Preoperative Differentiation of Pancreatic Cystic Neoplasm Subtypes on CT-Based Radiomics: SCN, MCN And IPMN

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Research

Keywords: pancreatic cystic neoplasm, radiomics, contrast-enhanced computed tomography, pancreatic phase, differential diagnosis

Posted Date: October 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-968579/v1>

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Abstract

Background:

The serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) comprise the large proportion of pancreatic cystic neoplasm (PCN). The appropriate clinical management of MCN and IPMN is extremely essential to improve the 5-years survival rate for the early detection of pancreatic cancer. However, the differential diagnosis of patients with PCN before the treatment is still a tough challenge for all surgeons. Therefore, a reliable diagnosis tool is urgently required to be established for the improvement of precision diagnostics.

Method:

Between February 2016 and December 2020, 143 consecutive patients with PCN who were confirmed by postoperative pathology were retrospectively included in the study cohort, randomized into development and test cohort at the ratio of 7:3. The predictors of preoperative clinical-radiologic parameters were evaluated by the use of univariate and multivariable logistic regression analysis. A total of 1218 radiomics features were computationally extracted from the enhanced computed tomography (CT) of tumor region and a radiomics signature was established by the random forest algorithm. In the development cohort, the multi-class and binary-class radiomics models integrating preoperative variables and radiomics features were constructed to distinguish between the three types of PCN. The independent internal test cohort was applied to validate the classification models.

Result:

All preoperative prediction models were built by integrating the radiomics signature with thirteen diagnosis-related radiomics features and three important clinical-radiologic parameters of age, sex and tumor diameter. The multi-class prediction model presented an overall accuracy of 0.804 in the development cohort and 0.707 in the test cohort. The binary-class prediction models displayed the higher overall accuracy of 0.853, 0.866, 0.928 in the development dataset and 0.750, 0.839, 0.889 in the test dataset. In the test cohort, the binary-class radiomics models showed better predictive performances (AUC = 0.914, 0.863, 0.926) than the multi-class radiomics model (AUC = 0.850), with a large net benefit in the decisive curve analysis. The radiomics-based nomogram provided the correct predicted probability for the diagnosis of PCN.

Conclusion:

The proposed radiomics models with clinical-radiologic parameters and radiomics features helped predict the accurate diagnosis among SCN, MCN, and IPMN to advance personalized medicine.

Introduction

Pancreatic cancer is a highly aggressive and malignant gastrointestinal tumor with the lowest 5-year survival of 10% for all cancers [1, 2]. Pancreatic cancer is estimated to be the second cause of cancer-associated death in the next few decades in the USA [3]. However, once the apparent clinical symptoms are present, almost all the patients are diagnosed with the advanced stage [2, 4]. Currently, the early detection of pancreatic cancer is widely recognized to improve the patient health benefit of longer median survival times [5, 6]. The mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) among the pancreatic cystic neoplasm

(PCN) are the important precursor lesions to provide the greater likelihood for the screening and early diagnosis of pancreatic cancer[7, 8]. Consequently, the correct diagnosis of PCNs before the treatment is considerably essential for clinical decision support.

Pancreatic cystic neoplasms represent a heterogeneous group of cystic lesions that mainly consisting of serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), solid pseudopapillary neoplasms (SPN), and cystic pancreatic neuroendocrine tumor (PNET), in which the IPMN, SCN and MCN are the major types of the PCNs [9, 10]. The ability of differential diagnosis among three PCN subtypes of SCN, MCN and IPMN ahead of treatment is necessary to improve the management and clinical outcomes due to the variable potential of malignancy[11]. IPMN and MCN patients with a high rate of malignant potential are mostly required to either undergo the surgical resection or receive the lifelong follow-up for surveillance of disease progression [12, 13]. Conversely, SCN was considered as benign lesions; the surgery and follow-up are not recommended unless the specific symptoms exist[14].

The reported prevalence of pancreatic cystic neoplasms is dramatically increasing with the widespread recommendation of annual physical examinations [15]. Presently, the majority of PCNs are incidentally detected on the abdominal computed tomography (CT) examinations, and thus these CT scans provide the available imaging dataset for diagnostic studies [16]. The pancreatic protocol CT and gadolinium-enhanced MRI with MRCP are the main diagnostic imaging modalities for the identification of different PCNs subtypes, and the endoscopic ultrasonography (EUS) is recognized as the complementary means to obtain a more precise diagnosis [17, 18]. Although the promising advances in imaging techniques, the distinction between the various PCN types still represents a great clinical challenge for practicing physicians[19]. Consequently, the phenomenon of misdiagnosis for PCNs patients is commonly reported even in the renewed hospital of the big city[20].

The exponential advances in medical image analysis have facilitated the progression of the novel field called radiomics, which represents the processes for the high-throughput extraction of numerous quantitative features from medical images[21, 22]. Radiomics provides the great potential to assess the extensive inter-and intra-tumoural heterogeneity hidden in the radiologic images, as well-known as a non-invasive approach [23]. The role of radiomics is committed to becoming an important adjunct to clinical decision making in two aspects of diagnosis and prognosis[24, 25]. Previous studies suggested that widespread use of radiomics in pancreatic lesions have significantly improved the ability of diagnosis and clinical management[26–28]. Moreover, some recent studies indicate that radiomics hold great promise for differential diagnosis of PCN subtypes [29–31]. Nevertheless, there is still an urgent demand to improve the diagnosis performance of radiomics-based models.

Our study aims to construct an automated model to make the precise diagnosis of PCNs for precision medicine. The radiomics models consisting of clinical-radiologic parameters and radiomics features would improve the diagnosis accuracy and assist the involved physicians in making optimized treatment decisions to reduce the morbidity and mortality rates of pancreatic cancer.

Material And Methods

Patients

The retrospective study was approved by the ethics committee of the Institutional Review Board of Nanjing Drum Tower Hospital, and the informed consent from patients was waived.

Between February 2016 and December 2020, 302 consecutive patients with PCNs who underwent curative resection at our center were retrospectively evaluated (Fig. 1).

The inclusion criteria were as follows: (a) with the postoperative pathological diagnosis of MCN, SCN or IPMN; (b) with the identifiable cystic lesion in contrast-enhanced CT images within three weeks before curative resection; (c) without any systemic or focal therapy before CT examination and surgery; (d) with available clinicopathological parameters.

The exclusion criteria were as follows: (a) complicated with other hepatic-biliary-pancreatic malignant tumors (n = 27); (b) with artifacts on CT images in arterial phase or venous phase (n = 9); (c) with difficulty in outlining the margin of the tumor because of the size (the maximum diameter <1cm) and poor contrast of the lesion (n = 10).

Eventually, a total of 143 patients (median age, 53 years; interquartile range, 43-66 years; 77 females, 66 males) were enrolled in our study cohort. The dataset of patients with PCN was randomly divided into two groups at the ratio of 7:3, development and test cohort. The development cohort consisted of 102 patients (MCN 35, SCN 33, IPMN 34) and the test cohort consisted of 41 patients (MCN 10, SCN 14, IPMN 17).

Preoperative clinical data and postoperative pathological information of those patients were obtained from the electronic medical record system.

Ct Technique

All CT examinations were performed with a multidetector spiral CT scanner (LightSpeed, VCT, or Discovery HD750, GE Healthcare, US). The parameters of contrast-enhanced CT scans were as follows: tube voltage 120 kVp, tube current 250–300 mAs, slice thickness: 1.25mm, slice interval: 1.25mm, matrix: 512x512, rotation time: 0.6s, helical pitch 1.375, field of view: 35-40cm. All patients were required to fast for at least 6-8 hours before the CT scan and placed in the supine position with their arms raised during the scanning. The scan range was from the dome of the diaphragm to the lower pole of the kidney. After the unenhanced CT scan, the iodinated contrast agent (Omnipaque 350 mgI/mL, GE Healthcare, US) at a rate of 1.5 mL/kg per body weight was injected intravenously by the high-pressure syringe (Medrad Stellant CT injector system; One Medrad Drive Indianola, PA, US). The pancreatic phase, and portal venous phase of contrast enhancement were obtained respectively at 40-50 seconds and 65-70 seconds after the injection of the contrast agent. The mean interval between the CT scan and surgery was 8.5 ± 3.6 days (range, 7–20 days).

Ct Images Acquisition And Segmentation

The radiomics workflow is shown in Figure 2. The contrast-enhanced computed tomography images of PCNs with 1.25 mm thickness (DICOM) were obtained from the Picture Archiving and Communication System (PACS) in our hospital. The pancreatic phase of the contrast-enhanced CT images revealed the distinct regional difference in contrast sensitivity between the normal pancreas tissue and pancreatic cystic tumor, which was selected for analysis of the tumor heterogeneity and correlation with clinical parameters and imaging features. The regions of interest (ROIs) of the whole tumor area were automatically segmented with a deep-learning segmentation algorithm for the study. The segmentation images of all tumor regions were corrected on each section by two radiologists (Z.Y.F and W J, with 4 years and 10 years of experience in abdominal imaging, respectively) using the

ITK-SNAP (version 3.8.0, <https://www.itksnap.org/>), avoiding the pancreatic parenchyma and large vessels around the tumor and adjacent abdominal organs. Two radiologists were blinded to the clinicopathological information of all the patients during the period of segmentation. The radiologists performed the segmentation twice in a 2-week independently to evaluate inter- and intra-observer reproducibility to determine the stability of each radiomic feature extracted from the ROIs.

Radiomic Feature Extraction And Selection

The image pre-processing and radiomic feature extraction were implemented by the

Open-source Pyradiomics package (version 3.0.1, <https://github.com/Radiomics/pyradiomics>). Resampling-based approaches and normalization techniques were performed to improve the repeatability, stability, and accuracy of feature extraction. The voxel size of CT images was resampled to the $1 \times 1 \times 1 \text{ mm}^3$; images intensity was normalized by discretizing values of voxel intensity as 64 gray levels for the non-homogeneity of spatial intensity. A total of 1218 radiomics features were extracted from each of three-dimensional segmentation in the pancreatic phase, which consisted of the first-order statistics ($n = 19$), shape descriptors (3D, $n = 16$), 75 texture features (GLCM, GLSZM, GLRLM, NGTDM, GLDM; $n = 75$), wavelet decompositions ($n = 688$) and LoG-based features ($n = 430$). Subsequently, all feature values were centered and standardized by z-scores for all analyses.

The feature selection process was conducted to follow the three steps for identifying the robust characteristics. Before the feature screening, all data were normalized to range [0,1], avoiding the impact of significant discrepancy between the values. The specific process of feature selection was as follows. In the first step, we excluded the radiomic features with poor stability from the dataset (intraclass correlation coefficients lower than 0.75) in the assessment of test-retest and interobserver agreement. Subsequently, the Pearson correlation test was employed to filter out the redundant features with the average and absolute coefficient higher than 0.8. Ultimately, the Boruta algorithm was applied to select the important features for the establishment of radiomic signature by the Random Forest (RF) classifier, as high-related with differential diagnosis in the PCNs.

Model Development And Validation

We developed two types of preoperative radiomics models by RF classifier: the multi-class prediction model was constructed to discriminate three pancreatic cystic neoplasm subtypes; the binary-class prediction models made pairwise classification among three subtypes of MCN, SCN and IPMN. The above radiomics models included the radiomic signature and significant clinical-radiologic characteristics before surgery. The overview of the RF modeling process was shown in Figure 3. Univariate analysis of clinical-radiologic parameters with P value lower than 0.1 was entered into multivariable analysis. The final risk factors among the clinical and imaging features were selected using multivariable logistic regression by stepwise backward method to eliminate the non-significant features. All of models were validated in an independent test cohort.

Statistical Analysis

Shapiro-Wilk test and Levene test were used for normality and homogeneity of variances, respectively. Continuous variables were expressed as median with interquartile range in parentheses, and categorical variables were expressed as total numbers and frequencies. Univariate analysis was performed to analyze clinical-radiologic

parameters: Chi-square test, corrected chi-square test or Fisher test was used for categorical variables; independent sample t-test or Mann-Whitney U test was used for continuous variables. Multivariate logistic regression analysis was applied to select the important predictors of clinical parameters. The radiomics signature was built based on the selected radiomics features by the packages “Boruta” in R. The receiver operating characteristic (ROC) analysis was used to evaluate predictive efficiency of the model. And the area under ROC curve (AUC), sensitivity and specificity were obtained to assess the performance of the prediction model. Decision curve analysis was performed to evaluate the net benefits of the prediction models. The statistical analysis was conducted with software (R, version 4.1.0, <http://www.r-project.org>). A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

Patients Characteristics of the Study Cohorts

The preoperative clinical-radiologic characteristics of all PCN patients were found no significant difference in the development and test cohort, as shown in Table 1. From February 2016 and December 2020, there was a total of 143 pancreatic cystic neoplasms patients enrolled in our study cohort, including 45 MCN patients, 47 SCN patients and 51 IPMN patients. The proportion of males and females in the population of MCN, SCN and IPMN patients was 1:6.5, 1:2.9, and 1:0.4; the median age with interquartile range was 60 (47.75, 68.25) years, 55 (44.00, 62.00) years and 66 (61.00, 71.00) years, respectively. Comparison of consistency between preoperative radiological and postoperative pathological diagnosis, the result showed that diagnostic accuracy and precision of preoperative imaging findings in PCNs patients were relatively low. The rate of accurate diagnosis was 16.67%, 10.64% and 56.86%, respectively for the MCN, SCN and IPMN. Among the three subtypes, the percentage of PCNs patients with ambiguous diagnosis was separately 73.33%, 70.21%, and 39.22% (MCN, *n* = 33; SCN, *n* = 33; IPMN, *n* = 22). In our institution, the misdiagnosis rate of MCN, SCN, IPMN patients was 10.00%, 19.15%, and 3.92%, respectively.

Table 1
The clinical and imaging Characteristics of PCN patients in development and test cohort

characteristic	Development cohort (n=102)	Test Cohort (n=41)	p Value
Age	54.5 (43.0, 66.0)	61.0 (42.0, 67.0)	0.449
Sex	59 (57.8%)	18(43.1%)	0.132
Female	43 (42.2%)	23 (56.1%)	
Male			
Primary tumor type	35 (34.3%)	10 (24.4%)	0.670
MCN	33 (32.4%)	14 (34.1%)	
SCN	34 (33.3%)	17 (41.5%)	
IPMN			
Chronic pancreatitis	7(6.9%)	4 (9.8%)	0.558
Present	95(93.1%)	37(90.2%)	
Absent			
Abdominal symptom	53(52.0%)	22(53.7%)	0.855
Present	49(48.0%)	19(46.3%)	
Absent			
History of Diabetes	7(6.9%)	5(12.2%)	0.300
Present			
Absent	95(93.1%)	36(87.8%)	
Serum AFP (ng/ml) *	2.0 (1.3, 3.1)	1.8 (1.3, 2.6)	0.115
Serum CA19-9 (U/ml) *	10.2 (6.3, 15.5)	10.4 (6.5, 10.4)	0.641

Note: Except where indicated, data are numbers of patients, with percentages in parentheses. AFP = a-fetoprotein, CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CA125 = carbohydrate antigen 125, CA724 = carbohydrate antigen 724, CA242 = carbohydrate antigen 242, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALB= albumin.

*Data are medians, with parentheses are the interquartile range.

characteristic	Development cohort (n=102)	Test Cohort (n=41)	p Value
Serum CEA (ng/ml) *	0.8 (0.5, 1.8)	1.0 (0.5, 2.0)	0.250
Serum CA125 (U/ml) *	8.7 (5.4, 11.1)	9.3 (6.8, 11.6)	0.507
Serum CA72-4 (U/ml) *	1.5 (1.0, 2.7)	1.7 (1.1, 3.1)	0.809
Serum CA242 (U/ml) *	4.3 (3.0, 7.6)	4.0 (2.3, 6.1)	0.724
Serum ALT (U/L) *	15.9(11.9, 22.4)	18.7(15.2, 23.9)	0.554
Serum AST (U/L) *	18.7(15.2, 23.9)	18.8(16.0, 24.0)	0.746
Serum ALB (g/L) *	40.1(39.5, 42.1)	40.8(38.6, 42.5)	0.465
Lesion location	33(32.4%	19(46.3%)	0.370
Head and neck	50 (49.0%)	16(39.0%)	
Body and tail	12(11.8%)	2(4.9%)	
Uncinate	7(6.9%)	4(9.8%)	
Diffuse			
Tumor diameter (cm) *	2.83(1.85, 4.63)	2.81(2.17, 4.15)	0.857
Tumor number	79(77.5%)	29(70.7%)	0.400
Solitary	23(22.5%)	12(29.3%)	
Multiple			
Mean CT value (HU)	37(-8, 64.2)	26(-10, 59)	0.381
Calcification			0.595
Present	16(15.7%)	5(12.2%)	
Absent	86(84.3%)	36(87.8%)	
pancreatic duct dilatation			0.06
Present	55(53.9%)	30(73.2%)	
Absent	47(46.1%)	11(26.8)	
Bile duct dilatation			0.808
Present	14(13.7%)	5(12.2%)	
Absent	88(86.3%)	36(87.8%)	
Note: Except where indicated, data are numbers of patients, with percentages in parentheses. AFP = a-fetoprotein, CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CA125 = carbohydrate antigen 125, CA724 = carbohydrate antigen 724, CA242 = carbohydrate antigen 242, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALB= albumin.			
*Data are medians, with parentheses are the interquartile range.			

Univariate And Multivariate Analysis Of Clinical-radiologic Parameters

Table 1 showed the researchers retrospectively collected and analyzed baseline characteristics that were considered clinically relevant with the outcome of diagnosis. Univariate logistic regression analysis of the clinical data and radiological features indicated that the age, sex, abdominal symptom, serum tumor markers [alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA)], serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), tumor diameter, calcification, bile duct dilatation and lesion location were statistically significant ($P < 0.1$) between the three subtypes in the development cohort. Next, the significant variables were entered into multivariate logistic regression to obtain the risk factors for diagnosis of PCNs. The statistical data of multivariate analysis was completely shown in Table 2. The result indicated that the age ($P = 0.001, 0.005, 0.041$), sex ($P = 0.005, 0.041, 0.017$) and tumor diameter ($P < 0.000, 0.020, 0.021$) were independent risk factors for differential diagnosis between MCN and SCN, MCN and IPMN, SCN and IPMN.

Table 2
Multivariate Logistic Regression analysis of risk factors in development cohort

	MCN vs SCN		MCN vs IPMN		SCN vs IPMN	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
age	0.863(0.792, 0.941)	0.001*	0.598(0.418, 0.857)	0.005*	0.693(0.487, 0.985)	0.041*
sex	0.122(0.010, 1.549)	0.005*	32.017(1.564, 65.520)	0.041*	262.102(9.525, 725.121)	0.017*
Abdominal symptom	1.353(0.296, 6.180)	0.696	0.042(0.000, 4.422)	0.182	0.031(0.000, 2.951)	0.135
CEA	3.660(0.831, 16.112)	0.086	2.236(0.089, 56.235)	0.625	0.611(0.026, 14.307)	0.759
AFP	2.261(0.958, 5.336)	0.062	1.266(0.429, 3.730)	0.669	0.560(0.192, 1.629)	0.287
ALT	0.828(0.668, 1.026)	0.084	1.022(0.720, 1.450)	0.905	1.233(0.893, 1.703)	0.202
AST	1.151(0.914, 1.448)	0.232	0.779(0.484, 1.254)	0.303	0.677(0.415, 1.103)	0.118
Tumor diameter	1.3104(1.160, 11.126)	0.000*	33.913(1.732, 66.388)	0.020*	33.446(1.709, 645.413)	0.021*
Calcification	3.234(0.534, 19.577)	0.201	1.463(0.000, 30.172)	0.994	45.249(0.000, 94.340)	0.994
Bile duct dilatation	2.316(0.075, 60.672)	0.657	0.368(0.004, 34.070)	0.665	0.172(0.003, 11.115)	0.408
Lesion location	2.136(0.075, 60.672)	0.657	17.143(0.001, 214.380)	0.242	69.886(0.001, 403.815)	0.483
Note: Numbers in parentheses are the 95% confidence interval. CI: confidence interval; *, $P < 0.05$.						

Radiomic Feature Selection And Signature Construction

Among 1218 radiomics features extracted from CT images, 866 features were selected by evaluation of the intraclass correlation coefficient (ICC > 0.75). Then, the Pearson correlation test was used to exclude 722 features with high correlation coefficients.

The Boruta algorithm was conducted to screen 13 features to construct a radiomics signature by RF analysis. The important features selected from Boruta algorithm were presented in Figure 4. The radiomics signature demonstrated good prediction ability with the out-of-bag (OOB) error of 0.317 and a C index of 0.772 in the test cohort, and the diagnosis performance was summarized in Table 3.

Table 3
Diagnosis performance of the radiomics signature in the development and test cohort

Development cohort							Test cohort					
P/T	SCN	MCN	IPMN	Pre	Rec	F1	SCN	MCN	IPMN	Pre	Rec	F1
SCN	23	5	4	0.719	0.697	0.708	6	0	2	0.750	0.429	0.546
MCN	7	29	1	0.784	0.829	0.806	2	9	2	0.692	0.692	0.692
IPMN	3	1	29	0.879	0.853	0.866	6	1	13	0.650	0.765	0.698
Total	33	35	34	OA	0.794		14	13	17	OA	0.683	
Note: T, True type; P, Predicted type; Pre, Precision; Rec, Recall; OA: Overall accuracy. Precision = Tree Position/(Tree Position + False Position); Recall = Tree Position/(Tree Position + False Negative); F1-score = 2 × Precision × Recall/(Precision + Recall).												

Prediction Models Development And Validation

The radiomics-based models were established by three significant clinical-radiologic parameters at multivariable analysis and radiomics signature in the development cohort.

The multi-class prediction model indicated that the classification error (out-of-bag estimate) reached stable with the minimum value of 19.61%, when the number of trees was more than 500 and three variables were tried at each split. Figure 5 illustrated the relationship between error rate and the number of trees in the process of multi-class model construction. In the development dataset, the multi-class radiomics model had an overall accuracy of 0.804 and the respective precision of 0.800, 0.727 and 0.929 for SCN, MCN and IPMN (Table 4). In the test dataset, the overall accuracy to classify the triple tumors was 0.707 and the precision of identification severally for SCN, MCN and IPMN was 0.750, 0.667 and 0.722.

Table 4
Diagnosis performance of the multi-class prediction model in the development and test cohort

Development cohort							Test cohort					
P/T	SCN	MCN	IPMN	Pre	Rec	F1	SCN	MCN	IPMN	Pre	Rec	F1
SCN	24	2	4	0.800	0.727	0.762	6	0	2	0.750	0.429	0.546
MCN	8	32	4	0.727	0.914	0.810	3	10	2	0.667	1.000	0.800
IPMN	1	1	26	0.929	0.765	0.839	5	0	13	0.722	0.765	0.743
Total	33	35	34	OA	0.804		14	10	17	OA	0.707	
Note: T, True type; P, Predicted type; Pre, Precision; Rec, Recall; OA: Overall accuracy.												

Table 5A. Diagnosis performance of the SCN-MCN model in the development and test cohort

Development cohort						Test cohort				
P/T	SCN	MCN	Pre	Rec	F1	SCN	MCN	Pre	Rec	F1
SCN	27	4	0.871	0.818	0.844	8	0	1.000	0.571	0.727
MCN	6	31	0.838	0.886	0.861	6	10	0.625	1.000	0.769
Total	33	35	OA	0.853		14	10	OA	0.750	

Table 5B. Diagnosis performance of the MCN-IPMN model in the development and test cohort

Development cohort						Test cohort				
P/T	MCN	IPMN	Pre	Rec	F1	MCN	IPMN	Pre	Rec	F1
MCN	33	3	0.917	0.943	0.930	10	3	0.769	1.000	0.869
IPMN	2	31	0.939	0.912	0.925	0	14	1.000	0.823	0.903
Total	35	34	OA	0.928		10	17	OA	0.889	

Table 5C. Diagnosis performance of the SCN-IPMN model in the development and test cohort

	Development cohort					Test cohort				
P/T	SCN	IPMN	Pre	Rec	F1	SCN	IPMN	Pre	Rec	F1
SCN	29	5	0.853	0.879	0.866	11	2	0.846	0.786	0.828
IPMN	4	29	0.879	0.853	0.866	3	15	0.833	0.882	0.857
Total	33	34	OA	0.866		14	17	OA	0.839	

Note: T, True type; P, Predicted type; Pre, Precision; Rec, Recall; OA: Overall accuracy.

The binary-class radiomics models were composed of three classification models to distinguish between SCN and MCN; MCN and IPMN, SCN and IPMN. The SCN-MCN model, MCN-IPMN model and SCN-IPMN model showed the overall accuracy of 0.853, 0.928, 0.866 in the development cohort, and 0.750, 0.889, 0.839 in the test cohort. For the SCN-MCN model, the precision was 0.871 and 0.838 in the development dataset (Table 5A). For MCN-IPMN model, the precision was 0.917 and 0.939 in the development cohort (Table 5B). Meanwhile, the precision of SCN-IPMN model was 0.853 and 0.879 in the development cohort in Table 5C.

All binary class prediction models virtually presented the higher overall accuracy and F1-score than the multi-class prediction model both in the development and test cohort. Especially, the model for diagnosis classification of MCN and IPMN yielded favorable predictive performance. By analyzing ROC curve in the test cohort, the multi-class radiomics model integrating radiomic and clinical-radiologic features improved the diagnostic accuracy efficacy, compared with the radiomics signature (Figure 6). The value of AUC was 0.772 and 0.850, respectively. However, the binary-class radiomics model showed the best discriminatory ability, with the value of AUC was 0.914 for SCN and MCN, 0.863 for SCN and IPMN, 0.926 for MCN and IPMN in the test cohort.

The calibration curve demonstrated that the model-predicted subtype was well-calibrated with the pathologically confirmed subtype in the binary-class radiomics models (Figure 7). With decision curve analysis, three binary-class prediction models displayed a great net benefit under the suitable range of threshold probabilities in the test dataset (Fig. 7). As shown in Figure 8, the nomogram was performed to visualize the binary-class radiomics models and provide the predicted probability of tumor subtypes for the individuals.

Discussion

The study had retrospectively enrolled patients with pathologically diagnosed as three subtypes of PCNs to predict the precise histological types preoperatively. The RF classifier was the optimal algorithm selected from the multiple radiomics methods used to construct of all the models. Ultimately, all the classification models were composed of the three significant clinical-radiologic characteristics (age, sex, tumor diameter) and radiomics signature with thirteen radiomics features in the development cohort.

Compared to previous studies, our study had a distinct advantage in the image segmentation method. The ROI of cystic neoplasms was achieved by using automatic segmentation via a new deep-learning network system. The explicit introduction of targets' geometric information in the deep learning network was helpful to obtain a better segmentation boundary[32]. The proposed segmentation method leads to significant improvements in the stability and robustness of radiomic features.

Two types of classification models were developed to make a more accurate and precise diagnosis of MCN, SCN, and IPMN. The binary-class prediction models displayed a higher overall accuracy both in the development and test datasets than the multi-class prediction model. Apparently, the binary-class radiomics models showed better predictive performances with high AUC values than the multi-class radiomics model in the test cohort. Among the three binary-class classification models, the SCN-IPMN model provided the highest value of AUC and presented the excellent net benefit in the analysis of decision curves in the test cohort. Using the nomogram to visualize diagnosis prediction models, the analysis of nomogram indicated that radiomics models had a potential ability for differentiation diagnosis of cystic pancreatic neoplasms.

Therefore, the commitment of our research was to enhance diagnosis efficacy of preoperative prediction model, compared with other clinical and radiomics models in the previous study. Furthermore, our result was consistent with the other research. Dmitriev et al. found that the ensemble classifier combining of the RF and Convolutional Neural Networks algorithm was established by 14 selected quantitative features (age and gender, cyst location, intensity and shape features) outperformed the conventional clinical model (accuracy 83.6% vs. 62%)[33]. Shen et al. found that the RF model including 4 important clinical characteristics (age, gender, serum CA 19-9, serum CEA) and 5 radiomics features from CT images presented the highest discrimination ability of differential diagnosis for SCN, MCN and IPMN than the SVM model and the ANN model (84% in the training dataset and 80% in the validation dataset)[30]. In our study, the distinctive radiologic characteristics were selected to implement the clinical and radiomics features for diagnosis prediction of three subtypes. The wavelet-based and log-based radiomics features occupied an important place in the signature. According to the previous reports, the above radiomics features would represent the heterogeneity of tumor tissue and tumor microenvironment from multiple dimensions of the space. The binary class model showed a better overall accuracy of 85.3%, 86.6%, 92.8% in the development cohort and 75.0%, 83.9%, 88.9 % in the test cohort. The radiomics models all achieved the great value of AUC and calibration results in the test cohort.

Currently, the treatment protocols of MCN, SCN, and IPMN are significantly different in the clinical management of surgery and surveillance. According to current evidence and guidelines, the resection is recommended for MCN which is larger than 40mm or in the presence of symptoms and risk factors, otherwise the follow-up should be performed for screening of disease progression[12]. IPMN are recommended to undergo surgical resection and receive lifelong postoperative surveillance, with evidence of IPMN recurrence or IPMN-associated aggressive malignancy development[34]. Once the diagnosis of SCN is clear, the patients with symptoms of compressing the adjacent organs are only recommended to require surgery; follow-up is required to be continued based on the presence of clinical symptoms after one-year surveillance for asymptomatic SCN. Improving diagnosis accuracy is urgently needed to make personalized and precision medicine become a reality for every patient.

Our research has some limitations. First, all the datasets were from a single medical center and the number of included PCNs patients was slightly limited, although the internal validation was applied to enhance the reliability of radiomics models. Second, the study was a retrospective analysis which resulting in potential selection bias. Third, all of the contrast-enhanced CT images were acquired with the same CT scanner and fixed parameters. Therefore, the reproducibility and stability of radiomics features extracted from CT images required further validation in the multiple brands of CT scanners. Finally, the dataset was only committed to classifying the three most common pancreatic cystic neoplasms. In the future, the other cystic subtypes will be included in the dataset.

Conclusion

In conclusion, the radiomics model consisting of clinical-radiologic characteristics and radiomics features based on enhanced CT images demonstrates the promising diagnosis performance and discrimination ability for the subtypes of pancreatic cystic neoplasms. And the binary-class prediction models are superior to the multi-class prediction model in an overall accuracy of diagnosis. Further studies are required to improve the clinical utility of the radiomics models to help surgeons provide precise diagnosis information for PCNs patients.

Abbreviations

SCN

serous cystic neoplasm

MCN

mucinous cystic neoplasm

IPMN

intraductal papillary mucinous neoplasm

PCN

pancreatic cystic neoplasm

SPN

solid pseudopapillary neoplasm

CT

computed tomography

PNET

cystic pancreatic neuroendocrine tumor

EUS

endoscopic ultrasonography

PACS

picture archiving and communication system

ROIs

regions of interests

RF

random forest

ROC

receiver operating characteristic

AUC

the area under the receiver operating characteristic curve

AFP

alpha-fetoprotein

CEA

carcinoembryonic antigen

ALT

serum alanine aminotransferase

AST

serum aspartate aminotransferase

OOB

out-of-bag

Declarations

Acknowledgements

We would like to express our great appreciation to the R Development Core Team and contributors for R packages used in our study. We thank Jun Ma for supporting the new deep-learning network system to obtain a better segmentation boundary.

Authors' contributions

S.Xu, F.Zhang, J.Wu and N.Tang collected data; S.Xu, F.Zhang, J.Wu and N.Tang analyzed data; S.Xu, F.Zhang, J.Wu and J.He participated in research design; S.Xu, F.Zhang, N.Tang and J.He contributed to the writing of the manuscript discussing data and supervised the study; and all authors read and approved the final manuscript.

Funding

This project is supported by China's Ministry of Science and Technology (No. 2020YFA0713800), and the National Natural Science Foundation of China (No.12090023).

Availability of data and materials

The data is not available because of patients' privacy.

Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. The requirement for written informed consent was waived due to its retrospective nature.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

References

1. Siegel, R.L., et al., *Cancer Statistics, 2021*. CA Cancer J Clin, 2021. **71**(1): p. 7-33.
2. Chen, X., et al., *Cell death in pancreatic cancer: from pathogenesis to therapy*. Nat Rev Gastroenterol Hepatol, 2021.
3. Mizrahi, J.D., et al., *Pancreatic cancer*. Lancet, 2020. **395**(10242): p. 2008-2020.
4. Ho, W.J., E.M. Jaffee, and L. Zheng, *The tumour microenvironment in pancreatic cancer - clinical challenges and opportunities*. Nat Rev Clin Oncol, 2020. **17**(9): p. 527-540.
5. Pereira, S.P., et al., *Early detection of pancreatic cancer*. Lancet Gastroenterol Hepatol, 2020. **5**(7): p. 698-710.

6. Singhi, A.D., et al., *Early Detection of Pancreatic Cancer: Opportunities and Challenges*. Gastroenterology, 2019. **156**(7): p. 2024-2040.
7. Munigala, S., A. Gelrud, and B. Agarwal, *Risk of pancreatic cancer in patients with pancreatic cyst*. Gastrointest Endosc, 2016. **84**(1): p. 81-6.
8. Lennon, A.M., et al., *The early detection of pancreatic cancer: what will it take to diagnose and treat curable pancreatic neoplasia?* Cancer Res, 2014. **74**(13): p. 3381-9.
9. van Huijgevoort, N.C.M., et al., *Diagnosis and management of pancreatic cystic neoplasms: current evidence and guidelines*. Nat Rev Gastroenterol Hepatol, 2019. **16**(11): p. 676-689.
10. Kromrey, M.L., et al., *Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study*. Gut, 2018. **67**(1): p. 138-145.
11. Keane, M.G. and E. Afghani, *A Review of the Diagnosis and Management of Premalignant Pancreatic Cystic Lesions*. J Clin Med, 2021. **10**(6).
12. *European evidence-based guidelines on pancreatic cystic neoplasms*. Gut, 2018. **67**(5): p. 789-804.
13. Tanaka, M., *Clinical Management and Surgical Decision-Making of IPMN of the Pancreas*. Methods Mol Biol, 2019. **1882**: p. 9-22.
14. Yoon, J.G., et al., *Pancreatic cystic neoplasms: a review of current recommendations for surveillance and management*. Abdom Radiol (NY), 2021. **46**(8): p. 3946-3962.
15. Pandey, P., et al., *Follow-up of Incidentally Detected Pancreatic Cystic Neoplasms: Do Baseline MRI and CT Features Predict Cyst Growth?* Radiology, 2019. **292**(3): p. 647-654.
16. Okasha, H.H., et al., *Cystic pancreatic lesions, the endless dilemma*. World J Gastroenterol, 2021. **27**(21): p. 2664-2680.
17. Du, C., et al., *Comparison of endoscopic ultrasound, computed tomography and magnetic resonance imaging in assessment of detailed structures of pancreatic cystic neoplasms*. World J Gastroenterol, 2017. **23**(17): p. 3184-3192.
18. Carmicheal, J., et al., *Elevating pancreatic cystic lesion stratification: Current and future pancreatic cancer biomarker(s)*. Biochim Biophys Acta Rev Cancer, 2020. **1873**(1): p. 188318.
19. Tirkes, T., et al., *Pancreatic cystic neoplasms and post-inflammatory cysts: interobserver agreement and diagnostic performance of MRI with MRCP*. Abdom Radiol (NY), 2021. **46**(9): p. 4245-4253.
20. Cahalane, A.M., et al., *Which is the best current guideline for the diagnosis and management of cystic pancreatic neoplasms? An appraisal using evidence-based practice methods*. Eur Radiol, 2016. **26**(9): p. 3121-8.
21. Gillies, R.J., P.E. Kinahan, and H. Hricak, *Radiomics: Images Are More than Pictures, They Are Data*. Radiology, 2016. **278**(2): p. 563-77.
22. Lambin, P., et al., *Radiomics: the bridge between medical imaging and personalized medicine*. Nat Rev Clin Oncol, 2017. **14**(12): p. 749-762.
23. Lambin, P., et al., *Radiomics: extracting more information from medical images using advanced feature analysis*. Eur J Cancer, 2012. **48**(4): p. 441-6.
24. Limkin, E.J., et al., *Promises and challenges for the implementation of computational medical imaging (radiomics) in oncology*. Ann Oncol, 2017. **28**(6): p. 1191-1206.

25. Liu, Z., et al., *The Applications of Radiomics in Precision Diagnosis and Treatment of Oncology: Opportunities and Challenges*. Theranostics, 2019. **9**(5): p. 1303-1322.
26. Virarkar, M., et al., *Update on quantitative radiomics of pancreatic tumors*. Abdom Radiol (NY), 2021.
27. Machicado, J.D., E.J. Koay, and S.G. Krishna, *Radiomics for the Diagnosis and Differentiation of Pancreatic Cystic Lesions*. Diagnostics (Basel), 2020. **10**(7).
28. Dalal, V., et al., *Radiomics in stratification of pancreatic cystic lesions: Machine learning in action*. Cancer Lett, 2020. **469**: p. 228-237.
29. Xie, T., et al., *CT-Based Radiomics Analysis for Preoperative Diagnosis of Pancreatic Mucinous Cystic Neoplasm and Atypical Serous Cystadenomas*. Front Oncol, 2021. **11**: p. 621520.
30. Shen, X., et al., *A Contrast-Enhanced Computed Tomography Based Radiomics Approach for Preoperative Differentiation of Pancreatic Cystic Neoplasm Subtypes: A Feasibility Study*. Front Oncol, 2020. **10**: p. 248.
31. Wei, R., et al., *Computer-Aided Diagnosis of Pancreas Serous Cystic Neoplasms: A Radiomics Method on Preoperative MDCT Images*. Technol Cancer Res Treat, 2019. **18**: p. 1533033818824339.
32. Ma, J., J. He, and X.P. Yang, *Learning Geodesic Active Contours for Embedding Object Global Information in Segmentation CNNs*. Ieee Transactions on Medical Imaging, 2021. **40**(1): p. 93-104.
33. Dmitriev, K., et al., *Classification of Pancreatic Cysts in Computed Tomography Images Using a Random Forest and Convolutional Neural Network Ensemble*. Med Image Comput Comput Assist Interv, 2017. **10435**: p. 150-158.
34. Marchegiani, G., et al., *Oncocytic-type intraductal papillary mucinous neoplasms: a unique malignant pancreatic tumor with good long-term prognosis*. J Am Coll Surg, 2015. **220**(5): p. 839-44.

Figures

Figure 1

Flowchart show the criteria of Inclusion and exclusion for the enrollment in this study. PCN, pancreatic cystic neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; IPMN, intraductal papillary mucinous neoplasm.

Figure 2

Diagram represents the radiomics workflow of this study. The workflow includes image acquisition, image segmentation, feature extraction and selection, model construction and evaluation.

Figure 3

The overview of the Random Forest modeling process. OOB, out-of-bag.

Figure 4

The importance of radiomics features in feature selection with Boruta algorithm. Thirteen important features were retained with the highest rank score in the importance.

Random Forest Model

Figure 5

The selection of the number of trees in the model construction. The red line represented the error of MCN subtype; the blue line represented the error of SCN subtype; the green line represented the error of IPMN subtype; the black line represented the out-of-bag error (OOB error).

Figure 6

Receiver operating characteristic (ROC) curve of all radiomics models in the test cohort.

Figure 7

The calibration curve and decision curve analysis of binary class models in the test cohort: the calibration curve analysis of SCN-MCN model, SCN-IPMN model and MCN-IPMN model were shown in (a), (b) and (c), respectively; the results of decision curve analysis were separately shown in (d), (e) and (f).

Figure 8

Nomogram of radiomics-based binary-class models for predicting the classification risk.