

# The Natural History of the Incidentally Discovered Small Simple Pancreatic Cyst: Long-Term Follow-Up and Clinical Implications

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**OBJECTIVE.** The purpose of our study was to determine the natural history of small ( $\leq 2$  cm) simple pancreatic cystic lesions.

**MATERIALS AND METHODS.** A retrospective review was performed of patients with long-term follow-up who were diagnosed with small ( $\leq 2$  cm) simple pancreatic cysts on sonography or CT from 1985 to 1996. Long-term surveillance included radiographic surveillance of 5 years or longer, clinical follow-up of 8 years or longer, or response to questionnaire or telephone inquiry 8 year or longer after the original diagnosis. Cause of death was recorded for patients who died within 5–8 years of diagnosis. Patients were excluded if a history of pancreatitis or systemic cystic disease existed.

**RESULTS.** Seventy-nine patients had small simple pancreatic cysts. Forty-nine (62%) had adequate radiologic, clinical, or questionnaire follow-up. Of the 22 patients with radiologic follow-up, 13 (59%) had cysts that remained unchanged or became smaller (mean size, 8 mm; mean follow-up, 9 years), and nine (41%) had cysts that enlarged, from a mean of 14 mm to a mean of 26 mm (mean follow-up, 8 years). Of the 27 patients with clinical or questionnaire follow-up (mean follow-up, 10 years), none developed symptomatic pancreatic disease. Eighteen patients (23%) died within 8 years without adequate radiologic follow-up, none of pancreas-related causes. Twelve patients (15%) were lost to follow-up.

**CONCLUSION.** Although small, incidental, simple pancreatic cysts of 2 cm or smaller may enlarge over a prolonged time, morbidity or mortality due to these small simple cysts is extremely unlikely, and observation appears to be a safe management option.

**G**iven the high spatial resolution of modern sonography, MRI, and thin-collimation MDCT, simple pancreatic cysts are being found with increasing frequency. In a recent retrospective review of abdominal MRI examinations, 20% of patients were found to have pancreatic cystic lesions, with 94% of these being unilocular simple cysts, 82% being smaller than 1 cm in diameter, and only 26% being related to a history of pancreatitis [1]. Pancreatic cysts are often incidental findings occurring in patients who have no symptoms referable to the pancreas. Preoperative characterization of simple pancreatic cysts as neoplastic or nonneoplastic, benign or malignant, is often impossible. Radiologists are often uncertain about what recommendations should be made when these asymptomatic pancreatic cysts are detected, and clinicians are often uncertain how to manage them. In one recent series, only 4% of asymptomatic pancreatic cysts proved to be pseudocysts [2]. Furthermore, in the absence of systemic cystic disease such as von Hippel-

Lindau disease, polycystic kidney disease, or cystic fibrosis, true epithelial cysts are considered rare [3]. Therefore, most incidental pancreatic cystic lesions are assumed to be cystic neoplasms. Because of the as-yet-undefined but nevertheless present risk of malignancy, the aggressive approach of surgical resection of these pancreatic cysts has been advocated by some authors [2, 4, 5]. This recommendation is in contradistinction to the prevailing practice at our institution for small cystic lesions of 2 cm or smaller. Because of the frequent incidental finding of a simple pancreatic cyst and the aggressive management advocated at some centers, the aim of this retrospective study was to evaluate the natural history of incidental, small, simple pancreatic cysts to help formulate appropriate management guidelines.

## Materials and Methods

Institutional review board approval was obtained before the initiation of this retrospective study. Using an institutional radiologic coding sys-

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## Incidentally Discovered Pancreatic Cysts

<b>TABLE 1</b> Long-Term Radiologic Follow-Up in 22 Patients with a Simple Pancreatic Cyst of 2 cm or Smaller		
Follow-Up Finding	Cyst Size	
	Increased	Stable or Decreasing
Number (%)	9 (41)	13 (59)
Mean age (yr)	68	65
Mean cyst size (mm)		
At original diagnosis	14 (range, 7–20)	8 (range, 3–15)
At final radiologic follow-up	26 (range, 10–50)	<sup>a</sup>
Mean follow-up interval (yr)	8	9
Anatomic location of cyst		
Head	4	7
Body	2	5
Tail	3	1

<sup>a</sup>Five patients had cysts that were unchanged in size, and eight patients had cysts that were not detected on follow-up imaging.

tem and subsequent review of reports and (when available) films, we identified patients who were diagnosed with one or more small ( $\leq 2$  cm) simple pancreatic cysts on sonography or CT from 1985 to 1996. A cutoff of 1996 was used to ensure adequate follow-up, which was defined as 5 years or longer of imaging follow-up, 8 years or longer of clinical follow-up at our institution, or follow-up via satisfactory response to a health questionnaire relating to the history of a pancreatic disease (mailed  $\geq 8$  years after diagnosis). This follow-up health questionnaire asked patients whether they had any new diagnosis of pancreatic tumor or pancreatic disease since their last Mayo Clinic appointment and whether they had undergone an abdominal CT, sonography, or MRI examination. Details of any new diagnoses were obtained, and copies of the outside imaging or medical records were sought. If patients did not respond to the questionnaire, we attempted to contact them by telephone to obtain the same information. To obtain clinical or imaging information from outside institutions, we asked patients to sign an authorization for release of medical information to our institution. Patients were excluded if they had biochemical evidence of, or a clinical diagnosis of, pancreatitis, a history of von Hippel-Lindau disease, polycystic disease of the kidney or liver, or cystic fibrosis [6–9]; or if they died from unrelated causes within 5 years of detection of an incidental cyst. Clinical histories before and after cyst detection were reviewed. Radiologic

<b>TABLE 2</b> Clinical or Questionnaire Follow-Up in 27 Patients with a Simple Pancreatic Cyst of 2 cm or Smaller	
Data Sought	Finding
Number	27
Mean age (yr) at diagnosis	64
Mean cyst size (mm) at initial diagnosis	10 (range, 4–20)
Anatomic location of cyst	
Head	11
Body	12
Tail	4
Mean follow-up (yr) (to time of last follow-up, questionnaire, or death)	10 (range, 8–16)
Any known disease related to pancreas (other than known cyst)	
Yes	0
No	27

(sonographic, CT, and MRI) and endoscopic studies were reviewed. Pathology and cytology results were reviewed when available. Causes of death for patients who died within 5 years of the diagnosis of incidental pancreatic cyst were delineated through mechanisms previously elucidated (clinical history, telephone call to relatives).

### Results

Seventy-nine patients were identified with simple pancreatic cysts of 2 cm or smaller (age range, 15–87 years; mean age, 66 years). Sixty-seven (85%) were female and 12 (15%) were male. Twelve patients (15%) were lost to all follow-up, and 18 patients (23%) died within 8 years of unrelated causes. Forty-nine patients (62%) had follow-up as follows: 22 with 5 years or longer of radiologic follow-up, nine with 8 years or more of follow-up through clinical notes; and 18 with questionnaire follow-up 8 years or more after their original diagnosis of simple pancreatic cyst. A pathologic diagnosis was obtained in only one patient, who underwent surgery at another institution and was found to have a pseudocyst, although there was no history of pancreatitis.

Table 1 summarizes the long-term follow-up of the 22 patients with radiologic studies. In the nine patients with enlarging cysts, the cysts grew at a rate of up to 8 mm/year. None

<b>TABLE 3</b> Data for 18 Patients Who Died Within 8 Years of Diagnosis of a Simple Pancreatic Cyst of 2 cm or Smaller	
Patient Data	Finding
Number	18
Mean age (yr) at diagnosis	68
Mean cyst size (mm) at diagnosis	9 (range, 3–18)
Mean follow-up (yr) (to time of death)	3.4
Any known disease related to pancreas (other than known cyst)	
Yes	0
No	18

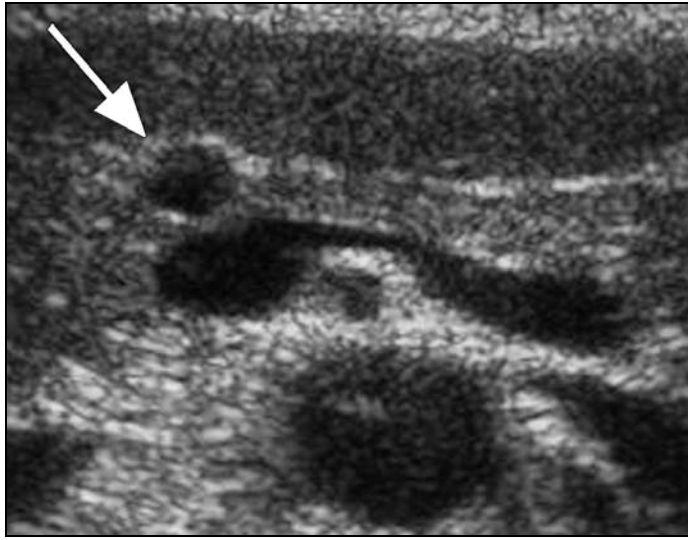
of these patients became symptomatic. One additional patient with an enlarging cyst died after 3 years of congestive heart failure and is not included in this group. Of the 13 patients with radiologic follow-up who did not have cysts that enlarged, five had pancreatic cysts that were unchanged in size (Fig. 1), and eight had cysts that were not seen on follow-up CT or sonography. None of these 13 patients developed symptomatic pancreatic disease.

Table 2 summarizes the follow-up from 27 patients with clinical follow-up material at our institution or with questionnaire follow-up. None of these patients had any symptomatic or other evidence of pancreatic disease.

Eighteen patients died within 8 years (mean, 3.4 years; range, 1 month–7 years) of the detection of their simple pancreatic cyst. Relatives indicated that there was no known pancreatic disease in any of these patients (Table 3). Only two patients were found to have had autopsies, and no pancreatic abnormality was mentioned in either autopsy report.

### Discussion

Our retrospective study attempts to document the natural history of simple pancreatic cysts of 2 cm or smaller. In the subgroup of 22 patients who were followed up radiologically, these small pancreatic cysts remained stable or were not present on follow-up imaging in 59% of patients. In contrast, these cystic lesions did increase in size in 39% of patients, only one of whom underwent surgical resection, which provided a diagnosis of pancreatic pseudocyst. In the subset of 27 patients with 8 years of clinical or historical follow-up, no patient (0%) was found to have developed pancreatic disease. In fact, no pa-



**Fig. 1.**—45-year-old woman with history of chronic hepatitis C. Transverse sonogram shows 8-mm simple cyst (arrow) at neck and body of pancreas that was stable in size for more than 7 years.

tient in either group is known to have died of pancreas-related causes. Finally, in the 18 patients who died within 8 years of the diagnosis of a simple pancreatic cyst, none was found to have died of pancreas-related causes. On the basis of these findings, we conclude that radiologic and clinical observation of incidentally discovered, small, simple pancreatic cysts appears to be safe in most such patients. The optimal interval for follow-up scanning is unknown, but annually is probably sufficient.

The differential diagnosis of a small and simple pancreatic cyst is broad, and such cysts may be neoplastic or nonneoplastic. Neoplastic causes include mucinous cystic neoplasm (MCN), branch duct intraductal papillary mucinous neoplasm (IPMN), and serous cystadenoma. Other cystic neoplasms such as cystic islet cell neoplasms, cystic degeneration of ductal adenocarcinoma, and solid pseudopapillary neoplasm of the pancreas are rare. Nonneoplastic cysts may be congenital, such as cysts associated with von Hippel-Lindau disease, polycystic kidney disease, and cystic fibrosis. The rare true cysts and lymphoepithelial cysts are also nonneoplastic. Nonneoplastic acquired cysts include pancreatic pseudocysts, retention cysts, and parasitic cysts [3]. Although most incidentally discovered pancreatic cysts of 2 cm or larger are neoplastic, and 50% of incidental cysts smaller than 2 cm are considered by some to be IPMN or MCN, which are presumably premalignant lesions [2], fewer than 5% of incidental pancreatic cysts smaller than 2 cm are frankly malignant [2]. Cysts with

complex features such as internal septa, mural nodules, or mural enhancement have a greater likelihood of being malignant and were excluded from our study.

In their recent study, Fernandez-del Castillo et al. [2] recommend that patients with incidental pancreatic cystic lesions smaller than 2 cm should be observed, whereas those with cystic lesions greater than 2 cm should be managed according to age, with young and middle-aged patients undergoing resection. Older or less medically fit patients could undergo endoscopic sonography with fine-needle aspiration and resection only if mucin; a high level of carcinoembryonic antigen; or mucinous epithelium, malignant cells, or neuroendocrine cells were present in the aspirate. If small cystic lesions enlarge on follow-up imaging, further workup can be initiated once a cyst becomes 2 cm, with our evidence supporting the fact that this period of observation does not portend an adverse outcome for the patient. Many neoplasms responsible for an incidental pancreatic cystic lesion grow slowly and are more likely to be benign than malignant (e.g., serous cystadenoma and branch duct IPMN). In patients with benign disease, close observation will hopefully obviate unnecessary surgery.

We observed a lack of consistency in the follow-up of patients in our institution. In part, this appeared to stem from differing recommendations by radiologists who interpreted the scans—for example, whether the radiologist recommended either referral to a pancreatic specialist or follow-up imaging, or

merely described the cystic lesion but made no recommendations. Follow-up intervals recommended by the radiologists were variable, and in many cases subsequent scanning was performed for an indication other than pancreatic cyst. This is probably a fair reflection of what happens in the wider community, because no accepted guidelines exist for the management of these small simple pancreatic cystic lesions. Either the patients in our study were followed up with surveillance by way of transabdominal imaging, or their cystic lesions were considered to be benign and were not further pursued. One patient underwent ERCP, which was unable to further characterize the cystic lesion, but none had endoscopic sonography or cyst aspiration. However, endoscopic sonography was not in common use during the years covered by our study.

Endoscopic sonography is now used widely in some centers, and many patients with pancreatic cystic lesions at our institution now undergo endoscopic sonography unless age or comorbidity makes it irrelevant. In addition to assessment for internal septa and mural nodules, endoscopic sonography can assess for ductal communication [10, 11]; and with endoscopic sonography guidance, it is possible to perform fine-needle aspiration of a cyst's contents [12].

The presence of mucinous epithelial cells distinguishes IPMN and MCN from serous cystic neoplasm and pseudocyst [13]. In contrast, the presence of glycogen-containing cells is diagnostic of serous cystadenoma [14, 15]. Unfortunately, the sensitivity of fine-needle aspiration to correctly diagnose the cause of these lesions is unknown. Analysis of cyst contents for viscosity, mucus, amylase, carcinoembryonic antigen, CA-125, and other tumor markers may help in further refining the diagnosis [13, 16]; however, results are often inconclusive. Typically, at our institution, an asymptomatic cyst of smaller than 1 cm will be followed up with sonography or CT. Asymptomatic cysts of about 1–2.5 cm will be evaluated with endoscopic sonography and, often, with fine-needle aspiration. Patients with asymptomatic cysts greater than 2.5 cm and patients with symptomatic cysts of any size may be offered surgery.

Our study has several weaknesses. The principal limitation of our study is the lack of pathologic diagnosis of these cystic lesions. However, although the cysts could have been neoplastic, and 10 cysts are known to have increased in size, it is important that none caused any morbidity or mortality. Because

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we could not ethically perform a prospective study in which pathologic proof was obtained, it was necessary to rely on long-term imaging and clinical follow-up. Another shortcoming caused by the necessity for prolonged follow-up is the technical limitations of older imaging technology, with the CT and sonographic equipment of 8–19 years ago being inferior to today's scanners. With the higher resolution of modern imaging technology, more and smaller lesions are likely to be detected than was the case in our study period. Our ability to characterize these lesions accurately as being simple versus complex cystic masses is greater now than it was in the past. Therefore, we would expect that patient outcomes should, if anything, be better in patients who are followed now by surveillance imaging than in our study patients.

Finally, an inherent limitation of this study is the potential for bias related to patients lost to follow-up. It is possible that a patient could have been diagnosed at our institution as having a simple pancreatic cyst and then experienced mortality or morbidity and returned to a local medical provider, unknown to our study. In addition, some patients were excluded on the basis of death within 8 years of diagnosis due to causes unrelated to the pancreas before sufficient follow-up could be obtained. Although we could find no evidence

of pancreatic disease in our follow-up, it is difficult to completely exclude the possibility of pancreas-related disease in these patients.

In conclusion, an incidentally discovered simple pancreatic cystic lesion of 2 cm or smaller is highly unlikely to cause morbidity or mortality and, if confirmed to be a simple cystic lesion by high-quality transabdominal sonography, thin-collimation CT, MRI, or endoscopic sonography, it may safely be observed. About half of these lesions may eventually grow to be larger than 2 cm, at which time more invasive management may be required.

### References

1. Zhang X, Mitchell DG, Dohke M, et al. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. *Radiology* 2002;223:547–553
2. Fernandez-del Castillo C, Targarona J, Thayer S, et al. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. *Arch Surg* 2003;138:427–434
3. Tanno S, Obara T, Izawa T, et al. Solitary true cyst of the pancreas in two adults: analysis of cyst fluid and review of the literature. *Am J Gastroenterol* 1998;93:1972–1975
4. Horvath KD, Chabot JA. An aggressive resectional approach to cystic neoplasms of the pancreas. *Am J Surg* 1999;178:269–274
5. Gasslander T, Arnelo U, Albiin N, Permert J. Cystic tumors of the pancreas. *Dig Dis* 2001;19:57–62
6. Ros PR, Hamrick-Turner JE, Chiechi MV, et al. Cystic masses of the pancreas. *RadioGraphics* 1992;12:673–686
7. Hough DM, Stephens DH, Johnson CD, Binkovitz LA. Pancreatic lesions in von Hippel-Lindau disease: prevalence, clinical significance, and CT findings. *AJR* 1994;162:1091–1094
8. Neumann H, Dinkel E, Brambs H, et al. Pancreatic lesions in von Hippel-Lindau syndrome. *Gastroenterology* 1991;101:465–471
9. Cahill ME, Parmentier JM, Van Ruyssevelt C, Pauls CH. Pancreatic cystosis in cystic fibrosis. *Abdom Imaging* 1997;22:313–314
10. Brugge WR. The role of endoscopic ultrasound in pancreatic disorders. *Int J Pancreatol* 1996;20:1–10
11. Maguchi H, Osanai M, Yanagawa N, et al. Endoscopic ultrasonography diagnosis of pancreatic cystic disease. *Endoscopy* 1998;30[suppl]:A108–A110
12. Lewandrowski K, Lee J, Southern J, Centeno B, Warshaw A. Cyst fluid analysis in the differential diagnosis of pancreatic cysts: a new approach to the preoperative assessment of pancreatic cystic lesions. *AJR* 1995;164:815–819
13. Adsay NV, Klimstra DS, Compton CC. Cystic lesions of the pancreas: introduction. *Semin Diagn Pathol* 2000;17:1–6
14. Van Dam J. EUS in cystic lesions of the pancreas. *Gastrointest Endosc* 2002;56[4 suppl]:S91–S93
15. Yasuhara Y, Sakaida N, Uemura Y, et al. Serous microcystic adenoma (glycogen-rich cystadenoma) of the pancreas: study of 11 cases showing clinicopathological and immunohistochemical correlations. *Pathol Int* 2002;52:307–312
16. Nguyen G, Suen KC, Villanueva R. Needle aspiration cytology of pancreatic cystic lesions. *Diagn Cytopathol* 1997;17:177–182

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