

Pancreatic Cysts 3 cm or Smaller: How Aggressive Should Treatment Be?¹

Dushyant V. Sahani, MD
 Anuradha Saokar, MD
 Peter F. Hahn, MD, PhD
 William R. Brugge, MD
 Carlos Fernandez-del Castillo, MD

Purpose:

To retrospectively determine the frequency of malignancy in small (≤ 3 cm) pancreatic cysts, to evaluate whether cyst morphologic features can help predict the presence of malignancy, and to determine the natural history of small pancreatic cysts at follow-up imaging.

Materials and Methods:

Institutional review board approval was obtained; informed patient consent was not required. By means of a computerized search, 510 patients with pancreatic cysts that had been detected at computed tomography (CT) or magnetic resonance (MR) imaging were identified. Cysts that were 3 cm or smaller at surgery or endoscopic ultrasonography (US)-guided cyst fluid aspiration and biopsy were included. Eighty-six patients—31 men and 55 women aged 24–89 years—fulfilled the criteria. Patients underwent surgery or were monitored with endoscopic US-guided cyst fluid analysis, cytologic analysis, and follow-up imaging. Imaging findings were compared with surgical and pathology records and with endoscopic US features. Positive predictive values (PPVs) for benignity and malignancy were calculated on the basis of cyst size and absence or presence of septa in the cysts.

Results:

Forty-eight patients underwent surgery, and 38 were treated nonsurgically. Seventy-five patients had benign cysts; eight, borderline (malignant) neoplasms; and three, carcinoma in situ lesions. The PPV of small pancreatic cysts for prediction of benignity was 87% (75 of 86 patients). Thirty-six patients had unilocular cysts (35 with benign lesions, one with borderline neoplasm). The PPV of unilocular cysts for prediction of benignity was 97% (35 of 36 patients). Fifty patients had septated cysts; seven of these patients had borderline neoplasms, and three had carcinoma in situ lesions. For prediction of malignancy in small cysts, the PPV of septa was 20% (10 of 50 patients), which was significantly higher than the 3% (one of 36 patients) PPV of unilocular cysts ($P = .042$). No significant changes in cyst morphologic features were seen in patients who were followed up with imaging for a mean period of 21.8 months.

Conclusion:

The majority ($n = 75$) of small pancreatic cysts were benign. Thirty-six cysts were unilocular, and virtually all of these ($n = 35$) were benign. The presence of septa was associated with borderline or in situ malignancy in 20% (10 of 50) of cases.

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¹ From the Departments of Radiology, Division of Abdominal Imaging (D.V.S., A.S., P.F.H.), Gastroenterology (W.R.B.), and Surgery (C.F.), Massachusetts General Hospital, White 270, 55 Fruit St, Boston, MA 02114. From the 2004 RSNA Annual Meeting. Received October 20, 2004; revision requested December 27; revision received March 10, 2005; accepted April 27; final version accepted May 5. Address correspondence to D.V.S. (e-mail: dsahani@partners.org).

Extensive use of high-quality abdominal imaging has resulted in an increased number of patients who receive a diagnosis of pancreatic cysts (1–3). The majority of these lesions are found to be cystic neoplasms of the pancreas and not pseudocysts (1). Very often cystic neoplasms are detected incidentally and are small at the time of detection (1). To our knowledge, there are no explicit guidelines for the treatment management of small cystic tumors of the pancreas (1–6). Despite recent advances in cross-sectional imaging, the inability to fully characterize small pancreatic cysts is a common problem (3,5). Concern that many of these lesions may be premalignant or malignant has led to recommendations that all cystic pancreatic lesions be resected (3,7,8). However, this treatment strategy is impractical, because 30%–40% of these lesions may be benign serous cystadenomas (4,9).

Therefore, the purpose of our study was to retrospectively determine the frequency of malignancy in small (≤ 3 cm) pancreatic cysts, to evaluate whether the morphologic features of cysts can help to predict the presence of malignancy, and to determine the natural history of small pancreatic cysts at follow-up imaging.

Materials and Methods

Patient Population

Institutional review board approval was obtained for this retrospective study; informed patient consent was not required. This study was Health Insurance Portability and Accountability Act compliant. We searched our radiology database (FolioViews, version 4.2; Next Page, Draper, Utah) that contained data on all of the radiologic examinations performed and reported at our institution from January 1998 through March 2004 for data on pancreatic cysts detected at computed tomography (CT) and/or magnetic resonance (MR) imaging. We identified 510 patients with cystic lesions of the pancreas that had been identified at CT and/or MR imaging.

One hundred twenty-two patients

with prior clinical and laboratory evidence of pancreatitis were excluded. Criteria for the diagnosis of pancreatitis were elevated serum amylase or lipase levels and/or imaging evidence of pancreatic inflammation, pancreatic ductal calcification, or atrophy. Of the remaining 388 patients, 313 (80.6%) had cysts 3 cm in diameter or smaller at the time of initial detection. Of these 313 patients, 244 (78.0%) had pancreatic cysts that had been incidentally detected.

Only those patients who had undergone either surgery with corresponding histopathologic analysis or endoscopic ultrasonography (US)-guided cyst fluid aspiration and biopsy for cytologic, biochemical, and tumor marker analyses were included in the study. All patients with nondiagnostic cytologic results ($n = 26$)—because of insufficient tissue or specimen contamination—were excluded. Two hundred one patients who had undergone serial imaging but no intervention to determine the nature of the cyst also were excluded from the study. Similarly, patients who had more than one cyst with the dominant cyst being larger than 3 cm in diameter were not included in the study. Patients who previously had undergone pancreatic surgery for a cystic or solid lesion and developed a new pancreatic cyst that was seen on follow-up images also were excluded.

A total of 86 patients (31 men, 55 women; age range, 24–89 years; mean age, 68 years) met the selection criteria and constituted our study population. Of the 86 patients, 52 had undergone CT only, 20 had undergone MR imaging only, and 14 had undergone both CT and MR imaging. We (A.S., D.V.S.) recorded these patients' clinical presentations, imaging features, and pathologic and surgical findings. The absence or presence of symptoms and the type of symptoms, when present, also were recorded. Patients were considered to have an incidentally detected pancreatic cyst if the cyst was discovered during evaluation for a different medical problem. Symptoms that were considered to be related to pancreatic cysts included abdominal pain, weight loss, palpable

mass, jaundice, and diarrhea with malabsorption. The likelihood of malignancy in the incidentally detected small cysts was determined.

Imaging Protocols

CT.—A variety of imaging protocols and equipment were used during the 6-year period. Helical CT with a single-detector row unit (GE HighSpeed; GE Medical Systems, Milwaukee, Wis) or multi-detector row unit (with four, eight, or 16 detector rows) (GE LightSpeed; GE Medical Systems) was performed in all patients. Routine abdominal CT beginning 60–70 seconds after intravenous injection of contrast material was the most commonly performed examination. For routine CT scanning, 120–150 mL of nonionic contrast material (300–350 mg/mL) was injected at a rate of 2.5–3.0 mL/sec, and images were acquired at a 5-mm section thickness after a 70-second delay. The field of view was adjusted according to the size of the patient. In patients known or suspected to have a pancreatic lesion, a dedicated pancreatic CT protocol was used as either the initial or the follow-up study.

After nonenhanced CT acquisitions in the liver and pancreas were performed, 150 mL of nonionic contrast material (300 mg of iodine per milliliter) was injected at a rate of 4–5 mL/sec and two acquisitions were performed. Pancreatic phase imaging was performed 45 seconds after contrast material injection by obtaining 1.25-mm or larger sections through the pancreas. Portal venous phase imaging with 5-mm-thick sections followed at 70 seconds after

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contrast material injection. For pancreatic phase imaging, the field of view was 28 cm; for the other phases, the field of view was adjusted according to the size of the patient. Other less commonly used protocols were CT angiography and hematuria protocols.

MR imaging.—MR imaging was performed with a 1.5-T system (Signa, software version 8.3; GE Medical Systems) by using a phased-array torso coil. For evaluation of the pancreas, T2-weighted fast spin-echo (5,000/100 [repetition time msec/echo time msec], 90° flip angle, 34-cm field of view, 3-mm section thickness, 256 × 192 matrix) and T1-weighted in-phase (150/4.2) and out-of-phase (150/2.1) spoiled gradient-echo images (90° flip angle, 36-cm field of view, 4-mm section thickness, 256 × 160 matrix) were obtained. Subsequently, fat-suppressed fast spoiled gradient-echo dynamic MR imaging (150/2, 70° flip angle, 36-cm field of view, 4-mm section thickness, 256 × 160 matrix) through the pancreas was performed after the injection of 0.1 mmol of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Montville, NJ) per kilogram of body weight during the arterial (20 seconds), portal venous (70–80 seconds), and equilibrium (180 seconds) phases. In addition, coronal and transverse half-Fourier single-shot fast spin-echo images were obtained for MR cholangiopancreatography. For thin-section MR cholangiopancreatography, a 4–5-mm section thickness, 40-cm field of view, and 256 × 256 matrix were used. For thick-slab MR cholangiopancreatography, a 50–60-mm section thickness, 26-cm field of view, and 256 × 256 matrix were used.

Image Analysis

The CT and MR images were retrospectively reviewed by consensus between two radiologists (D.V.S. with 9 years experience, A.S. with 2 years experience), who were aware of the diagnosis of cystic pancreatic lesion but blinded to the results of the pathologic and cyst fluid analyses. The numbers, sizes, and locations of the cysts and the morphologic features of the cysts, such as presence or absence of calcifications, septa,

and/or mural nodules on CT and MR images, were recorded. When multiple cysts were present within the pancreas, the diameter and morphologic features of the largest of the smaller (≤ 3 cm) cysts, along with the previously described features other than size, were recorded. Peripancreatic abnormalities, including lymphadenopathy, vascular involvement, peripancreatic fat infiltration, and metastasis, were noted. Peripancreatic lymphadenopathy was diagnosed when the short-axis diameter of the lymph node was greater than 10 mm. In patients in whom multiple images were obtained, the size and morphologic features of the cyst depicted on the first image were recorded.

Endoscopic US

Several gastroenterologists (including W.R.B.) with 2–10 years of experience performed the endoscopic US examinations. Endoscopic US was performed by using the GFUM-20 radial or linear scanning echoendoscope (Pentax, Orangeburg, NY) at 7.5 and 12.0 MHz. The following information regarding the morphologic features of the cysts from the endoscopic US report was recorded (A.S.): cyst diameter and presence or absence of septa, a solid component, and/or lymphadenopathy.

Endoscopic US–guided Cyst Fluid Aspiration

All patients who underwent endoscopic US also underwent endoscopic US–guided cyst fluid aspiration and cytologic analysis with use of a 19- or 22-gauge needle (Wilson Cook, Winston-Salem, NC; or Mediglobe, Tempe, Ariz) that was occluded with a stylet. The cyst fluid was analyzed for biochemical (ie, amylase) or tumor (ie, carcinoembryonic antigen) markers. According to information cited in the report on cytologic and cyst fluid analyses, all examined patients had adequate samples for cytologic and cyst fluid analyses.

The cytologic findings described in the pathology report were reviewed (A.S.). Whenever possible, a specific diagnosis such as pseudocyst, mucinous cystic neoplasm, or serous cystadenoma was given on the basis of the cyst fluid

cytologic, biochemical, and tumor marker analysis findings. A carcinoembryonic antigen level higher than 200 ng/mL indicated mucinous cystic neoplasm, and a carcinoembryonic antigen level lower than 5 ng/mL indicated serous cystadenoma. Cysts lacking malignant cells at cytologic analysis were considered to be benign. When cyst fluid and cytologic analysis results were definitively negative for malignancy but did not yield a precise diagnosis, the lesion was considered to be a benign unclassified cyst.

Surgery and Histopathologic Analysis

The type of surgical procedure performed was recorded (A.S.). The gross and microscopic descriptions of the resected specimens cited in the pathology reports were reviewed (A.S.). The gross findings noted were lesion size and presence or absence of septa and/or mural nodules. At microscopy, on the basis of the most aggressive histologic epithelial changes and according to the World Health Organization classification system, pancreatic cysts were classified as benign, borderline (malignant), or malignant (10). For this analysis, we grouped the tumors into two main categories—benign and malignant—with the latter category including borderline neoplasms, carcinoma in situ lesions, and invasive cancers. The degree of peripancreatic extension, including the nature of the resected lymph nodes, also was assessed. The imaging and histopathologic findings were then correlated.

Comparisons and Follow-up

CT and MR imaging findings were compared with endoscopic US report, surgical, and cytologic-histologic findings. The patients who were treated nonsurgically underwent imaging surveillance to ensure the cysts remained stable. A greater than 5 mm growth of the cyst in any dimension, changes in the morphologic features of the cyst such as development of solid components or peripheral or septal calcification, pancreatic duct dilatation, biliary obstruction, lymphadenopathy, metastasis, vascular encasement, and infiltration of peripan-

creatic tissues were considered signs of malignancy. Reduction in the size or complete resolution of the cyst at follow-up imaging was considered a confirmation that the cyst was benign.

Statistical Analyses

We calculated the positive predictive values of small size (≤ 3 cm) and the absence or presence of septa for diagnosing a pancreatic cyst as benign or malignant by using 2×2 contingency tables. Analyses were performed by using computer software (Excel; 2002 Microsoft, Redmond, Wash). The probability of malignancy in small septated cysts compared with the probability of malignancy in small unilocular cysts was determined by using the χ^2 test (2002 Microsoft). A *P* value of less than .05 was considered to indicate a significant difference.

Results

Clinical Findings

Fifty-eight (67%) of the 86 patients had incidentally detected pancreatic cysts with complaints unrelated to the cysts. Twenty-five (29%) patients reported having abdominal pain or discomfort, two (2%) patients presented with

weight loss, and one (1%) patient had symptoms of malabsorption. Of the 58 patients with incidentally detected cysts, seven (12%) had cysts that were included in the malignant category (five with borderline neoplasms, two with carcinoma in situ lesions).

Numbers, Locations, and Sizes of Cysts at Imaging

A total 111 pathologically verified cysts were identified in 86 patients. More than one cyst was detected in 17 patients: Ten patients had two pancreatic cysts, six had three cysts, and one had four cysts. Fifty-five cysts were located in the head of the pancreas; 28 cysts, in the body; and 28 cysts, in the tail. The sizes of the cysts ranged from 7 mm to 3 cm (mean, 19.2 mm).

Thirty-six (42%) patients had unilocular cysts, and 50 (58%) had septated cysts. No cyst in our study group had a solid component at imaging or histopathologic analysis. No peripancreatic abnormalities in the form of lymphadenopathy, fat infiltration, vascular involvement, or metastasis were documented in any patient.

Surgery and Histopathologic Analysis

Forty-eight patients underwent surgical resection for 60 cysts. Twenty-three pa-

tients underwent the Whipple procedure; 19 patients, distal pancreatectomy; and six patients, middle pancreatectomy. Thirty-seven patients had benign cysts: mucinous cystadenoma in 13 patients, side-branch intraductal papillary mucinous neoplasm in 14, serous cystadenoma in three, pseudocyst in two, cystic neuroendocrine tumor in two, lymphoepithelial cyst in one, and unclassified cyst (sclerosing benign cyst in one patient, benign multicystic lesion with squamous differentiation in one patient) in two.

Eleven patients were assigned to the malignant cyst group: Eight patients had borderline tumors (six with side-branch intraductal papillary mucinous neoplasms, two with mucinous cystic neoplasms), and three had carcinoma in situ lesions (two with side-branch intraductal papillary mucinous neoplasms, one with mucinous cystic neoplasm). None of the patients had invasive cancer at histopathologic analysis. One patient underwent surgery after initial conservative management. In this patient, follow-up CT and endoscopic US images obtained at 2-year follow-up showed increased cyst size and the development of a solid component. The cytologic findings correlated with the imaging findings. Results of the first cytologic examination were negative for malignant cells, whereas results of the cytologic examination performed at 2 years showed malignant cells. After resection, this patient received a diagnosis of side-branch intraductal papillary mucinous neoplasm with carcinoma in situ.

Of the 48 patients who underwent surgical resection, 16 had unilocular cysts and 32 had septated cysts. Fifteen of the 16 patients with unilocular cysts had benign lesions, and one (with an intraductal papillary mucinous neoplasm) was assigned to the malignant cyst group (Fig 1). The intraductal papillary mucinous neoplasm had borderline changes at histopathologic analysis, without evidence of invasive carcinoma or carcinoma in situ. Of the 32 patients with septated cysts, 22 had benign lesions and 10 were assigned to the malignant cyst group (seven with borderline neoplasms, three with carcinoma in situ

Figure 1

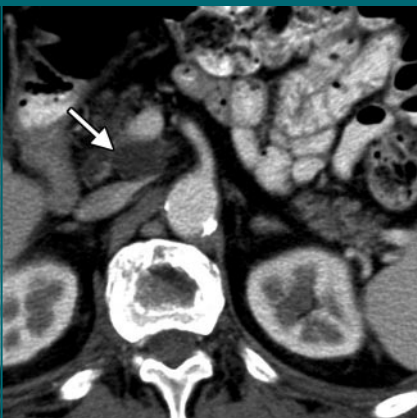


Figure 1: Transverse contrast material-enhanced CT scan of abdomen in 65-year-old woman. A unilocular cyst (arrow) in the uncinate process of the pancreas was detected incidentally and confirmed to be benign intraductal papillary mucinous neoplasm after surgery.

Figure 2

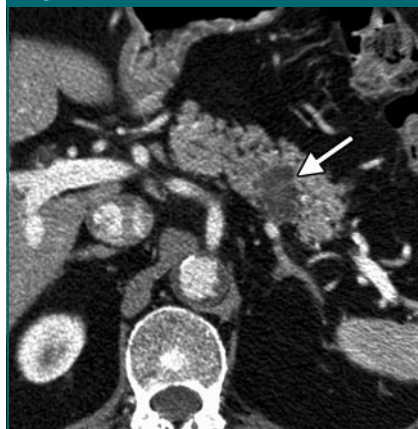


Figure 2: Transverse contrast-enhanced CT scan of abdomen in 70-year-old man with abdominal pain. A 2.7-cm septated cyst (arrow) is seen in the tail of the pancreas and was proved to be an intraductal papillary mucinous neoplasm with borderline changes at histopathologic analysis.

Figure 3

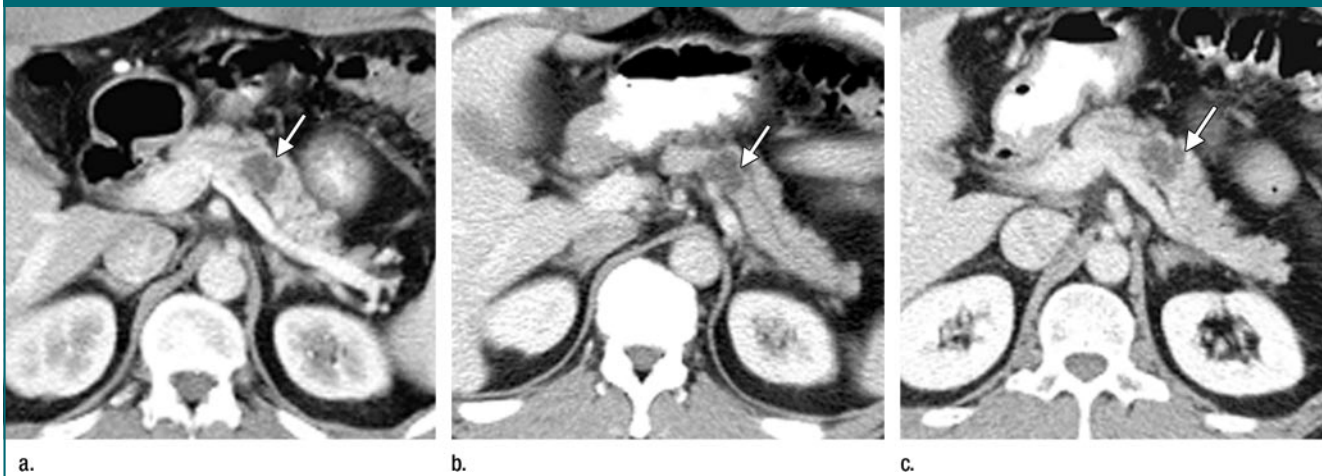


Figure 3: (a–c) Serial transverse contrast-enhanced CT images of abdomen in 69-year-old man. A 2.7-cm intraductal papillary mucinous neoplasm (arrow) involving the body of the pancreas was confirmed at endoscopic US–guided aspiration and biopsy and remained unchanged during the 2-year follow-up.

Table 1

Positive Predictive Values for Detection of Specific Pancreatic Cyst Types

Pancreatic Cyst Type	Positive Predictive Value*
Benign, ≤3 cm	87 (75/86)
Benign, unilocular	97 (35/36)
Malignant, septated	20 (10/50)

* Data are percentages. Data in parentheses are numbers of patients used to calculate the percentages.

Table 2

Detection of Benign and Malignant Pancreatic Cysts Based on Presence or Absence of Septa

Pancreatic Cyst Type	Benign Cysts	Malignant Cysts		
		Borderline	Carcinoma in Situ	Invasive Cancer
Unilocular	35	1	0	0
Septated	40	7	3	0
Total	75	8	3	0

Note.—Data are numbers of patients.

lesions). None of the septated cysts showed invasive carcinoma (Fig 2). None of the patients had malignant peripancreatic lymphadenopathy at histopathologic analysis.

Nonsurgical Management

Thirty-eight patients with 51 pancreatic cysts were treated conservatively. Twenty of these 38 patients had unilocular cysts, and 18 had septated cysts. No solid components or enlarged peripancreatic lymph nodes were seen at initial endoscopic US. In all of these patients, a diagnosis of benign lesion was established after endoscopic US–guided cyst fluid analysis and cytologic analysis.

Of the 38 patients who were treated nonsurgically, 29 underwent imaging follow-up for a mean period of 21.8

months. Five of these patients had a greater than 5 mm reduction in the size of the cyst at follow-up imaging: Three had complete resolution of the cyst, and two had a marked reduction in cyst size. Aside from the one patient who had side-branch intraductal papillary mucinous neoplasm with carcinoma in situ (described earlier), none of these conservatively treated patients had an increase in cyst size or changes in the morphologic features of the cyst at follow-up imaging to suggest progression to malignancy (Fig 3). In addition, none of these patients had pancreatic or biliary ductal dilatation or obstruction, peripancreatic lymphadenopathy or fat infiltration, vascular encasement, or metastasis to suggest malignancy at follow-up imaging.

Comparison of Imaging and Histopathologic Findings

A total of 75 (87%) of the 86 patients had benign cysts, eight (9%) had borderline neoplasms, and three (4%) had carcinoma in situ lesions. Thirty-six (42%) patients had unilocular cysts: 35 had benign lesions, and one had a borderline neoplasm. Fifty (58%) patients had septated cysts. Ten of these patients had cysts assigned to the malignancy category: seven with borderline neoplasms and three with carcinoma in situ lesions. The positive predictive values for the detection of benignity and malignancy based on cyst size and absence or presence of septa are given in Table 1. Overall, one of the 36 patients with unilocular cysts, compared with 10 of the 50 patients with septated cysts,

received a diagnosis of either borderline neoplasm or carcinoma in situ ($P = .042$). A breakdown of the numbers of patients with benign and malignant cysts as a function of the presence or absence of septa is presented in Table 2. The distributions of patients with unilocular and septated cysts are shown in Tables 3 and 4, respectively. All 11 patients assigned to the malignant cyst group had mucin-producing neoplasms. The various benign lesions included in our study are shown in Table 5.

Discussion

Performing CT and MR imaging by using thin sections through the pancreas has resulted in increased detection of pancreatic cysts (1). Other factors such as optimization of the timing of the contrast agent injection and imaging during the appropriate vascular phase after contrast agent injection also have contributed to this improved detection. Insufficient information on the biologic behavior of small pancreatic cysts has resulted in an absence of clear-cut guidelines for the management of these

lesions (1–6). Because of the known risk of malignancy in cystic neoplasms of the pancreas, investigators have recommended the resection of all pancreatic cysts (3,7,9). However, this treatment strategy seems overly aggressive given that 80.6% of the cysts described in our database were 3 cm in diameter or smaller at the time of detection and that 78.0% of these cysts were incidentally detected. These findings highlight the need to single out small pancreatic cysts for further study.

At present, published literature on the natural history of small pancreatic cysts is limited. However, studies pertaining to pancreatic cysts of all sizes have revealed that small pancreatic cysts are less likely to be malignant (3,4,6). In the Fernandez-del Castillo et al study (1), only 10 (20%) of 51 small cysts were malignant. In our series of 86 patients with small pancreatic cysts, 75 patients (87%) had benign lesions, 11 (13%) had malignant lesions (eight with borderline neoplasms and three with carcinoma in situ lesions at histopathologic analysis), and none had invasive malignancy. For patients with pancreatic cysts 3 cm or smaller, the positive predictive value for a benign diagnosis was 87%. These findings are contradictory to those reported by Spinelli et al (2), who found that cyst size did not enable the prediction of malignancy. All of the malignant cysts in our series were noninvasive; this factor further supports the contention that small mucin-producing neoplasms may have low malignancy potential. None of the pancreatic cysts in our series contained invasive carcinoma.

Furthermore, the pancreatic cysts in 58 (67%) of the 86 patients were detected incidentally. Of these 58 patients, seven (12%)—five with borderline neoplasms and two with carcinoma in situ lesions—were assigned to the malignant cyst group; the remaining patients had benign cysts. Investigators in a previous study (1) found that 3.5% of the small incidentally detected cysts in their series were malignant.

It is well recognized that the detection of a solid component within a pancreatic cyst is a strong indicator of malignancy (3,4). Although the identification of septa within a pancreatic cyst is not always associated with malignancy, it can be a cause for concern (4). Septa can be associated with a malignant or potentially malignant mucinous cystic neoplasm as well as a benign serous cystadenoma (11,12). We attempted to determine whether morphologic features such as septa are associated with a higher incidence of malignancy in small cysts. In our series, only one of the 36 patients with unilocular cysts had borderline malignant changes, without carcinoma in situ or invasive cancer. This result highlights the fact that small pancreatic cysts without septa or solid components are almost always benign. The positive predictive value of 3 cm or smaller unilocular cysts for the detection of benignity was found to be 97%. On the other hand, 10 of the 50 patients with septated cysts had malignant lesions—seven had borderline neoplasms, and three had carcinoma in situ lesions—whereas none of these patients had invasive malignancy. The positive predictive value of septa for the detection of a more aggressive histologic tumor type was 20%, which implies that the detection of septa within small cysts is not a good determinant of malignancy, but it does increase the level of suspicion.

Since Compagno and Oertel (13,14) described the potential malignant nature of mucinous cystic neoplasms, it has been assumed that all mucinous cystic neoplasms will transform into malignancies. However, subsequent study results have suggested that carefully selected patients can be treated

Table 3

Distribution of Unilocular Pancreatic Cysts in 36 Patients

Unilocular Cyst Type	No. of Patients
Pseudocyst	5
Mucin-producing neoplasm	18
Benign, unclassified	11
Serous cystadenoma	1
Neuroendocrine tumor	1

Table 4

Distribution of Septated Pancreatic Cysts in 50 Patients

Septated Cyst Type	No. of Patients
Pseudocyst	2
Mucin-producing neoplasm	29
Benign, unclassified	14
Serous cystadenoma	2
Neuroendocrine tumor	1
Other	2

Table 5

Distribution of Benign Pancreatic Cysts in 75 Patients

Benign Cyst Type	No. of Patients
Pseudocyst	7
Mucin-producing neoplasm	34
Benign, unclassified	25
Serous cystadenoma	3
Neuroendocrine tumor	2
Other	4

nonsurgically (3–6,15). The criteria for nonsurgical management in these studies were variable and included young age, absence of symptoms, small cyst size, absence of a solid component, identification of the typical morphologic features of serous cystadenomas, and absence of mucin in the cyst aspirate. In these studies, almost all of the pancreatic cysts were stable at serial imaging surveillance. The few cysts that demonstrated growth at serial imaging had benign features at histopathologic analysis following resection. Spinelli et al (2) reported that 15 (19%) of the 79 patients who underwent follow-up imaging in their study had cyst growth, and in 11 of these 15 patients, the cysts were malignant at resection. The mean diameter of the cysts that showed growth was 3.5 cm, while the mean diameters of the cysts that remained stable or decreased in size were 1.9 and 2.6 cm, respectively.

In our series, nearly all of the patients who did not undergo surgery and were treated conservatively had no interval cyst growth or change in cyst characteristics at follow-up CT or MR imaging for a mean of 21.8 months. In only one patient, who initially was treated conservatively, the cyst increased in size and had a solid component at 2-year follow-up imaging. In this patient, results of the initial cytologic examination were negative for malignant cells, while results of the second cytologic examination were positive for malignancy. The final diagnosis in this patient was side-branch intraductal papillary mucinous neoplasm with carcinoma in situ. These results support the hypothesis that the majority of small pancreatic cysts are benign and have stable size and morphologic features at follow-up and that interval cyst growth or changes in cyst morphologic features, such as the development of mural nodules, calcification, or dilatation of the pancreatic duct or bile duct, should be viewed with suspicion for malignant transformation. Therefore, in the absence of symptoms, these cysts can be safely managed with imaging surveillance.

There were some limitations in our

study. The section thickness selected for CT was not kept constant: The patients who were examined with a dedicated pancreas protocol technique were imaged by using a section thickness of 1.25 mm, while other patients were imaged by using a section thickness of 5.0 mm. This may have affected our ability to assess morphologic features such as thin septa or small mural nodules. Because our institution is a tertiary referral center for treatment of pancreatic diseases, the data in our series may not have been representative of the true frequency of malignancy in small cysts in the general population. The degrees of complexity of the cysts at imaging also may have influenced the decision to perform endoscopic US-guided aspiration and surgery. Because surgical resection was not performed in all patients, we relied on a combination of biochemical markers, tumor markers, and cytologic cyst fluid findings to establish the diagnoses. Although none of these findings represents a reference standard, the combination of findings of various cyst fluid and cytologic analyses is complementary in establishing the nature of pancreatic cysts (16).

In addition, nine of the 38 patients who were treated nonsurgically were lost to follow-up. No attempts were made to contact these patients or their primary care physicians to follow up the status of their pancreatic cysts. Likewise, we do not know the outcomes of the patients who had pancreatic cysts 3 cm or smaller but did not meet our eligibility criteria of histopathologic verification and therefore were not a part of the study. Finally we did not evaluate the incidence of malignancy in the pancreatic cysts that were larger than 3 cm.

The natural history of small pancreatic cysts is not yet clearly understood. Although mucin-producing neoplasms are considered potentially malignant if they are left in situ, the transformation from a benign to a malignant histologic type may take several years, and it is not clear if this occurs in all cases. Therefore, it may be prudent to observe these lesions for an extended period. However, serial imaging performed for a prolonged period that reveals no

change in the size or morphologic features of a lesion may lead to a loss of interest on the part of the patient and thus adversely affect his or her compliance with follow-up. This phenomenon could be a potential problem for some patients.

In conclusion, the majority (87%) of the small (≤ 3 cm) pancreatic cysts in our study were benign. Some pancreatic cysts can contain carcinoma in situ, although this finding is uncommon, whereas invasive carcinoma is very rare. Small unilocular cysts are almost never malignant, and the detection of septa at imaging does not definitively indicate malignancy. However, incidentally detected small cysts should not be disregarded, because a small percentage (13% in our study) of them can be a more aggressive histologic type. On the basis of our results, we believe that small incidentally detected pancreatic cysts can be safely monitored with imaging. Changes in the size or morphologic features of a cyst at follow-up imaging should raise suspicion for malignancy and prompt one to perform either resection or cyst aspiration for cytologic analysis.

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