Clinical Significance of Pancreatic Calcifications: A 15-Year Single Center Observational Study

Wei Wang

Ruijin Hospital, Shanghai Jiao Tong University

Li Chai

Ruijin Hospital, Shanghai Jiao Tong University

Naiyi Zhu

Ruijin Hospital, Shanghai Jiao Tong University

Qingrou Wang

Ruijin Hospital, Shanghai Jiao Tong University

Weimin Chai

Ruijin Hospital, Shanghai Jiao Tong University

Baiyong Shen (✉ shenby@shsmu.edu.cn)

Ruijin Hospital, Shanghai Jiao Tong University

Research Article

Keywords: pancreatic calcifications, chronic pancreatitis, non- chronic pancreatitis diseases, malignancy

Posted Date: July 27th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-646216/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objective

Pancreatic calcifications (PC) are considered specific for chronic pancreatitis (CP), but PC may also be present in non-CP diseases. The aims are to understand the pattern of calcifications in different diseases and to determine they were related to malignant diseases.

Methods

A retrospective study was performed including patients with PC or CP undergoing surgery in the Department of General Surgery of Ruijin Hospital from January 2003 to June 2018.

Results

PC were observed in 168 (4.5%) of the 3755 patients with pancreatic diseases. The majority of patients with PC had three kinds of CP (73.2%) while 26.8% had other five kinds of non-CP diseases. The incidences of PC in the pancreatic diseases were lower than these in previous studies. In patients with non-CP diseases, the incidence of PC in malignant intraductal papillary mucinous neoplasm (IPMN) was significantly higher than benign IPMN (8.3% vs. 0.7%, $p = 0.004$). In 204 patients with CP, pancreatic calcification (OR = 3.7), advanced age (> 55 years), high BMI (> 24 kg/m²), parenchymal atrophy and pancreatic mass were independent predictors for malignancy. In patients of CP with pancreatic mass (n = 81), the ability of PC (OR = 28.6) to predict malignancy increased nearly sevenfold.

Conclusion

The disease spectrum with PC was very diverse but the incidences of PC in the pancreatic diseases were low. PC may be related to malignant IPMN in non-CP diseases and is related to malignancy in the patients with CP, including the cases without pancreatic mass.

Introduction

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.^[1] In the course of the disease, patients with CP are at higher risk for the development of pancreatic ductal adenocarcinoma (PDAC) because of the chronic inflammation, with a standardized incidence ratio of 26.3 to 27, and an overall lifetime risk of 4%.^[2, 3]

The most widely used diagnostic criteria for CP include the Japanese Pancreas Society (JPS) criteria, Ammann's (Zurich Workshop) criteria, and Mayo scoring system. Apart from the tissue diagnosis, the

presence of stones in the pancreatic ducts and calcifications in the pancreatic parenchyma, have long been considered specific for CP. [4, 5]

However, pancreatic calcifications (PC) have also been noted in patients with many other pancreatic diseases.[6] The pattern of calcifications in different diseases is not clear, and whether PC were associated with malignancy of pancreatic diseases is not determined because there are very few articles focusing on these issues and most of them have small sample sizes. [7, 8]

The present study was conducted to understand the spectrum of diseases that can lead to PC, and to explore whether a pattern of PC is associated with malignant pancreatic diseases to provide more targeted information for the selection of other examinations, particularly in the setting of CP and clinical decision-making.

Materials And Methods

Data source and patient population

Using the electronic and paper records of the Department of General Surgery & Research Institute of Pancreatic Disease in Ruijin Hospital, we performed a retrospective longitudinal cohort study including consecutive patients of CP and PC undergoing surgery from January 2003 to June 2018. All the patients provided written informed consent for the surgical procedures. Every patient underwent detailed evaluation after hospitalization, including laboratory blood tests, serum tumor markers, contrast enhanced CT, contrast enhanced MRI, and EUS or PET / CT if required. A routine multidisciplinary team (MDT) discussion was held for every patient before surgery to determine the individual therapeutic strategy, including the preoperative diagnosis, and indication for resection. [9]

All the diagnoses of CP or non-CP diseases and their malignancies were confirmed histopathologically. If malignant disease (such as PDAC) coexists with CP, it was called malignant CP. We applied WHO-defined criteria to confirm the diagnosis of malignant SPT, namely angioinvasion, perineural invasion, or deep invasion into the surrounding tissue, or metastasis. [10, 11]

Definitions

Calcifications were defined as discrete, hyperattenuating foci on non-contrast CT images. The metrics to measure the pattern of calcifications in and around the pancreatic tumors/neoplasms were as follows: (1) Number (single or multiple) and position (head, body and tail) of calcifications. (2) Location of calcifications - Calcifications were considered intraductal (intraductal stones) if they were located within the main pancreatic or branch ducts and were surrounded by hypodense fluid. Calcifications located within the pancreatic tissue and completely surrounded by it, and apparently not connected with the pancreatic ducts, were considered parenchymal. Intralesional calcification was defined as calcification within the lesion, including wall of the cyst, septa, and mural nodules. Calcification around the pancreatic lesions was defined as calcification pushed aside by the lesion and not assessed as intralesional

calcification.^[12] (3) Distribution of calcifications - If the calcifications were observed in any particular part of the parenchyma of pancreas such as the uncinata process, head, body, or tail of the pancreas, then it was considered to have segmental distribution while in patients with diffuse distribution the calcifications were located throughout the entire parenchyma of pancreas.^[7] (4) Morphology of calcification - Eggshell calcifications was defined as linear calcium deposits in the wall or septae. Punctate or point calcifications were defined as calcifications of ≤ 5 mm in diameter, and coarse calcifications were defined as calcifications of ≥ 5 mm. "Cyst wall" indicates calcification that was found beside the cyst, and "septum" indicates calcification that was present in the cyst bulkhead. A central calcified scar consisted of calcified septations radiating outwards with a sunburst or stellate appearance called as stellate central calcifications. ^[6, 8, 12]

Pancreatic cystic lesions were defined as those exhibiting a round or oval shape with a recognizable wall, and attenuation similar to that of water with no enhancement after the administration of contrast medium, and the presence of enhancing solid components in less than 50% of the lesion. A solid lesion was defined as a discrete mass of soft-tissue attenuation with the enhancing solid portion involving more than 90% of the lesion. A solid and cystic lesion was defined as a lesion in which the enhancing solid component involved 50–90% of the lesion. ^[13]

The main pancreatic duct (MPD) was labelled as dilated if its diameter was more than ≥ 4 mm in the head of pancreas, ≥ 3.5 mm in the body, or ≥ 1.5 mm in tail region. ^[14, 15] Pancreatic atrophy was deemed present when the anteroposterior width of the pancreas was less than 1 cm in more than half of the pancreas and was confirmed histopathologically.^[16] The common duct was considered dilated when its transverse short-axis dimension was > 7 mm. ^[17]

Patients were labelled as smokers if they smoked ≥ 100 cigarettes in their lifetime. Patients were considered alcohol drinkers if they consumed ≥ 15 drinks (100-150-gram alcohol) per month on an average and no binges.^[18]

Suspicious lymph nodes were defined as those with a short axis diameter > 1 cm, abnormal round morphology, heterogeneity, or central necrosis. Vascular invasion was said to be present if the tumor abutment was more than 90° of the circumference of the superior mesenteric artery, total occlusion of major peripancreatic arteries, or the tumor abutted more than 180° of the circumference of the portal vein or superior mesenteric vein.^[19]

CT examination

The CT images were first screened and evaluated by radiologist (Li Chai). Then the results were submitted to two radiologists for further evaluation, with 5 years (Qingrou Wang) and 13 years (Naiyi Zhu) of experience in this field, respectively. The discrepancies between the three readers' interpretations were submitted to an imaging seminar, which was led by a senior radiologist (Weimin Chai) with more than 25 years of experience in this field, to resolve the discrepancies by consensus. The radiologists were both

blinded to the pathology results and the clinical outcomes. [8] All discussion and results were recorded by the junior radiologist and approved by the team members.

All the patients underwent at least one plain or enhanced abdominal CT examination. We selected and analysed the abdominal CT images performed at the time of first admission. For routine CT examination of the upper abdomen, we used a threshold of > 160 HU to indicate calcification and patients were placed in a supine position, and scanned from the top of the diaphragm to the lower edge of the both kidneys. Patients were kept fasting for more than 8 hours and were asked to drink about 800-1000ml of water before the CT examination to fill the upper gastrointestinal tract. Conventional upper abdominal CT scanning protocol included spiral scanning, 120 kVp, dynamic mA technology, noise index (NI) (about 10–12 Hu), thickness/interval (2.5-5mm), and the pitch (less than 1). For enhanced CT examination of the upper abdomen, patients were asked to breath-hold, followed by injection of 80-100ml of non-ionic iodine contrast agent (about 1.5 ml/kg) with high pressure syringe at 2.5–3.5 ml/s flow rate, and images were obtained in arterial phase (35–40 seconds after the onset of injection) and a venous phase acquisition (60–70 seconds). For the pancreatic dynamic enhanced CT, the total dose of intravenous contrast medium used was 600 mgI/kg, and the intravenous bolus injection was finished within 30 seconds. Three or four-phase CT acquisition was performed, with an arterial-phase image acquired at 20–30 s, pancreatic-parenchymal-phase image at 35–50 s, portal venous-phase image at 60–70 s, and delayed-phase image at 120–180 s. For image 3D-reconstruction, the thickness of the images in the arterial and portal phases was less than 1 mm, and the post-processing methods included MPR (multi-planar reformat), MIP (maximum intensity projection), VR (volume rendering), and CPR (curved planar reconstruction).

Statistical analysis

Quantitative data were presented as mean $\pm$ standard deviation (mean $\pm$ SD), and analyzed by the *t*-test if normally distributed, or by the Wilcoxon rank-sum test in case of skewed distribution. Categorical data were presented as frequency (percentage) and analyzed by a χ^2 -test, with or without Yates' correction for continuity or Fisher's exact test where appropriate. The determination of our variables was based on previous studies, and are shown in Table S1 and later in Table S4. [7, 8, 20] Multiple logistic stepwise regression analysis was used to determine the independent risk factors for the development of PDAC in patients with CP. All the statistical analyses were performed using the SPSS version 22.0 software (Statistical Packages for Social Sciences, Chicago, IL, USA). A *p* value of < 0.05 was considered statistically significant.

Results

Patients

PC were observed in 168 (4.5%) of the 3755 patients with pancreatic lesions treated during the study period and the incidences of PC in the pancreatic diseases were lower than these in previous studies

(Table 1). Among these 168 cases with PC, the most common disease was three kinds of CP (73.2%). Other non-CP diseases (26.8%) included five pancreatic diseases such as pseudopapillary tumors (SPT), serous cystic neoplasm (SCN), pancreatic neuroendocrine tumors (P-NETs), malignant intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) (Fig. 1).

Table 1
Histological diagnosis of patients with pancreatic calcifications

Calcification				
	n	n	%	Previous study
CP	168	96	57.1%	68% [4]
CP + IPMN	2	2	100%	/
PDAC ^a	2086	25	1.2%	4% [4]
SPT	223	15	6.7%	30% [3]
SCN	381	12	3.1%	30% [3]
P-NETs	345	10	2.9%	20–22% [3]
IPMN ^b	363	5	1.4%	20%-80% [3]
MCN	187	3	1.6%	15% [3]
	3755	168	4.5%	/
^a : including the 34 patients with CP and PDAC (Calcification, n = 26; no Calcification, n = 8), not including 424 patients whose clinical diagnosis was PDAC but only received palliative care or bypass surgery with no histopathological evidence ^b : not included two patients with CP combined IPMN, and 4 out of 5 cases were malignant. Abbreviations: CP, chronic pancreatitis; IPMN, Intraductal Papillary Mucinous Neoplasm; PDAC, Pancreatic ductal adenocarcinoma; SPT, Solid pseudopapillary tumors; SCN, Serous Cystic Neoplasm; P-NETs: Pancreatic Neuroendocrine tumors; MCN, Mucinous Cystic Neoplasm.				

CT features of PC

In the patients with non-CP diseases, there were no intraductal stones. Segmental PC(s) in the lesion or around the lesion in pancreatic parenchyma was the major feature of these non-CP diseases. Pancreatic intraductal stones combined with parenchymal calcifications was the major feature of CP and malignant IPMN (Table S2, Table 2).

Table 2
Pancreatic calcifications on computed tomography

Cal. morphology ^a	Pse.+Cal. ^b (n = 7)	SPT (n = 15)	SCN (n = 12)	P-NETs (n = 10)	IPMN (n = 5)	MCN (n = 3)
Eggshell-like	0	12 (80%)	0	0	0	0
Point cal. at the edge	7 (100%)	3 (20%)	0	6 (60%)	4 (80%)	2 (66.7%)
Stellate central cal.	0		9 (75%)	0	0	0
Central cal.	0		0	2 (20%)	0	0
Septal cal.	0		3 (25%)	0	0	1 (33.3%)
Not at the site of lesions ^c	0		0	2 (20%)	1 (20%)	0
^a : the definitions of calcification(s) morphology were show in the first part of “Definitions”; cal., calcification(s); ^b : Pancreatic pseudocyst whose pancreatic calcification(s) at the site of or the edge of the cystic lesions; ^c : Point calcification(s) does not at the site or the edge of the solid or cystic lesions.						

Among the 155 patients with PC whose imaging were performed in our hospital, the sensitivity and specificity of combined pancreatic intraductal and parenchymal calcifications for the diagnosis of CP or CP combined with IPMN was 72.7% (80/110) and 100% (45/45), respectively. (Table S3).

PC and malignancy

Among the malignant diseases such as malignant CP, P-NET, IPMN, and MCN, the incidence of PC was significantly higher in patients with malignant IPMN compared to benign IPMN (8.3% vs. 0.7%, $p = 0.002$) (Table 3).

Table 3
Pancreatic calcifications and malignancy of diseases.

	Benign		Malignant		P value
	Calcification		Calcification		
CP (n = 191)	157	85(54.1%)	34	25 (73.5%)	0.038
P-NETs (n = 345)	334	6 (1.8%)	11	1 (9.1%)	0.205
SPT (n = 223)	177	15 (7.8%)	31	0 (0.0%)	0.236
IPMN (n = 363) ^b	303	2 ^a (0.7%)	60	5 (8.3%)	0.002
MCN (n = 187)	159	4 (2.5%)	28	1 (3.6%)	0.560

^a: not included the patients whose preoperative CT examinations were performed at other hospitals. ^b: including the 2 patients with CP and IPMN. Abbreviations: CP, chronic pancreatitis; P-NETs: Pancreatic Neuroendocrine tumors; IPMN, Intraductal Papillary Mucinous Neoplasm; MCN, Mucinous Cystic Neoplasm.

Independent predictors of malignancy in CP

In the series of 204 patients with CP, there were 34 cases with PDAC (malignant CP group). (Table S1) Using a stepwise - logistic regression analysis, only the age at admission (> 55 years), parenchymal atrophy, body mass index (> 24 kg/m²), PC and the presence of pancreatic mass were shown to be the independent risk factors for the development of PDAC (Table 4).

Table 4

Logistic Regression Analysis for Identifying Independent Risk Factors for the Development of PDAC in CP^a

Risk Factors	Odds Ratio	<i>p</i> value
All patients (n = 204 ^b)		
Age at admission: >55 years	4.5	0.049
Atrophy of the parenchyma	9.8	0.001
Body mass index: >24 kg / m ²	4.2	0.047
Pancreatic calcification	3.7	0.035
Pancreatic mass	24.4	0.000
Patients with Pancreatic mass (n = 81 ^c)		
Age at admission: >55 years	16.9	0.008
Common bile duct (CBD)dilation or CBD stent implantation	0.2	0.032
Pancreatic calcification	28.6	0.000
Atrophy of the parenchyma	8.3	0.007
Patients without Pancreatic mass (n = 110 ^d)		
^a : PDAC pancreatic ductal adenocarcinoma; CP, chronic; ^b : included the 13 patients whose imaging were performed at other hospitals; ^c : including the data of 25 patients with PDAC, the data of 13 patients was excluded, including these with pancreatic pseudocyst (n = 5), these with IPMN (n = 2), and these whose imaging examinations were performed at other hospitals (n = 6); ^d : only 6 patients with PDAC, which is not enough for establishing a regression model.		

The cases with pancreatic mass underwent further analysis. Using univariate analysis, multiple factors were shown to differentiate benign versus malignant pancreatic mass as shown in Table S4. On multivariate logistic regression analysis, the age at admission (> 55 years), CBD dilation or CBD stent implantation, parenchymal atrophy, and PC were found to be the independent predictors of PDAC (Table 4).

Discussion

The results of our cohort study suggest that the majority (73.2%) of patients with PC had CP and 26.8% had other pancreatic diseases. This observation is consistent with that of the previous study by Campisi *et al.*^[7] But the disease spectrum was more diverse in our study than that reported by Campisi *et al.* In the CP spectrum, there were three kind of CP, including benign CP, malignant CP and CP combined with IPMN in our study. The non-CP diseases include not only the P-NETs, the IPMN, the SCN, but also the SPT

and the MCN. In addition to that, the rate of malignant CP was high (14.9% in our series vs. 3.9% in Campisi's study) (Fig. 1, Table 1).

One of the key features of CP is the presence of pancreatic intraductal stones and diffuse distributed parenchymal calcifications. Together, these features have high sensitivity (72.7%) and specificity (100%) for diagnosing CP. (Table S2, Table 2). All our findings are similar to the revised Japanese clinical diagnostic criteria for CP. [4] But our series also showed that there is a small possibility of presence of P-NETs or malignant IPMN which can mimic CP (Table S2).

The other key points for the differentiation of CP and non-CP were the presence of typical features of the non-CP diseases. (Table S2, Table 2). The curvilinear or peripheral eggshell-like calcifications were the main feature of SPT. Point or block calcification(s) at the edge of the lesion was found in malignant IPMN (80%), P-NETs (60%), MCN (66.7%) and SPT (20.0%). Stellate central calcification was the main finding of SCN (Table 2, Table S2). These findings of SPT were slightly different from that of the previous studies, where the calcifications of SPT were characteristically peripheral and punctate. [21] The calcifications of P-NETs were usually focal, coarse, irregular, and centrally located, [22, 23] calcifications of MCN were peripheral eggshell or focal punctate calcifications, [24] calcifications of IPMN were punctate calcifications (87%) and coarse calcification (33%). [25, 26] In our series, one of the important identification points was that calcifications of pseudocyst are located in the cystic wall, whereas in the non-CP diseases, the cystic pancreatic lesions usually have only segmental calcifications.

The second important purpose of this study was to determine whether PC can be used to suggest a diagnosis of malignancy. On a whole, the presence of diffuse distribution of parenchymal calcifications alone and intraductal stones alone ruled out malignancy with high specificity (95.1% and 94.3% respectively) (Table S3). But in our study group, the majority of the patients had CP and IPMN with only one case of mixed ductal-endocrine carcinoma of the pancreas and mucinous cystadenocarcinoma each. Also, the difference in the incidence of PC was significantly lower in benign IPMN than malignant IPMN ($p = 0.002$) in our study. Previous studies have also reported that the presence of coarse calcifications is associated with high risk for malignancy. [27] Not much is known about PC and malignancy in other non-CP diseases, and some of our results were somewhat contradictory. In MCN, multilocular macrocystic lesions and lesions with calcifications in the wall had a higher risk of malignancy. [28] But in our study we could not find any difference between the benign and malignant group (2.5% vs. 3.6%, $p = 0.560$), which similar to that reported by Wu *et al.* [29]. In a previous study, 7 of 10 P-NETs with calcifications had malignant features, unlike the observations of this study. [6] However, in SPT, PC was not useful to differentiate the benign and malignant forms of SPT as found in this study and previous studies (Table 3). [6, 10, 11]

There are few studies showing that PC is associated with cancer. [2, 3] In a study ($n = 48$) reported by Mohamed *et al.*, [8] the presence of a pancreatic mass in CP is suggestive of malignancy, especially when PC are observed. Our results in agreement with these that PC was found to a risk factor with the highest

odds ratio. We also found that presence of PC, in combination with other variables, such as advanced age (> 55 years), high BMI (> 24 kg/m²), atrophy of the parenchyma and pancreatic mass, were shown to be independent predictors of PDAC but with the lowest odds ratio (Table 4). This may be due to the patients were all received surgical treatment or the number of patients were relatively large in our study. And, on the other hand, the PC is an important warning sign for malignancy who had surgical indication, even the patients had no pancreatic mass.

Common bile duct dilation or bile duct stenting was a protective factor (OR = 0.2, $p = 0.032$). This was contrary to the observations made by previous study.^[8] But a similar study by Ruan *et al.*^[30] showed that dilated bile ducts passed through the lesions in 79.17% of massforming CP and in 16.67% cases of pancreatic carcinoma ($p < 0.001$). The double duct sign, which indicates the expansion of both the pancreatic duct and the bile duct, was similar in both groups. However, the number of cases were small (massforming CP, $n = 24$; pancreatic carcinoma, $n = 30$). The rate of calcification in massforming CP was significantly more than in pancreatic carcinoma cases (58.3% vs. 10%, $p < 0.001$). In our study, the incidence of calcification in CP with PDAC was more than CP without PDAC cases (75.0% vs. 22.6%, $p = 0.000$ (Table S4).

About 5–10% of "mass-forming" pancreatitis often masquerades as PDAC. due to overlap of the imaging findings.^[31, 32] In this study, we found that suspicious lymph nodes, abutment or encasement of the arteries around the pancreas, venous involvement, and the tumor size have no ability to differentiate between CP and CP with PDAC. Many other clinical features such as the duration of symptoms before admission, jaundice, high-colored urine, diabetes mellitus, total bilirubin levels, and the carbohydrate antigen 19 – 9 (CA19-9), the carbohydrate antigen 125 (CA125) were insignificant using logistic regression, which are in agreement with these in preivout studies.^[20, 33–36] However, the appearance of these clinical features should raise the suspicion of PDAC and may complement other clinical findings to improve diagnostic accuracy.^[34]

Our study has some limitations. First, the sample size was relatively small. Second, only the patients undergoing surgery were included. This method guaranteed the accuracy of the diagnosis, but many patients with PC were not included in our study who received medical or endoscopic intervention therapy. Third, because the focus of this study was PC, findings of imaging modalities other than CT were not studied. Also, the morphological features of bile ducts and pancreatic ducts, including the double duct sign and whether they passed through the lesion or interrupted the lesion areas, were not further evaluated. Fourth, this study was retrospective in nature. The technical parameters adopted in different periods were slightly different. The scan thickness of 5mm in the early-phase of the study could have increase the risk of overlooking PC. Future larger prospective studies are required to validate the findings of this study. Finally, we were not sure whether the CT scan parameters of other hospitals were consistent with those of our hospital. However, during the pre-operative discussion at our pancreatic center, the imaging data of other hospitals was reviewed and no inconsistency with regards to the presence of PC was found.

In summary, the incidences of PC in the pancreatic diseases were lower than these in previous studies, but the disease spectrum, including three kind of CP and five kind of non-CP diseases, was more diverse than these in previous studies. On the other hand, PC may be related to malignant IPMN. And, PC, in combination with other variables, were shown to be related to PDAC in the setting of CP, not only in cases with pancreatic mass, but also in cases without pancreatic mass.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not Applicable.

Availability of data and material: The datasets to support the findings of this study are included within the article, including figure 1, tables and supplementary tables. Any other data used to support the findings of this study are available from the corresponding author upon request.

Competing interest: The authors declare that there are no competing interests associated with the manuscript.

Funding: None.

Author contributions

Study concept and design: Wei Wang, Baiyong Shen, Weimin Chai; Acquisition of data: Li Chai, Wei Wang; Evaluating CT examinations: Li Chai, Weimin Chai, Naiyi Zhu, Qingrou Wang; Analysis and interpretation of data: Wei Wang; Drafting the paper: Wei Wang; Critical revision of the paper for important intellectual content: Wei Wang, Weimin Chai; Statistical analysis: Wei Wang; Study supervision: Baiyong Shen, Weimin Chai, Wei Wang.

Acknowledgements: None.

References

1. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. *Pancreatology*. 2016; 16: 218–224.
2. Wang W, Liao Z, Li G, et al. Incidence of Pancreatic Cancer in Chinese Patients with Chronic Pancreatitis. *Pancreatology*. 2011;11: 16–23.
3. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. *Am J Gastroenterol*. 2017;112(9):1366–1372.
4. Reddy NG, Nangia S, DiMagno MJ. The Chronic Pancreatitis International Classification of Diseases, Ninth Revision, Clinical Modification Code 577.1 Is Inaccurate Compared With Criterion-Standard Clinical Diagnostic Scoring Systems. *Pancreas*. 2016;45:1276–1281.

5. Raimondo M, Imoto M, DiMagno EP. Rapid endoscopic secretin stimulation test and discrimination of chronic pancreatitis and pancreatic cancer from disease controls. *Clin Gastroenterol Hepatol*. 2003;1: 397–403.
6. Javadi S, Menias CO, Korivi BR, et al. Pancreatic Calcifications and Calcified Pancreatic Masses: Pattern Recognition Approach on CT. *AJR Am J Roentgenol*. 2017;209: 77–87.
7. Campisi A, Brancatelli G, Vullierme MP, et al. Are pancreatic calcifications specific for the diagnosis of chronic pancreatitis? A multidetector-row CT analysis. *Clin Radiol*. 2009; 64:903–911.
8. Mohamed A Jr, Ayav A, Belle A, et al. Pancreatic cancer in patients with chronic calcifying pancreatitis: Computed tomography findings - a retrospective analysis of 48 patients. *Eur J Radiol*. 2017;86: 206–212.
9. Yusheng Shi, Yue Wang, Jian Wang, et al. Learning curve of robot-assisted middle pancreatectomy (RMP): experience of the first 100 cases from a high-volume pancreatic center in China. *Surg Endosc*. 2020;34(8):3513–3520.
10. Bosman, FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours of the Digestive System. Vol 3. 4th ed. Geneva, Switzerland: WHO Press; 2010.
11. Park JK, Cho EJ, Ryu JK, et al. Natural history and malignant risk factors of solid pseudopapillary tumors of the pancreas. *Postgrad Med*. 2013; 125: 92–99.
12. Masahiro Tsujimae, Atsuhiko Masuda, Hideyuki Shiomi, et al. Significance of pancreatic calcification on preoperative computed tomography of intraductal papillary mucinous neoplasms. *J Gastroenterol Hepatol*. 2019;34(9):1648–1655.
13. Jeon SK, Lee JM, Joo I, et al. Nonhypervascular Pancreatic Neuroendocrine Tumors: Differential Diagnosis from Pancreatic Ductal Adenocarcinomas at MR Imaging-Retrospective Cross-sectional Study. *Radiology*. 2017;284: 77–87.
14. Stevens T, Lopez R, Adler DG, et al. Multicenter comparison of the interobserver agreement of standard EUS scoring and Rosemont classification scoring for diagnosis of chronic pancreatitis. *Gastrointest Endosc*. 2010; 71:519–526.
15. Hughey M, Taffel M, Zeman RK, et al. The diagnostic challenge of the sequelae of acute pancreatitis on CT imaging: a pictorial essay. *Abdom Radiol (NY)*. 2017;42:1199–1209.
16. Hirano K, Tada M, Isayama H, et al. High alcohol consumption increases the risk of pancreatic stone formation and pancreatic atrophy in autoimmune pancreatitis. *Pancreas*. 2013;42: 502–505.
17. Padilla-Thornton AE, Willmann JK, Jeffrey RB. Adenocarcinoma of the uncinate process of the pancreas: MDCT patterns of local invasion and clinical features at presentation. *Eur Radiol*. 2012; 22:1067–1074.
18. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med*. 2009;169: 1035–1045.
19. Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. *Radiology*. 2014;270: 248–260.

20. Kamisawa T, Wood LD, Itoi T, et al. Pancreatic cancer. *Lancet*. 2016; 388:73–85.
21. Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. *Radiology* 1996; 199:707–711
22. Lesniak RJ, Hohenwarter MD, Taylor AJ. Spectrum of causes of pancreatic calcifications. *AJR Am J Roentgenol*. 2002, 178: 79–86.
23. Poultides GA, Huang LC, Chen Y, et al. Pancreatic neuroendocrine tumors: radiographic calcifications correlate with grade and metastasis. *Ann Surg Oncol*. 2012, 19(7):2295–2303.
24. Verde F, Fishman EK. Calcified pancreatic and peripancreatic neoplasms: spectrum of pathologies. *Abdom Radiol (NY)*. 2017;42(11): 2686–2697.
25. Perez-Johnston R, Narin O, Mino-Kenudson M, et al. Frequency and significance of calcification in IPMN. *Pancreatology* 2013; 13:43–47.
26. Kawamoto S, Lawler LP, Horton KM, Eng J, Hruban RH, Fishman EK. MDCT of intraductal papillary mucinous neoplasm of the pancreas: evaluation of features predictive of invasive carcinoma. *AJR* 2006; 186:687–695.
27. Masahiro Tsujimae, Atsuhiko Masuda, Hideyuki Shiomi, et al. Significance of pancreatic calcification on preoperative computed tomography of intraductal papillary mucinous neoplasms. *J Gastroenterol Hepatol*. 2019;34(9):1648–1655.
28. Procacci C, Carbognin G, Accordini S, et al. CT features of malignant mucinous cystic tumors of the pancreas. *Eur Radiol* 2001; 11:1626–1630.
29. Wu BU, Sampath K, Berberian CE, et al. Prediction of malignancy in cystic neoplasms of the pancreas: a population-based cohort study. *Am J Gastroenterol*. 2014;109: 121–129; quiz 130.
30. Ruan Z, Jiao J, Min D, et al. Multi-modality imaging features distinguish pancreatic carcinoma from mass-forming chronic pancreatitis of the pancreatic head. *Oncol Lett*. 2018;15: 9735–9744.
31. Gandhi NS, Feldman MK, Le O, et al. Imaging mimics of pancreatic ductal adenocarcinoma. *Abdom Radiol (NY)*. 2018;43(2):273–284.
32. Gerstenmaier JF, Malone DE. Mass lesions in chronic pancreatitis: benign or malignant? An "evidence-based practice" approach. *Abdom Imaging*. 2011;36: 569–577.
33. Mayerle J, Kalthoff H, Reszka R, et al. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. *Gut*. 2018; 67:128–137.
34. Su SB, Qin SY, Chen W, et al. Carbohydrate antigen 19 – 9 for differential diagnosis of pancreatic carcinoma and chronic pancreatitis. *World J Gastroenterol*. 2015; 21:4323–4333.
35. O'Brien DP, Sandanayake NS, Jenkinson C, et al. Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. *Clin Cancer Res* 2015; 21: 622–631.
36. Dimastromatteo J, Brentnall T, Kelly KA. Imaging in pancreatic disease. *Nat Rev Gastroenterol Hepatol*. 2017; 14:97–109.

Figures

Figure 1

Disease spectrum of patients with pancreatic calcifications. CP: Chronic pancreatitis; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; SPT: Solid pseudopapillary tumors; SCN: Serous cystic neoplasm; P-NETs: Pancreatic neuroendocrine tumors; MCN: Mucinous cystic neoplasm.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.docx](#)