFR2 has been tested in clinical trials
Magnetic Resonance Imaging (MRI)	Hyperpolarized (HP) ^{13}C MRI	• Hyperpolarized ^{13}C MRI focuses on the metabolic processes in tumors • ^{13}C pyruvate is commonly used because it plays a central role in energy metabolism, specifically glycolysis, which is altered in many cancers, including pancreatic ductal adenocarcinoma (PDA) • It has shown promise in mouse models and has been found to be safe and feasible in initial human studies

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