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Artificial Intelligence-Augmented Imaging for Early Pancreatic Cancer Detection

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Abstract
Background: Pancreatic ductal adenocarcinoma (PDA) is a highly lethal malignancy, often diagnosed at an advanced stage due to its insidious progression and the absence of effective early detection strategies. Accurate diagnosis and staging are critical for optimizing treatment selection and improving patient survival. Contrast-enhanced computed tomography (CT) remains the diagnostic standard for PDA; however, its sensitivity is limited by interobserver variability and the frequent absence of overt morphological abnormalities in early stage disease. ***Summary:*** Artificial intelligence (AI) has emerged as a promising tool for overcoming the inherent limitations of conventional radiologic assessment by leveraging radiomics and deep learning models to extract subtle imaging signatures of PDA that are imperceptible to the human eye. AI-driven models have demonstrated the ability to detect pre-diagnostic PDA on CT scans months to years before clinical presentation by identifying textural and structural changes in the pancreas. Furthermore, automated volumetric pancreas segmentation enhances reproducibility and facilitates the discovery of imaging biomarkers associated with early carcinogenesis. Despite these advances, key challenges remain, including dataset heterogeneity, model interpretability, and prospective validation in real-world clinical settings. ***Key Messages:*** AI-driven approaches offer a transformative opportunity to augment CT-based PDA detection, reduce diagnostic uncertainty, and facilitate earlier intervention. However, robust external validation, integration into clinical workflows, and prospective trials are essential to establish AI as a reliable adjunct in PDA diagnosis and staging.

Introduction

Pancreatic ductal adenocarcinoma (PDA) remains among the most lethal malignancies. It is a leading cause of cancer-related mortality and is projected to become the second deadliest cancer in the USA by 2030 [1]. The prognosis remains poor, with most cases diagnosed at a locally advanced (LA) or metastatic stage. Only 13.6% of PDA cases are detected while still localized and potentially resectable [2]. In 2024, the incidence-to-mortality ratio of PDA was 1.28, indicating that nearly every diagnosed individual eventually succumbs to the disease [1]. This high mortality rate is primarily driven by the symptom-driven detection paradigm, where more than 85% of cases are diagnosed at an unresectable stage, restricting treatment to palliative care [3, 4].

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PDA differs from most other major malignancies in lacking a standardized screening strategy for sporadic cases, which account for the vast majority (85–90%) of diagnoses [5]. While hereditary PDA allows for the identification of high-risk individuals (HRIs) through genetic testing and structured surveillance programs [6, 7], sporadic PDA arises in individuals with no known familial predisposition, making pre-symptomatic detection particularly challenging. Consequently, early detection of sporadic PDA presents the greatest opportunity to improve overall survival, as even modest gains in early diagnosis could lead to significant reductions in mortality on a national scale [8]. These challenges highlight the pressing need for more effective early detection strategies to enhance resectability rates and long-term survival outcomes.

Advances in multimodal therapy have significantly improved outcomes for patients with LA and borderline resectable (BR) PDA, further reinforcing the importance of early detection. Data from recent studies indicate that patients achieving a major pathologic response following systemic chemotherapy and tailored neoadjuvant regimens can attain a median overall survival exceeding 60 months, a marked improvement over historical outcomes [9–11]. These findings highlight a paradigm shift – early detection not only increases the likelihood of surgical resection but also maximizes the benefits of modern treatment strategies. If PDA is detected even at an LA/borderline resectable stage, contemporary therapeutic regimens can significantly extend survival. Therefore, targeted early detection has the potential to transition the treatment paradigm from palliative management to curative-intent interventions, ultimately improving long-term survival in this historically lethal disease.

Limitations of Conventional Imaging in Detecting Early Stage PDA

Despite advancements in imaging technology, conventional methods remain inadequate for detecting PDA at its earliest and most treatable stages [12–14]. Contrast-enhanced computed tomography (CT), the current diagnostic standard, relies on macroscopic tumor visualization. However, pancreas at the pre-diagnostic stage of PDA is frequently morphologically normal. Retrospective analyses indicate that over 50% of PDA cases exhibit no discernible abnormalities on pre-diagnostic imaging [12, 13], underscoring the inherent limitations of conventional CT in detecting subtle parenchymal changes associated with early tumorigenesis. This limitation results in the failure to capture disease during its subclinical phase, when intervention could be most effective. Subtle imaging abnormalities observed in pre-diagnostic PDA, such as pancreatic duct cutoff or mild dilatation, lack specificity and are frequently overlooked in clinical practice. These findings are often present 3–36 months before clinical diagnosis but are also commonly seen in individuals without PDA, reducing their predictive value and contributing to high false-positive rates [14, 15]. Additionally, interpretation of these subtle features is highly subjective, with low inter-reader agreement among radiologists, further compounding diagnostic variability and the likelihood of missed early stage tumors. Standard imaging techniques also fail to capture dynamic alterations in pancreatic morphology and function over time, limiting their utility in longitudinal screening strategies and significantly undermining the success of early detection frameworks.

Additionally, PDA progresses rapidly, transitioning from subclinical disease to advanced-stage disease within an estimated 12–18 months. Conventional imaging modalities are inherently limited in detecting the subtle parenchymal changes preceding tumor formation, as these alterations often manifest at textural or molecular levels beyond the resolution of standard imaging [16–18]. This diagnostic latency significantly impacts patient outcomes, as surgical resection – the only potentially curative intervention – is feasible only for tumors detected at an early stage [19]. Without a paradigm shift in imaging methodologies, the clinical window for early detection and intervention remains critically narrow.

This review examines AI-driven advancements in volumetric pancreas segmentation and early detection of PDA, highlighting key limitations of conventional imaging modalities in detecting early stage disease. Given the widespread use of CT as the primary imaging modality due to its standardized acquisition protocols and operator independence, the focus remains on CT-based AI applications. Additionally, we discuss challenges limiting clinical integration, including dataset heterogeneity, lack of prospective validation, and the need for standardized frameworks to mitigate false-positive and false-negative findings in early detection models.

AI-Driven Pancreas Segmentation: A Critical Enabler for Early PDA Detection

Volumetric pancreas segmentation is extremely critical for early detection on imaging, as subtle parenchymal changes often remain undetectable on standard imaging, necessitating precise volumetric analysis to identify pre-diagnostic alterations [14, 20]. However, manual segmentation of the pancreas is a labor-intensive and inherently inconsistent process due to the organ's irregular shape, variable positioning, and complex interface with surrounding structures [21]. Even among experienced radiologists, segmentation is time-consuming and subject to high inter- and intra-reader variability, introducing inconsistencies that hinder reproducibility in biomarker discovery and clinical diagnostics [22]. Given these

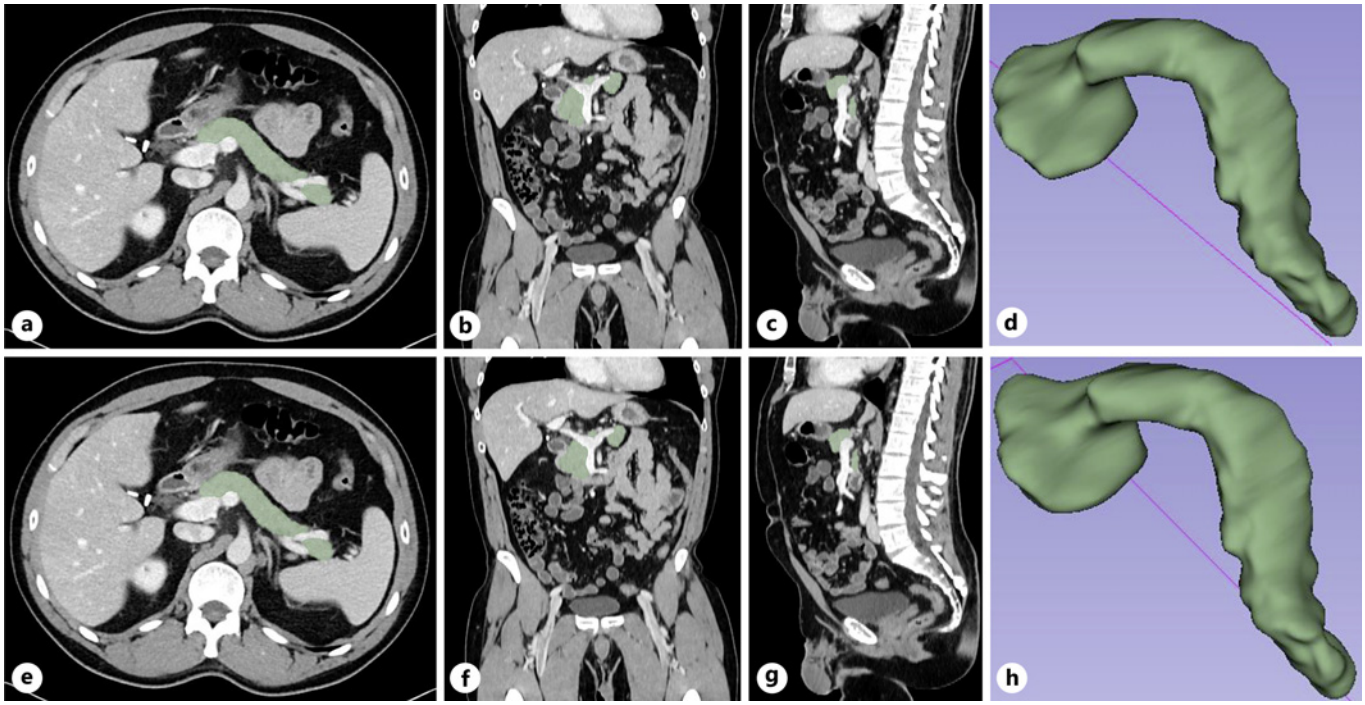

Fig. 1. Volumetric pancreas segmentation: radiologist vs. AI model: radiologists-derived pancreas segmentations were displayed in panels (**a–c**), while panels (**e–g**) illustrate the segmentations generated by the AI model. The high dice similarity coefficient (DSC) of 0.96 indicates excellent consistency between the two methods and the AI model's segmentations closely mirror those of the radiologists across all imaging planes: axial (**a**, **e**), coronal (**b**, **f**), and sagittal (**c**, **g**). 3D renderings of the segmentations from both the radiologists and AI model are provided in panels (**d**) and (**h**), respectively.

constraints, manual segmentation is neither scalable nor feasible for widespread implementation in risk-stratified screening programs or large-scale studies assessing pancreatic imaging biomarkers.

AI-powered pancreas segmentation offers a scalable, objective, and reproducible alternative to manual delineation (shown in Fig. 1). Deep learning models trained on large, multi-institutional datasets have demonstrated near-expert performance in automated pancreas segmentation, achieving high Dice Similarity Coefficients (DSC) and strong concordance with radiologist-annotated volumes [20–25]. The DSC is a statistical metric used to evaluate the accuracy of segmentation models by quantifying the spatial overlap between AI-generated and ground-truth segmentations. Its values range from 0 (no overlap) to 1 (perfect overlap), with higher values indicating superior segmentation performance. Similarly, the CCC assesses volumetric agreement between predicted and reference pancreas segmentations, measuring both precision and accuracy. A CCC value closer to 1 reflects high concordance, reinforcing the reliability of AI-driven segmentation for clinical application [22]. By providing accurate volumetric pancreas assessments, AI-driven segmentation facilitates the extraction of subtle imaging biomarkers, enabling the identification of textural and morphometric changes that precede clinical PDA diagnosis. Moreover, automated segmentation minimizes human-induced variability, enhances efficiency in radiomics workflows, and enables real-time pancreas analysis in routine clinical practice.

AI-Augmented CT Imaging for Detection of PDA at the Pre-Diagnostic Stage

Recent advancements in machine-learning-driven radiomics have enabled the quantification of subvisual pancreatic changes that precede clinically detectable PDA [14, 26–28]. One such approach, the Radiomics-Based Early Detection Model (REDMOD) [14], was developed to assess structural and textural alterations in the normal-appearing pancreas on pre-diagnostic CT scans obtained months to years before a clinical PDA diagnosis (shown in Fig. 2). In a recent case-control study, REDMOD was applied to a dataset comprising 155 pre-diagnostic CTs (median lead time: 398 days) and 265 CTs from age-matched controls. Radiomic feature extraction yielded 88 first-order and gray-level texture metrics, of which 34 were selected through a least absolute shrinkage and selection operator (LASSO) approach. The dataset was split into a training subset (292 CTs: 110 pre-diagnostic, 182 controls) and a test subset (128 CTs: 45 pre-diagnostic, 83 controls), ensuring robust model validation. In the test subset, REDMOD achieved an AUC of 0.98 (95% CI, 0.94–0.98), a sensitivity of 95.5% (85.5–100.0), a specificity of 90.3% (84.3–91.5), and an

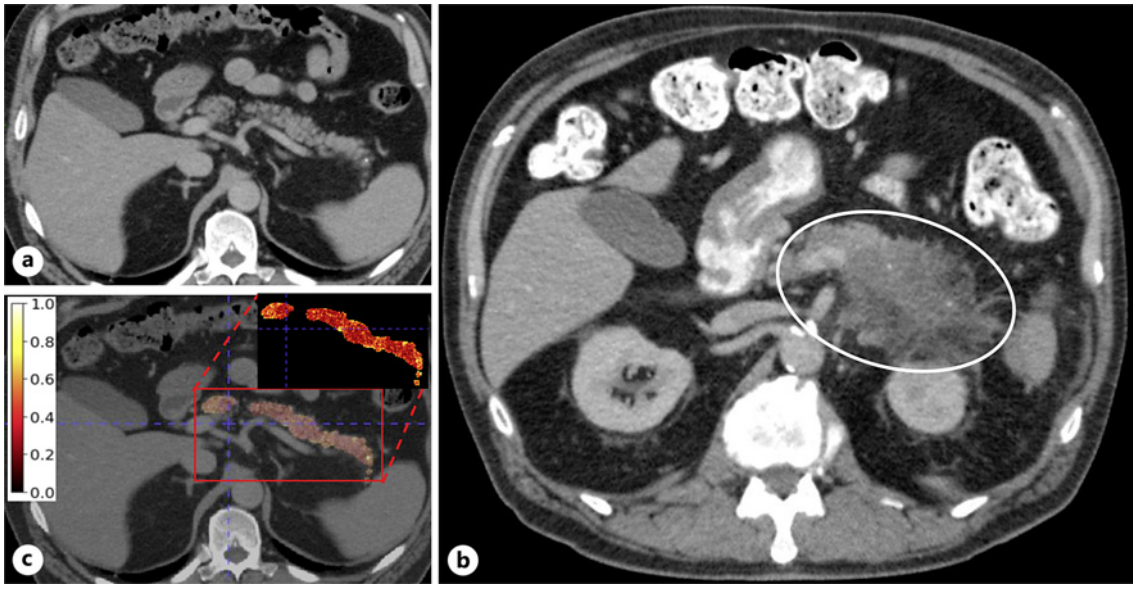

Fig. 2. Pre-diagnostic (**a**) and diagnostic (**b**) CT of a 65.9-year-old male: the pre-diagnostic CT scan showed a pancreas with no significant structural abnormalities. However, about 2.9 years later, the patient was diagnosed with a large PDAC (white oval). A radiomics texture map (**c**), generated using the REDMOD algorithm, is superimposed on the pre-diagnostic CT image. This map visualizes the spatial distribution of the wavelet-filtered gray-level co-occurrence matrix informational measure of correlation 2 (GLCM-IMC2), which was one of the key gray level features used in the REDMOD prediction model.

accuracy of 92.2% (86.7–93.7) at a median lead time of 386 days (range: 97–1,092 days). The model's high specificity persisted when validated on independent datasets, achieving 92.6% specificity in an internal validation set (n = 176) and 96.2% in a public NIH dataset (n = 80). A direct comparison with radiologists demonstrated the superiority of REDMOD, as expert readers assessing the same CTs achieved an AUC of only 0.66 (0.46–0.86), with fair inter-reader agreement (Cohen's kappa = 0.3). Furthermore, radiologists frequently misclassified indirect imaging findings – such as focal atrophy or ductal dilatation – as indicative of PDA in controls, leading to false-positive rates as high as 18%. This finding underscores the lack of specificity of traditional radiologic interpretation for early PDA detection.

To elucidate the biological relevance of the extracted radiomic features, an ablation study systematically removed feature classes to assess their contribution to model performance. Textural heterogeneity features from gray-level co-occurrence matrices (GLCM) emerged as the most predictive, aligning with prior evidence that pancreatic carcinogenesis induces microarchitectural remodeling before the formation of a discrete mass [29, 30]. To ensure real-world applicability, REDMOD underwent robustness testing using simulated variations in image acquisition and radiomic processing workflows. Despite perturbations, the model consistently maintained high predictive accuracy, confirming its generalizability across diverse imaging conditions [31]. These results demonstrate that AI-powered radiomics can detect biologically relevant pre-diagnostic pancreatic remodeling, offering a novel pathway toward earlier PDA detection in asymptomatic individuals.

Several independent studies have corroborated these findings. A study by Qureshi et al. [26] employed AI-based radiomic analysis on pre-diagnostic CT scans and identified subtle pancreatic changes that precede clinical PDAC diagnosis. Their model utilized a naïve Bayes classifier and achieved an 86% accuracy in predicting future PDA development. Similarly, Chen et al. [28] leveraged machine-learning-based radiomic analysis on a large, multi-institutional dataset. Notably, their model outperformed radiologists in identifying PDAC lesions, particularly for tumors smaller than 2 cm, a size threshold where human interpretation is notably unreliable. Further supporting these findings, Javed et al. [27] conducted a study utilizing AI-driven analysis of pancreatic subregions, demonstrating that PDA development is associated with distinct morphologic and textural changes in specific regions of the pancreas in pre-diagnostic CTs. By evaluating localized pancreatic alterations rather than whole-organ changes, this study refined risk prediction methodologies, aligning with REDMOD's findings that early tumorigenic processes manifest in subtle, quantifiable radiomic patterns. Collectively, these studies underscore the potential of AI-powered radiomics to enhance early PDAC detection, supporting a paradigm shift toward preemptive identification of HRIs before conventional imaging reveals overt malignancy.

AI-driven radiomics models for early PDA detection can extend beyond direct pancreatic imaging by incorporating systemic changes that precede clinical diagnosis. Cancer-induced metabolic alterations, particularly in body composition, have emerged as potential biomarkers for early detection [32]. Longitudinal studies indicate that PDA induces significant reductions in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) well before diagnosis [33]. These findings align with prior evidence that cachexia – a condition characterized by progressive muscle loss – can manifest even in the preclinical stages of pancreatic cancer [34], further reinforcing the potential for systemic biomarkers in early detection. Despite its promise, AI-driven body composition analysis faces critical clinical challenges. A primary limitation is the requirement for serial CT imaging to track longitudinal changes in metabolic parameters, which is not routinely available outside of specific high-risk cohorts or surveillance programs. Systemic metabolic changes are also not unique to PDA – conditions such as diabetes, chronic inflammation, and other malignancies can induce similar alterations, leading to high false-positive rates when these features are used in isolation [35, 36]. Furthermore, cachexia progression varies among patients, making it difficult to define standardized cutoffs for risk stratification. While integrating systemic imaging biomarkers with pancreatic-specific radiomic features could improve specificity, large-scale, multi-institutional prospective validation studies are required before this approach can be incorporated into routine clinical practice.

AI-Augmented CT Imaging for Detection of PDA at the Diagnostic Stage

Another significant clinical issue is the missed detection of incidental PDA on routine imaging, including more advanced tumors that remain undiagnosed due to inadequate pancreatic evaluation, suboptimal contrast timing, or limitations in image quality [37, 38]. These cases, where a pancreatic lesion is present but not identified at the time of imaging interpretation, are categorized as "missed PDA." Such diagnostic oversights underscore the urgent need for improved imaging protocols and AI-driven tools capable of enhancing pancreas-specific assessments and increasing the detection rates of subtle, early PDA features that are frequently overlooked in routine evaluations.

A crucial step in AI-powered PDA detection is accurate tumor localization on cross-sectional imaging, which is typically achieved using pancreatic segmentation masks that delineate the gland and the tumor [39–41]. Convolutional neural networks (CNNs) trained for pancreas segmentation serve as the foundation for PDA detection models. One such AI system was trained on 696 portal-phase diagnostic CTs with PDAC and 1,080 control images, achieving an impressive 92% accuracy on an internal test set (1,238 cases: 409 PDAC, 829 controls) and 86% accuracy on an external dataset (194 PDAC, 80 controls). Furthermore, this model demonstrated robust performance when applied to a simulated high-risk cohort, achieving 95% accuracy in cases where the PDA-to-control ratio was adjusted to reflect the estimated 3-year risk of sporadic PDA in individuals with new-onset diabetes (NOD) and an END-PAC score ≥3. Notably, although trained exclusively on larger tumors, the model successfully detected PDA in pre-diagnostic CTs acquired 3–36 months before clinical diagnosis, achieving an 84% accuracy rate, reinforcing its potential for early detection [39].

Another AI-based system, PANDA [40] (Pancreatic Cancer Detection with Artificial Intelligence), demonstrated high accuracy in PDA detection even when trained on non-contrast CTs, an imaging modality previously considered suboptimal for pancreatic cancer detection. Trained on a dataset of 3,208 patients, PANDA achieved an AUC of 0.986–0.996 across multiple validation cohorts, significantly outperforming radiologists in sensitivity (by 34.1%) and specificity (by 6.3%). Importantly, PANDA maintained over 90% sensitivity for detecting stage 1 and 2 PDACs – a key benchmark for effective early detection strategies. In real-world clinical evaluations involving 20,530 patients, the model identified pancreatic malignancies missed by standard-of-care radiology reports, demonstrating its potential for opportunistic screening in asymptomatic populations. Further reinforcing the diagnostic power of deep learning on CECT, Liu et al. [42] developed a CNN that accurately distinguished pancreatic cancer from non-cancerous tissue. Their model demonstrated excellent sensitivity (0.97–0.99) and specificity (0.99–1.00) on local Taiwanese test sets and notable generalizability with an AUC of 0.92 in a cross-racial US external validation cohort, also outperforming radiologists' sensitivity in local evaluations. However, the robustness of this external validation for specific PDA detection has been questioned, as the publicly available external dataset utilized contained a heterogeneous mix of pancreatic pathologies (including neuroendocrine tumors and intraductal mucinous neoplasms) rather than solely PDA cases, directly impacting the reported generalizability for PDA [43]. Beyond CNN-based detection models, hybrid AI approaches that integrate deep learning with radiomic feature extraction and texture analysis have been explored to enhance early stage PDA detection [44, 45]. One study trained a machine-learning classifier on radiomic features extracted from manually segmented 3D pancreas volumes, achieving an AUC of 0.99 and an accuracy of 99.2% in a validation set of 125 CT scans [46]. A complementary approach utilized a patch-based AI model, dividing the pancreas and surrounding regions into smaller segments

to improve localized tumor identification. This system, evaluated on 436 PDA cases and 479 healthy controls, demonstrated >85% accuracy across both Taiwanese and US datasets, with a sensitivity exceeding 90% for detecting stage 1 and 2 tumors [47, 48]. To address the critical challenge of model generalization in diverse clinical settings, Qu et al. [49] introduced a causality-inspired intervention method for CECT-based diagnosis. By actively reducing the influence of confounding image features, their model achieved an encouraging average accuracy of 0.87 across three independent test sets, signaling a promising direction for enhancing the real-world applicability of AI diagnostic tools. The diagnostic utility of AI is also being actively explored using non-contrast CTs (NCCTs). Qiu et al. [50] proposed a novel multiresolution-statistical texture analysis architecture for radiomics-based PDA diagnosis on NCCTs, reporting an AUC of 0.79 on their test set. More recently, addressing both early diagnosis and model robustness on NCCT, Li et al. [51] developed a causality-driven graph neural network which demonstrated stable accuracies ranging from 0.81 to 0.85 across independent multicenter test cohorts, underscoring the evolving potential of AI even in the absence of intravenous contrast.

Challenges, Limitations, and Future Directions in AI-Augmented Imaging for PDAC Detection

Despite advances in deep learning and radiomics, integrating AI-driven imaging tools into clinical workflows for PDA detection remains challenging. A major limitation is the scarcity of well-curated, pre-diagnostic imaging datasets, essential for training and validating AI models capable of recognizing subclinical pancreatic changes. Unlike malignancies with established screening pathways, PDA lacks standardized surveillance for HRIs, limiting access to routine early stage imaging. This results in a small pool of annotated pre-diagnostic CTs, restricting AI model development and generalizability. Variability in imaging acquisition and annotation across institutions further complicates standardization, increasing the risk of overfitting and reducing clinical applicability.

Publicly available datasets, while valuable for external validation, often lack histopathologic confirmation, consistent annotations, and imaging quality control [52]. Approximately 25% of these datasets include biliary stents, which introduce bias by inadvertently associating stents with PDAC, distorting AI predictions [53]. Many studies fail to account for such biases, artificially inflating performance metrics and limiting real-world translation. Mitigating these issues requires standardized dataset curation, bias reduction strategies, and rigorous validation across diverse imaging protocols. Ensuring robust generalization across varied patient demographics, imaging protocols, and scanner vendors remains a primary objective. Future efforts must not only emphasize curated multi-institutional datasets but also explore advanced computational strategies such as domain generalization, federated learning, and causality-inspired model architectures [49, 51] to mitigate dataset shift and enhance real-world performance.

Interinstitutional variability in imaging acquisition further limits AI model generalizability. Differences in scanner technology, contrast timing, resolution, and reconstruction techniques create inconsistencies in AI-driven pancreas segmentation and lesion detection. Multi-institutional collaboration is critical to harmonizing imaging protocols and establishing large-scale registries of annotated pre-diagnostic and diagnostic CTs. Open-access repositories and federated learning frameworks can support decentralized AI model training, preserve patient privacy while improving adaptability. However, to truly propel the field towards clinical utility, future data collection efforts require meticulous optimization. This includes establishing standardized, multicentric prospective data registries with harmonized imaging acquisition protocols (including consistent contrast phases, slice thickness, and reconstruction kernels) and structured, granular clinical annotations. Such datasets should ideally capture the full spectrum of disease, from HRIs with normal-appearing pancreases on pre-diagnostic CTs to those with early and late-stage tumors, and crucially, must incorporate longitudinal follow-up with linked genomic, proteomic, and clinical outcomes data. Furthermore, enhancing dataset organization necessitates common data models, robust de-identification protocols that preserve crucial metadata, and Findable, Accessible, Interoperable, Reusable (FAIR) data principles to maximize their value for developing and validating AI tools that meet pressing clinical demands for early and accurate PDA detection.

Clinical adoption of AI requires a multidisciplinary approach, involving radiologists, gastroenterologists, oncologists, and AI experts to refine models and ensure they capture clinically relevant imaging markers. Prospective trials are necessary to validate AI in PDA risk stratification and early detection. Explainability remains a critical concern – black-box models lacking transparency reduce clinician trust and regulatory approval. While techniques like gradient-weighted class activation mapping (Grad-CAM) have been used in some diagnostic PDA models to visualize regions of model focus [39], the development and rigorous validation of more advanced and clinically intuitive XAI methods are crucial for demystifying AI decision-making and fostering widespread clinical adoption. Future AI systems should incorporate heatmaps, uncertainty quantification, and explainable AI methodologies to facilitate clinical integration.

Future Clinical Trial Considerations for AI-Augmented PDA Detection

Validating AI-driven PDA detection requires prospective, multi-institutional trials with risk-stratified cohorts. HRIs, such as those with glycemically defined NOD with END-PAC scores ≥3, should be prioritized. Randomization, while ideal, presents ethical challenges, as withholding AI-augmented imaging from high-risk individuals could delay diagnosis. A dual-cohort design comparing serial AI-enhanced CT imaging versus standard clinical monitoring offers a pragmatic alternative. Primary endpoints should include time-to-diagnosis from glycemically defined NOD onset, while secondary endpoints should evaluate stage at detection, AI specificity versus radiologists, false-positive impact, and overall survival outcomes.

Ethical considerations include radiation exposure, false positives, and incidental findings. Serial imaging must be optimized to balance detection benefits with safety concerns. Bias mitigation is critical to ensure AI models generalize across diverse populations and imaging protocols. Data harmonization efforts, including standardized contrast-enhanced imaging protocols and multi-site validation, will improve AI reproducibility. Passive EMR surveillance of observational cohorts can increase statistical power, enabling a comprehensive evaluation of AI's impact on shifting the diagnostic trajectory toward curative intervention. Integration with biobanking efforts will also support biomarker discovery, expanding AI's role in a broader multimodal PDA detection strategy.

Conclusion

AI-driven imaging has the potential to transform early detection of PDA by identifying pre-diagnostic pancreatic changes, integrating systemic biomarkers, and improving the accuracy of lesion detection. Despite advances in deep learning, major challenges remain, including dataset limitations, interinstitutional imaging variability, and the need for prospective clinical validation. Standardizing data acquisition, ensuring bias mitigation, and improving model interpretability are essential for AI tools to achieve clinical integration. Future efforts should focus on establishing large, multi-institutional datasets, refining AI algorithms to enhance specificity, and conducting prospective trials in high-risk populations to assess clinical impact. AI will require a multidisciplinary approach, leveraging expertise in radiology, oncology, and computational science to optimize early detection strategies and improve patient outcomes.

Conflict of Interest Statement

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Author Contributions

Ajit H. Goenka, MD: conceptualization, writing – original draft, writing – review and editing, and supervision; Ajith Antony, MD, Armin Zarrintan, MD, and Murlidhar Murlidhar, MBBS: data curation, investigation, and writing – original draft; Sovanlal Mukherjee, PhD: writing – review and editing, resources, and supervision; Khurram Bhinder, MBBS: investigation, data curation, and writing – original draft.

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