Review

Artificial intelligence in pancreatic cancer

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Abstract

Pancreatic cancer is the deadliest disease, with a five-year overall survival rate of just 11%. The pancreatic cancer patients diagnosed with early screening have a median overall survival of nearly ten years, compared with 1.5 years for those not diagnosed with early screening. Therefore, early diagnosis and early treatment of pancreatic cancer are particularly critical. However, as a rare disease, the general screening cost of pancreatic cancer is high, the accuracy of existing tumor markers is not enough, and the efficacy of treatment methods is not exact. In terms of early diagnosis, artificial intelligence technology can quickly locate high-risk groups through medical images, pathological examination, biomarkers, and other aspects, then screening pancreatic cancer lesions early. At the same time, the artificial intelligence algorithm can also be used to predict the survival time, recurrence risk, metastasis, and therapy response which could affect the prognosis. In addition, artificial intelligence is widely used in pancreatic cancer health records, estimating medical imaging parameters, developing computer-aided diagnosis systems, etc. Advances in AI applications for pancreatic cancer will require a concerted effort among clinicians, basic scientists, statisticians, and engineers. Although it has some limitations, it will play an essential role in overcoming pancreatic cancer in the foreseeable future due to its mighty computing power.

Key words: Artificial intelligence, machine learning, pancreatic cancer, early detection, prognosis prediction

Introduction

Pancreatic cancer (PC) is the deadliest form of all cancer. The five-year relative survival rate for PC is only 11% in the USA, which is the lowest among all cancers [1]. There were 495773 new cases and 466003 deaths from PC worldwide in 2020, accounting for 2.6% of all new cancer diagnoses and 4.7% of all cancer deaths, respectively [2]. In China, the incidence and mortality of PC among tumors are 2.47% and 3.64%, respectively [3]. The main reason for such a poor prognosis of PC is the late diagnosis, with only about 20% of patients being diagnosed at an early stage. Most patients have non-specific first symptoms, such as jaundice, fatigue, change in bowel habits, and indigestion, that make it difficult to distinguish from non-cancer diseases [4]. Most chemotherapy [5-7], targeted therapy [8], and immunotherapy [9-11] are ineffective because most patients are already in the progressive stage with local invasion and distant metastases at the detection time [12,13]. A multicenter study demonstrated that patients with PC detected by screening had a 5-year survival rate of 73.3% and a median survival time of 9.8 years, compared with 1.5 years for patients with PC seen by non-screening [14]. To diagnose early-stage PC accurately is desperately needed [15,16].

Radiographic imaging-based investigations [17-20] are fundamental techniques in PC screening, including endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), etc. Related techniques based on the above methods, such as EUS-guided fine needle aspiration (FNA) and biopsy (FNB), contrast-enhanced EUS (CE-EUS), CT (CE-CT), MRI (CE-MRI), and positron emission tomography-computed tomography (PET/CT), can further improve the accuracy of diagnosis. However, screening in the asymptomatic population is not
recommended due to the economic burden and the relatively low incidence of PC in the general population [21,22]. Also, early PC lacks biomarkers. Carbohydrate Antigen 19-9 (CA19-9), the best-validated biomarker in PC, does not have enough accuracy and specificity in screening early PC [23,24]. Thus, many scientists are working to develop new early screening methods. Meanwhile, it is also essential to use better ways to assess treatment efficacy and prognosis, which will facilitate the development of appropriate clinical treatment options and critical drugs [25,26].

Artificial intelligence (AI) is a branch of computer science dedicated to producing a new kind of intelligent machine that can respond similarly to human intelligence [27]. Nowadays, many researchers are attempting to apply AI to the medical field, including healthcare [28], oncology [29], cardiology [30], and more. Compared with traditional biometric methods, AI has greater flexibility and scalability, which allows it to be deployed for many tasks. Another advantage is its ability to integrate a large number of different data types and understand complex relationships between variables in a flexible, trainable manner. As the scale of medical data continues to expand and computer computing power continues to improve, AI is showing more and more advantages in processing big data. In clinical practice, AI can perform routine tasks consistently, freeing up physicians' time to solve more complex clinical problems [27,31]. For PC, AI-assisted diagnostic techniques are also gaining more attention. The 2020 AI and Early Detection of Pancreatic Cancer Virtual Summit discussed and highlighted the potential of AI in the early diagnosis of PC [32]. In the recent meeting of The Alliance of Pancreatic Cancer Consortia, the discussion focused on imaging methods and the use of AI for the early detection of PC [33].

Despite the unparalleled advantages of AI, there are still many concerns about its application in the clinical field. For example, no one model can solve all problems, and all models have their range of adaptation [34]. There is a risk that AI algorithms may ignore specific differences, such as gender and race, which can lead to bias because of the heterogeneity between the training set and other patients [35-37]. AI also faces many ethical issues in clinical practice, such as the need for researchers and healthcare organizations to protect data from hacking for patient privacy. Healthcare systems should strive to ensure that the benefits of AI are passed on to all patients they serve, not just those with access to more resources. Also, it is difficult to assign liability for medical malpractice arising from defects in AI [37,38]. In addition, AI's transparency and interpretability are challenged by factors such as patient privacy, algorithm interpretability, publication bias, etc. [39,40]. Most of the AI devices approved by the FDA have only undergone retrospective studies. The lack of prospective studies may lead to unexpected conditions during the clinical application of AI devices [41,42]. Solving these problems is a key point for the future of AI in clinical applications.

In this review, using "artificial intelligence", "machine learning", and "pancreatic cancer" as the keywords, we searched the relevant literature published by July 2022 in PubMed, Embase, Web of Science, and other databases. We summarized the application of AI in several aspects of PC. Compared with the existing studies, our review summarizes more comprehensively [43,44]. We outlined how AI could help in medical image analysis, pathological examination, and biomarkers in the tumor diagnosis process. In prognosis respect, the AI analysis includes survival time, recurrence risk, metastasis, and therapy response. Finally, we summarized the current status of AI in PC and discussed the future challenges and directions for the field.

State-of-the-art AI Algorithms involved in Pancreatic Cancer

Machine Learning

Machine learning (ML) is a subfield of AI that solves the problem of how to build computers that improve automatically through experience (Figure 1). Based on a large amount of feature data, ML can use specific algorithms to learn how to accomplish a task [45]. In today's medical field, there is a massive amount of data generated every day, and it becomes a challenge to integrate this data to make predictions. The most significant advantage of ML is the ability to integrate vast amounts of data and combine the observed and predicted quantities in nonlinear and highly interactive ways [46]. ML techniques can be broadly classified based on the type of labels. Based on labels, machine learning can be classified as supervised, unsupervised, semi-supervised, and reinforcement learning. There is also ensemble learning that integrates multiple algorithms (Figure 2A-2E).

Receiver operating characteristics (ROC) curves help organize ML classifiers and visualize their performance. ROC curve is a line graph plotted with sensitivity as the vertical coordinate and (1-specificity) as the horizontal coordinate. The area under the ROC curve (AUC) is the evaluation metric, and the larger the AUC value, the better the corresponding algorithm performs [47]. Other metrics, including accuracy, sensitivity, specificity, F1-Score, positive
predictive value (PPV), and negative predictive value (NPV), are also commonly used to evaluate the result of the ML [48].

**Supervised Learning**

Supervised learning is constructing a model in which each observation vector has a corresponding response variable. In other words, all data is labeled. By fitting a model that relates responses to predictors, supervised learning can accurately predict future observed responses or better understand the relationship between responses and predictors [49,50]. Examples of such algorithms include Logistic Regressions (LR), Decision Trees (DT), Support Vector Machines (SVM), Naïve Bayes (NB), Artificial Neural Networks (ANN), etc., and the best application scenario for each algorithm varies [51]. In this review, most of the algorithms used in PC are supervised learning. A typical application of supervised learning algorithms is the precise diagnosis, including detection, grading, and differential diagnosis, using radiomics, digital pathology slides, or biomarkers. The prognosis of PC is also widely used to predict survival time, recurrence rate, metastasis, and therapy response.

**Unsupervised Learning**

Unsupervised learning means we can know the observation vector, not the associated response. In other words, all data is unlabeled. Using the observation vector’s data makes it possible to perform clustering, correlation evaluation, dimensionality reduction, etc. [50,52]. Examples of such algorithms include K-mean clustering [53], Principal Component Analysis (PCA) [54], Non-negative Matrix Factorization (NMF) [55], etc. The application of unsupervised learning in PC is relatively rare, but there have been attempts to do so, including classification [56], feature extraction of CT images [57,58] or pathological slides [59], and estimation of medical imaging parameters [60].

**Semi-supervised Learning**

As its name suggests, semi-supervised learning is somewhere between supervised and unsupervised learning, allowing the use of large amounts of available unlabeled data in combination with small labeled datasets in many use cases. Semi-supervised learning can utilize a small amount of labeled data to obtain better performance than supervised learning while utilizing less labeled data to achieve the same level of performance close to that of supervised learning [61,62]. Examples of such algorithms include generative models, self-training, co-training, graph-based learning, Semi-supervised support vector machines, etc. [61,63].

The application of semi-supervised learning is mostly seen in medical imaging. Supervised learning algorithms may lack annotated data because annotation of medical imaging data is time-consuming and requires a high level of expertise. By using semi-supervised learning algorithms, the task of segmentation or diagnosis using medical images can be accomplished with fewer annotations [64]. For example, CT images of PC can be used for segmentation and diagnosis [65].

![Deep Learning, Machine Learning, Artificial Intelligence](https://www.thno.org)

**Figure 1.** The relationship between artificial intelligence, machine learning, and deep learning. Artificial intelligence refers to the use of machines to simulate human intelligence. Machine learning is a subfield of artificial intelligence, which mainly studies how to simulate or realize the learning function in human intelligence. The deep learning model is a subset of machine learning, which is a model combining multi-layer neural networks.
Reinforcement Learning

The reinforcement learning process is guided by a specific goal. Agents interact with the unknown environment and get reward or punishment feedback from the environment. Then, it uses this feedback to train itself and collect experience and knowledge about the environment to achieve specific goals [66]. Reinforcement learning can also be combined with deep learning to become deep reinforcement learning. It uses dynamic data and labels to bring feedback signals into the learning process rather than constructed, static dataset labels as in traditional machine learning [67].
Reinforcement learning algorithms are commonly used in decision-making in the medical field. Due to the heterogeneity of patients’ conditions and treatment responses, it is challenging to realize precision medicine. Reinforcement learning can construct dynamic treatment regimens that consider the immediate effect of treatment and the long-term benefit to the patient [68,69]. For PC, reinforcement learning algorithms can generate high-quality treatment plans for pancreas stereotactic body radiation therapy (SBRT) to achieve optimal metering distribution [70].

**Ensemble Learning**

Rather than a single algorithm, ensemble learning seamlessly integrates various machine learning algorithms into a unified framework, typically for supervised learning. Specifically, ensemble learning samples the data and produces prediction results using multiple learners. The above results are combined, and the errors of individual learners are potentially compensated by other learners, resulting in better prediction performance [71,72]. Depending on whether the different learners are independent of each other, the ensemble approach can be divided into two main frameworks: the dependent and independent [71]. The output of each learner of the dependent framework affects the next learner, which is represented by AdaBoost in the “Boosting” algorithm [73]. In an independent framework, individual learners can output in parallel, which is represented by Random Forest (RF) in the “Bagging” algorithm [74]. Both dependent and independent frameworks have applications in diagnosing [75-77] and prognosis [78-81] PC.

**Deep Learning**

Deep learning (DL) is a subset of ML algorithms (Figure 1). It allows a machine to feed raw data and automatically build complex concepts. Take image recognition as an example. The mapping from many different pixels to an image is very complex. DL solves this difficulty by decomposing the complex mappings required to recognize an image into a series of simple nested mappings. The algorithm can be divided into one visible layer and several hidden layers. The visible layer is where the image is fed, while hidden layers are where the algorithm gradually extracts the features from the image [82,83]. Compared to shallow ML and traditional data analysis methods, DL models have superior performance in many applications, especially in domains with extensive and high-dimensional data. However, shallow ML performs better for low-dimensional data, especially when a limited training set [84]. With the significant development of computer technology, many DL algorithms, such as Convolutional Neural Networks (CNN), Recurrent Neural Networks (RNN), MultiLayer Perceptron (MLP), Generative Adversarial Networks (GAN), and Deep Belief Networks (DBN), have been widely used in the field of oncology (Figure 3) [85-87].

**AI in Tumor Diagnosis Process**

Reading medical images to make judgments is essentially a problem of recognizing complex
patterns, which computers can be trained using ML models to achieve efficient and repeatable recognition. AI can play a role in several steps in medical image-based PC diagnosis, including image reconstruction, segmentation, and detection, characterization, grading of pancreatic disease based on image features. Using similar techniques, AI can also identify digitized histopathology slides. It can potentially improve the accuracy, reproducibility, and efficiency of diagnosis using histological sections. In addition, the computer can analyze biomarker information with high throughput and accuracy, thus identifying tumor-related biomarkers more efficiently and using this information for diagnosis.

**AI in Medical images-based diagnosis**

Imaging techniques play an essential role in the diagnosis of PC. Current clinical imaging modalities include EUS, CT, MRI, and PET, with different advantages and disadvantages in clinical applications (Table 1). In the traditional process of medical image analysis, experienced radiologists are required. With AI technology, it is possible to free imaging physicians from tedious and repetitive labor to handle tasks that require more creativity.

**Table 1. Advantages and disadvantages of imaging modalities for pancreatic cancer**

| Modality | Advantages | Disadvantages |
|----------|------------|---------------|
| EUS      | High-resolution; Useful in tissue sampling | Invasive; Operator dependent |
| CT       | High spatial resolution; Widely available | Poor contrast resolution |
| MRI      | High contrast resolution; High sensitivity to small tumor and metastasis | Limited availability; Image artifacts |
| PET      | Provides functional metabolic information | Poor spatial and contrast resolution; Physiological FDG uptake disturbance |

Radiomics refers to the high-throughput extraction of many image features from radiographic images, which may be challenging to recognize or quantify by the human eye. Radiomics can be used to identify lesions, allowing for early detection and diagnosis of disease. Also, radiological features can predict prognoses, such as survival, tumor metastasis, and treatment response, and correlate with genomic, transcriptomic, or proteomic features [88-91]. Conventional workflow in radiomics usually contains four steps: image acquisition, segmentation, feature extraction, and analysis [92]. For image acquisition, standard protocols are needed to minimize confounding variables [93]. Segmentation involves identifying the images’ regions of interest (ROIs) and defining the boundaries in the pictures. While this step can be done manually by practiced radiologists, many ML methods have been used for image segmentation [88,94,95]. The dice similarity coefficient (DSC), used to measure the similarity of two sets, is the most used metric in evaluating segmentation performances. In some research, segmentation performances also used Hausdorff distance and intersection over union for evaluation [96]. The next step is extracting radiomics features from ROIs, including histogram-based, texture-based, model-based, transform-based, and shape-based features. Radiomic features are usually numerous, highly correlated, and redundant features that need to be filtered out before they can be used for model building [91,94]. The final step is to build a predictive model using ML and evaluate the model’s performance.

**Endoscopic Ultrasound**

EUS is widely used in diagnosing pancreatic lesions because it provides high-resolution images of the pancreas without being disrupted by gas, bone, or subcutaneous fat. EUS and its related techniques, such as CE-EUS and EUS elastography, show high specificity and sensitivity in diagnosing pancreatic diseases. Furthermore, it is frequently used to identify regional lymph nodes and assess the relationship of tumors to nearby vascular structures [19,97]. In addition, EUS can guide tissue sampling to obtain pathological information about the cancerous tissue [20,98]. The disadvantage is that EUS is an invasive procedure with a risk of pancreatitis or bleeding. The method is also demanding on the operator, and improper handling may reduce the accuracy of the diagnosis [99,100]. As early as 2001, scientists had researched using neural networks to enhance EUS to detect and diagnose PC. Many studies have emerged in recent years (Table 2) [101-112].

AI in EUS is frequently used to aid in the differential diagnosis of PC and other conditions. In our statistics, a few studies applied AI in the differential diagnosis of PC. The overall AUC, accuracy, sensitivity, and specificity were 0.940-0.986, 80%-98.26%, 87.59%-100%, 50%-93.38%, respectively [101-109]. Udriştoiu et al. combined CNN and long short-term memory (LSTM) neural networks to construct an ML algorithm for differential diagnosis of focal pancreatic masses, using multi-sequences EUS (grayscale, color Doppler, arterial and venous phase contrast-enhancement, and elastography). Their model achieved high AUC and accuracy among the studies [105]. Kuwahara et al. used CNN (ResNet-50) in turn to extract image features and distinguish between benign and malignant intraductal papillary mucinous neoplasm (IPMN) [110].
The physician can also use AI in EUS for pancreas segmentation. Iwasa et al. analyzed 100 patients with different PC. Segmentation was performed using U-Net with 100 epochs and was evaluated with 4-fold cross-validation. The median intersection over the union of all cases was 0.77 [111].

Zhang et al. developed a station classification model and a pancreas segmentation model for EUS training and quality control. The DSC of the pancreas segmentation model was 71.5%, and the accuracy of the station recognition model reached 82.4% [112].

### Computed Tomography

CT is the dominant imaging modality for diagnosing and staging PC, which is more widely available and less expensive than other imaging modalities. Due to the high spatial resolution of CT, it can be used for diagnosing and staging the tumor, identifying vascular involvement, tumor resectability analysis, etc. However, the tumor may not be visible due to the poor contrast resolution of CT. With the use of multiplanar reformations, 3D techniques, and spatial and temporal resolution improvement, CT has achieved high sensitivity (96%) in tumor identification [18,97]. AI can assist CT-based diagnosis in many ways, including pancreas segmentation, diagnosis and staging of PC, differential diagnosis, and resectability analysis (summarized in Table 3).

In our statistics, several studies focused on PC or PC precursor lesions diagnosis or prediction by AI-assisted CT. Their AUC, accuracy, sensitivity, specificity were 0.79-0.999, 77.66%-99.2%, 76.64%-100%, 85.59%-98.5%, respectively [113-122]. The method of Chu et al. [120] has the highest accuracy (99.2%) among the studies. 190 pancreatic ductal adenocarcinoma (PDAC) patients and 190 healthy control cases with 64-MDCT scans were included, and 0.75-mm slices of venous phase images were chosen for segmentation and radiomics analysis. Images were manually segmented, and their features were extracted by a binary mask and selected by minimum-redundancy maximum-relevancy feature selection. Finally, an RF classifier was constructed to classify PDAC from the normal pancreas. All of the PDAC cases were correctly classified. Only one normal case from a renal donor was classified as PDAC, giving an AUC of 0.999, an accuracy of 99.2%, a sensitivity of 100% and a specificity of 98.5%.

Some studies focused on the differential diagnosis of pancreatic disease. Ikeda et al. investigated a neural network classifier for the differential diagnosis of PDAC and mass-forming pancreatitis, with an AUC of 0.866 [123]. Chen et al. combined imaging features and enhanced CT texture analysis. Then they used LASSO and RFE_LinearSVC algorithms to select features to differentiate pancreatic serous cystadenomas (SCN) from pancreatic mucinous cystadenomas (MCN), with an AUC of 0.932 [124]. Ren et al. extracted 792 radiomics features from the late arterial and portal venous phases of CE-CT. They then used an RF classifier for differential diagnosis between pancreatic adenosquamous carcinoma (PASC) and PDAC and achieved an AUC of 0.98 [125]. Xie et al. extracted and screened ten optimal imaging features and applied an RF algorithm to build a Rad-score to discriminate between MCN and atypical SCN. The method achieved an AUC of 0.97 [126]. Li et al. extracted 1409 features from 65 patients with PDAC and 20 patients with CP, using the optimal features to build an RF to achieve an AUC of 0.968.
radiomics features from the portal phase of multidetector computed tomography (MDCT). After removing irrelevant features and Bonferroni correction, four features by LASSO regression were still significantly associated with focal-type autoimmune pancreatitis (AIP) and PDAC. The LASSO logistic regression formula was used to obtain the rad-score for discriminating focal-type AIP from PDAC (AUC 0.97) [127]. In addition to using traditional algorithms (PyRadiomics), Ziegelmayer et al. used deep CNN for radiomics feature extraction. For the prediction of AIP or PDAC, an extremely randomized tree classifier was fit on the extracted features with an AUC of 0.90 [128]. Yang et al. adopted the RF method to construct a diagnostic prediction model based on textural parameters of CE-CT images to discriminate between SCN and MCN [129].

Table 3. Application of AI based on CT in the differential diagnosis of pancreatic cancer and other pancreatic tumors

| Reference | Sample size | Data source | Algorithms | Aim | Best result |
|-----------|-------------|-------------|------------|-----|-------------|
| Ma et al. [113] | 3494 images from 190 cases | CE-CT | CNN | PC diagnosis | Accuracy (95.47%), Sensitivity (91.58%), Specificity (98.27%) |
| Liu et al. [114] | 338 cases | CE-CT | faster R-CNN | PC diagnosis | AUC (0.903), Precision (76.64%) |
| Si et al. [115] | 143,945 images from 319 cases | CE-CT | ResNet18, U-net32, ResNet34 | PC diagnosis | AUC (0.871), Accuracy (82.7%), Sensitivity (86.8%), Specificity (69.5%) |
| Qiu et al. [116] | 312 cases | Plain CT | MSTA architecture, SVM | PDAC diagnosis | AUC (0.88), Accuracy (81.19%), Sensitivity (76.64%), Specificity (85.59%) |
| Qureshi et al. [117] | 216 cases | CE-CT | RFE, NB | PDAC prediction | Accuracy (86%) |
| Ebrahimian et al. [118] | 103 cases | DECT | RF | Benign vs Malignant Pancreatic Lesions | AUC (0.94), Accuracy (89%), Sensitivity (90%), Specificity (88%) |
| Chakraborty et al. [119] | 103 cases | CE-CT | RF, SVM | Predict High Risk IPMN | AUC (0.81) |
| Chu et al. [120] | 380 cases | MDCT | RF | PDAC detection | AUC (0.999), Accuracy (99.2%), Sensitivity (100%), Specificity (98.5%) |
| Mukherjee et al. [121] | 420 cases | CE-CT | KNN, SVM, RF, and XGBoost | PDAC prediction | AUC (0.98), Accuracy (92.2%), Sensitivity (95.5%), Specificity (90.3%) |
| Polk et al. [122] | 51 cases | CE-CT | LR | IPMN malignancy prediction | AUC (0.93) |
| Ikeda et al. [123] | 71 cases | CE-CT | NN | PDAC vs mass-forming pancreatitis | AUC (0.916) |
| Chen et al. [124] | 100 cases | CE-CT | LASSO, SVM (RFE, LinearSVC) | SCN vs MCN | AUC (0.932), Sensitivity (87.5%), Specificity (82.4%) |
| Ren et al. [125] | 112 cases | CE-CT | RF | PASC vs PDAC | AUC (0.98), Accuracy (94.5%), Sensitivity (98.3%), Specificity (90.1%), PPV (91.9%), NPV (97.8%) |
| Xie et al. [126] | 216 cases | CE-CT | RF | MCN vs atypical SCN | AUC (0.734), Accuracy (72.8%), Sensitivity (74.8%), Specificity (70.5%), PPV (73.2%), NPV (79.8%) |
| Li et al. [127] | 97 cases | MDCT | LASSO regression | focal-type AIP vs PDAC | AUC (0.97), Accuracy (94%), Sensitivity (95%), Specificity (93%) |
| Ziegelmayer et al. [128] | 86 cases | CE-CT | Deep CNN+ Extremely Randomized Trees | AIP vs PDAC | AUC (0.90), Sensitivity (89%), Specificity (83%) |
| Yang et al. [129] | 78 cases | CE-CT | RF+ LASSO | MCN vs SCN | AUC (0.77), Accuracy (85%), Sensitivity (85%), Specificity (83%) |
| Gao et al. [143] | 170 cases | CE-CT | mRMR+ LASSO | MCN vs SCN | AUC (0.91), Accuracy (85%), Sensitivity (92%), Specificity (81%) |
| Panda et al. [130] | 1917 images | Venous phase CT | 3D CNN | Pancreas segmentation | DSC (91%), HD (0.15mm) |
| Mahmoudi et al. [131] | 157 cases | CT | 3D CNN, U-Net, TauNet | PDAC segmentation | DSC (60.6%), Precision (57.8%), Recall (78.0%), HD (3.71mm) |
| Huang et al. [132] | 170 cases | CE-CT | U-net | PNET segmentation, grading and volumetry | DSC (81.8%), AUC (0.87) |
| Lim et al. [133] | 1006 cases | CE-CT | 3D U-Net | Pancreas segmentation and volumetry | DSC (84.2%), Precision (86.9%), Recall (84.2%) |
| Boers et al. [134] | 1995 images | Venous phase CT | 3D U-net | Pancreas segmentation | DSC (78.1%) |
| Xie et al. [135] | 82 cases | CE-CT | RSTN | Pancreas segmentation | DSC (84.53%) |
| Wang et al. [65] | 800 images | Venous phase CT | IGA-Net | Pancreas segmentation; NP vs PDAC | DSC (60.29%), Sensitivity (99.75%), Specificity (96.50%) |
| Zhou et al. [136] | 14 cases | 4DCT | ResNet-50, FPN | Tumor positioning | DSC (98%) |
| Abel et al. [137] | 221 images | Venous phase CT | mNet | PCL detection | Sensitivity (78.8%) |
| Lyu et al. [138] | 47 cases | CE-CT | DLIR-H | PC resectability prediction | AUC (0.91), Sensitivity (97%), Specificity (87%) |
| Chang et al. [139] | 401 cases | CE-CT | SVM+ LASSO | PDAC grading | AUC (0.961), Accuracy (90.1%), Sensitivity (88.6%), Specificity (91.7%), PPV (92.1%), NPV (88.0%) |
| Luo et al. [140] | 112 cases | CE-CT | CNN | PNET grading | AUC (0.82), Accuracy (82.1%), Sensitivity (88.3%), Specificity (84.6%) |
| Wan et al. [57] | 137 cases | CE | SAE+ mRMR+ SVM | PNET grading | AUC (0.715, SAE-based model), (0.771, hybrid feature-based model) |
| Wan et al. [58] | 114 cases | CE | SAE+ SVM/MLR/ANN | PNET grading | AUC (0.845, SVM) (0.856, MLR) (1.00, ANN) |

Abbreviations: 4DCT: four dimensions CT; AIP: autoimmune pancreatitis; ANN: artificial neural network; AUC: area under the curve; CE-CT: contrast-enhanced CT; CNN: convolutional neural network; CT: computed tomography; DECT: dual energy CT; DLIR: deep learning image reconstruction; DSC: dice similarity coefficient; FPN: feature pyramid network; HD: Hausdorff distance; IGA-Net: Inductive Attention Guidance Network; IPMN: intraductal papillary mucinous neoplasm; KNN: k-nearest neighbor; LASSO: least absolute shrinkage and selection operator; MCN: pancreatic mucinous cystadenoma; MDCT: multidetector CT; MLR: multivariable logistic regression; mRMR: minimum redundancy; MSTA: multiresolution-statistical texture analysis; NP: normal pancreas; PDAC: pancreatic ductal adenocarcinoma; PCL: pancreatic cystic lesion; PNET: pancreatic neuroendocrine tumor; RF: random forest; RF: recursive feature elimination; RSTN: recursive feature elimination; SAE: sparse autoencoder; SCN: pancreatic serous cystadenoma; SVM: support vector machine.
Several studies used AI-assisted CT for pancreas or PC segmentation. Their DSCs ranged from 60.6% to 91% [65,130-135]. Panda et al. developed a two-stage 3D CNN model based on a modified U-net architecture. 1917 portal venous phase CT scans with normal pancreas were used for training, validation, and testing. The mean DSC of their method was 91%, the highest among the studies. The authors also demonstrated that their approach could be applied to CT images containing PC (mean DSC=0.96) [130]. Zhou et al. developed a 4DCT-based method for tumor positioning without pancreas segmentation. Using 4DCT, they built a digitally reconstructed radiograph dataset for each patient, with clinical target volume (CTV) contours labeled. Then the datasets trained the ResNet and FPN algorithm to predict CTV. DSC of their method was 98%, which shows the accuracy of the positioning [136].

For other applications of AI in CT, Abel et al. developed and evaluated an algorithm based on a two-step nnU-Net architecture for automated detection of pancreatic cystic lesions (PCL) in CT [137]. Lyu et al. used high strength levels of the DL image reconstruction (DLIR-H) algorithm to predict the resectability of PC [138]. Chang et al. extracted radiomics features of CE-CT images by the SVM model and generated a radiomics signature by the LASSO model for the preoperative prediction of histological grades of PDAC. The radiomics signature for the training set and external validation data had an AUC of 0.961 and 0.770, respectively [139]. Luo et al. built a CNN-based model to analyze CE-CT images for pancreatic neuroendocrine neoplasms (PNET) grading [140]. Wan et al. built handcrafted, SAE, and hybrid features-based SVM prediction models for PNET grading. Among them, the hybrid feature model performs best (AUC 0.771) [57].

In addition to using CT image features to aid the precise diagnosis of PC, some studies attempted to improve CT image quality. Ohira et al. constructed a deep CNN that generates virtual monochromatic images from single-energy computed tomography (SECT) images for improved PC imaging quality [141]. Noda et al. used a DL image reconstruction algorithm to reconstruct dual-energy computed tomography images, thus assisting PC diagnosis [142].

### Magnetic Resonance Imaging

MRI is of great value in diagnosing PC due to its ability to collect many types and superior soft-tissue contrast. The best application circumstances for MRI include: (1) detection of small non-contour-deforming tumors, (2) evaluation of local extension and vascular encasement, and (3) determination of lymph node, liver, and peritoneal metastases [17,144]. However, MRI is usually more expensive than CT. Also, metal implants may cause image artifacts and hinder imaging [145]. The applications of AI in MRI-based diagnosis include pancreas segmentation, PC classification, and grading (summarized in Table 4) [56,146-152].

Li et al. collected four modalities of MRI for PC segmentation. Since MRI image labeling is time-consuming and laborious, they attempted to train the algorithm on labeled MRI images in one

### Table 4. AI-based on MRI is applied in the differential diagnosis of pancreatic cancer and other pancreatic tumors

| Reference | Sample size | Data source | Algorithms | Aim | Best result |
|-----------|-------------|-------------|------------|-----|-------------|
| Li et al. [146] | 267 samples from 4 modalities (T1, T2, T2, DWI, 68, DWI, 68, AP; 64) | T1, T2, DWI, AP MRI | UDA+ meta learning+ GCN | PC segmentation | DSC (62.08%, T1), (61.35%, T2), (61.88%, DWI), (60.43%, AP) |
| Chen et al. [147] | 73 cases | multi-sequences MRI | Spiral-ResUNet | PC segmentation | DSC (65.60%), Jaccard index (49.64%), HD (7.27mm), Recall (76.69%), Precision (62.96%) |
| Li et al. [148] | 56 DCE MRI sets | DCE MRI | CNN (SGDM) | PDAC segmentation | DSC (71%), HD (7.36mm), MSD (1.78mm) |
| Goldenberg et al. [149] | 30 mouse models | T1 relaxation, CEST, and DCE MRI | SVM | PC classification | Accuracy (87.5%), CEST (85.1%), DCE |
| Cui et al. [150] | 202 cases | T1-w, T2-w, CET1-w MRI | LA8SSO | BD-IPMN grading | AUC (0.903), Specificity (94.8%), Sensitivity (73.4%) |
| Corral et al. [151] | 139 cases | multi-sequences MRI | CNN | IPMN classification | AUC (0.783), Specificity (75%), Specificity (78%), PPV (73%), NPV (81%) |
| Hussein et al. [56] | 171 cases | T2 MRI | SVM, RF, 3D CNN | IPMN classification | Unsupervised: Accuracy (58.04%), Sensitivity (58.61%), Specificity (41.67%); Supervised: Accuracy (84.22%), Sensitivity (97.2%), Specificity (46.5%) |
| Cheng et al. [132] | 60 cases | CE-CT, T2 MRI | LR, SVM | Malignant IPMN prediction | MRI+SVM: AUC (0.940), Accuracy (86.7%), Sensitivity (95.7%), Specificity (81.1%), PPV (73.5%), NPV (96.8%) |

**Abbreviations:** AUC: area under the curve; BD-IPMN: branching type IPMN; CEST: chemical exchange saturation transfer; CNN: convolutional neural network; DCE: dynamic contrast enhancement; DSC: dice similarity coefficient; GCN: Graph Convolutional Networks; HD: Hausdorff distance; IPMN: intraductal papillary mucinous neoplasm; LR: logistic regression; MLP: multilayer perceptron; MSD: mean surface distance; NPV: negative predictive value; PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; PPV: positive predictive value; RF: random forest; SGDM: stochastic gradient descent with momentum; SVM: support vector machine; UDA: unsupervised domain adaptation; AP MRI: atrial phase MRI; DWI: diffusion weighted imaging.
modality and test the model’s performance in another modality to achieve unsupervised labeling of MRI images. The DSC of their methods on different models are 62.08% (T1), 61.35% (T2), 61.88% (DWI), and 60.43% (AP) [146]. To achieve pancreas segmentation, Chen et al. developed a spiral-transformation algorithm to map 3D images onto a 2D plane. Combined with U-Net, their method has a relatively high mean DSC (65.60%) [147]. Liang et al. trained the CNN with Stochastic Gradient Descent with Momentum algorithm, and their method got 71% DSC [148].

Four teams used AI-assisted MRI to classify or grade PC. Goldenberg et al. built three groups of tumor models with different types of PDAC cells. The method of support vector machine predicted the correct tumor model with 87.5% (CEST MRI) and 85.1% accuracy (DCE MRI) [149]. Cui et al. used multivariate logistic regression to analyze the extracted MRI image features, and the AUC of their method was 0.903 [150]. Corral et al. used a CNN to classify IPMN. Sensitivity and specificity to identify high-grade dysplasia or cancer were 75% and 78%, respectively. Moreover, the AUC was 0.78 [151]. Hussein et al. were among the few teams using an unsupervised learning algorithm. 3D CNN was used to classify IPMN. Their method’s accuracy, sensitivity, and specificity were 58.04%, 58.61%, and 41.67% [56].

Cheng et al. compared the predictive value of two medical imaging methods for predicting malignant IPMN. Radiomics features were extracted from arterial and venous phase images of CT and T2-weighted images of MRI, respectively. The LASSO algorithm was used for feature selection, and LR and SVM algorithms were applied to construct radiomics models. The results show that the MRI-based model (AUC 0.940) has a better performance compared to the CT-based model (AUC 0.864) [152].

### Positron Emission Tomography

Positron Emission Tomography (PET) is a molecular imaging technique that has a vital role in diagnosing and staging tumors (Table 5). In combination with CT technology, PET/CT can help localize functional abnormalities and provide information on the biological characteristics of the tumors, such as metabolism, hypoxia, and proliferation [153,154]. Fluorine 18-fluorodeoxyglucose (FDG), a glucose analogue, is the most widely used radiotracer in PET. However, glucose metabolism is not specific, and physiological uptake of FDG by inflamed tissues may lead to false-positive results [155]. Also, FDG intake is reduced in patients with hyperglycemia, leading to a false negative result [156]. For PC, FDG-PET is more sensitive than CT for treatment monitoring after radiotherapy and description of recurrence after tumor resection [17].

| Reference | Sample Size | Data Source | Algorithm | Aim | Best result |
|-----------|-------------|-------------|-----------|-----|-------------|
| Li et al. [75] | 80 cases | PET/CT | HFB-SVM-RF | PC diagnosis | Accuracy (96.47%), Sensitivity (95.25%), Specificity (97.51%) |
| Liu et al. [157] | 112 cases | PET/CT | SVM | PDAC vs AIP | AUC (0.9668), Accuracy (89.91%), Sensitivity (85.31%), Specificity (96.04%) |
| Zhang et al. [158] | 114 cases | PET/CT | RF, adaptive boosting, SVM | PDAC vs AIP | AUC (0.93), Accuracy (85%), Sensitivity (86%), Specificity (94%) |
| Xing et al. [159] | 149 cases | PET/CT | XGBoost | PDAC grading | AUC (0.994) |

Abbreviations: AIP: autoimmune pancreatitis; AUC: area under the curve; CT: computed tomography; NP: normal pancreas; PASC: pancreatic adenocarcinoma; PDAC: pancreatic ductal adenocarcinoma; PET: positron emission tomography; RF: random forest; SVM: support vector machine.
Table 6. Application of AI based on pathological examination in the differential diagnosis of pancreatic cancer and other pancreatic tumors

| Reference | Sample Size | Data Source | Algorithm | Aim | Best result |
|-----------|-------------|-------------|-----------|-----|-------------|
| Song et al. [163] | 11 images from 7 cases | WSI | DCM+BAYES, KNN, SVM, ANN | SCN vs MCN | Accuracy (90%), Sensitivity (89%), Specificity (91%), PPV (91%), NPV (89%) |
| Song et al. [164] | 240 images | WSI | SVM | PDAC diagnosis and grading | For diagnosis: Accuracy (94.38%), Sensitivity (93.13%), Specificity (95.63%), PPV (95.78%), NPV (93.50%); For grading: Accuracy (77.03%), Sensitivity (74.38%), Specificity (79.69%), PPV (79.65%), NPV (75.40%) |
| Kriegsmann et al. [165] | 201 cases | WSI | CNN | PIN, PDAC identification | Balanced accuracy (73% for non-aggregated; 92% for aggregated) |
| Niazi et al. [166] | 33 cases | Ki67 stained slides | CNN | PNET identification | Accuracy (96.2%), Sensitivity (97.8%), Specificity (88.8%) |
| Vance et al. [167] | 31 cases | WSI and MxIF | RF | PDAC cell populations identification | Accuracy (90.0%) |
| Momeni-Boroujeni et al. [168] | 277 images from 75 cases | FNA | MNN | Benign vs malignant pancreatic cytology | Accuracy (100%) |
| Naito et al. [169] | 532 images | EUS-FNB | CNN | PDAC detection | AUC (0.9836), Accuracy (94.17%), Sensitivity (93.02%), Specificity (97.06%) |
| Kurita et al. [170] | 85 cases | Cyst fluid and EUS-FNA | NN | Benign vs malignant PCLs | AUC (0.966), Accuracy (92.9%), Sensitivity (95.7%), Specificity (91.9%), PPV (81.5%), NPV (98.3%) |

Abbreviations: ANN: artificial neural network; AUC: area under the curve; BAYES: Batesian classifier; CNN: convolutional neural network; DCM: direction cumulative map; FNA: fine needle aspiration; FNB: fine needle biopsy; KNN: k-nearest neighbor; MCN: pancreatic mucinous cystadenoma; NPV: negative predictive value; PC: pancreatic cancer; PIN: pancreatic intraepithelial neoplasia; PPV: positive predictive value; MNN: multilayer perceptron neural network; MxIF: cyclic multiplexed-immunofluorescence; NN: neural network; PDAC: pancreatic ductal adenocarcinoma; RF: random forest; PNET: pancreatic neuroendocrine tumor; SCN: pancreatic serous cystadenoma; SVM: support vector machine; WSI: Whole slide imaging.

Al-assisted Pathological Examination

In addition to the above radiographic images, The pathologist can apply AI to Hematoxylin and Eosin (H&E)-stained or immunofluorescent-stained whole slides images (WSI) for PC diagnosis [160]. FNA and FNB are essential diagnostic methods for suspended PC with high accuracy [161,162]. AI can assist in the diagnosis of PC by analyzing cytology and biochemical characteristics of FNA/FNB samples. Here, we summarized the application of AI in pathological examination (Table 6) [76,163-169].

Song et al. constructed a system to automatically segment epithelial cell nuclei on slide images and extract morphological features. They subsequently used multiple classifiers to demonstrate the effectiveness of the designed method in the differential diagnostic of SCN and MCN [163]. Using a similar approach, Song also worked on diagnosing and grading PDAC [164]. Kriegsmann et al. used CNN to construct models for automatic localization and quantification of tissue categories in whole tissue slides, including pancreatic intraepithelial neoplasia and PDAC [165]. Ki67 index has clear guidance for proliferation rate and grading of PNET. However, the non-specificity of Ki67 staining and counterstaining hinders the accurate quantification of the Ki67 index. Therefore, Niazi et al. proposed a DL method based on Ki67-stained biopsy images to distinguish NET from non-tumor areas automatically and achieved 97.8% sensitivity and 88.8% specificity [166]. Vance et al. combined WSI and cyclic multiplexed immunofluorescence to collect 31 markers of PDAC and used an RF algorithm to identify tumor cell populations, achieving an accuracy of 87% [76].

Momeni-Boroujeni et al. used a K-means clustering algorithm to segment cell clusters from FNA-based slides, extracted the morphological features of the cell clusters, and trained a multilayer perceptron neural network (MNN) with these features. Then tested their ability to discriminate between benign and malignant pancreatic cytology (accuracy 100%) [167]. Vance et al. trained the CNN using FNB-based slides to assess PDAC and achieved an AUC of 0.984 [168]. Kurita et al. combined biomarkers in the cyst fluid, cytological features obtained by FNA, and clinical variables to training neural networks for differentiating malignant and benign PCLs [169].

The applications of AI in Biomarkers

Biomarkers have a significant role in diagnosing, staging, and treating PC. The use of appropriate biomarkers for screening in high-risk populations is an essential aspect of the early diagnosis of PC. However, the current PC biomarkers lack sufficient sensitivity and specificity for clinical application [44,161,170]. Liquid biopsies allow a comprehensive cancer profile to be evaluated in a non-invasive and real-time manner and help discover more data for cancer research, including CTCs, cfDNA, exosomes, etc. The biomarkers in these data can be analyzed using AI for their association with diseases. With the expansion of data obtained from liquid biopsies, scientists can better apply AI to biomarker-based early diagnosis of cancers [161,171,172].
As summarized in Table 7, various biomarkers have been used to diagnose or detect PC with the aid of AI, including exosomes [173-175], proteins [176-179], cell-free DNA (cfDNA) [77], circulating microRNA [180], extracellular vesicles long RNA [181], gene expression pattern [182], etc. The above studies mainly contain two categories, 1) biomarkers were known, these data trained ML algorithms to obtain prediction models for PC [173,178,179,181,182], and 2) biomarkers were uncertain, features in the dataset needed to be extracted, then ML models were used to evaluate the value of these features in the diagnosis of PC [77,174-177,180].

Genomics

All cancers occur due to a series of mutations in the cellular genome. The most common driver genes of PDAC are KRA5, CDKNA2A, TP53, and SMAD4, and genetic alterations of the SWI/SNF and COMPASS complexes significantly impact PC. The genome can be used as biomarkers for PC diagnosis, and genome studies can also reveal features that make PC therapeutically susceptible [183].

A part of some researchers used AI to analyze the existing genomic data in the database to find their association with PC. Wang et al. used 78 PDAC samples from the GEO database as the training set. By combining Support Vector Machine Recursive Feature Elimination (SVM-RFE) and Large Margin Distribution Machine Recursive Feature Elimination (LDM-RFE) algorithms, they predicted seven differentially expressed genes as specific biomarkers for PC [184]. Ko et al. developed a Gene Vector for Each Sample (GVES) model, which generated vector representations of genes using gene expression and biological network data from the TCGA database. In cases of small sample sizes, GVES had good accuracy for predicting prognostic genes [185]. Cristiano et al. developed an approach to evaluate fragmentation patterns of cfDNA across the genome and constructed a gradient tree boosting (GBM) model to detect cancer. For PC, the AUC, accuracy, and specificity were 0.86, 67%, and 71%, respectively [77].

Table 7. Applications of artificial intelligence in biomarker-based pancreatic cancer diagnosis

| Reference                  | Sample Size | Data Source                      | Algorithm | Aim                          | Best result                      |
|----------------------------|-------------|----------------------------------|-----------|------------------------------|----------------------------------|
| Chen et al. [173]          | 28 samples* | DNA-PAINT (exosomes)             | LDA       | Cancer detection             | Accuracy (100%)                  |
| Zheng et al. [174]         | 220 cases** | MALDI-TOF-MS (exosomes)          | ANN       | Cancer discrimination        | AUC (0.86)                       |
| Ko et al. [175]            | 28 mice + 34 cases | ExoTENPO chip (exosomes)       | LDA       | PC diagnosis                 | Accuracy (100%)                  |
| Gao et al. [176]           | 199 cases   | SELDI-TOF-MS (proteomes)         | SVM, KNN, ANN | PC diagnosis                | AUC (0.971), Sensitivity (96.67%), Specificity (100%) |
| Yu et al. [177]            | 100 serum samples | SELDI-proteichip                 | DT        | PC prediction                | Sensitivity (88.9%), Specificity (74.1%) |
| Yang et al. [178]          | 913 serum samples | Multiple serum tumor markers | ANN, LR       | PC diagnosis                 | AUC (0.905), Accuracy (85.53%), Sensitivity (90.86%), Specificity (67.50%) |
| Qiao et al. [179]          | 136 cases   | CT images + serum tumor markers  | 2D-3D CNN | For image segmentation; PC vs CP | GBM                              |
| Cristiano et al. [77]      | 34 cases    | Cell-free DNA                    | GBM       | Cancer detection             | AUC (0.86), Accuracy (67%), Specificity (71%) |
| Alizadeh Savareh et al. [180] | 671 cases | GEO database (circulating microRNA) | PSO-ANN-NC A | PC diagnosis                | Accuracy (93%), Sensitivity (93%), Specificity (92%) |
| Yu et al. [181]            | 501 cases   | exLR                             | SVM       | PDAC detection               | AUC (0.960), Accuracy (90.43%), Sensitivity (93.39%), Specificity (85.07%) |
| Almeida et al. [182]       | 648 samples | Gene expression microarray       | ANN       | PDAC prediction              | F1-score (0.86), Accuracy (89.66%), Sensitivity (87.6%), Specificity (83.1%) |
| Yang et al. [197]          | 204 cases   | Liquid biopsy                    | KNN, SVM, LDA, LR, Naive Bayes | PC diagnosis and staging         | For diagnosis: AUC (0.95), Accuracy (92%), Sensitivity (88%), Specificity (95%) |
| Sinkala et al. [198]       | 185 cases   | TCGA database (proteins, miRNAs, miRNAs, and DNA methylation patterns) | NCA, SVM, DT, LR, ET, KNN | PC subtypes differentiation | Accuracy (98.7% for mRNA-based KNN classifier; 97.8% for the DNA methylation-based SVM classifier) |
| Zhang et al. [199]         | 1183 cases*** | LDI-MS                        | SVM       | Pan-cancer diagnosis and classification | For PC: Accuracy (100%) |

*Including 9 healthy samples, 10 breast cancer samples, 9 PC samples; **Including 79 breast cancer cases, 57 PC cases, 84 healthy controls; ***Including 97 PC cases.

Abbreviations: ANN: artificial neural network; AUC: area under the curve; CNN: convolutional neural network; CT: chronic pancreatitis; DT: decision tree; DNA-PAINT: DNA points accumulation for imaging in nanoscale topography; ET: ensemble tree; exLR: extracellular vesicles long RNA; GBM: gradient tree boosting; KNN: k-nearest neighbor; LDA: linear discriminant analysis; LDI-MS: laser desorption/ionization mass spectrometry; LR: logistic regression; MALDI-TOF-MS: matrix-assisted laser desorption/ionization time-of-flight MS; MLP: multilayer perceptron; NCA: neighborhood component analysis; PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; PPV: positive predict value; SELDI-TOF-MS: surface-enhanced laser desorption/ionization time-offlight mass spectrometry; SVM: support vector machine.
Transcriptomics

Both coding and non-coding RNAs are essential for gene expression. In addition to mRNAs directly related to protein expression, many non-coding RNAs are involved in or reveal tumor progressions, such as miRNA, IncRNA, and circRNA [186]. The study of PC transcriptomics helps to understand the mechanism of tumor progression and provides valuable prognostic markers [187].

Xuan et al. obtained miRNA-disease association data from the human miRNA-disease database and built a network representation learning and CNN-based model to predict disease miRNAs. The AUC of the model in PC miRNA prediction is 0.971 [188]. Some researchers have also identified biomarkers directly from pathological samples. Mori et al. directly sequenced the RNA from PDAC tumor tissues and normal tissues, and DL analyzed the data. The selected genes were all important prognostic factors for PC based on the TCGA database [189]. Alizadeh Savareh et al. identified a series of circulating miRNAs associated with PC by analyzing four GEO microarray datasets. The value of the top miRNAs was then assessed by ML methods (Particle Swarm Optimization (PSO) + ANN and Neighborhood Component Analysis (NCA)). The final model, which consist of five miRNAs (miR-663a, miR-1469, miR-92a-2-5p, miR-125b-1-3p and miR-532-5p), showed good diagnostic results on the investigated cases and validation set (Accuracy: 0.93, Sensitivity: 0.93, Specificity: 0.92) [180]. Yu et al. analyzed the extracellular vesicles’ long RNA profile of PDAC, chronic pancreatitis (CP), and healthy plasma samples. The d-signature was identified using an SVM algorithm to detect PDAC (0.960), identify resectable stage I/II cancer (AUC 0.949), and distinguish PDAC from CP (AUC 0.931) [181]. Almeida et al. identify five differentially expressed genes (AHNAK2, KRT19, LAMB3, LAMC2, and S100P) from a gene expression microarray meta-analysis to train an ANN to classify PDAC or healthy samples. The ANN model could classify the test samples with a sensitivity of 87.6% and a specificity of 83.1% [182].

Proteomics

Proteins are the performers of gene-encoded functions. Although proteins are the direct products of mRNA translation, many unexpected associations in the proteome are primarily absent in RNA. Tumor proteome is closely related to epithelial and mesenchymal markers, cell lineage sensitivity, etc. Interventions on the proteome also provide new avenues for tumor treatment [190].

Gao et al. used SELDI-TOF-MS to analyze serum proteomes from PC patients and healthy controls. SVM analysis of the spectra was used to generate a predictive algorithm based on maximally differentially expressed proteins between PC patients and healthy controls. Four significant peaks were used to build a classifier to distinguish PC patients from healthy controls. Combining the SELDI protein peaks and CA19-9, their classifier achieves the AUC of 0.971 [176]. Yu et al. used SDLDI-Proteinchip to analyze serum protein profiling from PC patients and healthy controls. A decision-tree algorithm was trained to separate PC from controls. The sensitivity and specificity of their method were 88.9% and 74.1%, respectively [177]. Yang et al. used three tumor markers (CA19-9, CA125, and CEA) from serum specimens to train the ANN model for PC diagnosis. The AUC, accuracy, sensitivity, and specificity were 0.905, 83.53%, 90.86%, 67.50%, respectively [178].

Exosomes

Exosomes are extracellular vesicles secreted by eukaryotic cells involved in intercellular communication containing nucleic acids, proteins, lipids, and glycoconjugates. It can regulate tumor cell proliferation, metastasis, Epithelial-to-Mesenchymal Transition (EMT), and angiogenesis during tumor development. In clinical practice, it can be used as a biomarker for tumor diagnosis, grading, and prognosis prediction [191,192]. Many studies have used exosomes to diagnose, treat, and monitor treatment response in PC [193].

Chen et al. developed a quantitative analysis platform for continuously quantifying multiple exosomal surface biomarkers from blood samples. Four exosomal surface biomarkers (HER2, GPC-1, EpCAM, EGFR) were immunostained to calculate the number. Linear discriminant analysis was further used to identify exosomes from pancreatic and breast cancer samples. The accuracy of their method was 100% [173]. Zheng et al. used sequential size exclusion chromatography (SSEC) to separate exosomes from human plasma. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) data of samples were collected, and a multi-classifier artificial neural network (denoted as Exo-ANN) model was used to identify pancreatic and breast cancer samples. The AUC of their method for PC was 0.86 [174]. Ko et al. developed a multichannel nanofluidic system to isolate exosomes with an ExoTENPO chip, profiled the RNA cargo inside these exosomes, and applied a linear discriminate analysis (LDA) algorithm to identify samples derived from PC patients. Eight exosomal mRNA biomarkers were identified in their mice studies and used to distinguish PC patients from healthy controls. All
samples (N=24) in the blinded test set were classified correctly [175].

Multi-omics

It is also possible to combine multiple types of biomarkers to detect PC. The analysis of multiple biomarkers revealed the complex molecular landscape of PC and offered the possibility of precision medicine [194-196]. Yang et al. constructed a multi-analyte panel, including extracellular vesicle miRNAs and miRNAs, cfDNA, and CA19-9. These data are used in the training of various ML algorithms. When applied to PDAC diagnosis, the model achieved an AUC of 0.95 and an accuracy of 92%. Furthermore, the model achieved an accuracy of 84% for disease staging [197]. Sinkala et al. extracted several types of biomarkers from the TCGA database. Then they used neighborhood component analysis (NCA) to identify biomarker sets. Different biomarkers trained several ML algorithms for PC subtypes differentiation [198]. Zhang et al. reported a laser desorption/ionization (LDI) mass spectrometry-based liquid biopsy for cancer screening and classification. The study included many cancer types, with 100% accuracy for PC detection in an internal validation cohort [199]. Cheng et al. deployed ALICE (Automated Liquid Biopsy Cell Enumerator) to identify and enumerate minute amounts of tumor cell phenotypes bestrewed in massive leukocytes and discovered two subpopulations of circulating hybrid cells from PC patients [200]. Qiao et al. used CT images to train a 2D-3D CNN model for pancreas segmentation and achieved an average DSC of 84.32%. The diagnostic performance (accuracy 87.63%, sensitivity 94.57%, specificity 93.25%, PPV 84.32%, NPV 90.34%) of CT combined with tumor marker (CA-50, CA-199, CA-242) was better than CT or serum tumor markers only [179].

AI in Prognosis

Accurately predicting the prognosis of PC has important implications for clinical decision-making. This information can help clinicians decide on treatment options, analyze the outcome of pancreatectomy, improve the management of patients, etc. However, classical prognostic factors, such as lymph node status and American Joint Committee on Cancer (AJCC) stage, are not entirely relevant in some long-term survivors [201,202]. Also, long-term survivors and general patients did not show significant differences in their mutation profiles [203]. These facts make it challenging to predict the prognosis of PC. Due to its excellent computational power, AI was used to analyze PC prognoses, including survival time [204-221], recurrence risk [78,221-224], metastasis [225-230], therapy response [79-81,231-240], etc.

Survival time

The non-invasive identification of specific imaging features (or signatures) that can predict tumor genomic alterations is termed “radiogenomics,” which integrates radiomics and genomics information. The gene expression profiles obtained in radiogenomics can be used as biomarkers to predict prognosis [241]. With the aid of ML, the radiologist used radiological images (CT, MRI) to detect multiple gene expression profiles in PC, including p53 status and PD-L1 expression [204], FAP expression [205], and ITGAV expression [206]. These genes had been shown to have predictive ability for the prognosis of PC.

Radiomics can also be applied alone for prognosis prediction. Xu et al. used EUS images to predict the prognosis of PC patients undergoing interstitial brachytherapy [207]. By extracting the radiomics features of FDG-PET [208,209] or CT [210-212] images and combining them with ML models, researchers could improve the accuracy of survival prediction for PC patients. In addition to direct extraction of image features, CT images have also been used to analyze patient body compositions [213] and tumor heterogeneity [214] in PC to predict survival.

In addition to the radioactive approach mentioned above, some non-imaging methods can predict PC survival. Walczak et al. and Aronsson et al. combined clinical variables (sex, age, year of diagnosis, tumor stage, etc.) with ANN algorithms to predict survival in PC (91% sensitivity and 38% specificity) [215] and invasive IPMN (82% accuracy and 83% precision) [216], respectively. Using the ML algorithm, Hayward et al. combined clinical variables and treatment records to predict PC clinical performance (patient survival time, quality of life scores, surgical outcomes, and tumor characteristics) [217]. Biomarker analysis is also a common approach in prognosis. Yokoyama et al. evaluated the methylation status of MUC1, MUC2, and MUC4 promoter regions and integrated these results and clinical pathologic features. Then they used SVM-, NN-, and multinomial-based methods to develop a prognostic classifier [218]. Winter et al. used the NetRank algorithm to filtrate marker genes prognostic for the outcome from PC gene expression profiles. Accuracies were assessed using SVM classifiers and Monte Carlo cross-validation [219]. A wavelet-based DL method was proposed by Tang et al. to select variables and predict prognosis for PC by training with multi-omics data (genomic, epigenomic,
and clinical cohort information). This method predicts prognosis better than the traditional LASSO model (AUC: 0.937 vs. 0.802) [220]. Beak et al. used multi-omics data to analyze survival and recurrence in PC, with data sources including whole-exome sequencing, RNA sequencing, microRNA sequencing, DNA methylation data, and other clinical data. LR analysis generally revealed the best performance for both disease-free survival (DFS) and overall survival (OS) (accuracy = 0.762 and AUC = 0.795 for DFS; accuracy = 0.776 and AUC = 0.769 for OS) [221].

**Recurrence risk**

Clinical features, such as CA19-9 level, tumor location, size, stage, and differentiation degree, are of considerable importance for predicting the risk of recurrence. Li et al. collected demographics and various biochemical and pathological variables of PDAC patients from multiple institutions and used six ML algorithms to construct predictive models. SVM and KNN models had the highest accuracy in predicting 1-year and 2-year recurrence (70.9% and 73.4%), respectively [222]. Lee et al. compared the effects of RF and Cox models on the prognosis of PDAC. Training these two models using multiple clinical variables yielded a mean c-index of 0.6805 and 0.7738 for the RF and Cox models, respectively [78].

In combination with clinical features from patients, radiomics features can be used to predict the risk of recurrence of PC. He et al. collected PDAC patients’ CT images performed three months after surgery for radiomics analysis. Using clinicoradiological information and radiomics feature jointly or separately, multivariable LR was applied to construct the local recurrences model of PDAC. The combined model achieved an AUC of 0.742 in the validation cohort, which is better than the clinicoradiological-only risk model (AUC 0.533), and the radiomics-only risk model (AUC 0.730) [223]. Li et al. preprocessed CE-CT and extracted and selected optimal radiomics features from intratumoral volume (ITV) and peritumoral volume (PTV). Then, ANN and LR models were employed to develop the ITV model, PTV model, combined model, clinical model, and radiomics-clinical model. Radiomics-clinical model outperformed other models in predicting 1-year recurrence (AUC 0.764 for validation set) and 2-year recurrence (AUC 0.773 for validation set) [224].

**Metastasis**

The lymph node metastasis status of PDAC significantly impacts the choice of treatment options, the risk of postoperative recurrence, and the overall survival rate of patients [242,243]. Therefore, correct prediction of lymph node metastasis status can enhance patient prognosis. An et al. analyzed preoperative DECT images of regional lymph node dissection in PDAC patients using the Res-Net 18 algorithm to classify lymph node metastasis. The authors compared the prediction effects of virtual monoenergic images at different voltages. 100 + 150 keV DECT yielded the best predictions (AUC 0.87). If key clinical features (CT-reported T stage, LN status, glutamyl transpeptidase, and glucose) are integrated can further improve the prediction of the model (AUC 0.92) [225]. Some studies employed CT radiomics for PC lymph node metastasis prediction, and they all applied multivariable LR to construct a radiomics-based model with AUCs ranging from 0.75 to 0.912 [226-228]. Shi et al. employed T2-weighted (T2WI) and portal venous phase (PVP) MRI images for lymph node metastasis analysis. Radiomics features were extracted by PHilgo software and selected by a gradient-boosting decision tree. T2WI combined with the PVP model has the best performance. The AUCs were 0.834 and 0.807 in the training and validation cohorts, respectively [229].

Liver metastases are more common after PDAC resection but are unpredictable and lead to a poorer prognosis. Zambrinis et al. performed liver radiomics analysis on preoperative CE-CT scans and developed an LR classifier to predict early liver metastasis. By incorporating preoperative clinicopathological variables with radiomics features, their model achieved an AUC of 0.76 [230].

**Therapy response**

AI has also been used to predict treatment responses, including chemotherapy, radiotherapy, immunotherapy, and surgery. Wei et al. used a variational autoencoder (VAE) algorithm to extract tumor transcriptome features. Regularized gradient boosted decision trees (XGBoost) were further used to predict chemotherapy drug response for cancer (for PC: AUROC 0.738; AUPRC 0.764) [80]. Cos et al. collected preoperative activity metrics (step count, heart rate, and sleep time series) from patients with the help of wearable devices and built ML models to predict whether the pancreatectomy achieved the desired outcome (the absence of postoperative pancreatic fistulae, etc.). Their model combined clinical characteristics and achieved an AUC of 0.7875 [231]. Facciorusso et al. developed ANN and LR models to predict pain response after repeat echoendoscopic celiac plexus neurolysis. The predictive performance of the ANN model was higher than the LR model (AUC 0.94 vs. 0.85) [232]. Using clinical data and MRI images, Kassis et al. distinguished two subtypes of PDAC (KRT81+ and KRT81-) by gradient boosted-tree algorithm.
Subsequently, they assessed chemotherapy response and survival stratified by subtype and radiographic characteristics. Patients with the KRT81+ subtype responded significantly better to gemcitabine-based chemotherapy than FOLFIRINOX (HR 2.33) [81]. Schperberg et al. combined clinical trials, drug-related biomarkers, and molecular profile information to construct an RF model to predict drug oncologic outcomes in randomized clinical trials. The Spearman correlation ($r_s$) between their predicted model’s and actual outcomes was statistically significant (progression-free survival (PFS): $r_s = 0.879$, overall survival (OS): $r_s = 0.878$, $P < .0001$) [79]. Nasief et al. collected CT images of patients during chemotherapy and compared the changes in radiomics features therein. Bayesian-regularization-neural-network was used to build a response prediction model with AUC of 0.98 for kurtosis–coarseness–NESTD (normalized-entropy-to-standard-deviation-difference) combination [233].

Stereotactic body radiotherapy (SBRT) is a therapeutic option in PC care, which permits the precise application of high-dose radiation in 1 to 5 fractions to a limited target volume. It has been proven that SBRT has significantly better outcomes than chemotherapy alone or in combination with conventional external-beam radiotherapy (EBRT) [244]. Several studies with radiomics have emerged to predict the response to SBRT. Based on the radiomics features of CT and clinical characteristics, Gregucci et al. applied a multivariate LR model to predict local response to SBRT for locally advanced PC (AUC 0.851) [234]. Based on CT radiomics features, Parr et al. used the gradient boosting machine model to construct OS (c-index 0.66) and recurrence prediction model (AUC 0.78) for PC following SBRT [235]. Simpson et al. extracted radiomics features from low field strength (0.35 T) MRI for predicting treatment response in PC patients undergoing SBRT. RF algorithm was adopted to construct a prediction model with the AUCs of 0.81 and 0.845 in two similar studies [236,237].

Immunotherapy has shown remarkable efficacy against various tumors, but PC has shown minimal response to immunotherapy. Tumor-infiltrating lymphocytes (TILs) have been proven to be associated with immunotherapy response [245], OS, and PFS [246]. Analysis of TILs may help identify PC patients most likely to respond to immunotherapy. Bian et al. developed an XGBoost-based model for preoperative prediction TILs in PDAC patients with CT radiomics features (AUC 0.79) [238]. Based on MRI radiomics features, Bian et al. also predicted Tumor-infiltrating CD8+ T cell [239] and other TILs [240] in PDAC patients with LDA-based model (AUC 0.76) and XGBoost-based model (AUC 0.79), respectively.

Some researchers have used ML to analyze the recovery condition of long-term survivors of PC. Kong et al. analyzed CT images by ML to determine changes in body composition (skeletal muscle, adipose tissue) in long-term survivors of pancreatic head cancer. They performed a multi-factor LR analysis of the factors affecting the changes in body composition. Their research concluded that long-term survivors of PC did not recover their preoperative body composition status, and preoperative sarcopenia and recurrence influenced body composition changes [247]. The tumor–stroma ratio (TSR) is an independent prognostic factor for solid tumors [248]. Based on MRI radiomics features, Meng et al. developed and validated an XGBoost classifier for evaluating TSR in patients with PDAC for interstitial targeted therapy selection and monitoring (AUC 0.78 in the validation set) [249].

### Other applications of AI in PC

In addition to the research mentioned above, AI has also been applied to many aspects of PC, including predicting gene mutation [250,251], nucleus segmentation [252], tumor target localization [253], and predicting the risk of ICU admission for PC patients [254], etc.

Electronic health records (EHR) are also considered to be useful for early screening of PC. In a workshop (Early Detection of Pancreatic Cancer: Opportunities and Challenges in Utilizing Electronic Health Records) held in March 2021, experts from multiple fields assessed the feasibility of AI-based data extraction and modeling applied to EHRs and identified future directions [255]. In another article published the same year, Malhotra et al. used logistic regression on EHRs to screen people at high risk of PC. Their method could indicate cancer risk over a decade before diagnosing PC patients [256]. Roch et al. developed a natural language processing-based pancreatic cyst identification system. It could search and identify keywords of pancreatic cysts based on electronic medical records (EMR), with sensitivity and specificity of 99.9% and 98.8%, respectively. This system could help capture patients at risk of PC [257].

Some studies have also focused on analyzing the omics of PC. Kim et al. classified PC using ML and DL to classify quantitative proteomics data [258]. Song et al. employed AI techniques to deconvolute spatial transcriptomics data to uncover the cell states and subpopulations based on spatial localization [259]. Bagante et al. integrated whole-exome sequencing data with the help of artificial neural networks for cell-of-origin pattern prediction and molecular subtypes classification of hepato-pancreato-biliary
cancers. Combining the clinical data and the above information, they also analyzed the prognosis of cancer patients using random survival forest and Cox analysis [260].

Some studies have attempted to apply DL to estimate medical imaging parameters. Misha et al. present an unsupervised physics-informed DL algorithm of intravoxel incoherent motion (IVIM) model called IVIM-NET \textsuperscript{optim} to fit diffusion-weighted imaging (DWI)-MRI data. MRI images of 23 PDAC patients showed IVIM-NET \textsuperscript{optim} superior performance to the least squares and Bayesian approaches at SNRs < 50 [60]. Ottens et al. presented various frameworks, including non-linear least squares (NLLS), Gated Recurrent Unit (GRU), FCN, LSTM, GRU, CNN, and U-Net, that analyze DCE-MRI concentration curves and output extended Tofts-Kety parameter estimates. Testing on 28 PC patients showed that GRU had the best performance [261].

Some researchers have attempted to develop new computer-aided diagnosis (CAD) systems. Li et al. constructed a Raman spectroscopic system using CNN models to efficiently distinguish between cancerous and normal pancreatic tissue. The AUCs of all three Raman image-based (1D, 2D Raman images, and 2D Raman PC1) methods were close to 0.99 [262]. Jadhav et al. developed a 3D virtual pancreatography system using ML algorithms for non-invasive diagnosis and classification of pancreatic lesions, the precursors of PC [263]. Dmitriev et al. developed a CAD system for classifying pancreatic cystic lesions based on RF and CNN. They proposed a visual analytics approach to uncover the system’s decision-making process [264]. Combining clinical and radiological characteristics, Kang et al. built LR and ML models to predict the risk of malignant IPMN. After 200 repetitions, the mean AUCs of their ML and LR models were comparable (0.725 vs. 0.725) [265].

**Challenges and Future Perspectives**

Although AI has many applications on PC, many challenges have remained (Figure 4). Data accessibility and bias may affect the effectiveness of AI predictions. In radiomics, the image’s quality may affect the construction of AI models. An assessment of quality gaps in public pancreas imaging datasets found that a substantial proportion of CT images were

![Figure 4](https://www.thno.org)

*Figure 4. Application of artificial intelligence in multiple related fields of pancreatic cancer. Artificial intelligence can use one type of data alone to make predictions about pancreatic cancer or integrate multi-omics information for analysis.*
unsuitable for AI due to biliary stents or other factors [266]. Minorities are often underrepresented in clinical trials, leading to biased results [267,268]. For AI, insufficient data on minorities may result in the inability to adequately assess patient diversity for algorithm development and testing.

Though radiomics is thought to hold promise for addressing many issues in cancer care, there are still some concerns, such as reproducibility. Variations include intra-individual test-retest repeatability, image-acquisition technique, multi-machine reproducibility, segmentation reproducibility, radiomics feature definition, parameter setting, and implementation. All challenge the reproducibility of radiomics [269-271]. To improve the reproducibility of radiomics, scientists have attempted many approaches. The repeatability of radiomics features can be assessed using consistency correlation coefficients (CCCs) [272]. In order to build a more reproducible model, only repeatable features should be retained for subsequent model construction. Many studies reuse the dataset from which the model was developed for validation, lacking validation from external datasets. Using an external dataset for validation can improve the reproducibility of the model. Since there are many mature algorithms and software for radiomics, standardizing the process of radiomics, including image acquisition, segmentation, and feature extraction, can help to improve reproducibility [269,271,273].

Due to the specificity of the medicine, an interpretable algorithm is preferred. A flawed algorithm can lead to terrible consequences. Hundreds of hospitals that used IBM Waston Health’s cancer AI algorithm for recommending treatments proved to have some errors in their operation [274]. However, a trade-off exists between performance and explainability at present. The DL models usually perform better, but they are often the least explainable because they are purely data-driven, and the underlying structures are challenging to interpret [32,275]. Three main approaches have attempted to address the interpretability of DL models: (1) proxy models, which use more traditional statistical models to explain the operational properties of DL; (2) visualization, which shows the internal mechanisms of DL models; and (3) internal interpretability approach, where the model can explain by itself which parts are essential [276,277]. This suggests that before CAD systems can be used in the clinic, they must be approved for safety and efficacy to avoid patient harm.

As knowledge of the disease continues to expand, the data collected will gradually increase, and clinical decision-making will become more and more complex. Training AI by a single type of medical image or biomarker is not perfect for the diagnosis and prognosis of PC. It should be noted that the study of multimodal features based on image and multi-omics is a new direction for future research. Despite the challenges of AI in PC, it will eventually emerge in all areas of PC due to its great advantage in integrating complex data. In clinical practice, building viable healthcare AI systems requires the joint work of experts in multiple fields, including clinicians, basic scientists, statisticians, and engineers. As AI technology advances and various experts collaborate, its features will become more powerful and accurate.

Conclusions

Here we summarized the applications of AI on PC. AI-based early screening may be a critical factor in improving the prognosis of PC patients. The combination of medical images and AI may become an essential part of CAD systems to assist physicians in making adequate and accurate diagnoses. In addition, the role of AI in multi-omics and pathology cannot be ignored. With the decrease in computing costs and improved computer technology and biotechnology, AI will make a fantastic process in the medical field. This progress requires a collaborative effort between clinicians, basic scientists, statisticians, and engineers. Despite some limitations, it will still dramatically improve many aspects of PC in the foreseeable future because of its powerful computing capabilities.

Abbreviations

4DCT: four dimensions CT; AIP: autoimmune pancreatitis; ANN: artificial neural network; AUC: area under the curve; BAYES: Batesian classifier; BD-IPMN: branching type IPMN; CE-CT: contrast-enhanced CT; CE-EUS: contrast-enhanced EUS; CEH-EUS: contrast-enhanced harmonic EUS; CNN: convolutional neural network; CEST: chemical exchange saturation transfer; CP: chronic pancreatitis; CPP: chronic pseudotumoral pancreatitis; CT: computed tomography; DCE: dynamic contrast enhancement; DCM: direction cumulative map; DECT: dual energy CT; DLIR: deep learning image reconstruction; DNA-PAINT: DNA points accumulation for imaging in nanoscale topography; DSC: dice similarity coefficient; DT: decision tree; ET: ensemble tree; exLR: extracellular vesicles long RNA; FNA: fine needle aspiration; FNB: fine needle biopsy; FPN: feature pyramid network; GBM: gradient tree boosting; GCN: Graph Convolutional Networks; HD: Hausdorff distance; IGA-Net: Inductive Attention Guidance Network; IPMN: intraductal papillary mucinous neoplasm; IoU: intersection over union;
KNN: k-nearest neighbor; LASSO: least absolute shrinkage and selection operator; LDA: linear discriminate analysis; LD-M5: laser desorption/ionization mass spectrometry; LR: logistic regression; LSTM: long short-term memory; MALDI-TOF: matrix-assisted laser desorption/ionization-time-of-flight MS; MC: pancreatic mucinous cystadenoma; MDCT: multidetector CT; MLP: multilayer perceptron; MLR: multivariable logistic regression; naïve Bayes; NCA: neighborhood component analysis; NN: neural network; NP: normal pancreas; PCL: pancreatic cystic lesion; PC: pancreatic cancer; PCN: pancreatic neuroendocrine tumor; PCL: pancreatic ductal adenocarcinoma; PET: positron emission tomography; PIN: pancreatic intraepithelial neoplasia; PNET: pancreatic neuroendocrine tumor; PPV: positive predictive value; PASC: pancreatic adenousomas carcinoma; PC: pancreatic cancer; PCL: pancreatic cystic lesion; PUDAC: pancreatic ductal adenocarcinoma; PC: pancreatic cancer; PPC: pancreatic polypeptide; PCL: pancreatic cystic lesion; PUDAC: pancreatic ductal adenocarcinoma; SAE: sparse autoencoder; SCN: self-organizing map; SLM: stochastic learning machine; SNN: spike neural network; SVD: singular value decomposition; TIC: tissue inhibitor of metalloproteinases; TMA: tissue microarray; WSI: Whole slide imaging.

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