

Appropriate Interval for Imaging Follow-up of Small Simple Pancreatic Cysts

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ABSTRACT

Context: The frequency at which patients should undergo follow-up imaging of small pancreatic cysts is problematic because different medical societies have different follow-up guidelines.

Objective: To determine whether short-term follow-up of small pancreatic cysts is necessary to detect pancreatic cancer or cystic neoplasia.

Design: We retrospectively reviewed all abdominal magnetic resonance imaging (MRI) studies obtained in a geographically isolated health maintenance organization between January 1, 2012, and December 31, 2014, looking for pancreatic cysts. For each patient with one or more simple cysts, we recorded the size of the largest cyst. For patients with cysts, all their other computed tomography and MRI studies were reviewed to determine any change in size or morphology. The electronic medical record of every patient who underwent MRI was reviewed to determine development of pancreatic cancer.

Main Outcome Measures: Change in cyst size on images.

Results: Of 1946 patients, 342 were found to have at least 1 pancreatic cyst. A total of 228 patients had additional imaging from which to determine rates of change. The mean rate (standard deviation) of change for these cysts was 0.1 ± 2.0 mm/y. None of those cysts measuring 2 cm or smaller on MRI grew more than 5 mm in 2 years.

Conclusion: Our data validate the clinical efficacy of obtaining follow-up imaging no sooner than 24 months after the initial detection of a simple pancreatic cyst 2 cm or smaller. Patients with cysts are more likely to have pancreatic cancer, but earlier follow-up imaging would not change their diagnosis of pancreatic cancer.

METHODS

This study was approved by our institutional review board with a waiver of informed consent because it was a data-only retrospective review with no patient interactions. The study was compliant with the Health Insurance Portability and Accountability Act. We define small simple pancreatic cysts as those cysts 2 cm or smaller in maximal diameter that are unilocular or have only thin septations. We reviewed all abdominal magnetic resonance imaging (MRI) studies between January 1, 2012, and December 31, 2014, for patients who belonged to a geographically isolated health maintenance organization. All clinical information for these patients was available in an integrated electronic medical record that included all patient encounters.

All MRIs were performed on a GE 1.5T using a body coil (GE Signa HD, GE Medical Corp, Milwaukee, WI) or on a Philips 1.5T or 3.0T using a body coil (Philips Intera 1.5T or Ingenia 3T, Philips Healthcare, Andover, MA). Although the exact sequences used for each study varied according to the original indication for the study, almost every study included an axial T2-weighted sequence through the pancreas with and/or without fat saturation as well as at least 1 coronal T2-weighted or contrast-enhanced sequence. For every abdominal MRI performed during the study period, which we call the index MRI, at least 2 of the study coauthors reviewed the images to look for the presence of pancreatic cysts. Solid and part-solid cystic masses were excluded. However, multiseptated cysts were included if there was no mural nodularity or localized wall thickening (ie, contained only a few thin septations).

INTRODUCTION

The management of small pancreatic cysts is problematic. Small pancreatic cysts are a common finding in cross-sectional imaging of the abdomen, which is usually performed for reasons not related to pancreatic disease. Only a small percentage of these cysts have malignant potential. Different medical societies have different follow-up guidelines. The Fukuoka guidelines recommend that all cysts without nodularity or associated pancreatic duct dilation that measure between 1 cm and 2 cm in size be imaged every 6 to 12 months, whereas those less than 1 cm be imaged annually.¹ These guidelines make no recommendation to ever cease follow-up imaging. The American College of Radiology guidelines

for pancreatic cysts recommend that all cysts less than 2 cm be imaged in 1 year, with no further follow-up if stable at that time.² The American Gastroenterology Association recommends that cysts less than 3 cm be imaged after 1 year and then every 2 years, twice, for a total of 5 years of follow-up imaging.³

A recent study by Brook et al⁴ found that small pancreatic cysts in most patients remained stable during a median follow-up period of 2.2 years. However, 11% of these cysts demonstrated growth after an initial 1-year period of stability.⁴ We hypothesized that small pancreatic cysts do not require frequent or early follow-up imaging because these cysts are rarely the precursor to aggressive cancer.

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For each patient with a cyst, the largest cyst diameter was measured in the transverse plane. Patients with pancreatic cysts less than or equal to 5 mm were included only if the cyst could be confirmed on both the axial and coronal imaging planes. For every patient with a cyst, all other computed tomography (CT) and MRI studies between July 1, 2001, and June 1, 2016, were also reviewed to determine if there was any change in the size of their cyst. We reviewed the images of these cross-sectional imaging studies only if there was at least 3 months separating the study from the index MRI.

For every patient, we collected data on their age, sex, latest physician visit, and any diagnoses related to the pancreas, including pancreatic cancer, as of June 1, 2016. For patients with a diagnosis of pancreatic cancer, we reviewed their electronic medical records for the circumstances around which the diagnosis was ascertained. For all patients with a

pancreatic cyst, we reviewed their electronic medical records for any diagnosis of cystic neoplasia, including an intraductal papillary mucinous neoplasm, mucinous cystic neoplasia, or serous cystadenoma, and the circumstances around which any of these diagnoses were ascertained.

All statistical analysis was performed using Stata Version 11 (Stata Corp, College Station, TX).

RESULTS

We reviewed MRI studies for 1946 unique patients: 895 men and 1051 women. As shown in Table 1, the men in our study population were significantly older than the women, with an average age of 59.6 years vs 57.2 years. There were 342 patients whose index MRI demonstrated at least 1 pancreatic cyst, for an overall prevalence of 17.6%. Among these, 183 were women and 159 were men. There was no significant difference in mean age between the men and

women who had cysts. Among all women, 14.8% were found to have a pancreatic cyst, and 15.7% of men had a pancreatic cyst, which was not a significant difference (χ^2 , $p = 0.84$).

Older patients in our study were more likely to have cysts. We sorted patients using an age cutoff of 70 years. For both men and women, the prevalence of cysts was significantly higher in patients aged 70 years or older compared with those younger than age 70 years. Among men, the prevalence of cysts in those younger than age 70 years was 13.8% compared with 27.8% in the older patients (χ^2 , $p < 0.001$). The disparity was even more marked in women: 10.8% younger than age 70 years had pancreatic cysts vs 30.3% in older women (χ^2 , $p \leq 0.001$).

The size distribution of the largest cyst in each patient is presented in Figure 1. Mean size was 10.7 ± 9.1 mm, with an interquartile range (IQR) of 5 mm to 12 mm. There were 40 patients who had a cyst larger than 20 mm on their index MRI (11.7% of all patients with cysts), whereas only 13 patients (3.8% of all patients with cysts) had a cyst greater than 30 mm in maximum diameter on their index MRI.

Among the 342 patients with at least 1 pancreatic cyst, 228 underwent additional CT or MRI studies at least 3 months before or after the index MRI for whom we could determine an annual rate of change. The average time between imaging studies was 40.7 ± 32.4 months (IQR = 18.5-59.6 months). The average annual rate of change was 0.1 ± 2.0 mm/y (IQR = 0.0-0.6 mm/y).

An additional 27 patients all had at least 1 CT study after their index MRI in which no corresponding cyst or mass in the pancreas could be identified. In all but 1 of these 27 patients, the cyst seen on index MRI was less than 10 mm. Therefore, it is uncertain whether the cyst was too small to visualize with CT or if the cyst had resolved. The former scenario is more probable because a cyst could be identified by CT in several patients with cysts larger than 10 mm. Only 1 patient among these 27 had a 12-mm pancreatic body cyst on index MRI that we could not identify on CT obtained 20 months later (Figure 2).

Characteristic	All (N = 1946)	Men (n = 895)	Women (n = 1051)	p value
Age \pm SD, y (95% CI)	58.4 \pm 16.6 (48.7-69.6)	59.6 \pm 16.0 (51.8-70.4)	57.2 \pm 17.0 (46.8-68.9)	0.001
Total number of patients with cysts	342	183	159	0.63
Mean cyst size \pm SD, mm (95% CI)	10.7 \pm 9.1 (9.7-11.7)	10.6 \pm 8.7 (9.3-12.0)	10.8 \pm 9.5 (9.4-12.2)	0.86
Patients < 70 y with cysts	209	114	95	0.81
Patients \geq 70 y with cysts	133	69	64	0.57

CI = confidence interval; SD = standard deviation.

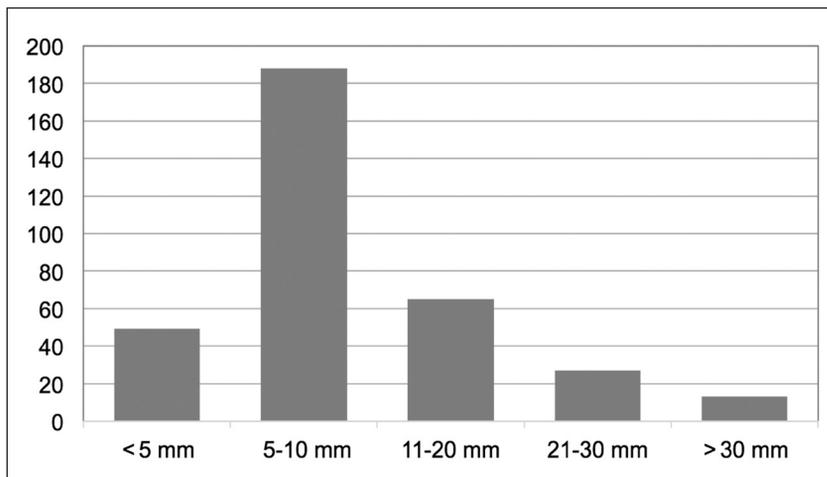


Figure 1. Size distribution of pancreatic cysts seen on index magnetic resonance imaging.

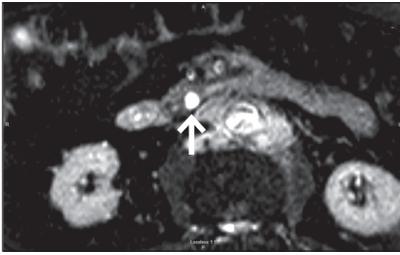


Figure 2A. Axial fat-saturated T2-weighted magnetic resonance image. The white arrow indicates a 1.2-cm simple cyst in the region of the uncinate process.

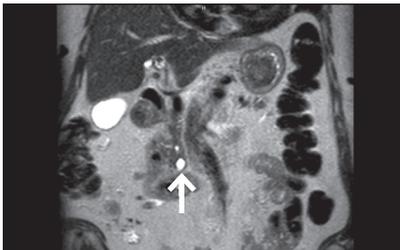


Figure 2B. Coronal T2-weighted magnetic resonance image demonstrating the same 1.2-cm pancreatic cyst.

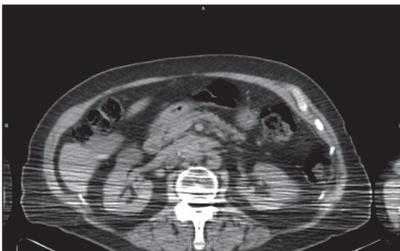


Figure 2C. Axial unenhanced computed tomography scan of the uncinate process performed 20 months after the images in Figures 2A and 2B were taken. This computed tomography scan does not show a low-attenuation lesion in the expected region of the cyst seen on previous magnetic resonance imaging.

Among the 189 patients with pancreatic cysts less than or equal to 20 mm who had additional imaging studies from which to calculate rates of change, the average annual rate of change was 0.07 ± 1.76 mm/y (95% CI = -0.18 to 0.32 mm/y).

Figure 3 plots the change in cyst size vs the duration of imaging follow-up for all 189 cysts that were 2 cm or less on index MRI. There was little change in size for most cysts. In fact, no cyst grew or shrank by more than 5 mm within 24 months after the index MRI. Only after 24 months did any cysts grow more

than 5 mm. We found only 1 instance in which a cyst 20 mm or smaller became larger than 20 mm within 2 years of the index MRI. This occurred for a 74-year-old woman noted to have a 20-mm cyst in the head of her pancreas, main pancreatic duct dilation to 6 mm, and a separate pancreatic mass, which proved to be cancer diagnosed at the time of the index MRI. This cyst enlarged to 22 mm as measured on a contrast-enhanced CT scan 8 months later.

Finally, we analyzed the prevalence of pancreatic cancer in patients with cysts and those without cysts. Ten of the 342 patients with cysts (2.9%) had or subsequently received the diagnosis of pancreatic cancer, whereas 22 of the 1604 patients without cysts (1.4%) had or subsequently received the diagnosis of pancreatic cancer, resulting in a significantly higher prevalence of pancreatic cancer in those patients with pancreatic cysts compared with those without pancreatic cysts (χ^2 , $p = 0.04$). Among the 10 patients with pancreatic cysts and cancer, 2 patients already carried a diagnosis of pancreatic cancer before their index MRI, whereas 7 others received their diagnosis of cancer within 6 weeks of their index MRI.

The 1 patient with a pancreatic cyst in whom the diagnosis of pancreatic cancer was determined after 6 weeks was a 77-year-old man with known pancreatic atrophy and multiple pancreatic body

and tail cysts, which were stable on MRI studies performed in 2011 and 2013. He presented in June 2015 with jaundice and abdominal pain, for which he underwent an MRI. This imaging demonstrated massive biliary and pancreatic ductal dilation without evidence of a discrete mass. The patient underwent endoscopic retrograde cholangiopancreatography, which revealed a friable adenocarcinoma in the ampulla. Routine-interval MRI for this patient would have been of doubtful utility in the early detection of the ampullary lesion.

Among the 1604 patients without cysts, 18 of the 22 patients with cancer already carried the diagnosis of pancreatic cancer or were diagnosed with pancreatic cancer within 6 weeks of their index MRI. In our study, 1 of 332 patients with a pancreatic cyst and without an initial cancer diagnosis, and 4 of 1586 patients without a cyst and without an initial cancer diagnosis, received a diagnosis of pancreatic cancer after 6 weeks from their index MRI, which is not statistically significant (Fisher exact test, $p = 0.99$).

Among the 342 patients with a pancreatic cyst, a diagnosis of intraductal papillary mucinous neoplasm or mucinous cystic neoplasia was confirmed by a pancreatic endoscopic ultrasonogram with fluid sampling in 7 patients. In 6 of these patients, ultrasonography was performed shortly after the index MRI finding of a pancreatic cyst. In 1 patient,

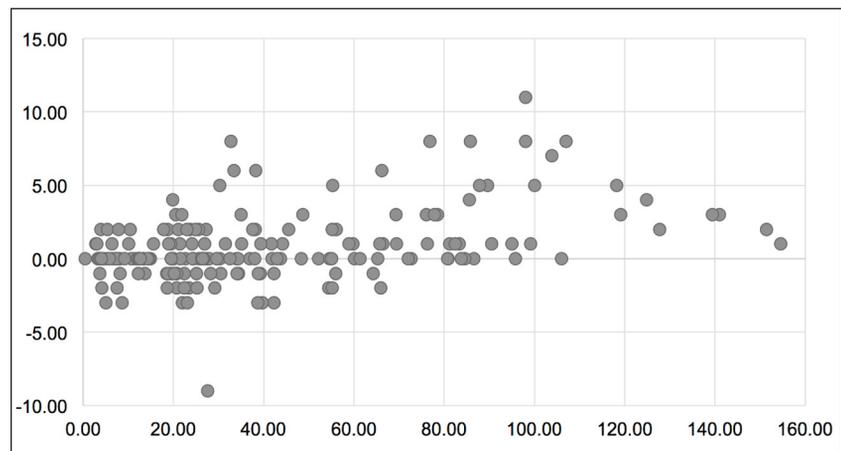


Figure 3. Plot of change in cyst size versus interval between imaging studies.^a

^a Vertical axis is change in cyst size (mm); horizontal axis is interval between imaging studies (months).

the ultrasound scan was obtained before the index MRI but was used to obtain a baseline for future follow-up. No patients had a diagnosis of an intraductal papillary mucinous neoplasm or mucinous cystic neoplasia during the clinical follow-up period in this patient cohort.

Four patients were found to have a pancreatic serous cystadenoma. One patient had a 5.1-cm cyst in the tail of the pancreas, and the diagnosis was made on the basis of the surgical specimen from distal pancreatectomy. Diagnosis for the remaining 3 patients was made on the basis of ultrasound fluid sampling. In 1 of these 3 patients, ultrasonography was performed 1 year after the index MRI but without interval imaging. The size reported on the ultrasonogram (1.8 cm) was similar to that measured on the index MRI (1.7 cm).

DISCUSSION

Pancreatic cysts are common, although estimates vary depending on the method of cross-sectional imaging. Laffan et al⁵ estimated a prevalence of 2.6% for unsuspected pancreatic cysts in their study of 2832 consecutive contrast-enhanced CT scans of the abdomen. The prevalence is much higher when MRI is the modality used to evaluate cysts. In a 2015 study, de Oliveira et al⁶ found an overall prevalence of 9.3% in their cohort of 2583 patients when their MRI reports were reviewed for the presence of cysts. In our patient population undergoing abdominal MRI, roughly 3 of every 20 patients had at least 1 cyst. Among our older patients, this rate increased to more than 1 in every 4 patients. Although these numbers are higher than those reported by the 2 studies mentioned earlier, they are similar to those reported by Lee et al,⁷ who estimated a prevalence of 13.5% in 616 consecutive patients undergoing abdominal MRI. These authors also noted an increasing prevalence with older age. In both studies estimating the prevalence of pancreatic cysts using MRI,^{6,7} patients aged 70 years and older demonstrated a much higher prevalence of cysts on MRI, with 30.7% of patients (65 of 212) having cysts in the study by de Oliveira et al⁶ and 40.2% of patients (43 of 107) in the study by Lee et al.⁷

The characteristics of cysts are important to the risk of malignancy. In a prospective study of 114 patients with pancreatic cysts and pathologic correlation of the surgically resected specimen, Sahani et al⁸ found that those associated with main pancreatic ductal dilation greater than 10 mm, mural nodularity, age older than 70 years, and cyst size larger than 3 cm correlated with aggressiveness of lesions, although only cyst size larger than 3 cm correlated with moderate or high-grade dysplasia vs low-grade dysplasia. Similarly, in a meta-analysis including 23 studies with a total of 1373 patients, Kim et al⁹ found that presence of mural nodules, followed by main pancreatic duct dilation, thick septum or wall, cyst size larger than 3 cm, and publication bias adjustment were all significant predictors of malignancy, whereas multilocularity and multiplicity of the cystic lesions did not reveal a statistically significant association with malignancy. In our study, we limited our final analysis to pancreatic cysts with a size less than or equal to 2 cm and without mural nodularity or masslike component specifically for these reasons. However, these types of cysts account for most cysts seen on MRI. In both MRI studies on the prevalence of pancreatic cysts mentioned earlier, approximately 12% of cysts had mural nodularity or thickened septations.^{6,7}

There have been relatively few studies on which to base our decisions for the management of these small pancreatic cysts, meaning those less than or equal to 2 cm. In 2005, Handrich et al¹⁰ published their study of 49 patients with small (≤ 2 cm) pancreatic cysts and a minimum of 5 years' radiologic or 8 years' clinical follow-up. They found that among the 22 patients with follow-up imaging studies, 13 had cysts that were stable or smaller on follow-up, whereas 9 patients' cysts were larger. Among the 27 patients with only clinical follow-up, none showed symptoms of pancreatic disease. Of the 18 patients who died during the minimum 8-year follow-up period, none died of pancreatic causes, according to their medical records.

Das et al¹¹ performed a retrospective study of 150 patients with cysts 1 cm or larger to determine growth rates during

a median follow-up of 32 months (IQR = 19-48 months). A total of 129 patients had cysts 3 cm or smaller, whereas only 21 patients had cysts greater than 3 cm. The authors found that only 5.6% of cysts smaller than or equal to 3 cm demonstrated any measurable growth, with an estimated median growth-free period of 103 months, whereas 44% of cysts larger than 3 cm demonstrated some growth, but even these had an estimated median growth-free period of 86 months.¹¹

Most recently, Brook et al⁴ performed a retrospective analysis of 259 subjects with small pancreatic cysts between 5 mm and 20 mm, with a minimum 6-month imaging follow-up. The median follow-up was 2.2 years, with an IQR of 1.2 to 3.9 years and a range of 0.5 to 11 years. The investigators found that cysts remained stable or shrank throughout the follow-up interval for 189 (73%) patients but grew larger for 70 (23%) patients. Among the 70 patients whose cysts grew, only 21 (30%) saw that growth occur during the first year; in the remaining patients, cyst growth occurred after at least 1 year of stability. The results from all of these studies suggest that early imaging may not be necessary for the follow-up of small cystic lesions of the pancreas.

In our patient population, the presence of pancreatic cysts was associated with an increased prevalence of pancreatic cancer. This finding concurs with the results of a recent large study of 2034 patients with pancreatic cysts and 6018 patients without pancreatic cysts in whom the presence of at least 1 pancreatic cystic lesion resulted in a 3-fold higher probability of pancreatic adenocarcinoma.¹²

A retrospective cohort study of adult patients with pancreatic cysts evident on medical record review found that patients could be stratified into low-, intermediate-, and high-risk categories on the basis of 4 cross-sectional imaging features: size, pancreatic duct dilation, septations with calcifications, and growth.¹³ Patients with cysts 2 cm or less with no other suspicious imaging features have a very low probability of malignancy developing ($\leq 0.6\%$), whereas these authors suggest that patients with cysts sized 1 cm to 3 cm that also have at least 1 suspicious imaging characteristic deserve close surveillance.¹³

Finally, Matsubara et al¹⁴ determined the relative risk of pancreatic cancer in patients with and without pancreatic cysts visualized on MRI and found that the presence of cysts was a significant risk factor for cancer, especially those cysts larger than 10 mm.

Our data validate the clinical efficacy of obtaining follow-up imaging no sooner than 24 months after the initial detection of a simple pancreatic cyst 2 cm or smaller for our own patient population. Cysts larger than 2 cm may not require more frequent imaging, but given the small numbers of larger cysts in this study, it may be premature to assume that larger cysts may be treated as conservatively as the more prevalent small cysts. Cystic masses were specifically excluded from this analysis and should be treated differently from the small unilocular cysts or cysts with only thin septations evaluated in this study. Unfortunately, the best interval for follow-up and the duration of follow-up cannot be answered by our data. Patients who are undergoing routine surveillance for active cancer should continue to have regular imaging irrespective of small pancreatic cysts.

CONCLUSION

Small unilocular or thinly septated pancreatic cysts do not require short-term follow-up. Our data show that if follow-up is to succeed in detecting change, the imaging interval should be long rather than short because short-term follow-up can lead to a false sense of security if there has been no change.

We recommend a follow-up imaging interval of no sooner than 24 months for patients with simple pancreatic cysts measuring 2 cm or less. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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