

Pancreatic cystic neoplasms: Adherence to management recommendations and associated endosonographic cyst characteristics

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Abstract

Background: The purpose of this study is to assess patients' compliance to recommendations after evaluation of pancreatic cystic neoplasm (PCN) with EUS and investigate how the presence of "worrisome" characteristics including cyst's size, main pancreatic duct dilation and presence of mural nodules might affect the adherence rates of management recommendations.

Methods: We performed a retrospective cohort study of patients at a private tertiary hospital who were referred for evaluation with EUS over a 5-year period (2015-2019), after the diagnosis of pancreatic cystic neoplasm during radiological imaging.

Results: We included 111 patients (mean age 64.1 years, SD = 13.9) with PCN. After the EUS examination, 16 patients were referred for surgical resection, 4 patients needed no further follow up and 91 patients were recommended to follow imaging surveillance. In total, 70 (63.1%) subjects adhered to surveillance recommendations. In the group of subjects who adhered to surveillance, cyst size ≥ 3 cm was found in 27 (38.6%) patients, main pancreatic duct diameter ≥ 5 mm in 12 (17.1%) subjects and only 3 (4.3%) pancreatic cysts demonstrated mural nodules. However, none of the aforementioned cystic "worrisome features" was significantly correlated with increased adherence to follow up ($p = 0.709$, $P = 0.642$ and $P = 0.630$, respectively).

Conclusions: Although the majority of patients with PCN adhered to given recommendations after EUS examination, the number of noncompliant subjects was noticeable. The presence of cystic "worrisome" features did not correlate with an increased compliance rate to suggested management plan. Further prospective studies are needed to elucidate the factors that may enhance patients' adherence.

Keywords: Adherence, endoscopic ultrasound, pancreatic cystic neoplasms, surveillance, "worrisome" features

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INTRODUCTION

The widespread use of cross-sectional imaging and the new advancements in high-resolution imaging technologies have resulted in increased detection of pancreatic cystic neoplasms (PCNs). In the majority of cases, PCNs are discovered incidentally during abdominal imaging for unrelated indications. Their prevalence in the general population approximates 8% (range 0.2–36.7%) and increases with age.^[1-3]

PCNs represent a broad spectrum of lesions with various characteristics and malignant transformation potential. They are classified into mucinous lesions including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), and non-mucinous lesions including serous cystic neoplasms (SCNs) and solid pseudopapillary neoplasms (SPNs). Mucinous lesions are characterized by a variable risk of progression to malignancy, estimated from 38% to 68% for main duct IPMNs (MD-IPMNs), 22% for branch duct IPMNs (BD-IPMNs), and from 7% to 12% for MCNs. SCNs maintain their benign nature, whereas the rarely encountered SPNs carry a low but established malignant potential.^[4,5]

Despite the low prevalence of malignancy in incidentally detected pancreatic cysts, their potential progression to malignancy over time has led several scientific associations to issue guidelines regarding optimal management.^[6-8] Regarding IPMNs, “worrisome features” like cyst size ≥ 3 cm, presence of a solid component or mural nodule within the cyst, and main pancreatic duct (MPD) dilation (diameter ≥ 5 mm) are considered to increase such a risk. Accordingly, patients should be given a recommendation to either follow-up these lesions with repeated MRI or, less frequently, proceed to surgical removal.

The target of any recommendation given to a patient with a PCN is to improve outcome by preventing the development of a pancreatic malignancy or by detecting it at an early stage. However, as many of the patients with PCNs remain asymptomatic, their adherence to follow-up can be problematic. Data pertaining to this issue are scarce and ambiguous. To address this matter, we conducted a study to evaluate patients’ adherence to recommendations given following PCN evaluation with endoscopic ultrasound (EUS). Moreover, we assessed whether the presence of “worrisome” cystic features is correlated with increased compliance to the instructions.

PATIENTS AND METHODS

Study design

This is a retrospective cohort study conducted in the gastroenterology department of a tertiary private hospital in Athens, Greece, during a 5-year period (2015-2019). The study included patients older than 18 years referred for EUS after the diagnosis of PCN during radiological imaging. The study was performed according to the World Medical Association Declaration of Helsinki and ethical approval had been received from the institutional ethics committee. Informed consent was obtained from each patient.

The electronic medical records of patients who met the inclusion criteria were reviewed, and individual telephone interviews were conducted to obtain information concerning adherence to given recommendations. We acquired follow-up data in terms of imaging tests done for surveillance and, in case of referral for surgical resection, whether surgery was performed and what was revealed during histologic examination. It was not obligatory that follow-up imaging tests and surgical resection would be performed in our center. However, our study group was keeping the electronic records of each patient after phone communication up to date, including imaging or histopathological results.

EUS Assessment

Prior to EUS performance, a detailed history from patients was obtained including pancreas-related symptoms (e.g., abdominal pain, nausea, weight loss, jaundice), new onset or recent deterioration of pre-existing diabetes, history of pancreatitis, and family history of pancreatic cancer. Results of recent laboratory tests including serum CA 19-9 levels were reviewed. Assessment of the PCN was performed by EUS. Procedures were carried out under deep sedation (including propofol) administered by an anesthesiologist. The following cyst characteristics were captured: size, MPD diameter, the existence of mural nodules or solid components, communication of the lesion with the MPD, and the presence of lymphadenopathy. EUS-guided fine needle aspiration (EUS-FNA) was performed at the endoscopist’s discretion, and cystic fluid was sent for amylase and carcinoembryonic antigen (CEA) measurements. Cytologic examination of the fluid or cyst wall nodules was also individually requested. Following the examination, according to the PCN type and the patient characteristics, all reports contained a written recommendation indicating further management (i.e., either no follow-up or radiological surveillance or surgical consultation) [Figure. 1]. The decision for the optimal management was based on EUS results in combination with

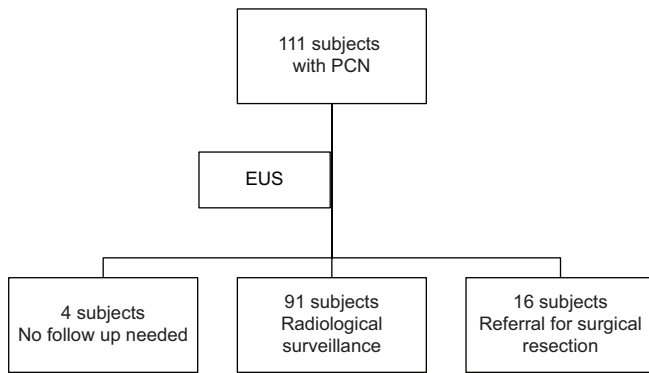


Figure 1: Recommendations made at termination of EUS examination

previous imaging modalities, according to the 2015 AGA guidelines.^[8] The following were considered “worrisome features”: size ≥ 3 cm, MPD diameter ≥ 5 mm, and presence of mural nodules. In case of one or more “worrisome features” of a lesion, the clinician thoroughly discussed the risks for malignant transformation and raised the concern for adherence to the written recommendation for each patient. No complementary cross-sectional imaging was demanded after the EUS examination in order to determine patients’ follow-up recommendation.

End points

The primary endpoint of the study was to investigate the adherence of patients with PCN to the written recommendation after EUS examination in our institution. The secondary endpoint was to assess whether the presence of any of the mentioned “worrisome features” resulted in increased compliance. Patients who could not be reached by telephone were considered as non-adherent with the suggested follow-up.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 software for Macintosh (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean (95% confidence interval) or median (interquartile range), depending on the normality of data distribution, and compared using the independent-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as frequency with percentages, and were analyzed using Pearson’s χ^2 test and Fisher’s exact test. The significance level was set at a value of $P < 0.05$.

RESULTS

A total of 111 patients underwent EUS for PCN from January 2015 to December 2019, met the inclusion criteria, and participated in the study. Table 1 shows patients’ baseline demographics as well as their clinical

Table 1: Patient demographics and clinical characteristics

Variable	Value
Age (mean \pm SD, y)	64.1 \pm 13.9
Female sex, n (%)	61 (55%)
Symptoms present, n (%)	34 (30.6%)
Pancreatitis, n (%)	12 (10.8%)
New onset DM, n (%)	5 (4.5%)
Deterioration of pre-existing DM, n (%)	3 (2.7%)
Family history of pancreatic cancer, n (%)	1 (0.9%)
Serum Ca 19-9 elevated (>37), n (%)*	5/43 (11.6%)
Index imaging method	
CT, n (%)	35 (31.5%)
MRI/MRCP, n (%)	48 (43.2%)
US, n (%)	14 (12.6%)

*Ca 19-9 was assessed in 43 out of 111 subjects. DM=Diabetes Mellitus, CT=Computed Tomography, MRI/MRCP= Magnetic Resonance Imaging/ Magnetic Resonance Cholangiopancreatography, US=Ultrasound

characteristics and index imaging method at diagnosis. PCNs’ morphological features (i.e., size, presence of mural nodules, and MPD diameter) and procedural details are presented in Table 2. Mean cyst size was 2.6 cm, and 52 of the 111 patients (46.8%) had at least one worrisome feature on EUS.

Compliance with recommended follow-up is shown in Table 3. Of note, 26 (23.4%) patients did not respond to our phone calls or their phone number was falsely captured, therefore were considered lost to follow-up and were included in the non-adherence group.

In total, 70 (63.1%) subjects adhered to surveillance recommendations in a mean follow-up duration of 35 ± 19.6 months. Having at least one worrisome feature was not associated with increased adherence rate ($p = 0.516$). More specifically, concerning the group of subjects who adhered to surveillance, cyst size ≥ 3 cm was found in 27 (38.6%) patients, MPD diameter ≥ 5 mm in 12 (17.1%) subjects and only three (4.3%) pancreatic cysts demonstrated mural nodules. However, none of the aforementioned “worrisome features” was significantly correlated with increased adherence to follow-up ($p = 0.709$, $P = 0.642$, and $P = 0.630$, respectively).

Table 2: Procedural data and cyst characteristics

Procedure/Cyst Characteristic	Value
FNA performed, n (%)	67 (60.4%)
Cystic fluid analysis performed (CEA, amylase), n (%)	24 (21.6%)
Cyst size (mean \pm SD, cm)	2.6 \pm 1.8
Cyst size ≥ 3 cm, n (%)	41 (36.9%)
MPD diameter, (mean \pm SD, mm)	3.4 \pm 2.18
MPD diameter ≥ 5 mm, n (%)	19 (17.1%)
Mural nodules/solid components, n (%)	4 (3.6%)
Presence of at least 1 worrisome feature*, n (%)	52 (46.8%)

FNA=Fine Needle Aspiration, CEA=Carcinoembryonic Antigen, MPD=main pancreatic duct, SD=standard deviation. *Worrisome features: size ≥ 3 cm, MPD diameter ≥ 5 mm, presence of mural nodule/solid component

Table 3: Worrisome features and compliance

	Compliant (n=70)	Non-Compliant (n=40)	P
Cyst Size			
<3 cm	43	26	P=0.709
≥3 cm	27	14	
MPD			
<5 mm	58	30	P=0.642
≥5 mm	12	10	
Mural Nodules			
Yes	3	1	P=0.630
No	67	39	
≥1 Worrisome Feature			
Yes	36	18	P=0.516
No	34	22	

MPD=Main Pancreatic Duct, SD=Standard Deviation

Out of the 16 subjects referred for surgical resection, 10 patients adhered to our recommendation and underwent pancreatectomy. Invasive adenocarcinoma was diagnosed in three of the 10 patients. Concerning the six ‘non-adherent’ patients, four followed imaging surveillance despite our recommendation for pancreatectomy, and two could not be reached by telephone. In the group of patients who received imaging surveillance as a recommendation, four were eventually diagnosed and/or died of pancreatic malignancy. One patient did not follow our recommendation for imaging surveillance and died 12 months after the first EUS due to pancreatic adenocarcinoma. Two other subjects, who belong to the compliance group and remain alive, were eventually diagnosed with neuroendocrine tumor after surgical resection, following four and eight imaging re-examinations, respectively. Finally, one patient who also belongs to the compliance group died of pancreatic adenocarcinoma 34 months after imaging surveillance with three EUS examinations and surgery following the last EUS.

DISCUSSION

Technological advancements and wide utilization of imaging modalities have increased the detection of PCNs. Mounting evidence has led international medical societies to publish algorithms for management of PCNs. However, data are controversial and proposed strategies differ, rendering the patient’s adherence to a consistent follow-up pattern quite challenging.^[9] According to our results, 63.1% of patients followed the given recommendation, whereas the presence of “worrisome features” (size ≥3 cm, MPD diameter ≥5 mm, and presence of mural nodules) did not increase compliance.

Adherence rate in our study appears to be concordant with a similar single center retrospective study conducted in 123 subjects with PCNs that showed 71.5% completion

of recommended follow-up.^[10] In contrast, two other studies found a compliance rate less than 50%. More specifically, in a cohort of 100 patients with incidentally identified pancreatic cysts, 47% of patients followed the recommended surveillance, whereas in the second study only 42% adhered to follow-up guidelines.^[11,12]

Satisfactory adherence rate to recommendations in our study could be explained by the fact that all patients received a written report following EUS examination, which included a specific surveillance recommendation. There is evidence that imaging reports including guidelines and recommendations may improve patients’ compliance. Schenck *et al.*^[11] proved that specific reference of the pancreatic cyst in the conclusion of the radiological report and particularly the recommendation for follow-up were both associated with compliance to surveillance. They also observed that even if the subjects adhered to surveillance, the pattern of adherence to guidelines varied broadly. Therefore, we feel a written report that clearly outlines a specific follow-up strategy is needed.

In our study, we showed that the presence of “worrisome features” does not increase adherence. Canakis *et al.*^[10] concluded that cyst size smaller than 1.5 cm was associated with incompleteness of follow-up, although statistical significance was not reached. Schenck *et al.*^[11] observed that the size and location of the lesion do not influence the compliance to follow-up, whereas MPD dilation and the absence of multiple cysts were predictors of higher adherence rates. Finally, Tabrizian *et al.*^[12] found a higher rate of failure to compliance when benign features of IPMNs were identified. Consequently, our results seem controversial in comparison to similar studies.

We chose to focus on cystic characteristics as they represent an objective parameter independent of demographic characteristics and socioeconomic status of participants. Previous studies have shown that socioeconomic status is not a predictor of surveillance for PCN.^[10,12] Tabrizian *et al.* found that patients with major co-morbidities were less adherent to follow-up of PCN (P < 0.01). Age above 68 years (P < 0.01) and American Society of Anesthesiology score of 3 or higher (P < 0.0001) also correlated with higher rates of failure of compliance.^[12] In addition, Canakis *et al.*^[10] emphasized two parameters that correlated with increased adherence rates: involvement of a documented primary care physician and organized follow-up by a gastroenterology specialty clinic. This suggests that proactive follow-up of these patients with a reminder telephonic call may improve their compliance. We observed that, following our telephonic call, a number

of non-adherent patients scheduled an appointment to see us in clinic.

Adherence to follow-up of PCN may also be influenced by emotional factors. The need for annual surveillance and the uncertain biological behavior of PCNs may generate negative emotions such as depression or anxiety contributing to significant disability and lower adherence rates. A medical-psychological approach is crucial after the diagnosis of a PCN in order to reassure adherence to the recommended strategy.^[13] There is evidence that individuals with PCN demonstrate decreased levels of anxiety or fear following EUS-FNA that is negative for malignancy.^[14] Studies that will investigate the psychological burden of patients with PCN and its association with adherence to recommendations as well as alternatives to minimize patient distress are needed.

The single-center design of our study enabled our physicians to maintain homogeneity of the whole process from diagnosis to management recommendation and follow-up. Accordingly, it has been shown in individuals at high risk for pancreatic cancer, that doctor–patient relationship increases adherence to recommendations.^[15] We regard this a strength of the present study. Nevertheless, the study is limited by its retrospective design along with the fact that our patient cohort in a private hospital may not be easily generalizable. In addition, 26 (23.4%) patients were lost to follow-up and adherence information were not available, despite the acquisition of data regarding their initial lesion.

In conclusion, we found that the majority of patients referred to our center for EUS after PCN evaluation followed the given recommendations. However, a lot of work can be done to improve patients' adherence to published guidelines. The lack of specific biomarkers that would potentially predict the malignant transformation of PCNs makes surveillance essential in order to detect cystic pancreatic neoplasms in early stages. This is especially important for high-risk patients with “worrisome features”, who did not demonstrate an increased compliance in our study. Clinicians should explain thoroughly the risk of malignant transformation for patients with PCNs that present “worrisome features” and enhance communication with patients using reminders for imaging tests through direct ways like e-mails and social media notifications. In addition, prospective studies are needed to further investigate the factors that may influence patients' adherence rates. Scientific associations should tailor guidelines so as to increase adherence rates to the suggested management plan. Surveillance can only be beneficial if it is adhered to by those who it is supposed to benefit. Our data suggests that significant improvements can be made.

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Conflicts of interest

There are no conflicts of interest.

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