

Nonsurgical Management of Asymptomatic Incidental Pancreatic Cysts

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See **Rodriguez JR et al** on page 72 for companion article in the July 2007 issue of *Gastroenterology*.

Background & Aims: Cystic lesions of the pancreas are detected more often nowadays. Many are considered pre-malignant and pancreatic resection is recommended. This study was undertaken to assess the natural course of asymptomatic pancreatic cysts and their malignant potential.

Methods: All patients referred for endoscopic ultrasound (EUS) between 1994 and 2003 because of pancreatic cystic lesions were included. **Results:** A total of 135 patients underwent EUS because of pancreatic cysts. Twenty-three patients were excluded because they were symptomatic or had pancreatic pseudocysts. The other 112 patients were diagnosed as having true pancreatic cysts. Fourteen of the 112 patients were referred for surgery based on either unfavorable EUS morphology or fine-needle aspiration results. In 4 (29%) of 14 surgical specimens, the histology was that of malignancy. An additional 8 patients with serous cystadenoma and pseudocysts were excluded from the analysis. The remaining 90 patients were defined as having indeterminate or mucinous cysts and were managed conservatively. The follow-up period lasted between 12 and 180 months (mean, 48 ± 33 mo). Malignancy was diagnosed in only 1 patient after 7 years of follow-up evaluation. None of the 57 patients available for clinical follow-up evaluation became symptomatic. The size of the cyst remained unchanged in 45 patients, increased in 2, and resolved in 9. Thirty-three patients were followed up through the Israel Registry: 31 were alive and 2 died from unrelated causes.

Conclusions: Our data suggest that a considerable number of asymptomatic pancreatic cystic lesions can be managed conservatively, at least for a mean period of 4 years. Malignant transformation in pancreatic cystic lesions probably is less frequent than previously reported.

Pancreatic cystic lesions are being identified increasingly because of the widespread use of imaging modalities such as computerized tomography (CT) and endoscopic ultrasound (US).¹⁻³ These cysts are composed of a variety of lesions, including inflammatory pseudocysts, serous cystadenoma, and mucinous cystic neoplasms. Patients with incidentally diagnosed pancreatic cysts generally are asymptomatic. Because asymptomatic serous cystadenomas have been reported to have a low malignant potential (<3%),⁴⁻⁹ they can be left alone along with inflammatory pseudocysts. However, the management of mucinous cystic neoplasms still is under debate. The malignant

potential of these tumors is reported to be considerable,^{10,11} even at the time of diagnosis of the lesion, leading to increasing numbers of referrals for pancreatic resections.¹²⁻¹⁴ Despite the improved surgical skills the morbidity and mortality rate of pancreatic resections still is significant.

To date, the existing methods to characterize pancreatic cysts lack the accuracy to distinguish between low- and high-risk lesions. The assessment of the cysts based purely on morphologic features cannot accurately distinguish the type of cyst or predict malignant transformation.^{1,2,14-18} Cytologic examination of the cyst contents often is nondiagnostic because of the inadequacy of the specimen acquired by the aspiration.^{1,2,17-19} Tumor marker levels in the aspirate have been reported as the best predictor of mucin-producing lesions,^{1,2} but they do not accurately reflect the risk of malignancy and they overlap with benign tumors.^{10,20} Therefore, the management of patients with pancreatic cysts remains a challenge.

Little information presently is available about the risk of a pancreatic cyst to develop malignant changes during a patient's lifetime. The aim of this study was to determine the natural history of asymptomatic pancreatic cystic lesions and to assess their malignant potential.

Patients and Methods

A single gastroenterology center's experience of consecutive patients with pancreatic cystic lesions referred for evaluation by EUS during a period of 10 years (from January 1994 to December 2003) is reported. Only asymptomatic patients with an incidental finding of a cystic lesion identified by abdominal imaging were eligible for the study. The medical records, EUS and CT records, and images of these patients were reviewed retrospectively.

All patients underwent an index EUS examination using a radial or curved linear-array echo endoscope. The data from all EUS procedures were entered into a standardized database. The diagnostic modalities used in the work-up of these lesions and the findings, such as size, location, and morphology, of the cysts were recorded. The specific morphologic characteristics of the cystic lesions that were assessed included the presence or absence of a cyst wall, a solid component, intracystic septa, and calcifications. A microcystic pattern of the cysts was regarded as compatible with a serous cystadenoma. A macrocystic pattern

Abbreviations used in this paper: CEA, carcinoembryonic antigen; CT, computerized tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration.

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Table 1. Patient Characteristics

Patients	Number (N = 112)
Male sex	33%
Mean age, y (±SD)	61 (15)
Mean cyst size, cm (±SD)	3.9 (2.1)
Cyst location	
Head/body-tail ratio	60/52
Mean follow-up period, mo (SD)	48 (33)

with an intracystic solid component was regarded as compatible with a mucinous neoplasm.

EUS-guided fine-needle aspiration (FNA) was performed when available using a 22-gauge needle. Cytopathologic assessment was performed by experienced cytopathologists. Aspirates were subdivided into diagnostic or nondiagnostic (in the case of acellular or hemorrhagic samples) groups. The diagnostic samples were defined as benign when normal cuboidal epithelium or inflammatory cells were seen, benign but with a malignant potential when mucin-producing cells were identified, and already malignant. The cyst fluid also was assessed for amylase and carcinoembryonic antigen (CEA) levels. High amylase levels (>5000 U/L)²⁰ in the aspirate were used to suggest an inflammatory nature of the cyst. The tumor marker CEA was measured using a solid-phase kit double-antibody sandwich immunoassay. It was used to differentiate mucinous from other lesions. CEA levels less than 5 ng/mL^{20,21} were used as diagnostic criteria for serous cystadenoma. The cut-off value of CEA greater than 25 ng/mL was used to support the mucinous nature of a cyst.

The decision to either follow-up a patient or to refer the patient for surgery was made by the referring physician after discussion with the patient. The histopathologic reports of the resected specimens were reviewed and classified according to the World Health Organization tumor classification system. Based on these reports, the patients were stratified into 2 groups: malignant and benign. Lesions were considered to be malignant whenever carcinoma in situ or invasive cancer was present, and benign when the diagnosis was that of a mucinous cyst adenoma, solid pseudopapillary tumor, serous cystadenoma, lymphangioma, pseudocyst, or other benign cystic condition. The outcomes of surgically treated patients also were recorded. The clinical data and imaging follow-up evaluations were obtained on a regular basis for the patients who did not undergo surgery. Additional information was obtained at the end of the study when the patients were recalled for a follow-up visit. A history of any symptoms was noted and all patients underwent pancreatic imaging by abdominal ultrasound, CT, or EUS. The examination was focused on the cyst diameter and the same morphologic criteria were used as during the index EUS procedure. Patients who were not available for clinical follow-up evaluation were followed up through the Israel Registry of Birth and Death (it is the most reliable source of information about whether a patient is still alive).

The primary outcome of the study was defined as a malignant progression by the end of the study period or associated death. The secondary outcome was defined as a change in the size of the cystic lesion and the development of symptoms.

Results

Patient Characteristics

During the 10-year period, 135 patients underwent EUS for the evaluation of pancreatic cystic lesions. Twenty-three patients were excluded. The remaining 112 patients' characteristics are presented in Table 1. Patients were predominantly women (67%, $P < .05$) with a mean age of 61 years (range, 32–77 y). The mean diameter of the cystic lesions was 3.9 ± 2.1 cm. Patients were followed up for a mean duration of 48 ± 33 months (range, 12–180 mo). The flow chart of the patients' outcome is shown in Figure 1.

Excluded Patients

Seventeen (13%) of the 135 patients were diagnosed as having pancreatic pseudocysts and therefore were excluded. Fifteen of them had a history of acute pancreatitis and the other 2 were diagnosed as chronic pancreatitis. On EUS, the cysts appeared as a simple cyst without septations, masses, or calcifications. FNA was performed in 4 patients, and yielded negative cytology in all of these cysts with CEA levels of less than 5 ng/mL and amylase levels of greater than 5000 U/L. All these patients were treated conservatively except 1 patient who became symptomatic during the follow-up period and needed drainage of the cyst. Six of 135 patients presented with pain, which seemed to be related to the pancreatic cysts. These patients also were excluded from further study.

Surgical Treatment and Pathologic Diagnosis

A total of 112 patients were diagnosed as having true pancreatic cysts. All were asymptomatic. Fourteen of the 112 patients were referred for surgery. EUS characterization of the resected cysts is shown in Table 2. All these patients had macrocystic-appearing cysts. A solid component was observed in 5 patients and distinct septations were found in 6. Thickened cystic walls were defined in 6 patients. Cyst fluid analysis data

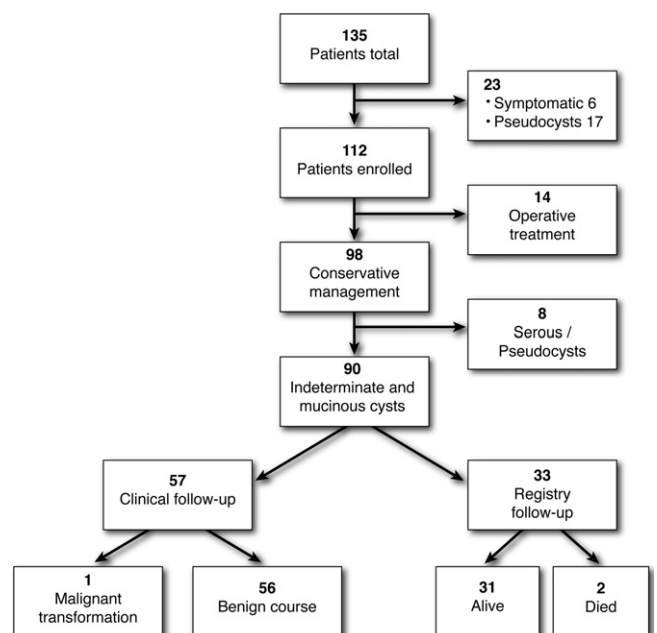


Figure 1. Flow chart of patients with pancreatic cysts.

Table 2. EUS Characteristics of Pancreatic Cysts

	Resected cysts (n = 14) (%)	Nonresected cysts (N = 98) (%)	P value
Cyst type			
Macrocytic	14 (100)	94 (96)	NS
Microcytic	0	4 (4)	
Solid component	5 (36)	12 (12)	.04
Septae	6 (43)	21 (21)	NS
Thickened wall	6 (43)	24 (24)	NS

were available for 10 patients. Cytopathologic assessment of the cyst content provided the diagnosis of malignancy in 2 patients, the diagnosis of a mucin-producing lesion in an additional 5 patients, and the diagnosis of a solid-cystic papillary tumor in 1 patient (Table 3). For the remaining 2 patients, FNA was not diagnostic. The CEA marker levels were greater than 25 ng/mL in 3 aspirates, including 1 cyst with nondiagnostic cytology.

The final pathologic diagnosis obtained at the time of surgery is shown in Table 4. Four of 14 (29%) lesions were defined as malignant and 10 were defined as benign. The malignant cysts included 2 mucinous cystadenocarcinomas with unequivocal tissue invasion, 1 intraductal papillary mucinous neoplasm with invasive cancer, and 1 ductal adenocarcinoma. The 2 patients with mucinous cystadenocarcinoma have survived 5 and 6 years, respectively, after pancreatic resection. The patient with an intraductal papillary mucinous neoplasm had presented with a cystic-appearing lesion and was not considered to have intraductal papillary mucinous neoplasm until the pathologic specimen was analyzed. The benign resected tumors were found at pathology to include 5 mucinous neoplasms, 2 serous cystadenomas, 1 solid and cystic papillary tumor, 1 lymphangioma, and 1 pseudocyst. All of these patients were alive at the end of the study period.

Conservative Management and Follow-Up Results

Ninety-eight (88%) of 112 patients were managed conservatively. The morphologic characteristics on the EUS images of these patients are presented in Table 2. Thirty-one of these patients underwent EUS-guided FNA. Based on cytology and biochemical and tumor marker analysis, their final diagnoses were as follows: pseudocysts (3 patients), mucinous cystic neoplasms (4 patients), and serous cystadenomas (5 patients). The remaining 19 aspirates were noncontributory, being either acellular or hemorrhagic (Table 3). These 19 patients, along with 67

Table 3. FNA Characteristics of Pancreatic Cysts

FNA	Resected cysts (N = 10) (%)	Nonresected cysts (N = 31) (%)
Cytology		
Inflammatory	0	3 (10)
Serous	0	5 (16)
Mucinous benign	5 (50)	4 (13)
Mucinous malignant	2 (20)	0
Other	1 (10)	0
Nondiagnostic	2 (20)	19 (61)
CEA level >25 ng/mL	3 (30)	2 (6)

Table 4. Pathologic Diagnosis of Resected Cysts

	Resected cysts (n = 14)
Mucinous cystic neoplasm ^a	8
Benign	5
Borderline	0
Malignant	3
Serous cystadenoma	2
Inflammatory cyst	1
Others ^b	2
Ductal adenocarcinoma	1
All malignant lesions ^c	4

^aIPMT is considered a mucinous cystic neoplasm.

^bSolid and cystic papillary tumors, 1; lymphangiomas, 1.

^cIncludes 3 malignant mucinous cysts and 1 ductal adenocarcinoma.

patients (total, 86 patients) who did not undergo FNA were followed up without a definite diagnosis and were categorized as indeterminate cysts.

Our study consisted of 90 patients: 86 patients with indeterminate cysts and 4 patients with mucinous cystic neoplasms. Clinical follow-up data were available for 57 of the 90 (63%) patients. The clinical course of these patients is summarized in Table 5. All of these patients were followed up on a regular basis at the outpatient clinic and by one of the imaging modalities such as abdominal ultrasound, CT, or EUS.

Only in 1 of 57 patients was the diagnosis of a cystadenocarcinoma eventually made after a 7-year follow-up period. This patient had undergone several previous aspirations of the cystic fluid for assessment before the malignant transformation was documented. The patient was alive at the end of the follow-up period. In the other 56 patients a benign course of the pancreatic cystic lesion was documented. None of them became symptomatic during the follow-up period. In 9 patients, lesions resolved spontaneously, 2 of them being diagnosed previously as mucinous cystic neoplasms (based on cystic fluid analysis). Two cysts have increased in diameter on follow-up imaging study, but the patients refused further intervention. In the remaining 45 patients the lesions did not change in size, or even decrease.

Table 5. Outcome of Nonsurgical Patients (Mucinous and Indeterminate Cysts)

	No. of patients (n = 90)
Patients followed up clinically	57
Primary outcome	
Malignant transformation ^a	1
Associated death	0
Secondary outcome	
Cysts resolved spontaneously	9
Increased cyst size	2
No change in cyst size	45
Symptom development	0
Patients followed up by Registry	33
Alive	31
Died	2

^aDiagnosed on fluid aspirate cytology.

Thirty-three of these 90 patients, all with indeterminate cysts, were lost to clinical follow-up evaluation but were followed up through the Israel Registry of Birth and Death. According to the Registry, 31 patients are alive and 2 have died. The causes of death are unrelated to pancreatic pathology; 1 owing to intracerebral hemorrhage and the other owing to ovarian cancer.

Discussion

Pancreatic cystic lesions are much more common than previously reported. The increased use of abdominal imaging is contributing to the increased identification of asymptomatic pancreatic cysts.^{2,3,16} The spectrum of pancreatic cysts is wide and includes benign, premalignant, and malignant pathologies. There is considerable controversy about the management of such patients. The decision is complicated because of the lack of diagnostic methods to differentiate between the various pancreatic pathologies and because of the lack of data about the risk for malignant transformation. A number of publications have emphasized the need for surgical management in patients with mucinous or indeterminate cysts of the pancreas because of either the high potential for malignant transformation or because of undetected foci of invasive carcinoma at the time of diagnosis.^{22,23} The purpose of the present study was to determine the long-term outcome of incidentally diagnosed pancreatic cysts in a consecutive series of patients from a referral gastroenterology center.

We found that the natural course of incidental pancreatic cysts usually is benign after a median follow-up period of 48 months. One should be aware that *mucinous cystic neoplasm* is a pathologic diagnosis and it is not clear how many of our un-operated cysts were mucinous. Of 98 patients who were managed conservatively, at least 17 did not have a mucinous cystic neoplasm. The long-term follow-up evaluation indicated that the likelihood of malignant transformation in the other patients with indeterminate cysts was low. Furthermore, the outcome of the 4 patients with suspected mucinous cysts was benign as well. Therefore, our data suggest that a close follow-up evaluation of asymptomatic indeterminate pancreatic cysts is warranted. Only 1 of our 90 patients eventually was diagnosed as having a malignant lesion. Our data contradict previous studies that have reported rates of 20%–42% of (pre)malignant lesions in pancreatic cysts.^{1,2,12,24} One reason for the discrepancy between the literature and our population probably lies in the different study populations. Most series were generated from tertiary surgical departments, which may have led to a selection bias. These series were more likely to have included subsets of patients in whom (pre)malignant lesions are more likely and who are suitable for surgical treatment. Our study included all patients who were referred for EUS evaluation to a hospital-based gastroenterology department. Because most patients were managed conservatively in our study, the absolute incidence of premalignant lesions cannot be derived from our data. The incidence of true malignancy, however, is likely to be low because patients with regular follow-up for cancerous pancreatic lesions are unlikely to remain asymptomatic for such a long period. Thirty-three patients were not available for clinical follow-up evaluation. Their follow-up evaluation was based on the Israel Population Registry, which is a reliable source of information to follow up patients and their causes of death. These data confirmed that 31 patients were

alive at the end of the study period. Although the data on their pancreatic status were not available, the long-term survival of these patients decreases the likelihood of malignant transformation.

The number of patients in our study who were referred for surgery was 14. We only have retrospective data on the criteria used to submit patients for surgery. Some of the patients had surgery because of obvious malignancy on FNA. This group underwent more FNA analyses ($P = .008$) and more frequently had a pathologic diagnosis that prompted surgical intervention ($P = .001$). Most of these cysts were resected correctly, 4 had true malignancies, and 5 had mucinous cysts.

The current study had a relative low proportion of patients who underwent fluid aspiration. Having more cysts aspirated could provide a more accurate classification of the cystic neoplasms being followed up. On the other hand, the yield and sensitivity of aspirate analysis is far from satisfactory, and in many cases it does not allow for a final characterization of the cyst.

In conclusion, our data have shown that a considerable number of asymptomatic patients with pancreatic cysts lacking unfavorable findings seem to have a much more benign course than previously reported. Therefore, in such patients a close follow-up evaluation probably is warranted.

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