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Does Pancreas Cyst Size Correlate with the Risk for Malignancy?

REVIEW

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Abstract

Context: Some studies have suggested that small pancreas cysts can be observed. Large cysts or those with increasing size may require intervention. Mucin-producing or malignant cysts have been suspected by increased cyst fluid viscosity, elevated fluid CEA level, imaging features, and cytopathology.

Objective: The purpose of this analysis is to determine the actual correlation of pancreas cyst size and the presence of malignant or premalignant features.

Design: Retrospective study of all consecutive pancreatic cysts that were referred for analysis by endoscopic ultrasound (EUS) over an 18 month period at a single center academic tertiary referral institution.

Patients or Participants: A total of 65 cysts in 65 patients were examined (36 men, 29 women, mean age of 56.8 and 59.3 years, respectively).

Main outcome measures: The diagnostic predictability of pancreas cyst size alone to identify mucin-producing or malignant cysts and all nonmucinous cysts based on cytopathology.

Results: The mean 2D size of malignant or mucinous cysts was 9.88cm^2. The mean 2D size of all nonmucinous cysts was 16.4cm^2 but was not statistically significant (p=0.15). Pseudocysts tended to be larger and had a mean size of 22.5cm^2 and was statistically different in size from the malignant or mucinous cysts (p=0.044) as well as mean size of serous cysts (7.51cm^2, p=0.023). The difference in size between mucinous and serous cysts also was not statistically significant (p= 0.62).

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Conclusions: Pseudocysts have a larger mean size than malignant or mucinous cysts as well as serous cysts. However, the parameter of cysts size alone does not aid in differentiating mucinous and nonmucinous cysts. Cyst fluid analysis is essential to determine the type of cyst and optimal management.

Keywords
Mucinous pancreatic cysts, malignant pancreatic cysts.

Introduction

Many cystic lesions of the pancreas are found incidentally during radiographic imaging such as computerized axial tomography (CT) performed for other purposes. Some cysts may be benign such as simple cysts, serous cystadenoma, or pancreatitis-induced pseudocysts. Others, however, have malignant or pre-malignant characteristics such as mucinous cystic neoplasm (MCN), cysts of main or side-branch intraductal papillary mucinous neoplasm (IPMN), or cystic degeneration of neuroendocrine tumors or adenocarcinoma [1]

Differentiating these cysts is imperative to determine the proper management which may include invasive surgical resection of premalignant or malignant cysts. Imaging with high-resolution modalities such as endoscopic ultrasound can identify certain cyst features such as presence of layering debris in benign pseudocysts, microseptations of serous cysts, macroseptations of MCN, and cysts with communication or involvement of the pancreatic duct or its side-branches seen in IPMN [2, 3]. Cyst fluid aspiration by EUS-guided fine needle aspiration (FNA) can demonstrate increased viscosity of mucinous cysts. Furthermore, fluid from the cyst can be analyzed for levels of amylase, elevated in pseudocysts, and more importantly carcinogenic embryonic antigen (CEA) which is elevated in mucinous or malignant cysts [4]. Recently, cyst fluid DNA mutational analysis for K-ras-2 and loss of heterozygosity allelic alterations has been shown to assist in diagnosis of mucinous or malignant cysts [5].

Despite these features, some experts have advocated that the size of cysts alone can predict aggressive varieties and thus can be observed by noninvasive imaging tests such as CT. A recent study suggests that cysts less than 3cm in greatest diameter have the lowest potential for malignancy [6]. It has even been suggested that cyst fluid aspiration is not essential in small cysts and can be safely observed. Thus, the purpose of this analysis is to determine the actual correlation of pancreas cyst size and the presence of malignant or premalignant features.

Methods

This study was approved by the institutional review board.

Characteristics of subjects

All consecutive patients with pancreatic cysts that were referred over an 18 month period until November 2012 for evaluation by endoscopic ultrasound examination were included in this analysis. This included 65 cysts detected in 65 patients (36 men and 29 women with average age of 56.8 and 59.3 years, respectively, and a total age range of 32 to 88 years).

Endoscopic ultrasound examination

Aspiration of cyst fluid was accomplished by either a 19 or 22-guage needle after prophylaxis with either cefazolin or vancomycin. Fluid was aspirated with usually a single pass until complete collapse or until

the maximum ability of fluid withdrawal was achieved. Analysis included cytology, fluid and serum CEA, fluid amylase, and in certain cases mutational DNA analysis. Cyst measurement was reported as a square centimeter area derived from two dimensions from EUS imaging.

Fluid CEA elevation >192 mg/dL was used to define a mucinous cyst when combined with endosonographic features such as macroseptations and viscous fluid aspirate. In some cases, cytology revealed mucinous features and also confirmed malignancy in others. Serous cysts were identified by the microseptations seen by EUS, low level of fluid CEA, bland cytology and thin serous fluid. Pseudocysts were defined by inflammatory histology containing histiocytes and debris in the setting of acute or chronic pancreatitis along with low fluid CEA, high fluid amylase and the characteristic EUS appearance of a well-defined cyst without septations and containing layering debris.

The above cysts comprise the most common varieties and were thus examined. Other rare cysts include cystic and solid pseudopapillary tumors, lymphoepithelial cysts, and pancreatoblastoma. However, these have unique morphologies and cytologic findings, none of which were detected in this series of patients and thus were not included in the subject group or data analysis.

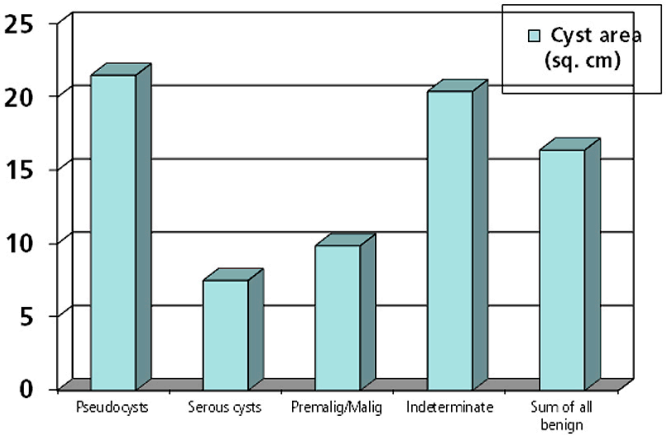
Statistical analysis

The data was analyzed and reported as a comparison of mean sizes of different subgroups of cysts using two-dimensional square centimeter area. Statistical significance was determined as a p value less than 0.05 and was calculated by two-tailed type 3 student t-test.

Results

Based on cytology of aspirates or histology of surgical specimens, 10 (15.4%) cysts were malignant or pre-malignant and included 5 (7.7%) mucinous cystic neoplasms, 2 (3%) side-branch intraductal papillary mucinous neoplasms, and 3 (4.6%) cases of cystic degeneration of pancreatic adenocarcinoma. The mean two-dimensional (2D) size of these malignant cysts based on EUS imaging was 9.88cm^2 (range of 1.7 to 16 cm^2). The mean 2D size of the remaining 55 benign cysts was 16.4cm^2 (range 2.1 to 31.5 cm^2 but was not statistically different from the group of malignant cysts (p=0.15). See **Figure 1**.

Figure 1: Comparison of size of varying groups of pancreas cysts. This depicts that pseudocysts tended to be larger than other cysts. The difference in size between malignant or mucinous cysts and all benign cysts was not statistically significant. The size of serous cysts also did not differ significantly from the mean size of the total benign cyst group or total malignant and premalignant cyst group.



The benign cysts included all nonmucinous or nonmalignant cysts such as pseudocysts, serous cystadenoma, or simple cysts. Pseudocysts tended to present at a larger size than other cysts at the time of initial imaging or detection due to symptoms. This group had a mean 2D size of 21.5cm^2 (n=35, range of 3 to 141 cm^2). Serous cysts were

identified by the EUS appearance, bland histology, lack of prior pancreatitis, low fluid CEA and variable fluid amylase with a mean 2D size of 7.51cm^2 (n=10). The remaining 10 (15.4%) cysts were classified as benign cysts of indeterminate variety. These cysts had a mean size of 8.6cm^2 (range of 2.2 to 31 cm^2).

A comparison of the mean size of malignant or mucinous cysts (9.88cm^2) to serous cysts (7.51cm^2) did not achieve statistically significant difference (p=0.62). However, there was significant difference between mean size of malignant or mucinous cysts and mean pseudocyst size (p=0.044).

Serous cyst mean size was compared to the mean size for the entire group of benign cysts and did not differ significantly (p=0.075). However, there was significant difference between mean sizes of serous cysts and pseudocysts (p=0.023).

Discussion

The differentiation of mucin-producing or malignant pancreatic cysts from nonmucinous varieties is imperative to determine appropriate management. Some experts have suggested that size is the most important predictor of malignant or premalignant features of pancreatic cysts [6, 7]. Some have demonstrated that cyst size larger than 3cm in a single dimension along with the presence of mural nodules particularly for IPMN are the major predictors of malignant progression [8]. Others have demonstrated that cyst fluid analysis such as CEA level, amylase, cytopathology, and DNA mutational analysis can aid in this diagnosis. This study, however, demonstrates that relying on radiographic size alone does not correlate well with the histologic diagnosis of pancreatic cysts.

Endoscopic ultrasound provides high resolution images that can aid in detection of features such as septations, mural nodules, or debris. Moreover, sampling of cyst fluid is easily achieved by EUS-FNA and enables fluid analysis. Cyst size can also be determined and monitored by EUS. However, as this study demonstrates, size is not a reliable factor for detection of malignant or premalignant cysts.

Pseudocysts tend to be larger at the time of diagnosis and usually are detected by imaging for symptoms of acute or chronic pancreatitis. There is statistically significant difference in size of pseudocysts from both malignant or mucinous cysts and benign serous cysts. However, many of these cysts tend to regress in size over time after the resolution of acute pancreatitis. Thus, the measurement of these cysts is highly dependent on the point in time of clinical follow-up.

In one recent study, changes in cyst size did not correlate with malignant transformation of branch-duct type IPMN. Rather, the presence of mural nodules within the cyst correlated with development of malignancy over a mean follow-up of 27 months [9]. Using size criteria, cysts exceeding 2cm in greatest diameter without a mural nodule or cysts smaller than 2cm but with a mural nodule have been both shown to have a 25% chance of malignant progression [10]. This suggests that cyst features rather than size may be more predictive of malignant progression in branch-type IPMN.

One study suggests that cysts exceeding a diameter of 3cm in size correlates with increased incidence of premalignant or malignant lesions based on CT scan size without fluid aspiration or analysis. This study also suggests that elevated serum CEA and elevated serum CA19-9 are also consistent with malignancy. Furthermore, the authors suggest no need for cyst aspiration and fluid analysis [11]. Yet, the sensitivity and specificity of these markers is unclear in this setting.

Recently, a study suggested that asymptomatic pancreatic cysts can be safely observed. Of 57 patients, cyst size did not change in 45 patients over a mean of 4 years [12]. However, some of these cysts were of indeterminate etiology and the duration of follow-up may have been too short for malignant

transformation. Moreover, this also bolsters the premise of our results that monitoring cyst size is not a reliable feature in following progression of pancreas cysts. The surgical approach to resection of pancreas cysts based entirely on radiographic appearance has been shown to result in several unnecessary operations as well as complications. In a study of 16 patients who underwent total pancreatectomy for presumed IPMN, 12 had actual premalignant or malignant features. Six patients had severe postoperative complications including two deaths. The authors suggested that more detailed imaging by EUS and fluid sampling could have aided in the decision to proceed to operation [13].

Previous investigators have demonstrated the importance of pancreas cyst characterization and aspiration for analysis by EUS in determining malignant or premalignant lesions. In a comparison using patients who underwent surgical resection of cysts, diagnostic EUS complemented by FNA accurately predicted malignancy in 88.9% of cases [14]. This demonstrates the overall significant influence on diagnosis and management of pancreas cysts by EUS examination.

International consensus guidelines have recently been established for the diagnosis and management of mucinous cysts and IPMN of the branch-duct type. The Sendai guidelines have carefully examined and recommended features of MCN and IPMN that should dictate a more aggressive approach. The consensus suggested that MCN and IPMN cysts that are >30mm in greatest diameter and have mural nodules or have increased in size recently are at the greatest risk of malignant transformation. The authors concluded that cysts that truly MCN by the other criteria mentioned previously should be resected regardless of size if the patient is an operative candidate as all MCNs have potential for malignancy. This includes cysts that are <30mm with or without a mural nodule. Thus, the consensus guidelines do not rely on size alone [15, 16].

These prior studies do demonstrate that larger size is an important factor that would be useful in determining whether a mucinous cyst has an increased risk of transformation from a premalignant to a malignant state. Many radiologists and clinicians often arrive at the conclusion that a very small pancreas cyst is clinically insignificant and can be observed periodically. However, cyst size alone used as screening criteria on radiographic imaging for all cysts is not an accurate methodology for predicting the course of pancreatic cysts. As our results demonstrate, there is no significant difference in size between mucinous and serous cysts. Pseudocysts may be larger than the other varieties but also have a different presentation including pancreatitis and symptoms often associated with compression of the gastrointestinal lumen. Thus, the usual incidental cyst should not be differentiated by size alone on a radiographic imaging test such as a CT scan. A high resolution imaging technique such as EUS may provide more detailed visualization of cyst for septations, mural nodules, and to possibly sample its contents for analysis of fluid CEA, CA 19-9, and cytology. Not every cyst will require sampling but can be directed by the findings of a high-resolution EUS image. Thus, initial cyst size alone on a radiographic study does not adequately triage the cyst into a reliable category that can predict its clinical course.

Summary

The gamut of pancreatic cysts includes benign cysts, inflammatory cysts, premalignant cysts, and cysts of malignant degeneration. Differentiating these cysts depends on a variety of factors including imaging features as well clinical symptoms and characteristics. While change in size of an identified pancreatic cyst has been shown to be an important feature of progression requiring intervention, this study demonstrates that initial cyst size at the time of detection does not correlate

well with the prediction of malignant potential. Endoscopic ultrasound exam with cyst fluid aspiration and analysis offers an opportunity to examine cysts identified radiographically with a higher-resolution modality. Moreover, the combination of clinical characteristics of the patient, imaging features, fluid viscosity, cyst fluid CEA and amylase levels, DNA mutational analysis of fluid, and cytopathology along with cyst size appears to be a more accurate predictor of the type of pancreas cyst. The optimal management of such patients depends on the analysis and interpretation of all of these factors rather than size alone.

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