

Artificial Intelligence in *Medical Imaging*

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Artificial Intelligence in Medical Imaging

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ABOUT COVER

Editor-in-Chief of *Artificial Intelligence in Medical Imaging*, Professor Xue-Li Chen is an expert in the field of biomedical photonics imaging as well as its application in early detection and accurate diagnosis of gastric cancer. Professor Chen has co-led the development of Cerenkov luminescence endoscope and further explored the application in early detection of clinical gastrointestinal tumors. Professor Chen has also developed the stimulated Raman projection tomography technology which can perform the volumetric imaging of single cells in a label-free manner. Professor Chen has served as the member of SPIE, OSA, IEEE, and as a committee member of the Branch of Contrast Technology in China Medicinal Biotech Association, the Nuclear Medicine Committee of Shaanxi Cancer Association, and the Shaanxi Society of Biomedical Engineering.

AIMS AND SCOPE

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

AIMI mainly publishes articles reporting research results obtained in the field of artificial intelligence in medical imaging and covering a wide range of topics, including artificial intelligence in radiology, pathology image analysis, endoscopy, molecular imaging, and ultrasonography.

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Artificial intelligence in pancreatic disease

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Abstract

In recent years, the application of artificial intelligence (AI) in radiology has been growing rapidly, fueled by the availability of large datasets, advances in computing power, and newly developed algorithms. Progress in AI applied to medical imaging analyses has transformed these images into quantitative data, termed radiomics. When combined with patients' clinical data, these models, when developed by machine learning, have the potential to improve diagnostic, prognostic, and predictive accuracy. Currently, limited literature is available on the use of radiomics for pancreatic disease. Here, we will review recent studies in the application of AI in a variety of pancreatic diseases, mainly involving lesion detection, tumor characterization, tumor grading, response, and prognosis evaluation. Finally, we will also discuss the challenges and prospects in the field of radiomics for pancreatic disease.

Key words: Artificial intelligence; Machine learning; Deep learning; Radiomics; Texture analysis, Pancreas

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Core tip: The integration of radiomics, clinical data, and advanced machine-learning methodologies will improve diagnostic, prognostic, and predictive accuracy in patients with pancreatic disease, and facilitate clinical decision and management towards precision medicine.

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INTRODUCTION

Artificial intelligence (AI) describes the use of computers to simulate performance and critical thinking equivalent to a human being. Its application in radiology has been growing rapidly, powered by the availability of large datasets, advances in computing power, and newly developed algorithms^[1]. The progress in AI of medical imaging analyses has converted these images into quantitative and minable data to facilitate better clinical decisions and management^[2,3]. This comprehensive method, when used to analyze high-dimensional quantitative features from multimodality medical images, is known as radiomics^[4].

To establish robust quantitative image analyses, standardized methodologies are required based on various image modalities, such as those of computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), especially for texture- and filter-based features^[5,6]. After the mining of correlations between these features and diagnosis/prognosis of tumors, tumors can then be decoded into different imaging phenotypes^[7]. These data are then combined with other patients' data to develop models that can potentially enhance diagnostic, prognostic, and predictive accuracy^[8]. Because these analyses are based on the standard of care images, it is imaginable that radiomics analysis will eventually become routine practice^[9,10].

There are three approaches to data-mining for radiomics, including hand-crafted features, deep features, and a hybrid method. Traditional radiomics is done with the computation of agnostic hand-crafted features, which are computed automatically by image analysis algorithms^[5]. For instance, texture analysis has been widely used to quantify intuitive qualities by measuring the spatial variation in pixel intensities on images. In contrast to traditional radiomics, deep-learning extracts deep features from medical images based on the specifications of a pre-defined task, including disease diagnostics, cancer type prediction, or survival prediction. These deep features can be obtained via various architectures, such as a convolutional neural network (CNN), to find the most relevant features related to a pre-defined task^[11]. Thus, they can automatically learn the best features for a given task, without the need for human involvement for feature design. Recent studies have shown better performance by deep learning methods over traditional radiomics^[12,13]. Besides, the hybrid method, which combines hand-crafted and deep features, could provide complementary information for the radiological evaluation in cancer patients^[14-16].

The currently available literature on the use of radiomics for pancreatic disease is limited. Here, we will review recent studies in the application of texture analysis and radiomics in pancreatic malignancy, mainly involving cancer detection, grading, response, and prognosis evaluation. We will also review the performance of radiomics in differentiating between pancreatic cancer and other benign pancreatic lesions, such as autoimmune pancreatitis (AIP) and mass-forming pancreatitis (MFP). Finally, we will discuss the challenges and prospects in the field of radiomics for pancreatic disease. A summary table (Table 1) is also presented based on our review of the recent literature.

PANCREATIC DUCTAL ADENOCARCINOMA

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the USA. The 5-year survival for PDAC is only 8%, due to its aggressive nature and late-stage presentation when discovered in most patients^[17]. Therefore, early detection of PDAC is critical, because surgical resection is the only method to cure this disease. In patients receiving a surgical intervention, the involvement of regional lymph nodes and residual tumor at the surgical margin are also important issues related to survival outcome. In patients with metastatic disease receiving chemotherapy or radiotherapy, the use of radiomics to predict treatment response is being investigated.

Early detection of pancreatic ductal adenocarcinoma

Radiomics might offer an advantage over other techniques in the early detection of PDAC. This is because the subtle difference of the texture patterns between early cancer and normal pancreas might be discernable using radiomic features prior to visual detection.

Chu *et al*^[18] used 3D CT radiomic features to differentiate PDAC and normal pancreas by manually segmented features of the pancreas. The dataset included 190

Table 1 Recent publications using artificial intelligence and radiomics in pancreatic disease

Ref.	Year	Disease	Number	Training/testing	Modality	Design	Feature selection	Results
PADC detection								
Chu <i>et al</i> ^[18]	2019	PDAC <i>vs</i> normal	190:190	255/125	CT	Retrospective	RF	Accuracy: 99.2%; AUC: 0.99
Liu <i>et al</i> ^[19]	2020	PDAC <i>vs</i> normal	370:320	PDAC: 295/256; Normal: 75/64	CT	Retrospective	CNN	Accuracy: 98.6-98.9%; AUC: 0.997-0.999
Li <i>et al</i> ^[21]	2020	LN metastasis	159	118/41	CT	Retrospective	LASSO	Combined model; AUC: Training/test = 0.944/0.912
Bian <i>et al</i> ^[22]	2019	LN metastasis	225	-	CT	Retrospective	LASSO	The arterial rad-score is associated with the risk of LN metastasis.
Hui <i>et al</i> ^[25]	2020	R0 <i>vs</i> R1 after PD	34:52	-	CT	Retrospective	SVM	AUC: 0.8614 Accuracy: 84.88%
Bian <i>et al</i> ^[26]	2020	SMV margin (R0 <i>vs</i> R1) after PD	127:54	-	CT	Retrospective	LASSO	AUC: 0.75
Zhang <i>et al</i> ^[28]	2018	POPF after PD	117	80/37	CT	Retrospective	LASSO	AUC: Training/test = 0.8248/0.7609
Xie <i>et al</i> ^[32]	2020	PFS and OS	220	147/73	CT	Retrospective	LASSO	Rad-score is better than clinical model and TNM system
Cozzi <i>et al</i> ^[33]	2019	OS and local control after SBRT	100	60/40	CT	Retrospective	Elastic net regularization, Cox regression models	Identify low and high-risk groups
IPMN								
Chakraborty <i>et al</i> ^[41]	2018	Low risk <i>vs</i> high risk	103	-	CT	Retrospective	RF, SVM	AUC: 0.77
Corral <i>et al</i> ^[42]	2019	Normal pancreas, low-grade dysplasia, high-grade dysplasia, and adenocarcinoma	139 (31:48:20:40)	-	MRI	Retrospective	Deep learning	AUC: 0.78
PNET								
Liang <i>et al</i> ^[49]	2019	Grade 1 <i>vs</i> 2/3	137	86/51	CT	Retrospective	LASSO	AUC: Training/test = 0.907/0.891
Gu <i>et al</i> ^[50]	2019	Grade 1 <i>vs</i> 2/3	138	104/34	CT	Retrospective	MRMR, RF	AUC: Training/test = 0.974/0.902
Bian <i>et al</i> ^[51]	2020	Grade 1 <i>vs</i> 2/3 (non-functional)	139	97/42	MRI	Retrospective	LASSO and LDA	AUC: Training/test = 0.851/0.736
Other pancreatic lesions								
Park <i>et al</i> ^[54]	2020	AIP <i>vs</i> PDAC	85: 93	60/29: 60/33	CT	Retrospective	RF	Accuracy: 95.2%; AUC: 0.975
Zhang <i>et al</i> ^[55]	2019	AIP <i>vs</i> PDAC	45: 66	-	PET/CT	Retrospective	RF, adaptive boosting, SVM	Accuracy: 85%; AUC: 0.93
Ren <i>et al</i> ^[56]	2019	MFP <i>vs</i> PDAC	79: 30	69/40	CT	Retrospective	Mann-Whitney U test, MRMR	AUC: 0.98

Mashayekhi <i>et al</i> ^[57]	2020	Functional abdominal pain, recurrent acute pancreatitis, chronic pancreatitis	20:19:17	-	CT	Retrospective	Isomap and SVM	Accuracy: 82.1%
Yang <i>et al</i> ^[58]	2019	Serous <i>vs</i> mucinous cystadenoma	53: 25	4:1	CT	Retrospective	RF	Accuracy: 83%; AUC: 0.75

AIP: Autoimmune pancreatitis; AUC: Area under receiver operating characteristic curve; CNN: Convolutional neural network; DFS: Disease-free survival; IPMN: Intraductal papillary mucinous neoplasms; LASSO: Least absolute shrinkage and selection operator; LDA: Linear discriminative analysis; LN: Lymph node; MFP: Mass-forming pancreatitis; MRMR: Minimum redundancy maximum relevance; OS: Overall survival; PD: Pancreaticoduodenectomy; PDAC: Pancreatic ductal adenocarcinoma; PET: Positron emission tomography; PFS: Progression-free survival; PNET: Pancreatic neuroendocrine tumor; POPF: Postoperative pancreatic fistula; RF: Random forest; SBRT: Stereotactic body radiation therapy; SVM: Support vector machine; SMV: Superior mesenteric vein.

patients with PDAC and 190 healthy controls, and was divided into 255 training and 125 validation cases. A total of 478 features was extracted, and 40 features were selected for analysis by a random forest (RF) classifier. The overall accuracy was 99.2%, and the area under the curve (AUC) was 99.9%. The results were encouraging for using radiomics in the early detection of PDAC, but a limitation of this study was that the manual segmentation of pancreas boundaries was a labor-intensive work and required expert knowledge of radiologists.

To overcome this limitation, Liu *et al*^[19] used CNN to distinguish 370 patients with pancreatic cancer and 320 normal controls. CT images were preprocessed into patches to classify as cancerous or non-cancerous. In local test sets, CNN-based analysis had an accuracy of 0.986–0.989 and AUC of 0.997–0.999. In the test set (281 pancreatic cancers and 82 controls) of a different country, the accuracy was 0.832 and AUC was 0.920. The sensitivity for tumors smaller than 2 cm was 92.1% in the local test sets and 63.1% in the other country test set. When compared with radiologists' interpretation, CNN-based analysis achieved higher sensitivity than radiologists. Therefore, this method could be incorporated into the development of computer-aided detection software for pancreatic cancer detection. In clinical practice, other benign lesions, such as MFP or AIP, might mimic PDAC. Whether CNNs can distinguish between PDAC and other pancreatic pathologies, such as pancreatitis and other pancreatic tumors, must also be further studied. Besides, about 11%–27% of pancreatic cancer is enhancing the pancreatic parenchyma and not visible on contrast-enhanced CT^[20]. It is interesting to see whether radiomics can detect this particular type of PDAC.

Predicting lymph node metastasis

Accurate identification of the extent of lymph node (LN) metastasis is critical for the determination of surgical methods in resectable PDAC.

Li *et al*^[21] developed a model integrating clinical data and imaging features extracted from venous phase CT to predict LN metastasis. Their study included 159 patients with PDAC (118 in the primary cohort and 41 in the validation cohort). A total of 2041 radiomics features were extracted, and 15 features were selected for constructing the radiomics signature in the primary cohort. A combined prediction model was built by integrating the radiomics signature and clinical characteristics selected by using multivariable logistic regression. The combined prediction model reached a better discrimination power than the clinical prediction model, with an AUC of 0.944 *vs* 0.666 in the primary cohort, and 0.912 *vs* 0.713 in the validation cohort.

Bian *et al*^[22] used arterial phase CT images to predict LN metastasis in 225 patients. A total of 1029 radiomics features of the arterial phase were extracted and then reduced using the least absolute shrinkage and selection operator logistic regression (LASSO) algorithm. Multivariate logistic regression models were used to analyze the association. The radiomics score (rad-score), which consisted of 12 selected features, was significantly associated with LN status, both in univariate and multivariate analyses. Higher arterial rad-score was also associated with LN metastasis. In the future, it is necessary to establish a one-to-one correlation between the imaging findings and the pathological evidence of LN metastasis.

Predicting surgical margin and postoperative pancreatic fistula after pancreaticoduodenectomy

In a pathological examination after pancreaticoduodenectomy (PD), a resection margin

without cancer cells in 1 mm is considered as R0; a resection margin with cancer cells in 1 mm is considered as R1. The preoperative identification of R0 and R1 is a determining factor for surgical decisions and prognosis^[23,24].

Hui *et al*^[25] retrospectively analyzed CT images of 86 patients (34 cases of R0 and 52 cases of R1) with pancreatic head PDAC and that underwent PD. The radiomics features were reduced using principal component analysis. The support vector machine (SVM) with a linear kernel was used to classify the resection margins with leave-one-out cross-validation. The results achieved an AUC of 0.8614 and an accuracy of 84.88%. Two features of the run-length matrix, which are derived from diagonal sub-bands in wavelet decomposition, showed significant differences between R0 and R1.

Similarly, Yun *et al*^[26] used a portal rad-score to predict pathologic superior mesenteric vein (SMV) resection margin in 181 patients. For each patient, 1029 radiomics features of the portal phase were extracted, which were reduced using the LASSO logistic regression algorithm. The rad-score was significantly associated with the SMV resection margin status. The portal rad-score had an accuracy of 71.3% and AUC of 0.750. Although radiomics seem promising in predicting SMV section margin, assessment of all pancreatic resection margins is needed to predict patients' outcomes. Furthermore, the radiomic features of mesopancreas (located between the superior mesenteric artery and the uncinate process) are more likely to predict the status of the section margin than those of a primary tumor, because it is regarded as the primary site of cancer cell infiltration^[27].

Zhang *et al*^[28] used radiomic features extracted from the portal venous phase CT for the preoperative prediction of postoperative pancreatic fistula (POPF) in 117 patients receiving PD. The rad-score was constructed by LASSO, and its performance was compared with standard pancreatic Fistula Risk Score. Their rad-score could predict POPF with an AUC of 0.8248 in the training cohort (80 patients) and of 0.7609 in the validation cohort (39 patients). In addition, the AUC of the rad-score was statistically higher than the Fistula Risk Score for predicting POPF in both cohorts.

Predicting therapy response

Many researchers have utilized radiomic features derived from pretreatment CT to identify imaging phenotypes that might predict the treatment response in patients with PDAC.

Chen *et al*^[29] assessed the response of pancreatic head cancer during chemoradiation therapy in 20 patients. They found that significant changes in CT radiomic features were observed during therapy based on quantitative analysis of daily CT. In cases of good response, patients tend to have large reductions in mean histograms of CT number and skewness, and large increases in standard deviation and kurtosis. Thus, a high reduction of these features might suggest early treatment response and could be used to identify patients that need therapeutic intensification.

Borazanci *et al*^[30] used texture analysis to predict treatment response to poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. In 13 patients with PDAC who have deoxyribonucleic acid damage repair deficiency mutations, exploratory analysis of index lesions revealed correlations between lesion texture features with overall survival (OS), and also with time on PARP inhibitors.

Yue *et al*^[31] stratified patients into low and high-risk groups using pre- and post-radiotherapy 18F-FDG-PET/CT images from 26 patients. A total of 48 texture and clinical variables were identified, and the prognostic heterogeneity features were selected using LASSO/elastic net regression and multivariate Cox analysis. After radiotherapy, the metabolic activity in the primary tumor was suppressed, and underlying tissue heterogeneity was reduced. The authors identified five significant variables: Age, node stage, variations of homogeneity, variance, and cluster tendency. These patients could be stratified into two risk groups: A low-risk group ($n = 11$) with a longer mean OS and higher texture variation ($> 30\%$), and a high-risk group ($n = 15$) with a shorter mean OS and lower texture variation ($< 15\%$). The authors concluded that locoregional metabolic texture response might predict clinical outcomes following radiotherapy.

Predicting prognosis

Recent studies have suggested that radiomic features extracted from CT and PET were predictive of the survival outcome of PDAC patients.

Xie *et al*^[32] developed a CT-based radiomics nomogram for survival prediction in patients with resected PDAC in 220 patients (training = 147; validation = 73). A total of 300 radiomic features were extracted, followed by LASSO with multivariate regression analysis. The rad-score was significantly associated with disease-free survival (DFS)

and OS. Radiomics nomogram could better predict survival than the clinical model, and the TNM staging system could. However, there was no association between the rad-score and recurrence patterns.

Cozzi *et al*^[33] used CT radiomics signature to predict clinical outcomes after stereotactic body radiation therapy in 100 patients (training = 60; validation = 40) and found a clinical-radiomics signature was associated with OS and local control.

The value of texture features to predict prognosis and help clinical management in PDAC patients has been evaluated in several studies. In patients undergoing surgical resection, Kim *et al*^[34] found that high grey-level non-uniformity values suggested shorter recurrence-free survival in 116 patients, suggesting that high tumor heterogeneity was a poor prognostic indicator. However, Yun *et al*^[35] found that lower average values with homogeneous features (lower standard deviation and contrast and higher correlation) were significantly associated with poorer DFS in 18 patients. They conjectured that homogeneous texture features could represent more aggressive tumor nature, resulting from higher cellular density or dense desmoplasia. Besides, Eilaghi *et al*^[36] found that high tumor dissimilarity (high heterogeneity) and low inverse difference normalized (low heterogeneity) were associated with better OS in 30 patients. Therefore, the results of correlations between tumor heterogeneity with surgical outcome were contradictory and need further investigation.

In patients with unresectable PDAC treated with chemotherapy, Cheng *et al*^[37] found pretreatment CT texture analysis was associated with PFS and OS in 41 patients. Besides, a combination of pretreatment standard deviation (spatial scaling factor = 3) with tumor size in the survival model performed better than the standard deviation alone. Similarly, Sandrasegaran *et al*^[38] found that texture features of the mean value of positive pixels and kurtosis at medium spatial filters had a significant correlation with OS in 60 patients.

Hyun *et al*^[39] evaluated intratumoral heterogeneity measured by 18F-FDG PET texture analysis in 137 patients. The best imaging biomarker for OS prediction was first-order entropy (AUC = 0.720), followed by total lesion glycolysis (AUC = 0.697), metabolic tumor volume (AUC = 0.692), and maximum standard uptake value (AUC = 0.625). Multivariable Cox analysis demonstrated that higher entropy was independently associated with worse survival. Thus, first-order entropy is a better quantitative imaging biomarker of prognosis than conventional PET parameters.

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS GRADE AND RISK

Intraductal papillary mucinous neoplasms (IPMN) represents 15%–30% of cystic lesions of the pancreas. They are premalignant tumors that can progress from low-grade dysplasia to high-grade dysplasia to invasive cancer, accounting for 20%–30% of pancreatic cancer^[40]. The ability to identify IPMNs with low or high risk and malignant transformation into invasive cancer would optimize treatment strategy and improve surgical decision-making.

Chakraborty *et al*^[41] retrospectively analyzed pancreatic cyst and parenchyma regions on preoperative CT in 103 patients with pathologically proven branch duct-IPMN to predict IPMN risk. Expert pathologists categorized IPMNs as low or high risk following resection. A total of 131 texture features were derived from each cyst and pancreas regions. Five clinical variables were combined with imaging features to design prediction models. Their results of CT features achieved an AUC of 0.77, and the combination model obtained an AUC of 0.81.

Corral *et al*^[42] developed a new deep learning protocol on MRI to identify neoplasia for IPMN in 139 cases. A computer-aided framework was designed using CNN to classify IPMN. Their cases included normal pancreas (20%), low-grade dysplasia (34%), high-grade dysplasia (14%), and adenocarcinoma (29%). The sensitivity and specificity of the deep learning protocol to detect dysplasia were 92% and 52%, and to detect high-grade dysplasia or cancer were 75% and 78%, respectively. The deep learning protocol showed accuracy (AUC = 0.78) comparable to current radiographic criteria (American Gastroenterology Association, AUC = 0.76; Fukuoka, AUC = 0.77). Their computer-aided frameworks could assist in identifying high-risk IPMN.

Hanania *et al*^[43] investigated 360 texture features on CT images in 53 patients with IPMN (34 high-grade and 19 low-grade). These authors identified 14 imaging features within the gray-level co-occurrence matrix that predicted histopathological grade. The most predictive feature differentiated low-grade and high-grade lesions with an AUC of 0.82 (sensitivity 85%, specificity 68%). Using a cross-validated design, the best logistic regression yielded an AUC of 0.96 (sensitivity 97%, specificity of 88%).

Permuth *et al*^[44] evaluated 38 IPMNs (20 benign, 18 malignant) with preoperative CT radiomic data and matched plasma-based miRNA genomic classifier data. The miRNA classifier, high-risk, and worrisome radiologic features had AUC values of 0.83, 0.84, and 0.54, respectively. Fourteen CT radiomic features differentiated malignant from benign IPMNs with an AUC of 0.77. Combining radiomic features with the miRNA classifier revealed an AUC of 0.92 and superior predictive performance than other models. This study suggested that radiogenomic approach might more accurately predict IPMN pathology than radiologic features in consensus guidelines.

PANCREATIC NEUROENDOCRINE TUMOR GRADES

Recent updates of the World Health Organization classification separate pancreatic neuroendocrine tumor (PNET) into two broad categories, including the Ki-67 proliferative index and mitotic counts: Well-differentiated PNET and poorly differentiated pancreatic neuroendocrine carcinoma (PNEC). The classification also incorporates a new subcategory of well-differentiated grade 3 (G3) PNET^[45]. The assessment of tumor grade is essential for the prediction of prognosis and choice of the proper treatment strategy.

D'Onofrio *et al*^[46] evaluated 3D CT-texture analysis in 100 patients with NET [grade 1 (G1) in 31, grade 2 (G2) in 52, and G3 in 17 cases]. Their results showed kurtosis was significantly different among the three groups, and entropy was significantly different between the G1 and G3 groups and between the G2 and G3 groups.

Guo *et al*^[47] evaluated CT images of 37 patients (G1 in 13, G2 in 11, and G3 in 13 cases). Arterial enhancement ratio and portal enhancement ratio showed the best sensitivity (0.86–0.94) and specificity (0.92–1.0) for differentiating G3 from G1/G2, while the mean grey-level intensity, entropy, and uniformity showed acceptable sensitivity (0.73–0.91) and specificity (0.85–1.0). Mean grey-level intensity also showed acceptable sensitivity (91% to 100%) and specificity (82% to 91%) in differentiating G1 from G2.

Canellas *et al*^[48] evaluated CT images of 101 patients (G1 in 63, G2 in 35, and G3 in 3 cases). The CT features predictive of G2/3 were size larger than 2.0 cm, presence of vascular involvement, pancreatic ductal dilatation, and lymphadenopathy. The texture parameter entropy was also predictive of more aggressive tumors. Tumors with high grade (G2/3), vascular invasion, and high entropy had shorter PFS after surgical resection.

Liang *et al*^[49] used arterial phase CT to preoperatively differentiate grade 1 and grade 2/3 NET of 137 patients (training = 86, validation = 51). The Mann-Whitney U test and LASSO were applied for feature selection, and an eight-feature-combined radiomics signature was constructed. The nomogram model combining the radiomics signature with the clinical stage had the best performance (training AUC = 0.907; validation AUC = 0.891). A significant correlation was found between the nomogram model and the Ki-67 index and the rate of nuclear mitosis. The survivals of predicted grade 1 and grade 2/3 groups were significantly different.

Gu *et al*^[50] used arterial and portal venous phase CT images for preoperatively predicting grade 1 and grade 2/3 NET in 138 patients (training = 104, validation = 34). A total of 853 radiomic features were extracted. Minimum redundancy, maximum relevance, and RF methods were adopted for the feature selection. The radiomics signature had a significant association with histologic grade. The nomogram incorporating independent clinical risk factor, tumor margin, and fusion radiomics signature showed strong discrimination in the training cohort (AUC = 0.974) and validation cohort (AUC = 0.902) with good calibration.

Bian *et al*^[51] used 3T MRI for the preoperative prediction of nonfunctional PNET grade in 139 cases (training = 97, validation = 42). The LASSO and linear discriminative analysis were used to select the features and to construct a radiomics model. The clinical model revealed an AUC of 0.769 in the training cohort and 0.729 in the validation cohort. The mixed model, which combined the radiomics signature and 14 imaging features, yielded AUC values of 0.870 and 0.701. Thus, the noncontrast MRI could be used as a screening tool to help differentiate G1 and G2/3 tumors.

Currently, most studies have attempted to differentiate between G1 and G2/3 PNETs. However, the 5-year survival rates were 75%, 62%, and 7% for G1, G2, and G3, respectively^[52]. It would be more valuable to show the diagnostic values of the nomogram model in differentiating G1/G2 and G3. Furthermore, the G3 tumors are divided into two subgroups: Well-differentiated PNETs G3 and PNEC^[53]. The prognosis of the two subgroups is also different. Further studies are now needed to

differentiate well-differentiated PNET G3 and PNEC, and between PNETs G1/G2 and G3.

PANCREATIC TUMOR CHARACTERIZATION

Autoimmune pancreatitis vs pancreatic ductal adenocarcinoma

AIP has similar clinical and radiological presentations to PDAC, but the treatments of these two entities are different. Patients with AIP might be treated with oral corticosteroids, but patients with PDAC need surgical resection and chemotherapy. Thus, the differentiation of these two entities is imperative to avoid unnecessary surgical resections in patients with AIP or delayed treatment in patients with PDAC.

Park *et al*^[54] used CT-based machine learning of radiomic features to distinguish AIP from PDAC. Eighty-nine patients with AIP and 93 patients with PDAC were retrospectively included. Four-hundred-thirty-one radiomic features were extracted, and a RF method was used to discriminate AIP from PDAC. The radiomic features help differentiate AIP from PDAC with a sensitivity of 89.7%, specificity of 100%, accuracy of 95.2%, and AUC of 0.975.

Zhang *et al*^[55] used 18F FDG PET/CT to distinguish AIP from PDAC in 111 patients (AIP = 45, PDAC = 66). They extracted 251 features from 2D and 3D images and recombined these features into five feature sets according to their modalities and dimensions. Four machine learning classifiers were evaluated. CT features and 3D features performed better than PET features and 2D features, respectively. Multidomain features were superior to single domain features. In addition, the combination of the SVM-recursive feature elimination feature selection strategy and linear SVM classifier had the best performance (AUC = 0.93, accuracy = 0.85). The radiomics model was significantly superior to both human doctors and clinical factors-based prediction models.

The results of these studies are encouraging. For future work, combined features extracted from CNNs and more clinical factors to differentiate these two diseases would be an interesting direction to pursue.

Mass-forming pancreatitis vs pancreatic ductal adenocarcinoma

Ren *et al*^[56] used arterial and portal phase CT texture analysis to differentiate 30 patients with MFP and 79 patients with PDAC. Arterial CT attenuation, arterial, and portal enhancement ratios of MFP were higher than PDAC. Arterial CT attenuation and pancreatic duct penetrating sign were independent predictors in multivariate analysis. AUC of imaging feature-based, texture feature-based in arterial and portal phases, and the combined models were 0.84, 0.96, 0.93, and 0.98, respectively. Thus, CT texture analysis holds great potential to differentiate MFP from PDAC.

Mashayekhi *et al*^[57] used CT radiomics to differentiate 56 patients with recurrent acute pancreatitis ($n = 20$), functional abdominal pain ($n = 19$), or chronic pancreatitis ($n = 17$). In 54 radiomic features extracted by one-vs-one Isomap SVM classifier, 11 radiomic features were significantly different between the patient groups with an overall accuracy of 82.1%.

Serous and mucinous cystadenomas

Yang *et al*^[58] used CT textural features in the differential diagnosis of pancreatic serous cystadenomas ($n = 53$) and mucinous cystadenomas ($n = 25$). Textural parameters were analyzed using RF and LASSO methods. Patients were divided into training and validation sets with a ratio of 4:1. Radiomic features were able to separate serous from mucinous cystadenomas in both the training group (slice thickness of 5 mm, AUC 0.72, accuracy 0.86) and the validation group (AUC 0.75, accuracy 0.83). These results might provide a noninvasive approach to determine whether surgery or imaging follow up is suitable for these patients.

CHALLENGES AND PROSPECTS OF ARTIFICIAL INTELLIGENCE IN THE PANCREAS

There are three main challenges for the application of AI in the pancreas. First, the image analysis methods are diverse and variable, so many study results are inconsistent and contradictory. To ensure the availability of accurate and reproducible radiomics data, the initiatives to standardize the development of quantitative imaging

biomarkers have recently been developed^[59]. Second, the public data of pancreatic imaging available for machine-learning is insufficient, because most early pancreatic lesions are small and occult, and require labor-intensive work from experienced radiologists to label the target lesion. Automatic detection and segmentation of these pancreatic lesions, either with or without the aid of a radiologist, is needed to solve this issue. Third, most studies are retrospective, with limited clinical, laboratory, and outcome data. Previous studies have shown that combined models of radiomic and clinical factors achieve better performance than each individual model. Upcoming prospective studies that combined radiomics and clinical data, even with genomic data, are warranted. Ultimately, it is only with the availability of robust integrated radiomics and comprehensive clinical data that we can proceed to deploy AI in daily practice to improve the care of our patients.

CONCLUSION

The pancreas has both an endocrine and an exocrine digestive function, and its imaging presentations are diverse and frequently pose a diagnostic dilemma in clinical settings. The use of AI will greatly facilitate accurate pancreatic lesion detection, characterization, treatment response evaluation, and prognosis prediction in these patients. Currently, radiomics is under rigorous investigation in various pancreatic diseases, and recent study results are promising. With the growth of advanced AI technology and the availability of standardized imaging data, it seems likely that we will accomplish the goal of precision medicine and increase patients' outcomes in the near future.

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