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ORIGINAL ARTICLE

Natural history of asymptomatic pancreatic cystic neoplasms

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Abstract

Background: The management of asymptomatic pancreatic cysts is controversial and indications for excision are based on pathology and natural history.

Objectives: This study aimed to examine outcomes of asymptomatic lesions using a protocol based on size and cyst fluid analysis.

Methods: Asymptomatic cysts were identified from a prospectively maintained database. Sequential cross-sectional imaging studies were assessed, and results of endoscopic ultrasound-guided aspiration were co-analysed.

Results: A total of 338 asymptomatic patients underwent evaluation. Overall, 84 cysts were <1.5 cm and 254 were ≥1.5 cm in diameter. Median patient follow-up was 5.1 years [interquartile range (IQR): 4.1–6.9 years]. In the group in which cysts measured <1.5 cm in diameter, median cyst size was 1.0 cm (IQR: 0.6–1.2 cm) at presentation and increased to 1.2 cm (IQR: 0.7–1.6 cm) during follow-up. Five (6.0%) patients underwent resection, all within 2 months of presentation. In the group in which cysts measured ≥1.5 cm in diameter, median cyst size was 2.5 cm (IQR: 2.0–3.4 cm) at presentation and increased to 2.7 cm (IQR: 3.0–4.2 cm). A total of 63 (24.8%) patients underwent resection. Surgery was performed with 2 months in 53 (84.1%) patients, within 12 months in four (6.3%) patients and at >12 months post-presentation in six (9.5%) patients. A total of 70.6% of resected specimens were identified as malignancies or mucinous lesions.

Conclusions: Asymptomatic cysts of <1.5 cm in diameter can safely be followed by imaging and are expected to undergo little change. A quarter of all asymptomatic cysts measuring ≥1.5 cm are appropriately resected based on imaging and cyst fluid analysis.

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Introduction

The widespread use of cross-sectional imaging has led to the more frequent identification of asymptomatic pancreatic cystic disease and reported prevalences increase with each incremental improvement in technology.[1–4] In a population of 24 039 patients undergoing computed tomography (CT) or magnetic resonance imaging (MRI) during the period 1995–2002, Spinelli and colleagues identified pancreatic cysts in 1.2% of patients, although 0.7% of the sample had no history of pancreatitis.[1] Subsequently, Laffan *et al.* reported a prevalence of 2.6% using multi-detector CT[2] and Lee *et al.* identified cysts in 13.5% of their cohort using MRI.[3] Most recently, Girometti *et al.* reported the prevalence of pancreatic cysts to be 44.7% in patients undergoing magnetic resonance cholangiopancreatography (MRCP) for non-pancreatic indications.[4]

The management of asymptomatic pancreatic cystic neoplasms remains controversial. The original approach to the management of cystic lesions in many centres was to offer resection for all mucinous lesions; however, better understanding of these lesions[5] means that the need for excision is now usually based on the likely pathology and natural history of the lesions identified. It is important that the type of cyst present is identified accurately at an early stage as the spectrum of histopathological possibilities is wide and includes some entities that require resection and others that can be safely observed.

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There is no doubt that patients with intraductal papillary mucinous neoplasms (IPMNs) involving the main duct (MD-IPMN) require resection,[6] as do those with mucinous cystic neoplasms (MCNs)[7] in view of the risk for malignant transformation. The optimal management of IPMNs arising from side branches (SB-IPMN) of the main pancreatic duct is less clear as their natural history and malignant potential are less well defined than those of the main duct variant.[8] However, as a recent study suggests a 20% incidence of malignancy at 10 years, it is clear that they require at least careful observation.[9]

It is apparent that cyst size alone is an inadequate factor with which to differentiate cyst types and need for resection.[10] Most centres have now developed pathways for the characterization of asymptomatic lesions based on a combination of cross-sectional imaging, endoscopic ultrasound (EUS) and cyst aspiration, and have consequently developed a selective resection policy.[11–22]

The present group has previously studied the natural history of indeterminate pancreatic cystic neoplasms[5] and devised an investigation and management protocol based on size and cyst fluid analysis.[23] The aims of this study were to examine the protocol in a larger series of asymptomatic patients and to confirm its validity.

Materials and methods

Details of all patients with pancreatic cysts managed by the multidisciplinary pancreas team are held in an institutional prospectively maintained database, established in 1999 following approval by this institution's review board. Patients were initially evaluated within either the Hepatopancreatobiliary Section of the Department of Surgery, or the Therapeutic Endoscopy Section of the Department of Gastroenterology. The pancreatic surgeons and a pancreatologist conduct a joint clinic which allows any patients in whom cystic lesions are identified in the morning clinic to undergo EUS in the afternoon. Patients for whom management decisions are complex are presented at a weekly hepatopancreatobiliary case conference attended by surgeons, gastroenterologists, radiologists and pathologists.

Data were collected prospectively using a standardized electronic data form that required conclusions on the aetiology of symptoms. Patients with vague or non-specific symptoms were considered asymptomatic, although they had originally prompted the imaging study that led to the discovery of the cyst. The database was interrogated to identify all patients who presented with asymptomatic pancreatic cysts from January 2000 to July 2009.

Demographic details collected included data on age, gender and cyst size. Patients were managed according to the algorithm used in this centre, which has been published previously[24] and is illustrated in Fig. 1. In brief, cross-sectional imaging studies were assessed and EUS-guided fine needle aspiration (EUS FNA) [sequentially: cytology + mucin, carcinoembryonic antigen (CEA) and amylase] was performed in patients with cysts measuring ≥1.5 cm. The size selected for routine aspiration was based on data published by the present group which correlated cyst size and location with ability to obtain a complete aspiration results profile.[23] Endoscopic US and aspiration were also employed intermittently on cysts irrespective of size, based on referral pattern. The cut-off level of CEA for the diagnosis of a mucinous lesion was 192 ng/ml as per the International Consensus guidelines.[8]

Patients presumed to have a diagnosis of MD-IPMN or MCN were advised to undergo resection, as were those with suspicious radiological features (cysts with associated mass, mural nodules, duct obstructions, cyst rim calcifications) or cytological atypia on cyst aspiration. The presence of mucin and the CEA were also considered in the diagnostic process, principally to diagnose MCN and SB-IPMN.

Individuals within the surveillance programme underwent sequential imaging studies. Subjects who developed radiological features suspicious for malignancy and those who became symptomatic during observation underwent secondary resection. In patients in whom cysts measured ≥1.5 cm in diameter, imaging was performed at 6-month intervals initially in order to obtain a perspective on cyst growth rates. If there was no significant growth during the first year, the interval was increased to 12 months. In patients in whom lesion diameter measured <1.5 cm, scans were performed at 12-month intervals. The choice of imaging modality (CT or MRI) depended on which modality best demonstrated the lesion at baseline. Repeat aspiration was performed for an increase in cyst size if the patient remained asymptomatic.

Indications for surgery and the findings of histopathological examination, including degree of dysplasia, were recorded for all patients undergoing surgery.

Data were expressed as the median and interquartile range (IQR).

Results

During the period January 2000 to July 2009, 540 patients were registered in the database and 338 (62.6%) of these were asymptomatic. The group included 228 women and 110 men with a median age of 67 years (IQR: 57–75 years). The median length of follow-up from the time of registration was 5.1 years (IQR: 4.1–6.9 years).

The median cyst size at presentation was 2.0 cm (IQR: 1.4–3.0 cm) and the maximal size was 15.0 cm. The cysts were divided into lesions measuring <1.5 cm and those measuring ≥1.5 cm in diameter for the purposes of further investigation. The rationale for choosing this cyst diameter for stratification is based on findings in prior studies that demonstrated that a diameter of 1.5 cm is required for successful EUS FNA as smaller diameters provide inadequate aspirate volumes for characterization.[24] At registration, 84 cysts were found to measure <1.5 cm and 254 to measure ≥1.5 cm in diameter.

Cysts of <1.5 cm in diameter

In the group in which cysts measured <1.5 cm in diameter, the median cyst size at presentation was 1.0 cm (IQR: 0.6–1.2 cm). In

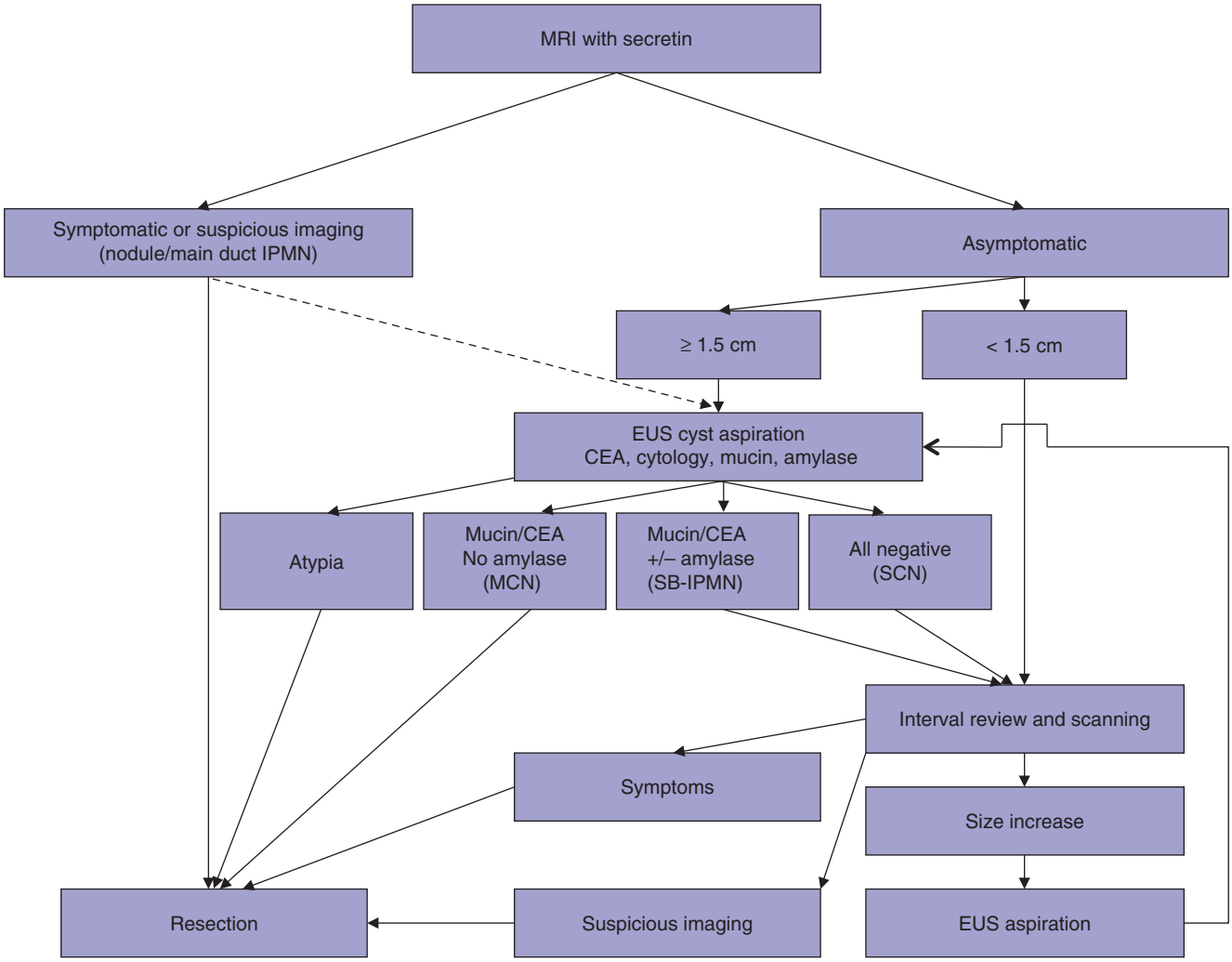

Figure 1 Algorithm for the management of pancreatic cystic neoplasia. MRI, magnetic resonance imaging; IPMN, intraductal papillary mucinous neoplasm; EUS, endoscopic ultrasound; CEA, carcinoembryonic antigen; MCN, mucinous cystic neoplasm; SB-IPMN, side-branch IPMN

four of the patients with lesions measuring <1.5 cm, mural nodules were identified on cross-sectional imaging; these patients underwent US-guided cyst aspiration. The fifth patient had a past medical history positive for renal cell carcinoma and was found to have a cystic lesion identified on routine follow-up imaging. The following patterns were seen in the four patients with suspicious imaging who underwent EUS: mucin and cellular atypia ($n = 1$); mucin and raised CEA ($n = 1$); mucin and mural nodule ($n = 1$), and mucin alone ($n = 1$).

Five (6.0%) patients in this group underwent resection, all within 2 months of initial presentation. Indications for surgery were suspicious findings during cyst evaluation (Table 1). The operations performed included four distal pancreatectomies and one pancreatoduodenectomy.

Histopathological findings are summarized in Table 2. Histopathology confirmed the lesions with a mural nodule and atypia

Table 1 Indications for primary and secondary operations undertaken in patients with asymptomatic pancreatic cysts

Indications for surgery	Cyst diameter: <1.5 cm ($n = 5$)	Cyst diameter: ≥1.5 cm ($n = 63$)
Operations performed after initial presentation and investigation, *n*		
Based on imaging protocol	5	53
Operations performed during surveillance, *n*		
Based on development of symptoms	0	2
Based on development of new features on imaging	0	6
Based on patient choice	0	2

Table 2 Final histopathological diagnoses based on examination of resection specimens

Histopathology	Cyst diameter: <1.5 cm (*n* = 5)	Cyst diameter: ≥1.5 cm (*n* = 63)
Mucinous cystic neoplasm, *n*	0	19
IPMN, *n*	2	16
Main	0	3
Side branch	2	11
Mixed-type	0	2
IPMN carcinoma, *n*	0	4
Main	0	3
Side branch	0	1
Mixed-type	0	0
Serous cystadenoma, *n*	1	14
Chronic pseudocyst, *n*	1	1
Neuroendocrine carcinoma, *n*	0	4
Mucinous adenocarcinoma, *n*	0	2
Ciliated foregut cyst, *n*	0	1
Developmental cyst, *n*	0	1
Lymphoepithelial cyst, *n*	0	1
Renal carcinoma metastasis, *n*	1	0

IPMN, intraductal papillary mucinous neoplasm.

to be SB-IPMNs, and the lesion in the patient with a history of renal carcinoma as a cystic renal metastasis. The patient in whom a positive staining for mucin emerged in conjunction with a raised CEA had a histological diagnosis of pseudocyst despite no clinical history suggestive of acute pancreatitis. The individual with isolated mucin staining was given a final histopathological diagnosis of a foregut cyst.

During the period of follow-up, the median cyst size increased from 1.0 cm (IQR: 0.6–1.2 cm) to 1.2 cm (IQR: 0.7–1.6 cm). No patient in the surveillance programme developed suspicious radiological findings and none of the patients became symptomatic. Furthermore, no additional operative procedures were performed.

Cysts of ≥1.5 cm in diameter

In the group in which cysts measured ≥1.5 cm, the median cyst size at presentation was 2.5 cm (IQR: 2.0–3.4 cm). A total of 53 (20.9%) patients underwent resection following multimodal assessment as per the protocol (Table 1); 48 of these patients underwent EUS and aspiration and the remaining five progressed directly to resection as a result of suspicious radiological findings. The median size of cysts in patients who underwent resection following the initial investigation was 2.9 cm (range: 1.5–15.0 cm).

During the follow-up of patients within the surveillance programme, the median cyst size increased to 2.7 cm (IQR: 3.0–4.2 cm). Within this cohort, a further 10 (3.9%) resections were performed in response to: the development of new radiological findings (n = 6); the development of symptoms (n = 2), and patient choice (n = 2). Four (6.3%) patients were operated within 12 months and six (9.6%) at ≥12 months post-presentation. The median size of cysts in patients who underwent resection following surveillance was 3.9 cm (range: 2.6–8.0 cm).

The two most common procedures were left pancreatectomy (n = 41) and pancreatoduodenectomy (n = 13). Total pancreatectomies were performed in three patients with MD-IPMN. Parenchyma-sparing resections were performed in six patients and included central pancreatectomy (n = 3), enucleation (n = 2) and uncinate resection (n = 1). There were no perioperative mortalities.

Histopathological findings in patients who underwent resection are summarized in Table 2. Of the 63 patients in whom cysts measured ≥1.5 cm, 19 had MCNs and eight had IPMNs with main duct involvement. This group also included two patients with mucinous adenocarcinomas and four with neuroendocrine carcinomas. The remaining lesions consisted of 12 SB-IPMNs and 18 benign lesions. Of the patients with SB-IPMNs, the indications for surgery were radiology and mucin (n = 5), radiology and raised CEA (n = 5), and radiology and atypical cytology (n = 2). Of those with a final histological diagnosis of serous cystic neoplasm (SCN, n = 14), the indications for surgery were: oligocystic lesion (n = 5), mucin on aspiration (n = 4), elevated cyst CEA (n = 1), elevated CEA and atypical cells (n = 1), large size (10 cm) (n = 1), and development of symptoms (n = 3). In the remaining four benign lesions, indications for resection were atypical cells (n = 2), radiology and mucin (n = 1), and size (n = 1; 6.0 cm).

In patients who underwent resection after a period of surveillance, histopathological findings in those who submitted to surgery within 1 year were MCN (n = 2), cystic neuroendocrine tumour (n = 1) and SCN (n = 1). Both MCNs had developed suspicious radiological features and the neuroendocrine tumour had increased in size. Of the six patients who underwent resection after 1 year, three underwent operations within 2 years and three were operated at a later time. Final histopathological findings in the patients who underwent surgery after 2 years of surveillance were all benign (SCN, n = 2; pseudocyst, n = 1) and surgery was indicated by the development of symptoms related to the cysts. Of the patients who underwent surgery within 2 years of presentation, one patient with a probable MCN developed new radiological features, and the other two, both of whom had suspected SB-IPMNs, requested surgery. Histopathology confirmed the findings and identified high-grade dysplasia in one of the patients with SB-IPMN.

Malignant and pre-malignant lesions

Overall, 68 (20.1%) of resections were performed in patients with initially asymptomatic cysts and 73.5% of these resection specimens revealed either malignant lesions or mucinous cystic lesions with malignant potential. Importantly, three of the MD-IPMNs and one of the SB-IPMNs revealed undiagnosed carcinomas

within the resection specimens. Only one of these had atypical cells on EUS FNA.

All of the three patients with MD-IPMN but without invasive carcinoma had evidence of dysplasia (high-grade, $n = 1$; moderate, $n = 1$; low-grade, $n = 1$). Similarly, both specimens of mixed-type IPMN showed dysplastic changes (high-grade, $n = 1$; low-grade, $n = 1$). In patients whose resection specimens showed SB-IPMN, the degree of dysplasia was unspecified in only three cases, and the remainder showed high-grade ($n = 3$), moderate ($n = 2$) or low-grade ($n = 5$) dysplastic changes within the cystic lesion.

In addition to the more common mucinous cystic lesions, two cases of mucinous adenocarcinoma with cystic change, four cases of neuroendocrine tumours with cystic change, and one renal cell carcinoma metastasis in a patient in whom resection was the appropriate treatment were identified.

Serous cystic neoplasms

In 15 patients, the final histopathological diagnosis was SCNs; 12 of these patients underwent primary resection and three developed symptoms during surveillance and underwent a subsequent operation. Of those undergoing primary resection following protocol evaluation, the indications for surgery were: appearance of a single cyst on imaging without any features to suggest SCN ($n = 5$); presence of mucin suggesting MCN ($n = 4$); elevated CEA ($n = 1$); oligocystic lesion with elevated CEA and atypical cells ($n = 1$), and large size (10.0 cm; $n = 1$).

Discussion

The primary finding of this study is that asymptomatic cysts are common: they were identified in 62.6% of patients in the pancreatic cyst database used in this study. This figure is comparable with the 71% reported by Ferrone *et al.* in a series of 401 patients[15] and identical to the 62% reported by Gaujoux and colleagues in a review of 1424 patients treated at the Memorial Sloan–Kettering Cancer Center over a 15-year period.[22] One strength of the current study's use of a prospective cohort is that it enables the accurate documentation of symptoms or the absence of symptoms for each cyst, something that is inaccurate in retrospective series. Thus, the present data provide a true reflection of the proportion of asymptomatic cysts referred for evaluation.

It is difficult to be certain of the prevalence of asymptomatic pancreatic cysts in the general population. There has certainly been a steady increase in prevalence as cross-sectional imaging has improved[1–4] and the latest technology suggests up to 44.7% of individuals may have small cysts.[4] Indeed, this is almost twice as high as the 24.3% reported in an autopsy series of 300 cadavers by Kimura *et al.*[25]

It is also clear from multiple centres that the increasing prevalence of cyst detection is associated with decreasing lesion size as a consequence of increases in awareness and the sensitivity of imaging.[12,15,19,22] This only increases the clinical challenges involved in determining which patients require resection. Ferrone *et al.* compared data for the periods 1997–2002 and 2004–2007, respectively, and noted that the proportion of asymptomatic patients investigated increased from 36% to 71%, and, correspondingly, the proportion undergoing surgery decreased from 80% to 50%.[15] In the present authors' experience, the median size of lesions sent for evaluation has halved from 4.0 cm to 2.0 cm over the last 5-year period.[5] Ferrone *et al.* reported a similar reduction in the size of lesions referred from 3.3 cm to 2.7 cm.[15]

In the present study, 20.1% of asymptomatic patients underwent resection, which is less than the proportions reported by other authors such as Correa-Gallego and colleagues who reported that 41% of asymptomatic patients underwent initial resection, with a further 13% undergoing surgery following a period of observation.[19] However, no-one developed cancer during this follow-up period, which is the longest in the literature. This suggests that contrary to the perception that an aggressive surgical approach should be applied in all patients with asymptomatic cystic pancreatic neoplasms, the vast majority of patients can be followed safely using the protocol suggested here. Ferrone and colleagues reported that 50% of their asymptomatic patients underwent surgery following initial investigation and that a further 8% did so after follow-up.[15] Many surgeons may have a lower threshold for operating on SB-IPMN lesions and MCNs, but this may be to the patients' detriment if they are asymptomatic.

There is little doubt within the pancreatic community that not all asymptomatic cystic lesions require resection and that a blanket policy of resection would be neither appropriate based on the indolent behaviour of many of these cysts nor, indeed, cost-effective.[26,27] The present authors believe that current management should be guided by EUS and aspiration with the development of management protocols.

Centres that deal with large numbers of cystic lesions have developed protocols for their management. However, there is no uniform agreement in relation to the cut-off size for investigation and, particularly, EUS-guided aspiration.[12–22] The algorithm used in Cleveland has a cut-off of 1.5 cm, below which EUS and aspiration are rarely performed. This size was chosen based on the likelihood that it would allow adequate fluid for analysis.[24] However, others use a threshold of 2.0 cm,[19,22] and some authors do not quote specific size criteria for the performance of second-line investigations.[13,17,18] A few centres advocate EUS in all patients with asymptomatic cysts.[16,20]

The interval for surveillance represents another factor on which there is no clear agreement, although many centres[21] have adopted guidelines based on those suggested by Allen and colleagues.[12] The Sendai consensus guidelines recommended annual follow-up for lesions measuring <1.0 cm, follow-up at intervals of 6–12 months for cysts measuring 1.0–2.0 cm in diameter, and follow-up at intervals of 3–6 months for larger lesions.[6] These guidelines were designed in relation to the surveillance of mucinous tumours rather than asymptomatic cysts and so their applicability is uncertain. Das *et al.* applied interval surveillance to 166 cysts believed to be mucinous neoplasms (117 MCNs and 49 SB-IPMNs).[14] Over a

median follow-up of 32 months, only 11% of these cysts were found to have grown and multivariate analysis showed that predictors of significant growth included the initial size of the cystic lesion and the presence of a mural nodule.[14] The authors noted that none of the cysts exhibited significant growth before 12 months. As a result, they concluded that a surveillance interval of 2 years would be adequate.[14] However, had such a policy been adopted in the current series, surgery would have been delayed in four patients with potentially malignant lesions who underwent resection.

One area of contention refers to the management of SB-IPMN. The risk for malignant transformation within this tumour is not well defined: the existing literature suggests rates of between 6% and 46%.[6,15,22,28–33] Most authors suggest a figure at the lower end of the scale and some suggest even lower rates as the current data are based on the findings of resection specimens. Indeed, Tanaka *et al.* suggested an incidence of 0–5% in asymptomatic SB-IPMNs.[6] The current guidelines suggest that these lesions should be subject to surveillance and that resection is indicated in mural nodules, a dilated main pancreatic duct or the development of symptoms.[6,34] Tanno *et al.* reported that only 11% of SB-IPMNs showed progressive changes and most of those without nodules remained unchanged over longterm follow-up.[32] The Indiana University group has also developed management protocols for pancreatic cystic lesions with the view to identifying those with high risk for malignant transformation.[35,36]

In the current study, one of the patients with SB-IPMN had an invasive carcinoma and three showed evidence of high-grade dysplasia; however, cytology was contributory in only one patient with dysplasia. These data are consistent with those from other series which claim that accurate prediction of carcinoma and high-grade dysplasia within SB-IPMNs is difficult to achieve.[9,19,39] Furthermore, it may not be possible to accurately determine the nature of a mucinous lesion preoperatively. Correa-Gallego *et al.* reported that this histological diagnosis was confirmed in only 64% of 50 patients undergoing resection of presumed SB-IPMN, and that 20% showed mixed-type IPMN with histological evidence of main duct involvement.[19] Another interesting aspect to this controversy concerns the patient's perspective. If a patient with an SB-IPMN is told that he or she has a 20% risk for cancer at 10 years, as recently suggested,[9] that no test is able to categorically indicate that the patient does not have cancer at presentation, and that the development of cancer is associated with reduced survival, it is not unreasonable to expect that many individuals will consider this 20% risk to be high and will opt for surgery, as did two patients in the current series. While accurate data are lacking, it is important that patients are fully informed of the risks and benefits of surveillance over resection and, furthermore, that attempts are made to gather more data on the natural history of this disease. The national risk for mortality in the USA is in the order of 3%[37] and has fallen to <1% in large-volume centres.[38] However, morbidity rates – currently in the order of 50%[37] – are clearly important in asymptomatic patients and must be taken into account when considering resection. Therefore, at present, as the natural history of SB-IPMN is unclear, a conservative approach would appear reasonable.[39]

One surprising finding to emerge from the present study refers to the difficulty of diagnosing SCN preoperatively. Only one of the cysts examined here had the typical features of a SCN: this was a 10-cm lesion. Of the remainder, five were oligocystic lesions of uncertain aetiology, and the others stained positive for mucin, had an elevated CEA or had atypical cells on aspiration cytology. Although such features are unusual for SCNs, these diagnostic dilemmas have been highlighted previously[40] and all series of asymptomatic pancreatic cysts will include SCNs among the lesions excised.

Conclusions

Asymptomatic cysts represent a common and important diagnostic dilemma, which, when identified, should be referred to a unit experienced in the management of pancreatic disease for evaluation and accurate characterization. This should include EUS aspiration for cysts of ≥1.5 cm in diameter. Lesions suspicious for malignancy and those believed to have a high malignant potential should be resected. Lesions with a low malignant potential should be subjected to clinical follow-up and imaging studies. In the present series, little change occurred in cyst size in lesions measuring <1.5 cm at presentation. However, an additional 20% of resections were performed for pancreatic cystic lesions measuring ≥1.5 cm at presentation in response to increases in size. Establishing a protocol for asymptomatic cysts based on aspiration results and imaging is more important than using size as a criterion on which to base management decisions and can avoid unnecessary resections.

Conflicts of interest

None declared.

References

1. Spinelli KS, Fromwiller TE, Daniel RA, Kiely JM, Nakeen A, Komorowski RA *et al*. (2004) Cystic pancreatic neoplasms: observe or operate. *Ann Surg* 239:651–657.
2. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S *et al*. (2008) Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 191:802–807.
3. Lee KS, Sekhar A, Rofsky NM, Pedrosa I. (2010) Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 105:2079–2084.
4. Girometti R, Intini S, Brondani G, Como G, Londero F, Bresadola F *et al*. (2011) Incidental pancreatic cysts on 3D turbo spin echo magnetic resonance cholangiopancreatography: prevalence and relation with clinical and imaging features. *Abdom Imaging* 36:196–205.
5. Walsh RM, Vogt DP, Henderson JM, Zuccaro G, Vargo J, Dumot J *et al*. (2005) Natural history of indeterminate pancreatic cysts. *Surgery* 138:665–670.
6. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M *et al*. (2006) International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 6:17–32.

7. Suzuki Y, Atomi Y, Sugiyama M, Isaji S, Inui K, Kimura W *et al*. (2004) Cystic neoplasm of the pancreas: a Japanese multi-institutional study of intraductal papillary mucinous tumour and mucinous cystic tumour. *Pancreas* 28:241–246.
8. Bassi C, Sarr MG, Lillemoe KD, Reber HA. (2008) Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. *J Gastrointest Surg* 12:645–650.
9. Sawai Y, Yamao K, Bhatia V, Chiba T, Mizuno N, Sawaki A *et al*. (2010) Development of pancreatic cancers during longterm follow-up of side-branch intraductal papillary mucinous neoplasms. *Endoscopy* 42:1077–1084.
10. Walsh RM, Vogt DP, Henderson JM, Hirose K, Mason T, Bencsath K *et al*. (2008) Management of suspected pancreatic cystic neoplasms based on cyst size. *Surgery* 144:677–684.
11. Handrich SJ, Hough DM, Fletcher JG, Sarr MG. (2005) The natural history of the incidentally discovered small simple pancreatic cyst: longterm follow-up and clinical implications. *AJR Am J Roentgenol* 184:20–23.
12. Allen PJ, D'Angelica M, Gonen M, Jaques DP, Coit DG, Jarnagin WR *et al*. (2006) A selective approach to the resection of cystic lesions of the pancreas: results from 539 consecutive patients. *Ann Surg* 244:572–582.
13. Lee SH, Shin CM, Park JK, Woo SM, Yoo JW, Ryu JK *et al*. (2007) Outcomes of cystic lesions of the pancreas after extended follow-up. *Dig Dis Sci* 52:2653–2659.
14. Das A, Wells CD, Nguyen CC. (2008) Incidental cystic neoplasms of pancreas: what is the optimal interval of imaging surveillance? *Am J Gastroenterol* 103:1657–1662.
15. Ferrone CR, Correa-Gallego C, Warshaw AL, Brugge WR, Forcione DG, Thayer SP *et al*. (2009) Trends in pancreatic cystic neoplasms. *Arch Surg* 144:448–454.
16. Grobmeyer SR, Cance WG, Copeland EM, Vogel SB, Hochwald SN. (2009) Is there an indication for initial conservative management of pancreatic cystic lesions? *J Surg Oncol* 100:372–374.
17. Sachs T, Pratt WB, Callery MP, Vollmer CM Jr. (2009) The incidental asymptomatic pancreatic lesion: nuisance or threat? *J Gastrointest Surg* 13:405–415.
18. Bose D, Tamm E, Liu J, Marcal L, Balachandran A, Bhosale P *et al*. (2010) Multidisciplinary management strategy for incidental cystic lesions of the pancreas. *J Am Coll Surg* 211:205–215.
19. Correa-Gallego C, Ferrone CR, Thayer SP, Wargo JA, Warshaw AL, Fernandez-del Castillo C. (2010) Incidental pancreatic cysts: do we really know what we are watching? *Pancreatology* 10:144–150.
20. Pausawasdi N, Heidt D, Kwon R, Simeone D, Scheiman J. (2010) Long-term follow-up of patients with incidentally discovered pancreatic cystic neoplasms evaluated by endoscopic ultrasound. *Surgery* 147:13–20.
21. de Castro SM, Houwert JT, van der Gaag NA, Busch OR, van Gulik TM, Gouma DJ. (2011) Evaluation of a selective management strategy of patients with primary cystic neoplasms of the pancreas. *Int J Surg* 9:655–658.
22. Gaujoux S, Brennan MF, Gonen M, D'Angelica MI, DeMatteo R, Fong Y *et al*. (2011) Cystic lesions of the pancreas: changes in the presentation and management of 1424 patients at a single institution over a 15-year time period. *J Am Coll Surg* 212:590–600.
23. Morris-Stiff G, Lentz G, Chalikonda S, Johnson M, Biscotti C, Stevens T *et al*. (2010) Pancreatic cyst aspiration analysis for cystic neoplasms: mucin or carcinoembryonic antigen – which is better? *Surgery* 148:638–644.
24. Walsh RM, Zuccaro G, Dumot JA, Vargo J, Biscotti CV, Hammel J *et al*. (2008) Predicting success of endoscopic aspiration for suspected pancreatic cystic neoplasms. *JOP* 9:612–617.
25. Kimura W, Nagai H, Kuroda A, Muto T, Esaki Y. (1995) Analysis of small cystic lesions of the pancreas. *Int J Pancreatol* 18:197–206.
26. Lim SJ, Alasadi R, Wayne JD, Rao S, Rademaker A, Bell R *et al*. (2005) Preoperative evaluation of pancreatic cystic lesions: cost–benefit analysis and proposed management algorithm. *Surgery* 138:672–679.
27. Das A, Ngamruengphong S, Nagendra S, Chak A. (2009) Asymptomatic pancreatic cystic neoplasm: a cost-effectiveness analysis of different strategies of management. *Gastrointest Endosc* 70:690–699.
28. Matsumoto T, Aramaki M, Yada K, Hirano S, Himeno Y, Shibata K *et al*. (2003) Optimal management of the branch duct type intraductal papillary mucinous neoplasms of the pancreas. *J Clin Gastroenterol* 36:261–265.
29. Irie H, Yoshimitsu K, Aibe H, Tajima T, Nishie A, Nakayama T *et al*. (2004) Natural history of pancreatic intraductal papillary mucinous tumour of branch duct type: follow-up study by magnetic resonance cholangiopancreatography. *J Comput Assist Tomogr* 28:117–122.
30. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA *et al*. (2004) Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg* 239:788–797.
31. Levy P, Jouannaud V, O'Toole D, Couvelard A, Vullierme MP, Palazzo L *et al*. (2006) Natural history of intraductal papillary mucinous tumours of the pancreas. *Clin Gastroenterol Hepatol* 4:460–468.
32. Tanno S, Nakano Y, Nishikawa T, Nakamura K, Sasajima J, Minoguchi M *et al*. (2008) Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: longterm follow-up results. *Gut* 57:339–343.
33. Crippa S, Fernandez-Del Castillo C, Salvia R, Finkelstein D, Bassi C, Domínguez I *et al*. (2010) Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. *Clin Gastroenterol Hepatol* 8:213–219.
34. Tang RS, Weinberg B, Dawson DW, Reber H, Hines OJ, Tomlinson JS *et al*. (2008) Evaluation of the guidelines for management of pancreatic branch-duct intraductal papillary mucinous neoplasm. *Clin Gastroenterol Hepatol* 6:815–819.
35. Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M *et al*. (2007) Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. *Ann Surg* 246:644–651.
36. Cauley CE, Waters JA, Dumas RP, Meyer JE, Al-Haddad MA, DeWitt JM *et al*. (2012) Outcomes of primary surveillance for intraductal papillary mucinous neoplasm. *J Gastrointest Surg* 16:258–267.
37. Mayo SC, Gilson MM, Herman JM, Cameron JL, Nathan H, Edil BH *et al*. (2012) Management of patients with pancreatic adenocarcinoma: national trends in patient selection, operative management, and use of adjuvant therapy. *J Am Coll Surg* 214:33–45.
38. Vollmer CM Jr, Sanchez N, Gondek S, McAuliffe J, Kent TS, Christein JD *et al*. (2012) Pancreatic Surgery Mortality Study Group. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg* 16:89–102.
39. Ball CG, Howard TJ. (2010) Natural history of intraductal papillary mucinous neoplasia: how much do we really know? *World J Gastrointest Surg* 2:368–372.
40. Huang P, Staerkel G, Sneige N, Gong Y. (2006) Fine-needle aspiration of pancreatic serous cystadenoma: cytologic features and diagnostic pitfalls. *Cancer* 108:239–249.