RESEARCH ARTICLE

REVISED Clinical and radiological features that predict malignant transformation in cystic lesions of the pancreas: a retrospective case note review [version 2; peer review: 2 approved]

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Abstract

Background: Pancreatic cystic lesions (PCL) are being detected with increasing frequency. Current methods of stratifying risk of malignant transformation are imperfect. This study aimed to determine the frequency of pancreatic malignancy in patients with PCL and define clinical and radiological features that predict malignant transformation in patients managed by surgery and/or surveillance.
Methods: A retrospective cohort of adults who were evaluated in a tertiary hepatopancreaticobiliary centre between January 2000 - December 2013 with a confirmed PCL and followed up for at least 5 years. All cystic lesions were discussed at a weekly multidisciplinary meeting.
Results: Of the 1,090 patients diagnosed with a PCL, 768 patients were included in the study: 141 patients were referred for immediate pancreatic resection, 570 entered surveillance while 57 had a malignant PCL which was unresectable at diagnosis (n=47) or were unfit for surgery (n=10). In those who were resected following presentation, malignancy was present in 38%. During follow-up 2% of those entering a surveillance programme underwent malignant transformation. Clinical and radiological features associated with a high-risk PCL included older age, symptoms, associated solid component or dilated main pancreatic duct. In intraductal papillary mucinous neoplasms, larger size was not a feature of malignant transformation (benign vs. malignant 30mm vs. 23mm; P= 0.012).
Conclusion: The sensitivity of standard diagnostic tests leading to immediate surgery for high-risk PCL (malignant or mucinous) was 92% but with a specificity of just 5%. Surveillance of PCL without high-risk features within a multidisciplinary meeting was associated with a low incidence of cancer development, supporting the use of worrisome clinical and radiological features in the initial stratification of PCL.

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 16 Jan 2020		✓ report
version 1 19 Feb 2019	✓ report	? report

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Pancreatic cystic lesion, IPMN, MCN, SCN, SPN, Pancreatic cancer, PNET

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REVISED **Amendments from Version 1**

We thank Prof Dennison and Dr Barresi for their review of our article.

As both reviewers noticed there was a discrepancy in median follow-up. This represented a transcription error in our results, which has been updated in our revised article.

In our study an MRI was performed in 34% and EUS in 39% of cases. As the reviewers highlight this rate is lower than what would be expected in current practice. Our study period ranged from 2000–2013 and before 2006 there were no guidelines for management, so greater variation in practice was seen. Current guidelines encourage greater use of MRCP, recognising that EUS and pancreatic protocol CT are acceptable alternatives and can provide complementary information. In a subsequent study by our group; we also observed that in certain patients with PCLs under surveillance, EUS can provide important additional information over cross-sectional imaging (Uribarri-Gonzalez L *et al.*, 2018)

Dr Barresi's suggested that several forms of imaging during the pre-operative period may reduce false positive rates in PCL. Recent guidelines suggest that MRCP has a diagnostic accuracy of multiple forms of imaging may improve diagnostic accuracies further. Importantly throughout our study all cases were regularly discussed at a multidisciplinary meeting, which is known to change management in up to a third of cases (Lennon *et al.*, 2014).

Our discussion has been modified to highlight the utility of novel endoscopic approaches (including experience from our group) as well as emerging fluid analysis methods.

Any further responses from the reviewers can be found at the end of the article

Introduction

Pancreatic cystic lesions (PCL) have become an increasingly common radiological finding, due largely to a greater availability and sensitivity of cross-sectional imaging. PCL are identified in 1.2–2.6%[1,2] of patients undergoing abdominal computed tomography (CT) and in up to 13.5% of patients undergoing an MRI for non-pancreatic indications[3]. PCL can represent a range of different lesions; the most common lesions are classified by the World Health Organisation pathologically as an intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystadenoma (SCA), solid pseudopapillary neoplasm (SPN), cystic pancreatic neuroendocrine tumour (PNET) or cystic degeneration of pancreatic ductal adenoacarcinoma (PDAC)[4].

It is estimated that 8% of all cases of PDAC arise from a PCL[5]. Detection therefore offers a significant opportunity for early curative intervention in a disease with a dismal prognosis. However the prevalence of these lesions is high and their natural history remains poorly understood. Malignant transformation of premalignant lesions is estimated to occur at a rate of approximately 0.95% per year[6] and studies that have followed mucinous lesions long-term, have suggested that those that undergo malignant transformation takes at least 5 to 10 years to develop invasive disease[7,8].

In accordance with international guidance, patients with PCL that are thought to be malignant or that are at high-risk of malignant transformation are referred for immediate surgical resection while other patients undergo regular surveillance with interval imaging[9]. In surveillance cohorts, PCL are usually smaller and without worrisome features. The exact clinical and radiological features, which predict mucinous subtypes that mandate, follow up or features which suggest malignant transformation, continue to be debated[9–14]. Recent retrospective cohort studies have shown that the 2012 international guidelines are more accurate than earlier guidance when triaging patients with PCL (PPV 88% vs. 67%, NPV 93% vs. 88%)[15,16], but highlighted that low-grade malignant lesions such as SPN, PNET and occasionally benign mucinous tumours can still be misclassified as no-risk or low-risk lesions using these criteria. Further studies from large patient cohorts who have undergone careful classification and long-term follow up are therefore required.

Study aims and objectives

The primary aim of this study was to predict the features of malignant transformation in a cohort of UK patients with a PCL referred to a tertiary hepatopancreaticobiliary (HPB) multidisciplinary team meeting (MDT).

Methods

Ethical consideration

The study protocol was reviewed by the Health Research Authority and deemed to primarily be an audit of current practice and therefore formal ethical review was not required.

Setting

A large regional hepatopancreaticobiliary cancer centre based across two tertiary-care hospitals; University College Hospital and the Royal Free Hospital, London.

Design

Retrospective case-note review.

Management

In the UK there are no national guidelines for the management of PCL so management is performed in accordance with the published International, European and AGA guidelines[9,17]. As management varies between these guidelines our centre has elected to discuss all cases of PCL at a weekly MDT meeting.

If the PCL is associated with no worrisome features, surveillance with interval imaging is the favoured management strategy. However patients with larger PCL with features suspicious of malignant transformation (solid component, dilated main pancreatic duct >6mm or associated symptoms e.g. jaundice) and without significant comorbidity were referred for surgery. Patients with features of malignant transformation but who were unsuitable for surgical resection (due to comorbidity or extent of disease) typically had the diagnosis confirmed histologically and were referred for oncological or palliative care.

Study definitions

A symptomatic PCL was defined as a lesion identified on imaging performed for the evaluation of attributable upper abdominal pain, obstructive jaundice or acute pancreatitis. For malignant lesions, weight loss, back pain and new-onset or deterioration of diabetes were also recognised to be associated symptoms.

If multiple PCL were present, the characteristics of the most significant cyst were reported (i.e. the largest cyst or the cyst with associated worrisome features).

Serum carcinoembryonic antigen (CEA) level >4.0 ng/mL and serum carbohydrate antigen 19-9 (CA 19-9) level >37 U/mL were considered to be elevated. In this study, all mixed type IPMNs (MT-IPMN) i.e. IPMN lesions which met criteria of both main duct and side branch lesions, were considered as main duct IPMNs (MD-IPMN). The PCL were further sub-classified on the basis of the most aggressive histological epithelial changes in accordance with the World Health Organisation (WHO) classification system[4]. Tumours were graded as having low or intermediate grade dysplasia, high-grade dysplasia including carcinoma *in situ* and malignant when invasive carcinoma was present, in line with the updated WHO classification of PCL[4]. Length of follow-up for the surveillance group was calculated from the time of the first cross-sectional imaging to the last cyst-related outpatient appointment. If patients did not attend clinic for any reason, interval imaging was used to define the last point of contact and to calculate the length of follow-up.

Inclusion criteria

Patients diagnosed with a PCL between January 1st 2000 and December 31st 2013 were included. Cases were identified primarily from records of the weekly HPB multidisciplinary team (MDT) meetings. In addition, the Pathology (CoPath histology database, Sunquest, Tucson AZ, USA), Endoscopy (GI reporting tool, Unisoft medical systems, UK) and Imaging (PACS: picture archiving and communication system, GE Healthcare, USA) databases were searched using the following terms; pancreatic cyst, serous cystadenoma, intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, mucinous cyst adenocarcinoma, solid pseudopapillary neoplasm, cystic pancreatic neuroendocrine tumour.

Exclusion criteria

After initial review, the following patients were excluded from the final analysis: patients < 18 years, patients with solid lesions, patients without cross-sectional imaging confirming the presence of a pancreatic cyst, patients with a confirmed inflammatory pancreatic cyst - defined as a cyst measuring more than 4cm on CT/MRCP and located within or adjacent to the pancreas with a documented history of acute or chronic pancreatitis. Four of these patients had an inflammatory cyst proximal to an obstructing pancreatic tumour but none developed *de-novo* pancreatic cancer during a median follow-up of 12 months.

Data recorded

Electronic medical records of the included patients were reviewed and information was recorded in an electronic spreadsheet; data obtained included demographic information (age, sex, hospital number), initial symptoms, history of pancreatitis or solid organ malignancy, family history of pancreatic cancer or relevant clinical syndrome. Recorded laboratory data including elevations in serum amylase, CEA and CA19-9. Baseline imaging (ultrasound, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP)), and endoscopic studies (endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA)) used in diagnosis were recorded. Features recorded from cross-sectional imaging included date of examination, size (maximal dimension), location and number of cystic lesions, presence of a solid component (mural nodules, solid component, calcification of the cyst or the wall, wall thickening), presence of septations, features of acute or chronic pancreatitis, dilatation of the pancreatic duct or biliary tree and communication of the cystic lesion with the main pancreatic duct or a side branch. For patients undergoing EUS-FNA or ERCP, imaging features at the time of the procedure were recorded as well as cytology, histology and biochemistry (CEA and amylase) results. Results of percutaneous biopsies or PET-CT scans were also recorded. For patients referred for surgery, date of operation, type of resection, final histology and length of follow-up including frequency of post-operative imaging, were recorded. For patients entered into a surveillance programme, length of surveillance, frequency of imaging and changes in size of the lesion during surveillance was also recorded.

Statistical analyses

Statistical Package for Social Sciences for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. Associations between malignancy and various clinical and radiographic characteristics were evaluated using a 2-sample *t* test for continuous variables, and a Chi-squared test for categorical variables.

Results

During the 14-year study period, 1090 patients with PCL were evaluated at the HPB MDT with rates new referrals increasing annually. 14 patients were under 18 years and were excluded from the study, as were 41 patients who had had a PCL identified on EUS but without available cross-sectional imaging. During follow-up of >12 months, 267 cysts were confirmed as pseudocysts, necessitating endoscopic or percutaneous drainage, and were also excluded. The study therefore included 768 patients, with a PCL necessitating surgery, oncologic management or surveillance [Figure 1].

Diagnostic work-up prior to MDT

97% (743/768) of patients assessed at the MDT had had a CT; the remaining 3% of patients underwent an MR / MRCP. 34% (259/768) of patients had both a CT and MRI as part of their diagnostic work-up. In patients with an indeterminate PCL, or worrisome feature on cross-sectional imaging, an EUS was performed in 39% (301/768), an ERCP in 9% (67/768) and a percutaneous biopsy in 4% (34/768).

Surgery

Of the 768 patient included in the study, 141 (18%) were referred for immediate surgical resection; a further 19 who were initially managed by surveillance eventually underwent pancreatic resection. 79 patients had an open or laparoscopic distal pancreatectomy with or without splenectomy, 65 had a Whipple's or pylorus-preserving pancreaticoduodenectomy, 10 had a total pancreatectomy and the remaining 6 patients had an enucleation [Table 1a and Table 1b]. The 30-day mortality following pancreatic resection for a PCL was 1% (2/160). Post-operatively, patients were followed up for a median of 15 (range 0–121) months.

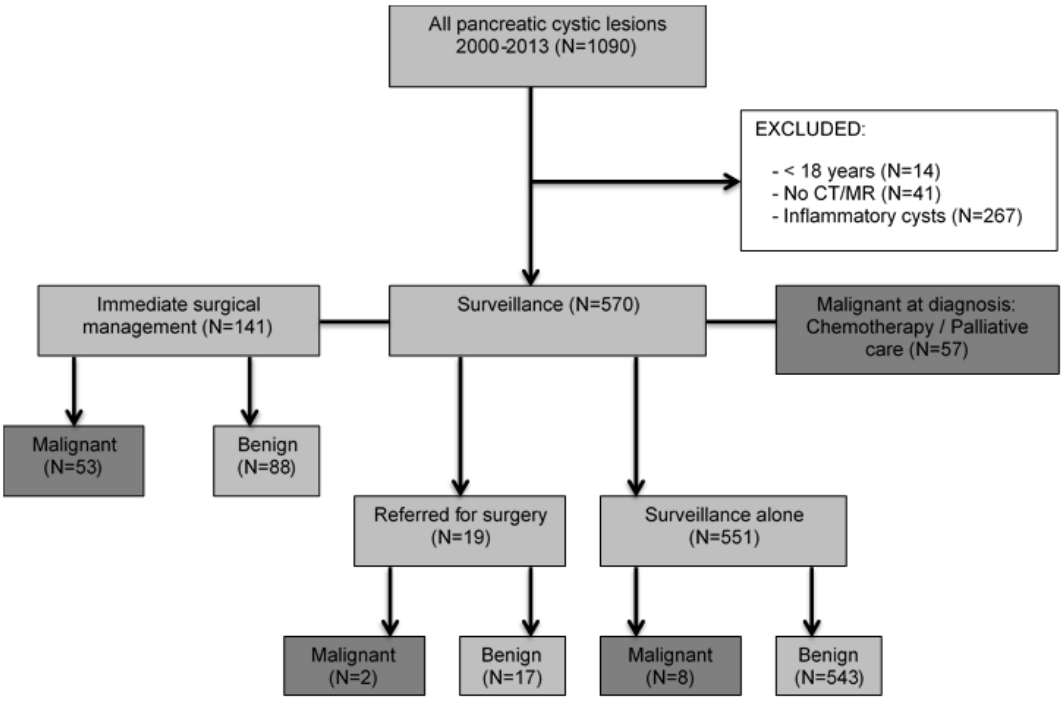

Figure 1. Management of pancreatic cystic lesions (PCL) discussed at multidisciplinary meeting (MDT) between 2000 and 2013.

Table 1a. Surgical resections performed.

Surgery (N=160)	N
Distal pancreatectomy +/- splenectomy	78
Pylorus-Preserving Pancreaticoduodenectomy (Whipple's Procedure)	65
Total pancreatectomy +/- splenectomy	11
Local excision	3
Distal pancreatectomy and splenectomy with subsequent completion pancreatectomy	3

Of the 56 patients who underwent pancreatic resection for malignant disease, 16 received adjuvant chemotherapy and 20% (11/56) died during follow-up. Of these, 9 cases were as a result of pancreatic cancer, one patient died unexpectedly while in hospital from an undetermined cause and one died from metastatic breast cancer.

Median survival following resection of a malignant PCL was 8 (range: 0–19) months for PDAC (no PCL), 16 (range: 0–91) months for a malignant IPMN, 32 (range: 5–84) months for a PNET, 26 (range: 7–35) months for a SPPN and 43 (range: 11–69) months for a malignant MCN.

Surveillance

During the study period 570 patients entered the surveillance programme. The median follow-up was 85 months (range, 0–1452 months) but dropout from surveillance was considerable after 12 months [Figure 2]. The median age of patients managed by surveillance was 67 years (range 20–92), which was older than those receiving surgical management. The median size of a cyst at entry to the surveillance programme was 20mm (range 3–130), which was smaller than all other management subtypes [Table 2].

Of the 451 patients with serial imaging during surveillance, 76 cysts (17%) increased in size, 272 remained stable, 50 decreased in size and 54 resolved [Table 3]. During follow up, 3% (19/570) of patients were ultimately referred to surgery and 2% (10/570) developed pancreatic cancer [Figure 1].

Of the 10 that underwent malignant transformation, nine of the PCL increased in size in addition to all developing worrying features [Table 4]. Seven of the 10 patients had an EUS; which was non-diagnostic in two cases and suggested benign pathology in the remaining cases. Only two of the 10 patients were ultimately referred for surgical resection; both had R0 resections and one developed recurrence at 13 months. The other eight patients were managed non-operatively, five having been discharged

Table 1b. Pathological diagnosis of patients undergoing immediate and delayed surgical management of a pancreatic cystic lesions (PCL).

Immediate surgical management (N=141)			
BENIGN – 62% (88/141)	**N**	**MALIGNANT 38% (53/141)**	**N**
IPMN (low-high grade dysplasia)	39	Malignant IPMN	16
Serous cystadenoma	19	Pancreatic neuroendocrine tumour	12
Mucinous cystic neoplasm (low-high grade dysplasia)	16	PDAC – cystic degeneration	8
Pseudocyst	9	Solid pseuopapillary neoplasm	7
Indeterminate cystadenoma	1	Mucinous cystic adenocarcinoma	5
Benign cystic teratoma (dermoid)	1	MCN adjacent to PDAC	1
Benign vascular lesion	1	Pancreatic metastasis (renal)	1
Mucinous non-neoplastic cyst	1	Pancreatic tumour with features of PDAC and PNET	1
Mild chronic pancreatitis + ductal dilation + mucinous concreations	1	Gastrointestinal stromal tumour	1
		Pancreatic desmoid tumour	1
Delayed surgical management (N=19)			
BENIGN – 89% (17/19)	**N**	**MALIGNANT – 11% (2/19)**	**N**
IPMN (low-high grade dysplasia)	5	Malignant IPMN	1
Serous cystadenoma	5	PDAC – cystic degeneration	1
Mucinous cystic neoplasm (low-high grade dysplasia)	3		
Pseudocyst	2		
Lymphoepithelial cyst	2		

IPMN: Intraductal papillary mucinous neoplasm, PDAC: pancreatic ductal adenocarcinoma

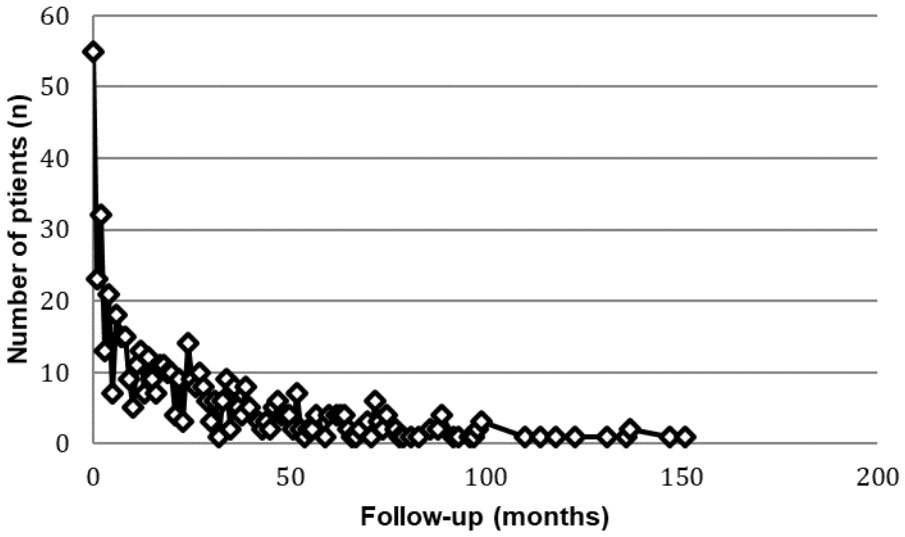

Figure 2. Duration of time spent in active surveillance for a pancreatic cystic lesions (PCL).

from active surveillance, as they were no longer fit for surgical resection. Two further patients were discharged from surveillance because the PCL was presumed to be an inflammatory cyst and one patient ultimately refused surgical intervention after developing unresectable pancreatic cancer [Table 4].

Of the 3% of patients in surveillance who were ultimately referred for surgery, 47% (9/19) were found to have a non-mucinous, non-malignant cyst on final pathology [Table 1b]. These patients had been in a surveillance programme for a median of 37 months prior to surgery (range: 7–64 months).

Table 2a. Comparison of clinical features by management subtype and cyst subtype for resected lesions.

Cyst	N	Median Age (range)	Male	Female	Symptoms	Clinical history of pancreatitis	Previous cancer	Family history of PDAC / syndrome	Median CA 19–9	Range CA 19–9
MANAGEMENT										
Immediate surgical management	141	61 (23–83)	40% (56)	60% (85)	50% (64)	23% (31)	11% (15)	4% (6)	15.3	(1.4–5604)
Surveillance	570	67 (20–92)	47% (266)	53% (304)	36% (182)	27% (153)	25% (142)	5% (30)	11.4	(<1–2102)
Chemotherapy / Palliative care (malignant at presentation)	57	69 (43–95)	63% (36)	37% (21)	76% (40)	20% (11)	16% (9)	4% (2)	106	(<1–4981)
SURGERY–BENIGN										
IPMN (benign)	44	65 (42–82)	52% (23)	48% (21)	49% (18)	33% (13)	12% (5)	0% (0)	15.75	(<1–460)
MCN	20	60 (27–76)	5% (1)	95% (19)	50% (7)	16% (3)	5% (1)	0% (0)	15	(1.4–36)
SCA	24	68 (49–78)	12% (3)	88% (21)	18% (3)	0% (0)	17% (4)	4% (1)	6.5	(1.4–49)
Pseudocyst	11	50 (34–66)	55% (6)	45% (5)	70% (7)	73% (8)	0% (0)	9% (1)	32	(8.8–5604)
SPN	7	28 (23–49)	0% (0)	100% (7)	33% (2)	14% (1)	0% (0)	0% (0)	6.45	(3.5–17.4)
SURGERY– MALIGNANT										
IPMN (malignant)	17	72 (54–81)	47% (8)	53% (9)	79% (11)	25% (4)	19% (3)	13% (2)	10.8	(8–19.6)
PNET	12	55 (36–77)	50% (6)	50% (6)	17% (2)	0% (0)	17% (2)	8% (1)	32.3	(16.9–108.2)
PDAC	9	68 (54–77)	55% (5)	44% (4)	75% (6)	33% (3)	0% (0)	0% (0)	37	(6–119.6)
MCN (malignant)	5	53 (41–69)	40% (2)	60% (3)	75% (3)	20% (1)	0% (0)	0% (0)	6	6

IPMN: Intraductal papillary mucinous neoplasm, PDAC: pancreatic ductal adenocarcinoma, MCN: Mucinous cystic neoplasm, SCA: Serous cystadenoma, SPN: Solid pseudopapillary neoplasm, PNET: Pancreatic neuroendocrine tumour

Table 2b. **Comparison of cross-sectional imaging features by management subtype and cyst subtype in resected pancreatic cystic lesions (PCL).**

Cyst	N	Median Size + range (mm)	Head / Neck	Body / Tail	Multiple pancreatic cysts	Solid component	Septations	Acute pancreatitis	Chronic pancreatitis	PD dilatation (>5mm)	PD com	CBD dilatation	LN enlargement	Vascular compromise	Concomitant cysts in other organs
MANAGEMENT															
Immediate surgical management	141	33 (3–230)	41% (58)	59% (83)	14% (20)	22% (31)	9% (13)	4% (5)	18% (25)	28% (39)	8% (11)	14% (19)	6% (9)	4% (6)	27% (38)
Surveillance	570	20 (3–130)	56% (315)	44% (245)	35% (197)	10% (59)	11% (65)	11% (64)	27% (154)	27% (151)	10% (56)	13% (72)	6% (35)	3% (14)	35% (202)
Chemotherapy/ Palliative care (malignant at presentation)	57	41 (7–250)	70% (40)	30% (17)	23% (13)	42% (24)	7% (4)	9% (5)	25% (14)	40% (23)	2% (1)	39% (22)	12% (7)	9% (5)	21% (12)
SURGERY - BENIGN															
IPMN (benign)	44	30 (11–130)	61% (27)	39% (17)	18% (8)	11% (5)	11% (5)	2% (1)	21% (9)	43% (19)	25% (11)	11% (5)	7% (3)	2% (1)	27% (12)
MCN	20	42.5 (18–120)	20% (4)	80% (16)	0% (0)	35% (7)	30% (6)	0% (0)	10% (2)	10% (2)	10% (2)	0% (0)	0% (0)	5% (1)	25% (5)
SCA	24	42.5 (14–159)	29% (7)	71% (17)	8% (2)	25% (6)	13% (3)	0% (0)	17% (4)	4% (1)	4% (1)	4% (1)	0% (0)	0% (0)	25% (6)
Pseudocyst	11	36 (20–90)	64% (7)	36% (4)	46% (5)	9% (1)	0% (0)	55% (6)	46% (5)	36% (4)	0% (0)	9% (1)	18% (2)	27% (3)	0% (0)
SPPN	7	59 (20–150)	0% (0)	100% (7)	0% (0)	29% (2)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	14% (1)	0% (0)	14% (1)
SURGERY - MALIGNANT															
IPMN (malignant)	17	23 (15–56)	53% (9)	47% (8)	29% (5)	18% (3)	0% (0)	6% (1)	29% (5)	47% (8)	0% (0)	47% (8)	0% (0)	0% (0)	53% (9)
PNET	12	23.5 (15–94)	25% (3)	75% (9)	17% (2)	33% (4)	0% (0)	0% (0)	0% (0)	0% (0)	17% (2)	0% (0)	8% (1)	0% (0)	33% (4)
PDAC	9	25 (15–59)	44% (4)	55% (5)	11% (1)	44% (4)	11% (1)	0% (0)	11% (1)	67% (6)	11% (1)	44% (4)	22% (2)	0% (0)	22% (2)
MCA	5	120 (23–230)	40% (2)	60% (3)	0% (0)	40% (2)	0% (0)	0% (0)	40% (2)	20% (1)	0% (0/	0% (0)	0% (0)	20% (1)	0% (0)

IPMN: Intraductal papillary mucinous neoplasm, PDAC: pancreatic ductal adenocarcinoma, MCN: Mucinous cystic neoplasm, SCA: Serous cystadenoma, SPN: Solid pseudopapillary neoplasm, PNET: Pancreatic neuroendocrine tumour, PD com: PD communication

Table 3. Proportion of pancreatic cystic lesions (PCL), which increased, decreased, remained stable or resolved while in surveillance with interval imaging.

	N = 452	Number PDAC	Median length of follow up	Range	Referred to surgery	Currently in active follow up
Increased	76	9	29	(0–137)	13 (1 malignant)	21
Stable	272	1	22	(0–151)	5 (1 malignant)	69
Decreased	50	0	24	(2–83)	1	12
Resolved	54	0	26	(3–147)	0	2

PDAC: Pancreatic ductal adenocarcinoma

Features of malignant transformation

During the study period, 16% (120/768) of patients were diagnosed with pancreatic cancer of whom 46% (55/120) underwent surgical resection. Of the patients initially referred for surgery, 38% (53/141) were diagnosed with a malignant pancreatic cyst compared to 2% (10/570) in the surveillance group [Figure 3]. 92% (110/120) of all patients with malignancy were diagnosed at the time the PCL was detected. The median age at diagnosis for a malignant PCL was 67 (23–95) years. 64% (67/105) were symptomatic. The median size of a malignant PCL at diagnosis was 35 (6–250) mm. 39% (47/120) had an associated solid component and 38% (45/120) had pancreatic duct dilation. Most patients developing malignancy did so within 2 year of diagnosis, but 30% underwent malignant transformation after more than 5 years follow up [Figure 4].

The overall sensitivity of current diagnostic tests leading to immediate surgery for high-risk PCL (malignant or mucinous) was high (92%) but specificity was low (5%). Table 2a. and Table 2b, compares cross-sectional imaging features by management and cyst subtype. Cysts that were malignant at diagnosis or were referred for immediate surgical resection were larger than cysts managed by follow-up surveillance. A mural nodule was an exceptionally rare radiological finding in patients in this study, but a solid component was present in 42% of patients with malignant cysts managed by chemotherapy and palliative care compared to 22% of PCL referred to surgery and only 10% of PCL entering surveillance. Pancreatic and common bile duct dilatation along with lymph node enlargement were also common features of malignant cysts managed non-operatively.

Clinical and radiological features which suggested malignant transformation were used to formulate a decision tree model, to guide management and counsel patients with a PCL from diagnosis and though surveillance [Figure 5].

Discussion

In this large cohort study of patients with a PCL referred to a tertiary referral HPB centre, most malignant lesions were detected within 1–2 years of diagnosis with a PCL or developed after substantial follow up (>5 years). This has been reported similarly by other groups and supports long-term surveillance for patients with mucinous PCL who are fit for surgical resection[18]. As expected, patients with high risk and worrisome features who were referred for immediate surgery had much higher rates of associated malignancy than those managed by surveillance with interval imaging (38% vs. 2%). However, although pre-operative investigations had a high sensitivity for detecting malignancy, they were associated with a poor specificity and a substantial proportion of patients underwent unnecessary surgery (21% of immediate and 47% of delayed pancreatic resections had completely benign disease e.g. SCN which would have never undergone malignant transformation). Other groups have reported similar findings with pre-operative cross-sectional imaging correlating with surgical pathological findings in only 30–74% of cases[19]. This is significant in this population as pancreatic resection has an associated morbidity (20.8–59%) and mortality of 0–7.1% (1% in our cohort) in high volume centres[20]. These findings suggests that current diagnostic tools used in pre-operative workup are imperfect[21,22], and improved tests and novel diagnostic adjuncts are required.

Pre-operative evaluation of PCL in this study was primarily dependent on clinical and radiological features, which were assessed during a weekly MDT meeting. Some groups have found serum CA 19-9 to be helpful in defining malignant transformation in PCL[23], but in this cohort it was not consistently elevated in any of the malignant subtypes. Cross-sectional imaging (CT and MR/MRCP) of the pancreas can effectively visualise septations, calcification, pancreatic or biliary duct dilation and the presence of solid components or enhancing mural nodules. In this cohort as in other studies[14], size alone was found to be a poor predictor of malignant transformation; the median size of resected benign IPMNs was larger than malignant IPMNs and with the exception of MCNs, the median size of all malignant PCL that were resected was less than 3cm. In this cohort, other features which suggested malignant transformation included the presence of associated symptoms, older age, solid component, pancreatic duct dilation and increasing size.

Given that cross-sectional imaging is an imperfect diagnostic tool it is often complemented by EUS in many centres, in order to provide additional imaging information and cytological and/or biochemical analysis of the cyst fluid. However there are also limitations to this technique and in this study no cases of malignant transformation were diagnosed cytologically pre-operatively. Low cytological yields from PCL have also been reported by a number of other groups[22,24–28]. Recently novel adjuncts to the

Table 4. **Characteristics of patients who developed malignant transformation during surveillance.**

Surgical management					
	Age	**Sex**	**Time to malignant transformation from diagnosis (months)**	**Route to diagnosis**	**Management**
1	77	M	18	Investigations for recurrent pancreatitis revealed a 2cm cyst in the uncinate. Entered surveillance, CA 19-9 rising 69.9 IU/ml. EUS-FNA revealed the cyst was communicating with a dilated main PD. Cytology non-diagnostic. ERCP – pathognomonic findings of MD-IPMN.	**Surgery:** Whipples. **Histology:** T2N0MXR0 tumour arising from a MD-IPMN. **Outcome:** No recurrence during 20-months of follow-up.
2	68	F	18	Imaging following acute necrotising gallstone pancreatitis revealed a 5.9cm cyst in the head of the pancreas with dilated main PD. Thought to be a symptomatic pseudocyst so a EUS guided cystenterostomy was performed. Following removal of the stents a small cyst persisted which had a solid component. CA 19–9 rising (1869.0 IU/ml). Repeat EUS-FNA: cytology consistent with a pseudocyst but cyst fluid CEA 105 ng/ml, amylase 1598 IU/L.	**Surgery:** Total pancreatectomy + splenectomy + PV reconstruction **Histology:** T3N1 (1/24) MxR0 PDAC + pseudocyst. **Outcome:** Adjuvant chemotherapy with gemcitabine. 13 months on PET-CT confirms recurrent disease – no further chemotherapy, asymptomatic.
Non-operative management					
	Age	**Sex**	**Time to malignant transformation from diagnosis (months)**	**Route to diagnosis**	**Management**
1	75	M	18	Right hemicolectomy for a Dukes B colorectal cancer, complicated by an anastomotic leak and prolonged ITU stay. Follow-up imaging revealed an incidental 23mm cyst in the pancreatic tail. EUS-FNA – cytology: atypical cells consistent with IPMN. 14 months later presented with jaundice. Cyst had increased to 3cm + solid component and dilated main PD. CA 19–9 rising (1879.0 IU/ml). Further EUS-FNA; cytology – atypia, histology - IPMN.	Resectable disease but patient refused pancreatic surgery. ERCP + metal stent inserted. Patient died 4 months later.
2	78	F	24	Admitted with deranged LFTs and abdominal pain. Imaging revealed cirrhosis and chronic pancreatitis + 12cm PCL with septations and a solid component. Developed nausea and weight loss so underwent percutaneous drainage of a presumed pseudocyst cyst at a local hospital. Follow-up imaging revealed unresectable PDAC with vascular incasement. EUS-FNA – cytology: well-differentiated PNET but IHC not supportive, CEA 36223 ug/L. Amylase < 3 IU/L.	Unresectable disease. Palliative care – died 3 months later.

Non-operative management					
	Age	**Sex**	**Time to malignant transformation from diagnosis (months)**	**Route to diagnosis**	**Management**
3	71	F	76	Imaging for autoimmune hepatitis revealed multiple incidental PCL with features of chronic pancreatitis. Thought to be multiple pseudocysts and therefore not actively followed-up. Patient requested a second opinion and when reimaged lesions had undergone malignant transformation.	Multiple comorbidities unfit for surgical resection – tissue diagnosis not pursued. Palliative care – subsequently died.
4	70	M	62	Family history of PDAC. Abdominal imaging for renal calculi revealed a 35mm cyst is the head of the pancreas with a dilated main PD and multiple other cysts. EUS-FNA; cytology consistent with low grade IPMN. CA 19-9 66 IU/ml. Discharged from active surveillance because of comorbidity after 18 months. Recommenced after 23 months & had developed a metastatic liver lesion of upper GI origin.	Unresectable disease. Palliative cisplatin + gemcitabine chemotherapy. Died 36 months later
5	81	M	24	Investigated for deteriorating blood sugars (recently diagnosed Type 2 DM). Abdominal CT: dilated PD without cause. EUS-FNA: 8mm multiloculated cyst in the pancreatic tail, with mural nodule. Cytology: possible mucin-secreting tumour but non-diagnostic. CA 19-9 101 IU/ml. Discharged from active surveillance as no longer a fit for surgical resection. Represented with metastatic PDAC 6 months later. ERCP + biliary brushings: IPMN with atypia.	Unresectable disease. Palliative care – subsequently died 36 months later.
6	71	F	19	Background of pancreatic trauma in 1971, requiring pancreatic surgery + drainage. Investigated for faecal inconsonance, colonic polyps and exocrine insufficiency with a CT pneumocolon. Found to a dilated main PD + 14mm cyst in the pancreatic tail, presumed due to trauma. Intermittent surveillance with colonic polyp surveillance via CT over 19 months. Developed significant weight loss and repeat imaging revealed unresectable disease. Cytology from pleural aspirate confirmed metastatic adenocarcinoma (? PNET).	Unresectable disease, palliative care, died 8 months after diagnosis.
7	78	F	73	Right hemicolectomy for Dukes B tumour, T3N0M0. During follow-up noted to have a dilated main PD. Over time became associated with a cystic and then a solid lesion. CA 19-9 rising (526.2 IU/ml). August 2012 – cytology from EUS-FNA suggestive of chronic pancreatitis but percutaneous biopsy confirmed moderately differentiated PDAC.	Locally advanced disease but unfit for surgical resection because of comorbidities. No chemotherapy, clinically stable 26 months after diagnosis.
8	87	M	12	CT pneumocolon for abdominal pain and diarrhoea revealed a dilated main PD and side branches with retroperitoneal LNs. Stable on imaging for 11 months then represented with jaundice and cholangitis. CA19-9 2102 IU/ml. ERCP + brushings – non diagnostic.	Unresectable disease. Multiple comorbidities. Refused chemotherapy. Histological diagnosis not pursued. Palliative care – subsequently died.

PDAC: Pancreatic ductal adenocarcinoma. PD: Pancreatic duct. EUS-FNA: Endoscopic ultrasound and fine needle aspiration. ERCP: Endoscopic retrograde cholangiopancreatography. LN: Lymph nodes. PCL: Pancreatic cystic lesion, DM: Diabetes mellitus, IHC: immunohistochemistry

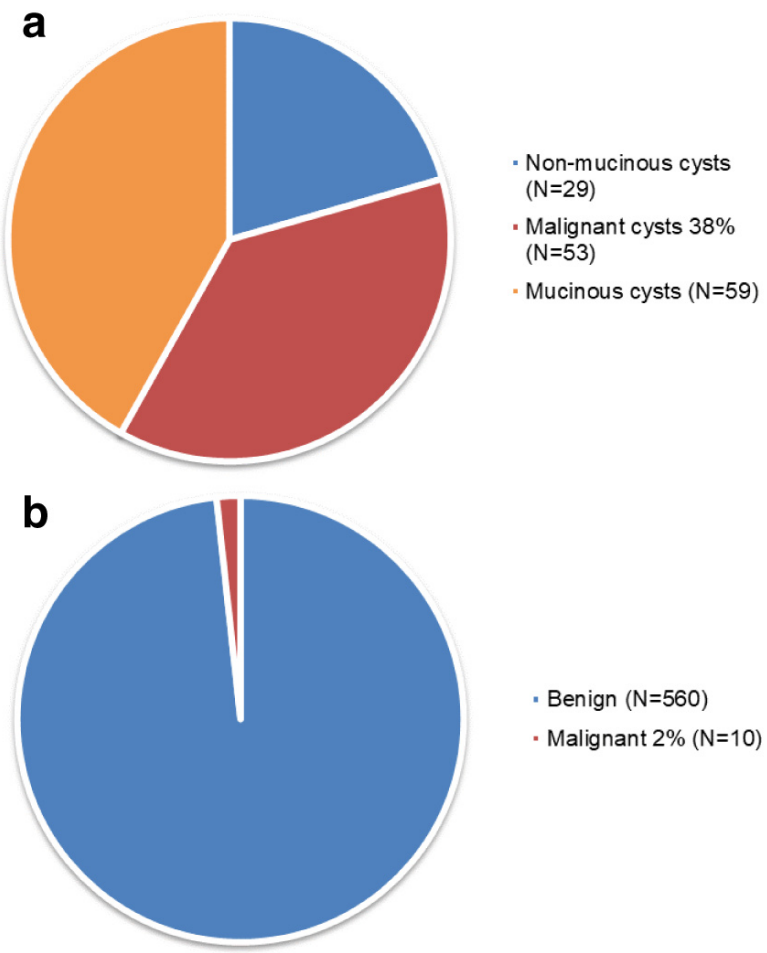

Figure 3. Incidence of pancreatic malignancy in surgical and surveillance cohorts (**a**) Immediate surgical management, (**b**) Surveillance: proportion that underwent malignant transformation.

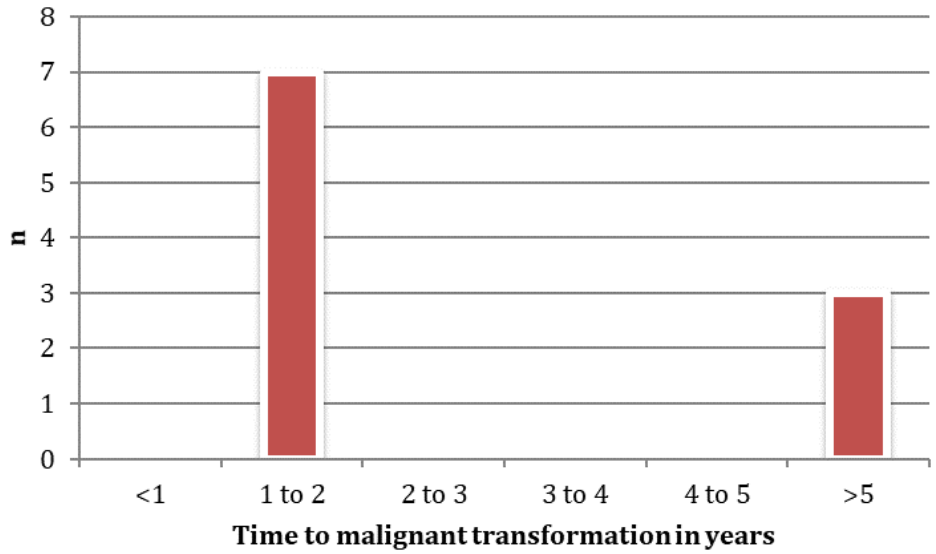

Figure 4. Time to malignant transformation in patients under surveillance for a pancreatic cystic lesions (PCL).

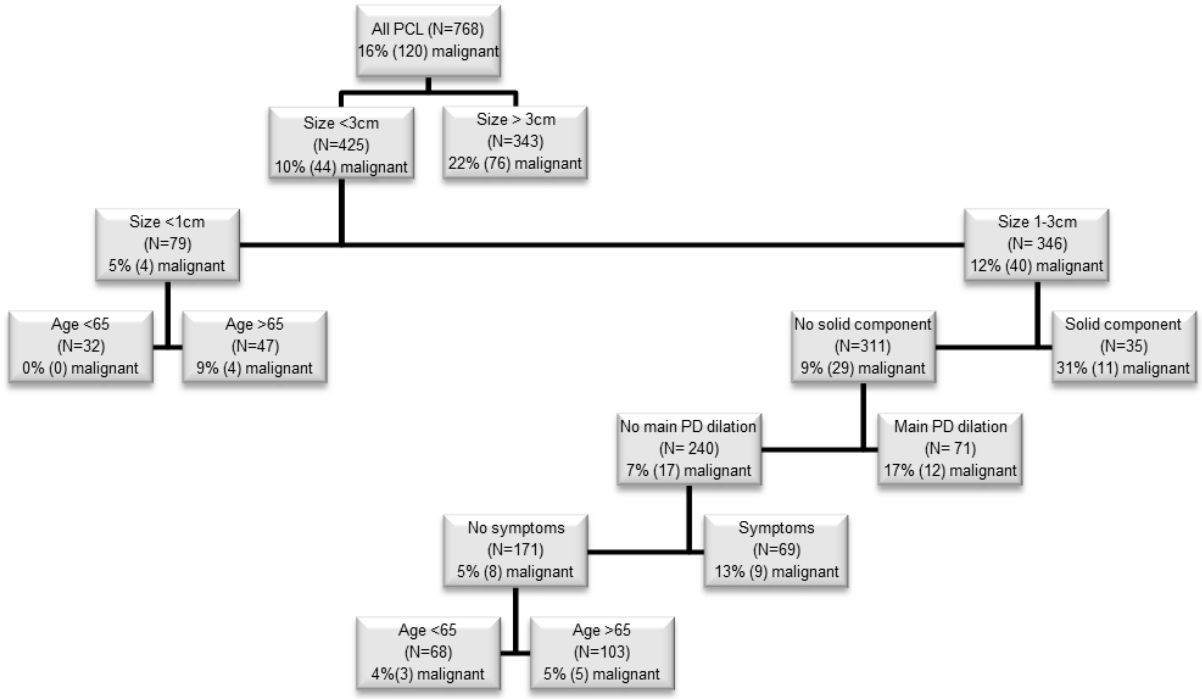

Figure 5. Recursive partitioning analysis: risk stratification for a PCL based on clinical and imaging features. PCL: pancreatic cystic lesion, PD: pancreatic duct.

EUS technique such as confocal endomicroscopy and through the needle biopsy forceps have been developed to improve the diagnostic accuracy of the technique[29,30]. Other groups have found that genetic markers in cyst fluid can aid differentiation of mucinous lesions[31]. These techniques may be incorporated in to diagnostic algorithms for PCL in the future.

Of the 10 patients in our surveillance group who ultimately developed pancreatic cancer, five had been discharged from active surveillance as they were no longer fit for surgical resection and two because they were thought to have inflammatory lesions. Of the two referred for surgery, one underwent a curative Whipple's resection and the other had a R0 total pancreatectomy and splenectomy but developed recurrence 13 months later. Patients undergoing malignant transformation were older than the majority of patients in surveillance so a lead-time bias may account for the initial peak in malignant transformation seen in this study. Large international surveillance cohorts have found similar rates of malignant transformation to that seen in this cohort[11,29–31].

Strengths and limitations

This study has several strengths; describing the clinical and radiological characteristics of a large cohort of patients with PCL, including a substantial surveillance cohort, with longterm follow up. An individual chart review of all patient electronic records facilitated accurate cyst diagnosis and characterisation in each case. This study unlike other cohorts[18], included patients with a history of acute and/or chronic pancreatitis. 33% of patients with a benign IPMN and 25% of patients with a malignant IPMN had a history of acute or chronic pancreatitis, confirming it is not a feature of inflammatory PCLs alone.

However, there were some limitations associated with this study. The overall rate of malignancy in this study was 16% (120/768). Other large HPB centres have reported similar rates of malignancy[11,30,31] and probably reflects increased rates of high risk referrals from surrounding hospitals as rates are considerably higher than those reported by community based population cohorts, suggesting that there is a cohort of largely low-risk patients who are managed outside of HPB centres[18]. This is important when interpreting the results of this study and the applicability of the recursive partitioning model.

In the surveillance cohort most patients did not undergo EUS or surgical resection as part of their management, therefore it was impossible to reliably classify cysts by histologic subtype so low-grade malignancy may have been under diagnosed. Although the study was conducted over a 14-year period, median follow-up in the surveillance cohort was 18 months, which may not have been long enough to capture all cases of malignant transformation and further longitudinal studies are needed to assess the long-term risk of cyst-related malignancy in this population.

Conclusions

In this large surveillance cohort from a tertiary referral HPB centre the overall rate of malignancy in PCL was 16%, which is lower than most surgical series but higher than community based studies. The majority of malignant lesions (92%) were detected

at the time of diagnosis. The sensitivity of current diagnostic tests leading to immediate surgery for high-risk PCL (malignant or mucinous) was high (92%) but specificity was low (just 5%). Surveillance of PCL without high-risk features was associated with a low incidence of cancer development (2%) supporting the use of worrisome clinical and radiological features (older age, symptoms, increasing size of the lesion and the presence of a solid component) in the initial stratification of PCL.

Data availability

Raw data used in this study can be found at Open Science Framework repository.

OSF: Dataset 1. UCL Pancreatic Cyst Registry, https://doi.org/10.17605/OSF.IO/7UPDM[32]

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Open Peer Review

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Version 2

Reviewer Report 20 January 2020

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✔ **Luca Barresi**
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The authors correctly interpreted my suggestions and modified the discussion of their study accordingly.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My field of research is pancreatology in general and cystic lesions of the pancreas in particular, with a specific interest in the diagnosis and stratification of the risk of malignancy through tissue acquisition.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 September 2019

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? **Luca Barresi**
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PCLs are more frequently being diagnosed due to the increased use of advanced radiological and endoscopic techniques. Often these lesions are asymptomatic and discovered incidentally, and only a small part will evolve towards aggressive lesions with metastatic potential. The problem of how to manage these lesions is discussed worldwide, and the continual publication of new diagnostic algorithms and guidelines is the best evidence that an approach shared by all clinicians is not currently available. In fact, both the diagnosis for type of lesion and the risk stratification for malignant evolution are currently very different in different centers, and often linked to the expertise available locally.

The study presented by Dr Keane et al. is a further confirmation of what has already been highlighted in many previous studies, namely that the stratification of the risk of malignancy using only the clinic and radiological features, in particular the CT scan, will inevitably lead to a high number of false positives, which will result in a considerable number of unnecessary pancreatectomies, and burdened by the known consequences of this surgery.
The study by our English colleagues confirms, in a large cohort of patients, against a high sensitivity, the low specificity of the clinical-radiological approach. The study is certainly well written, shows clear and detailed results, and supports the conclusions drawn by the authors. The statistical data are adequate for the evaluations carried out.

Noteworthy is that the follow-up of 18 months (on average) is too short to highlight the malignant evolution of these lesions, which have a very slow developing potential, as rightly pointed out by the authors themselves.

In addition, the authors report in the Abstract a selection of patients with at least 5 years of follow-up, which does not seem correct since the average follow up reported is only 18 months (to be corrected).

However, in addition to the main purpose of the study, the data presented confirm other interesting information that deserves to be emphasized:

1. It is interesting to note that in this study the majority of malignant lesions (92%) were highlighted at the first diagnosis of PCL. This was already observed in a previous study (reference in the study No. 18), where 74% of the malignant lesions were found within the first 3 months of initial diagnosis. This observation, translated into practical terms, means that the first approach to the patient with PCLs is fundamental because the clinician has the highest probability of observing the lesions that deserve surgical treatment. For this reason, the approach of our centre is to carefully study the lesions at the first diagnosis, in particular those with “worrisome features”, and to plan the first follow-up, for lesions that are not sent immediately to the surgery, at a short distance (usually 3 months, but certainly not more than 6) considering this control a sort of extension of the initial evaluation.

2. Despite point one, some lesions may degenerate even after having remained stable for more than 5 years. The study shows, in fact, a malignant evolution over 5 years from diagnosis in 30% of the lesions that degenerate during follow-up. It is also necessary to remember the possibility of occurrence of a pancreatic cancer concomitant but distinct from IPMN, an event not infrequent in this type of lesion, and also possible after the first 5 years of follow-up (3.5% at 10 years, and 12% at 15 years from the initial diagnosis)[1]. These data confirm that the guidelines of the American Gastroenterology Association (AGA)[2], whose recommendation to suspend the follow-up after 5 years of stability of the PCLs is risky and lacks justification. Follow-up should therefore continue indefinitely, as long as the patient remains fit for surgery.

3. The size of PCLs is of relative relevance to the stratification of the risk of malignancy (threefold increase in the malignancy risk for lesions >3 cm, instead the presence of mural nodules carries an eightfold increase in the malignancy risk). This has been highlighted in several studies, which is why the most widely used guidelines in the world, the International Consensus Guideline of Sendai-Fukuoka, last revised in 2017, have downgraded the size > 3 cm from "indication to surgery" of the first draft of 2006 (Sendai Guidelines) to lesions with "worrisome features", which means lesions with indication to perform other investigations (in particular an EUS-FNA), already in the 2012 revision (Fukuoka Guidelines), thus reducing the risk of unnecessary interventions.

4. Cytology on cystic fluid has a low diagnostic yield because of the paucity of cells dispersed in the cystic fluid. This is known and confirmed by multiple studies, which is why other methods of tissue acquisition (in particular EUS-through-the-needle biopsy) or *in situ* evaluation (with confocal laser endomicroscopy) have been used, with very encouraging results.

5. Both benign and malignant IPMN can occur with a certain frequency (about 25-30%) with acute or chronic pancreatitis. Therefore, finding a cystic lesion in a patient with recent acute (or chronic) pancreatitis is not diagnostic in all cases of pseudocyst. This is relevant and implies that the diagnostic evaluation should also be conducted on these PCLs.

6. Follow-up of lesions without "high risk stigmata" is a reasonable and relatively safe choice since only a small percentage (about 2% in this study) will degenerate during follow-up, as previously reported [3].

7. The presence of multiple (and sometimes contradictory) guidelines, and the need to adapt the approach to patients with PCLs certainly makes a shared approach valid and advisable through a multidisciplinary team that will evaluate and indicate the best management for the indeterminate and most suspected of degeneration PCLs.

In addition to these strengths of the study there are, however, also weaknesses:

1. In the study, magnetic resonance imaging (MRI) was used in only 34% of cases, with a prevalence of CT scanning. This may have reduced the diagnostic capacity of the radiologists since the spatial resolution of the MRI, and therefore the evaluation of the internal components of the PCLs, as well as the evaluation of the connection with the main pancreatic duct, is decidedly better with MRI. In addition, MRI easily highlights debris in pseudocyst, which is a specific aspect of pancreatic-peripancreatic collection (walled off necrosis), and absent in neoplastic PCLs. This aspect is not usually visible in CT scans.

2. The same goes for the limited use of the EUS in the study's cohort (39%, and only in patients with worrisome features), which has an even greater capacity than MRI in the evaluation of the internal structure of the PCLs to highlight possible microcystic components (highly suspect for serous cystadenoma, which were 15% of patients undergoing surgery), debris, small wall nodules (with the possibility also of differential diagnosis between mucus plug and epithelial nodules by means of contrast media) and evaluation of the connection with the main pancreatic duct for the diagnosis of IPMN.

I think it is highly likely that the use of such methods in all patients of the study would have significantly reduced the number of false positives and unnecessary surgery (in the study among the lesions that were indicated for surgery, 15% were serous cystadenomas and 7% pseudocyst).

But what could have contributed most to a better stratification of risk are the new methods, of which practically no mention is made in the work.

Even if needle-based endomicroscopy and EUS-through-the-needle biopsy were not used in the patients of this study (obviously, these were not available in the study period), it would be useful for the readers of this article to have at least a hint of what is currently feasible for our patients with PCLs.

Needle based endomicroscopy and tissue acquisition from the cystic wall with the EUS-through-the-needle biopsy have sufficient literature to be taken seriously as the new most credited methods for improving the diagnosis and stratification of risk for malignancy in PCLs. I strongly advise the authors to cite such methods, even briefly, underlining the importance they have assumed and will assume in the coming years.

Though, moreover, the analysis of the cystic fluid for the CEA is certainly not a perfect method, it is worth mentioning, perhaps by associating it with the evaluation of intracystic glucose, which seems promising and complementary to the CEA, and very easy to performe.

Last but not least, I would mention molecular biology on cystic fluid, which could be a turning point, as highlighted in recent studies, both in the diagnosis of the type of cysts and in the stratification for the risk of malignancy.

My suggestion is to review the discussion underlining the above points (both positive and negative) to provide readers with a more complete picture of the data highlighted by the study, and open a window on the principal changes across recent years, so as to make current the information that has emerged from this interesting retrospective assessment.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My field of research is pancreatology in general and cystic lesions of the pancreas in particular, with a specific interest in the diagnosis and stratification of the risk of malignancy through tissue acquisition.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 19 June 2019

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Particularly over the last two decades the increased number of cystic lesions of the pancreas (PCL) being identified has become a workload issue and the best management remains controversial. The workload problems, particularly for incidentally discovered lesions referred into tertiary centres, has prompted much discussion at National and International meetings with particular emphasis on attempts to define the cohort that could be safely managed conservatively. This is especially important with PCLs due to the essentially binary nature of the possible approaches and the consequences of inappropriate treatment. A proportion of PCLs will undergo malignant transformation and the consequences of this being missed have significant clinical, psychological and medico-legal repercussions. Conversely surgical intervention that proves to be unnecessary is costly and potentially associated with significant, avoidable morbidity and mortality. Thus a robust, evidence based approach to the management of PCLs is required to obviate these problems and reassure clinicians in lower volume centres in respect of the algorithm they employ.

Is the work clearly and accurately presented and does it cite the current literature?

The study presented by Keane *et al* represents a significant contribution to the literature from a high volume, internationally respected pancreatic unit. The presentation is clear and particularly the use of tables and diagrams helpful. Individual data are provided for those patients whose PCLs underwent malignant change while on the surveillance program. The literature is contemporary and relevant and of note is that the number is relatively small, dates back to 2004 and only contains 4 references in the last 5 years. This demonstrates the relative paucity of data and the difficulty in gathering data from a sufficient

number of patients together with a meaningful follow up period. This reflects the difficulty of identifying an appropriate cohort with a sufficient length of follow up to enable clinicians to produce clear and universally acceptable guidelines.

Is the study design appropriate and is the work sound?

The study is a retrospective case report series over a 14 year period, the importance of which relates to the large number of patients and the accurate follow up that has been possible for a significant length of time. The size of the series with 1,090 patients identified (with 768 available for the study following exclusion of those under 18, those with no cross sectional imaging available and 267 pseudocysts requiring drainage) and the large amount of data available allows firm conclusions to be drawn.
In the methods section of the abstract however it is stated that *"adults who were evaluated in a tertiary hepatopancreaticobiliary unit between January 2000 – December 2013 with a confirmed PCL and followed up for at least 5 years"* whereas the median follow up in the surveillance group was 18 months (range 0 – 151) and this should be clarified.

Are sufficient details of methods and analysis provided to allow replication by others?

The methodology is clearly described and appropriate. Detailed patient records had been electronically recorded for a sufficient length of time to ensure that a very large cohort with a detailed follow up enabling comprehensive and accurate data to be identified and collected. In addition to the usual demographic data this included family history, tumour markers, cross sectional imaging and EUS findings. This set of data is particularly valuable due to the lack of a significant change in routine clinical practice for the investigation of PCLs since the study period allowing the conclusions to be widely applicable.

If applicable, is the statistical analysis and its interpretation appropriate?

The statistical methods utilised SPSS for windows and the 2-sample t test is appropriate.

Are the source data underlying the results available to ensure full reproducibility?

The source data are not included in the paper but would be available.

Are the conclusions drawn adequately supported by the results?

The conclusions are supported by the results and the findings of this study are interesting and the conclusions important. The amount of data together with the inclusion of patients with acute and chronic pancreatitis is useful and reflects the "real world" presentation of the patients at HPB MDT meetings and provides additional reassurance to clinicians that the conclusions and advice will be applicable in everyday practice. The data are detailed but of particular importance are:

1. Estimation of ca19,9 was not helpful in malignant PCLs.
2. Cross sectional imaging alone can identify features associated with the development of malignancy.
3. Features that were identified to indicate malignant change were consistent with those previously described in other series.
4. The sensitivity of the traditional diagnostic methods was 92% but the specificity was only 5%.

One further interesting feature however was the size of the resected lesions. This study demonstrated that size *per se* could not be relied upon to predict malignancy and for IPMNs the size of lesions found to be

malignant following resection was smaller than benign lesions and in addition the median size of all resected PCLs found to have undergone malignant change was less than 3cm. This is important specifically for those patients presenting for the first time when traditionally it was felt that malignancy was unlikely if the lesion was less than 30 – 35mm. This point is further emphasised by the poor outcome of malignant PCLs with a median survival of 8 months (0 – 19).

Summary:

This is a well conducted study examining a large cohort of patients with PCLs which are a steadily increasing component of HPB MDTs. The management of these patients remains unclear and there is a relative paucity of data particularly examining a sufficiently large cohort with adequate follow up.
While the study supports the safety of surveillance of PCLs without malignant features and confirms that the incidence of malignant change is small, it also found importantly that size *per se* (as distinct from increase in size during surveillance) cannot be relied upon when predicting malignancy. This is an important finding when assessing patients at their first presentation.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am Professor of Hepatobiliary and Pancreatic Surgery at the University of Leicester and Consultant HPB Surgeon University Hospitals of Leicester NHS Trust. My main areas of research include Islet autotransplantation following total pancreatectomy, omega-3 fatty acids in malignancies of the pancreas and liver. I have over 380 peer reviewed publications the majority of which are HPB related.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.