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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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MINIREVIEWS

Artificial intelligence for pancreatic cancer detection: Recent development and future direction

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Abstract

Artificial intelligence (AI) has been increasingly utilized in medical applications, especially in the field of gastroenterology. AI can assist gastroenterologists in imaging-based testing and prediction of clinical diagnosis, for examples, detecting polyps during colonoscopy, identifying small bowel lesions using capsule endoscopy images, and predicting liver diseases based on clinical parameters. With its high mortality rate, pancreatic cancer can highly benefit from AI since the early detection of small lesion is difficult with conventional imaging techniques and current biomarkers. Endoscopic ultrasound (EUS) is a main diagnostic tool with high sensitivity for pancreatic adenocarcinoma and pancreatic cystic lesion. The standard tumor markers have not been effective for diagnosis. There have been recent research studies in AI application in EUS and novel biomarkers to early detect and differentiate malignant pancreatic lesions. The findings are impressive compared to the available traditional methods. Herein, we aim to explore the utility of AI in EUS and novel serum and cyst fluid biomarkers for pancreatic cancer detection.

Key Words: Artificial intelligence; Machine learning; Deep learning; Endoscopic ultrasound; microRNA; Pancreatic cancer; Pancreatic cyst

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Core Tip: Artificial intelligence (AI) aided endoscopic ultrasound (EUS) and microRNA analyses are sensitive and effective for pancreatic cancer detection with sensitivity of more than 95%. The size of pancreatic lesion does not affect the diagnostic performance by artificial intelligence. This will help overcome the delayed diagnosis and high mortality of pancreatic cancer. Recent studies showed that the speed of AI system in EUS can be performed in real time fashion. This will be adjunctive to the conventional EUS examination for future utility.

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INTRODUCTION

Pancreatic cancer has been notorious for late detection and high mortality rate[1,2]. The main contributing factor is the difficulty of diagnosis from imaging studies[3]. Differentiation between benign disease like chronic pancreatitis and malignancy is challenging[4]. Malignant pancreatic diseases [*i.e.*, pancreatic ductal carcinoma, intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasm] can present differently in radiologic imaging[3]. Endoscopic ultrasound (EUS) has been recognized as an effective method for detecting pancreatic cancer with a reasonable sensitivity but low specificity[5]. Compared to computed tomography (CT) and magnetic resonance imaging (MRI), EUS had a superior performance in small pancreatic tumors[6,7].

The use of computer aided diagnosis for cancer detection has been introduced since 1960[8]. In the past 10 years, the use of artificial intelligence (AI) has been exponentially increased in every field, including medicine[9-11]. Machine learning and deep learning are two major techniques in AI used for analyzing a large dataset and creating a predictive model[12-14]. The advance of AI in gastroenterology field has played an important role in pancreatic cancer regarding detection and survival prediction[15-17].

Given the emerging role of AI in this field, we conducted the systematic review on AI and pancreatic cancer with keywords of "artificial intelligence" and "pancreatic cancer" from PubMed and Institute of Electrical and Electronics Engineers databases. We aim to elaborate the advancement of AI application in pancreatic cancer detection by imaging studies focusing on endoscopic ultrasound and novel serum and cyst fluid marker analysis.

AI CONCEPT AND TERMINOLOGY

AI is the use of mathematical models and computer algorithms to mimic human intelligence. It has been increasingly used to predict risk and diagnose pancreatic cancer with imaging and personal health features[15,18-20]. Most medical AI is considered narrow AI, which focuses on single or limited tasks[19]. There are different AI techniques for creating predictive models, including machine learning and deep learning.

Machine learning is a subfield of AI that uses mathematical techniques to create a predictive model by recognizing patterns in the dataset without being explicitly programmed[18,19]. There are many machine learning algorithms available such as regression, decision trees, k-nearest neighbors, and neural network[21]. Machine learning shows great promise in medical research as it can detect complex patterns in a large dataset that human doctors would likely miss[22,23].

Deep learning, a subfield of machine learning, is basically a neural network with multiple hidden layers (usually a large number) to automatically detect higher-level features of input data. A neural network is also known as artificial neural network. As shown in Figure 1, neural network is a system of interconnected neurons with three type of layers: (1) Input layer; (2) Hidden layer; and (3) Output layer. Each layer

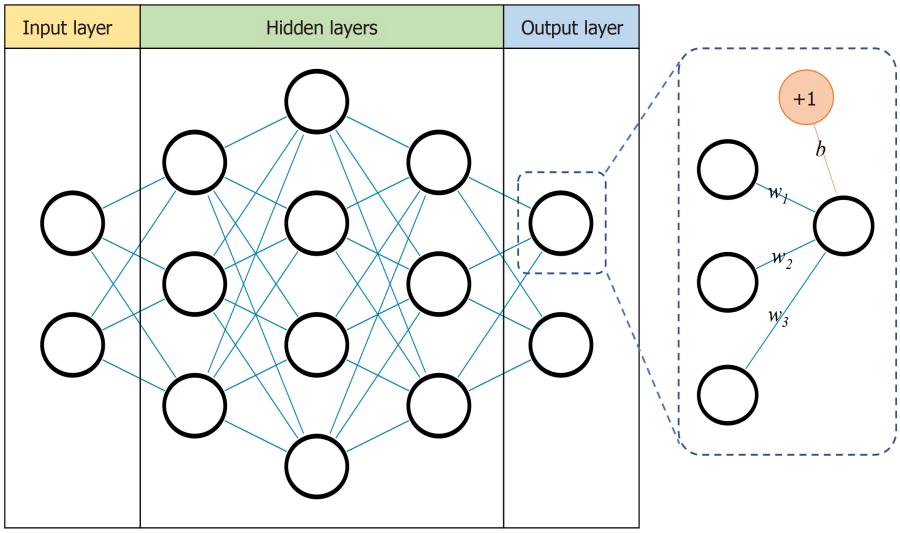

Figure 1 Neural network with input layer, hidden layers, and output layer. Each circle represents a neuron within the network. Within each neuron, weights and bias are applied to the input values to produce an output value. w: Weight; b: Bias.

amplifies certain aspects of the input that are important for discrimination by applying a weight to each input[24,25]. Besides requiring a large and well-annotated dataset, the major drawback of deep learning is a long training time, which could take hours or days. One method that can significantly improve the training time of deep learning is the use specialized hardware such as graphic processing unit or tensor processing unit[26].

A convolutional neural network (CNN) is a class of deep learning that apply a filter to capture the characteristic of the data. In image analysis, CNN use different filters to capture various aspects of the image[27,28]. The most significant advantage of CNN in the medical field is its ability to detect image features automatically and objectively, for instance, the detection of pancreatic cancer based on EUS images[19,29].

Three major types of machine learning problems are supervised learning, unsupervised learning, and reinforcement learning. Most machine learning problems in medicine are supervised learning, in which the response variable must be already known or labeled. To create a predictive model for solving supervised learning problem, the first step is the collection and annotation (label) of input data. The data is then divided into training and testing sets. The training data is used for training machine learning models, including applying different learning algorithms or architectures, optimizing model parameters, and selecting a final predictive model. Once the final predictive model is selected, the model will be evaluated using the testing data to assess the model performance on the data that has not been used before. These are common steps used to create a predictive model for both machine learning and deep learning[21,30]. In fact, the choice of using machine learning or deep learning usually depends on the type of inputs. Typically, CNN-based deep learning is the preferred choice for image classification. Additionally, deep learning model had a higher diagnostic ability than the subjective measurement of tumor feature values (tumor width, shape, and color) by doctors because of its objectivity[31-33].

APPLICATION OF AI IN IMAGING STUDIES FOR PANCREATIC CANCER DETECTION

Modern imaging modalities, including CT scan, MRI, ultrasound, and endoscopy, contain far more visual information than humans can distinguish with the naked eye[18]. Since 2010, significant progress has been achieved in applying AI to the gastroenterology imaging[15]. The pancreas is one of the most challenging organs in CT segmentation. Each patient produces more than 300 images that a radiologist must discern, creating intense reading efforts that sometimes succumb to unavoidable misdiagnosis[34]. Many machine learning and deep learning models have been created to aid physicians in making diagnosis based on medical imaging, including the detection of pancreatic neoplasms. There are two major types of AI systems used in the

detection of cancer: Computer-assisted detection (CADe) and computer-assisted diagnosis (CADx) and they serve different purposes. CADe systems are used for locating lesions in medical images. CADx systems characterize lesions and can distinguish between benign and malignant[35].

COMPUTED TOMOGRAPHY

CADx AI systems have been created with the analysis of segmented CT images of the pancreas. These systems work by creating an experimental group of image data and a control group of image data which are imported into a program. The data is fed through two matrices and a filter, statistics, and other data are applied. Then the pancreatic cancer and the normal control images are distinguished by data processing and statistical analysis[36].

An extension of CADx systems is the use of radiomics in CT images. Radiomics is an AI process that not only answers simple clinical questions (*e.g.*, benign or malignant), but can also be used to extract quantitative imaging features from radiology images to produce more detailed information about the areas of interest (*e.g.*, determining risk of malignancy in pre-malignant lesions)[18]. A study by Wei *et al*[37] used a machine learning based model to determine serous cystic neoplasms from non-serous cystic neoplasms based on 409 quantitative radiomic features from preoperative CT images. The model outperformed clinicians with an area under the receiver operating characteristic curve (AUC) of 0.84.

Segmentation of the pancreas in CT imaging is a difficult but essential task for a successful diagnosis of pancreatic cancer. The main challenges lie in its close proximity to other organs, shape variance and low contrast blurring[27,38-40]. Notably, the ideal type of CT imaging in patients with suspected pancreatic cancer is a contrast-enhanced, multidetector CT, which has sensitivity of 70% to 100% whereas traditional CT has an accuracy of 83.3%, sensitivity of 81.4%, and specificity of 43% for pancreatic adenocarcinoma detection[41].

Liu *et al*[42] used a faster region-based CNN (faster R-CNN) model to form a CADx to solve the challenging pancreas segmentation problem in CT images. Their faster R-CNN model assisted had an AUC of 0.96 and mean average precision of 0.7664, indicating a high discriminating ability and precision. Consequently, the time required to establish a diagnosis using their model was 3 s compared to 8 min by an imaging specialist. Another study used multi-scale segmentation-for-classification to detect pancreatic ductal adenocarcinoma (PDAC). This method functioned by performing tumor segmentation at the same time as tumor classification. This information was helpful for radiologists when determining tumor location. Their method reported a sensitivity of 94.1% and a specificity of 98.5%, implying that their model for tumor segmentation was strong in screening for PDAC[43]. Interestingly, Chu *et al*[44] used random forest algorithm to classify PDAC based on CT images. The overall accuracy, AUC, sensitivity, and specificity were 99.2%, 0.999, 100%, and 98.5%, respectively.

To classify pancreatic cancer, a custom method using a combination of support vector machine and random forest technology was applied to PET/CT images[45]. Their proposed model achieved accuracy of 96.47%, sensitivity of 95.23%, and specificity of 97.51%. They demonstrated that their model outperformed other models based on an external dataset.

MAGNETIC RESONANCE IMAGING

It is challenging to obtain multi-modal MRI images and then effectively fuse the information from these images due to the heterogeneity of the pancreas and the ill-defined tumor boundary[46-48]. PDAC diagnostic value by traditional MRI has an accuracy of 89.1%, sensitivity of 89.5.%, and specificity of 63.4%[41].

Barriers to machine learning algorithm development for MRI include limited availability of MRI data, reduced image quality, and unstandardized nature of MRI[49]. In addition, overfitting can be an issue due to small datasets in MRI and CNN studies[48]. However, CADx systems for the diagnosis of pancreatic cancer have been developed with MRI images. One study used a CNN was used for feature representation for IPMN diagnosis with MRI[47]. This approach led to a 30% improvement in specificity of IPMN diagnosis compared to single modality-based approaches (T1 or T2 imaging). The multi-modal fusion approach for IPMN detection had an accuracy of 82.80%, sensitivity of 83.55%, and specificity of 81.67%. It is only

needed to identify a single slice where pancreatic tissues could be obviously observed. Zhang *et al*[34] used support vector machine in combination with MRI detection to classify pediatric pancreatic cancer; their proposed model achieved a higher accuracy when compared to the normal detection algorithm. Corral *et al*[50] created a CNN which diagnosed intraductal papillary mucinous neoplasm (IPMN) on MRI images in 1.82 s with a sensitivity of 75% and specificity of 78%. Another study by Gao *et al*[51] created a deep learning model that graded pancreatic neuroendocrine tumors using MRI images, reaching an accuracy of 81.1% and AUC of 0.89. In a 2020 retrospective study, the research group assessed baseline CT images from 207 patients with proven PDAC and developed a machine learning model that used radiomics to predict molecular subtypes. The classification algorithm achieved a sensitivity, specificity and ROC-AUC of 0.84, 0.92, and 0.93, respectively[49]. Table 1 demonstrates the studies on CT and MRI of pancreatic cancer.

ULTRASONOGRAPHY

AI is used in transabdominal ultrasonography and endoscopic ultrasonography. In transabdominal ultrasonography, AI is used primarily for detecting liver fibrosis stage and chronic liver disease by using the histogram analysis and RGB-to-stiffness inverse mapping technique[19]. The role of transabdominal ultrasonography for pancreatic cancer detection is very minimal because the pancreas visualization is obscured by bowel gas. Due to this, there are no available studies in the evaluation of pancreatic cancer with transabdominal ultrasound.

ENDOSCOPIC ULTRASOUND

Among MRI, CT, and EUS, only EUS enables observation of the pancreas with high spatial resolution. EUS has higher tumor detection rates than contrast enhanced CT by allowing detection of the echo structure in lesions as small as 1 cm[52]. The sensitivity of EUS is superior to CT scan, 94% and 74%, respectively[5]. However, the accuracy of EUS is currently highly operator dependent.

There are previous studies on the application of AI in EUS for pancreatic cancer detection (Table 2). The overall accuracy of AI based approach were 80%-97% with sensitivity of 83%-100%. The findings are comparable to a sensitivity of 94% by endoscopist driven EUS according to the meta-analysis[5]. The first study of AI based EUS analyzed a single EUS image per patient obtained from the total of 21 patients[53]. Machine and human demonstrated a similar diagnostic performance. However, this study was done before the introduction of modern deep learning framework, which has demonstrated much better performance in general than earlier neural network architecture. Based on the observation that there is an age-related change of pancreas shape, Ozkan *et al*[54] used three different neural network models to classify pancreatic cancer in three age groups: Below 40, 40 to 60, and above 60. As a result, a higher performance was achieved by using a different model for each age group.

There were different techniques being used for image analyses and creating classification models in pancreatic cancer studies, including deep pocket inspection[55], support vector machine[56], region of interest, principal component analysis[57], neural network, and deep learning. We noticed that these requires were evolved with the major progress of AI development; machine learning techniques were used at the beginning and gradually evolved to CNN-based models (deep learning).

Interfering factors associated with misdetection of pancreatic cancer include chronic pancreatitis with more false negative results[4]. The compromised ability of pancreatic cancer detection in patients with chronic pancreatitis decreased to 54%-75%. Tonozuka *et al*[33] found that non-PDAC is the significant factor of misdetection which means the system tends to work towards preventing the overlooking of tumors than overdiagnosis of tumors. On the other hand, tumor size is not associated with misdetection. Thus, AI guided diagnosis can help with early detection of small tumor and prevent the progression of pancreatic cancer. Another consideration is that the control group with a few cases of mass forming pancreatitis makes the results not generalizable to the group of focal pancreatitis (pseudotumorous pancreatitis) as more included in Norton *et al*[53]. The main limitations of prior studies on AI-guided EUS diagnosis are small sample size. Data augmentation has been used to increase the number of images in later study[33]. Slow processing time and low-quality image are other constraints. They hinder the development of this approach to be real time

Table 1 Summary of studies assessing computed tomography and magnetic resonance using artificial intelligence-based approach for pancreatic cancer

Ref.	Overall dataset	Testing data	Model	Model performance on testing data					
				Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CT									
Zhu *et al*[43], 2019 (United States)	439 cases	23 cases	CNN	NA	NA	94.1	98.5	NA	NA
Liu *et al*[42], 2019 (China)	338 patients	100 patients	CNN	NA	0.9632	NA	NA	NA	NA
Chu *et al*[44], 2019 (China)	380 patients	125 patients	ML	99.2%	0.999	100	98.5	NA	NA
Li *et al*[75], 2018 (China)	206 patients	No separate testing data (10-fold CV)	CNN	72.8%[1]	NA	NA	NA	NA	NA
Wei *et al*[37], 2018 (China)	260 patients	60 patients	SVM	NA	0.837	66.7	81.8	NA	NA
MR									
Kaissis *et al*[49], 2020 (Germany)	207 patients	26 patients	ML	NA	0.93	84	92	NA	NA
Corral *et al*[50], 2019 (United States)	139 cases	No separate testing data (10-fold CV)	DL	NA	0.78[1]	92[1]	52%[1]	NA	NA
Gao *et al*[51], 2019 (China)	96 patients	No separate testing data (5-fold CV	DL	85.13[1]	0.9117[1]	NA	NA	NA	NA

[1]The performance was based on n-fold cross-validation on training data.

AUC: Area under the curve; CNN: Convolutional neural network; CT: Computed tomography; CV: Cross-validation; DL: Deep learning; IPMN: Intraductal papillary mucinous neoplasm; MR: Magnetic resonance; NA: Not available; NN: Neural network; NPV: Negative predictive value; PCA: Principal component analysis; PPV: Positive predictive value; SVM: Support vector machine.

analysis. Interestingly, real time EUS video using CNN for pancreas segmentation and station recognition has been studied[58]. The real-time system works as a monitoring safety net and remind endoscopist to make up the unobserved part. It can also increase trainee performance in learning how to detect pancreatic cancer using EUS, which can lead to the reduction of training time and cost.

AI also plays important role in two new EUS techniques, including contrast enhancing EUS (CE-EUS) and EUS elastography. CE-EUS is a technique that uses gas-containing contrast agents intravenously injected for better visualization and differential diagnosis of focal pancreatic lesions. A study found machine learning assisted CE- EUS provided higher sensitivity of 94% compared to 87.5% of qualitative CE-EUS without machine learning aid[59]. EUS elastography is a technique that measure the tissue stiffness, which help differentiate a mass from normal or inflammatory area. The real-time performance of neural network provided comparable efficacy to standard EUS elastography. The predictive performance of EUS elastography is similar to the b-mode EUS with AUCs of 0.94-0.965[60,61].

Regarding a real-time application, Marya *et al*[62] demonstrated the high accuracy of PDAC detection from other pancreatic diseases with AUC of 0.98. The author claimed that the speed of image processing is eligible for real-time system but it was not performed. Future application is warranted which can guide biopsy in patients with diffuse inflammation as chronic pancreatitis to avoid unnecessary biopsies.

AI has not only been studies in PDAC, but also in pancreatic cystic lesions. One study on the differentiation of malignant *vs* benign IPMN by EUS revealed the superior accuracy in identifying malignancy; 94% by AI *vs* 56% by the physician diagnosis performing EUS. However, the AI's prediction on EUS images was not performed during the EUS procedure in a real time. The real-time integration will help aid clinicians to make a clinical judgement[63]. EUS guided needle confocal laser endomicroscopy is a novel technique for pancreatic cystic lesions. A study was conducted in 15027 videos from 35 subjects with IPMN. The CNN algorithm for high grade dysplasia or adenocarcinoma diagnosis had higher sensitivity (83.3% *vs* 55.6%)

Table 2 Summary of endoscopic ultrasound using artificial intelligence-based approach studies pancreatic cancer and malignant pancreatic cyst detection

Ref.	Overall dataset	Testing data	Model	Model performance on testing data					
				Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Marya *et al*[62], 2020 (United States)	583 patients (1174461 images)	123 patients	CNN	NA	0.976	95	91	87	97
Tonozuka *et al*[33], 2020 (Japan)	139 patients (920 images)	47 patients (470 images)	CNN	NA	0.94	92.4	84.1	86.8	90.7
Ozkan *et al*[54], 2016 (Turkey)	332 images	72 images	NN	87.5	NA	83.3	93.33	NA	NA
Saftoiu *et al*[59], 2015 (Multicenter in Europe)	167 cases	15% of cases	NN	NA	NA	94.64	94.44	97.24	89.47
Zhu *et al*[56], 2013 (China)	388 images	50% of all data (200 trials)	SVM	93.86	NA	92.52	93.03	91.75	94.39
Zhang *et al*[55], 2010 (China)	216 patients	50% of all data (50 trials)	SVM	97.98	NA	94.32	99.45	98.65	97.77
Das *et al*[57], 2008 (United States)	319 images	50% of all data	NN	NA	0.93	93	92	87	96
Norton *et al*[53], 2001 (United States)	21 patients	4 patients	ML	80	NA	100	50	NA	NA
Elastography									
Saftoiu *et al*[61], 2012 (Multicenter in Europe)	258 cases	No separate testing data (10-fold CV)	NN	84.27[2]	0.94[2]	87.59[2]	82.94[2]	96.25[2]	57.22[2]
Saftoiu *et al*[60], 2008 (Denmark and Romania)	68 cases	No separate testing data (10-fold CV)	NN	NA	0.957[2]	NA	NA	NA	NA
IPMN									
Machicado *et al*[64], 2021 (United States)[1]	35 cases of EUS-nCLE (15027 frames)	No separate testing data (5-fold CV)	(1) CNN (segmentation); and (2) CNN (holistic)	(1) 82.9[2]; and (2) 85.7[2]	NA	(1) 83.3[2]; and (2) 83.3[2]	(1) 82.4[2]; and (2) 88.2[2]	(1) 83.3[2]; and (2) 88.2[2]	(1) 82.4[2]; and (2) 83.3[2]
Kuwahara *et al*[63], 2019 (Japan)	50 cases	No separate testing data (10-fold CV)	CNN	94[2]	NA	95.7[2]	92.6[2]	91.7[2]	96.2[2]

[1]Presented two designs of CNN algorithms: segmentation based model and holistic based model.
[2]The performance was based on n-fold cross-validation on training data.
AUC: Area under the receiver operating characteristic curve; CE-EUS: Contrast enhanced endoscopic ultrasound; CNN: Convolutional neural network; CV: Cross-validation; EUS-nCLE: Endoscopic ultrasound-guided needle based confocal laser endomicroscopy; IPMN: Intraductal papillary mucinous neoplasm; NA: Not available; NN: Neural network; NPV: Negative predictive value; PCA: Principal component analysis; PPV: Positive predictive value; SVM: Support vector machine.

and accuracy (82.9%-85.7% *vs* 68.6%-74.3%) than the Fukuoka and American Gastroenterology Association diagnostic criteria[64].

APPLICATION OF AI IN BIOMARKER ANALYSIS FOR PANCREATIC CANCER DETECTION

Conventional markers

The most used biomarker in monitoring pancreatic cancer is currently carbohydrate antigen (CA) 19-9[65]. It is usually used in monitoring progression and treatment of

pancreatic cancer due to the low specificity and sensitivity. The combined sensitivity and specificity were 78.2% and 82.8% respectively. The relatively low specificity and sensitivity, and low positive predictive value in asymptomatic patients, would indicate that CA19-9, would be a poor biomarker if applied as a screening test, causing unnecessary and wasteful workups for patients[66]. Another biomarker that has been explored is carcinoembryonic antigen (CEA), which exhibits an even poorer sensitivity and specificity for classifying pancreatic cancer than the CA19-9[65].

Some methods using more targeted screening have been suggested such as using multiple biomarkers together or screening only high-risk populations, but those have yet to be universally defined. A screening model was suggested to separate high risk populations into those with inherited pancreatic cancer and those who are at high risk for non-inherited. Even between those two categories non-inherited high-risk could only narrowed to individuals with new onset diabetes[66]. Using this as an example would still provide for a very large screening population with low sensitivity and specificity if only using CA19-9[67]. Other biomarkers have been identified that are present in early pancreatic adenocarcinoma but none of them alone have produced high enough quality data to prove even non-inferiority *vs* no screening, let alone CA19-9[66,68].

A study utilized neural network for multiple tumor marker analysis (CA19-9, CEA, and CA125) for pancreatic cancer diagnosis in 913 serum specimens. AUCs of neural network derived model was superior to logistic regression model with AUCs of 0.905 and 0.812, respectively. The diagnostic performance of single marker is lower than the AI model with AUCs of CA19-9, CA125, and CEA of 0.845, 0.795, and 0.800, respectively[69].

Kurita *et al*[70] used AI to differentiate between malignant and cystic lesions of the pancreas using a dataset consisting of biomarkers, sex, characteristics of cystic lesion, and cytology. It is worth noting that the authors clearly stated that the deep learning was used, but it is technically a neural network with two hidden layers; each layer contains nine nodes. In terms of discriminating performance of classifiers, their AI approach with an AUC of 0.966 well outperformed CEA (AUC = 0.719) and cytology (AUC = 0.739). Although this study is limited by its low sample size and retrospective nature, it showed that a predictive model based on a combination of biomarkers and other factors could achieve a higher performance in classifying the malignancy status of pancreatic cyst fluid in comparison to the use of single biomarker.

Novel biomarkers

In the past, conventional markers like CEA, CA72-4, CA125, and CA19-9, have been used to identify, differentiate, and monitor pancreatic cyst fluid. CA19-9 and CA125 can be used to assess for if a cyst has mucinous characteristics, while CEA can help to differentiate a malignant cyst from benign cyst[65,70]. Advances in genomic sequencing and identification have introduced the ability to isolate microRNA (miRNA) sequences in pancreatic cyst fluid and serum as potential biomarkers for pancreatic adenocarcinoma.

It was first suggested in 2010, that miRNA could be used as a marker for pancreatic adenocarcinoma. miRNA-21 and miRNA-155 in pancreatic juice were present in statistically significantly higher levels in pancreatic adenocarcinoma as compared to benign pancreatic cysts[71]. miRNA are exosome sequences that, in the setting of pancreatic adenocarcinoma, encode for proteins that are oncogenic or have tumor suppressor function. Several specific miRNAs have been identified to have a higher expression in pancreatic ductal adenocarcinoma, including miRNA-21 and miRNA-155[68]. These miRNAs are detected in the pancreatic juice. miRNAs are mostly expressed in pancreatic cyst fluid, but Yoshizawa *et al*[72] have gone on to examine miRNA in the urine. Looking the ratio of miR-3940-5p/miR-8069 in the urine of patients with pancreatic ductal adenocarcinoma, they found that an elevated ratio with an elevated CA19-9 better predicts pancreatic ductal adenocarcinoma than CA19-9 alone. These studies all examine the viability of miRNA in various types of fluid to detect disease states of the pancreas, none though utilize AI to determine which miRNA may produce the highest yield results. A limitation is that they represent small sample sizes with limited application at a population level.

Several studies have identified several miRNAs that potentially represent significant value in determining malignancy of pancreatic cystic lesion or identifying pancreatic adenocarcinoma at an early stage by AI, but each study has decided which miRNAs to utilize based on identifying and isolating very few sequences. Alizadeh *et al*[73], combined several AI and data mining techniques to best determine the miRNA sequences that have the greatest diagnostic and prognostic capabilities. Particle Swarm Optimization (PSO) and neural network, two forms of AI deep learning, identified a

set of five miRNAs: miR-663, miR-1469, miR-92a-2-5p, miR-125b-1-3p, and miR-532-5p. These were identified from 671 serum samples of patients with pancreatic ductal adenocarcinoma and healthy controls. This model had the greatest AUC score in differentiating pancreatic adenocarcinoma from controls with a sensitivity of 0.93, specificity of 0.92, and accuracy of 0.93.

Cao *et al*[74] employed machine learning to identify two panels of plasma miRNA to distinguish between chronic pancreatitis and pancreatic neoplasm from 361 plasma samples in China. Panel 1 consisted of miR-486-5p, miR-126-3p, and miR-106b-3p, and had an AUC of 0.891. Panel 2 consisted of miR-486-5p, miR-126-3p, miR-106b-3p, miR-938, miR26b-3p, and miR-1285, and had an AUC of 0.889. Both panels had a higher AUC than CA 19-9, which was 0.775.

The most robust path to create a new screening test for pancreatic adenocarcinoma must contain a combination of biomarkers and patient data to maximize both the sensitivity and sensitivity of the test[68,70,71,74]. AI creates the potential to assess patient characteristics, miRNA, and classical biomarkers, which allows for a comprehensive screening analysis of a patient. With the use of neural network and PSO, AI thinks, acts, and analyzes data at much faster speed and in more depth pattern recognition that forms the perfect environment for the development of high yield screening tests that have previously evaded us in diagnosing and screening for pancreatic cancer. Pancreatic juice for multiple exosomes of miRNA that are known to be associated with increased risk for pancreatic cancer, like oncogenes and tumor suppressor mutations, provides the opportunity to examine multiple pancreatic adenocarcinoma biomarkers with one test.

FUTURE PROSPECT

Pancreatic cancer is notorious for late detection. The studies on this area have been conducted mainly to identify the best approach for early detection by imaging studies and biomarkers. The advancement of EUS and the application of AI technology showed a promising performance. The modes of EUS: B-mode and elastography do not provide different accuracy and predictive value for pancreatic cancer. However, no data is available for EUS with contrast enhancement. B-mode which is generally used among centers can be the first step of AI implication. Ultimately, the data of imaging studies, biomarkers, and clinical parameters will be combined to build the sophisticated algorithm and implemented in the electronic medical records where clinicians use it as the predictive tool. There are a few limitations of AI application for EUS. First, the collection of EUS images as the big data is difficult. The collaboration of gastroenterologists, radiologists, and hospital administration will help facilitate the retrieval of images into the system. Multicenter participation is required to create the large dataset of EUS images of which it will optimize the efficiency of AI. The platform of dataset in one institution can be the good example that other centers can adopt and join the group. Second, the root of clinical decision based on AI results is possibly affected by the black box issue (inability to identify the ground of decision). Although there are ways that enable AI to be more interpretable, it is still an active area of research in computer science. Third, the diagnosis is most often made by examination of static images after EUS procedure. Further research on real-time implication of pancreatic malignant lesion diagnosis by AI method is warranted to aid clinician at the examination time to avoid unnecessary biopsy. Regarding biomarkers, although still a mainstay of current practice, the use of singular biomarkers like CA19-9, CEA, and CA-125, may soon become a thing of the past for pancreatic cancer detection. Recent studies showed that moving toward AI aided multiple fluid and serum analysis for biomarkers, like miRNA, potentially provide more sensitive and specific detection. AI not only provides a pathway for the computational, multilayered analysis of multiple patient variables and biomarkers, but also can provide indications for which of those EUS and biomarkers will be highest yield. Combining the knowledge in the field of and the capability of AI introduces a new world of exploration into both screening and diagnosis of pancreatic cancer. AI capabilities allow research to be more finely tuned and the implementation of the most effective method for research into developing screening and diagnostics for pancreatic adenocarcinoma and malignant pancreatic cysts.

CONCLUSION

AI applications for pancreatic cancer has are emerging. New studies come out and showed the promising results of AI in radiological imaging and biomarkers for pancreatic cancer detection. There are still some limitations which need to be addressed in the future studies before incorporating this technology in the clinical practice. The accuracy of AI aided EUS for pancreatic cancer diagnosis is high. However, it has been derived from the small training dataset. The generalizability needs to be considered before using it. Larger studies with population of various pancreatic diseases and third-party validation will demonstrate a greater confidence for adopting AI. For novel biomarkers, our review demonstrated that AI guided analysis of combination of candidate miRNAs have high predictive performance compared to standard tumor markers. The availability of miRNA testing is not widespread in every medical facility. To adopt this implication, further studies on the diagnostic performance are warranted to strongly support the evidence of utility.

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