ORIGINAL ARTICLE

Clinical, Radiological, Cytological and Biochemical Analysis of Pancreatic Cystic Lesions are Necessary prior to Definitive Therapeutic Planning

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ABSTRACT

Objective To retrospectively study the correlation between pre-operative morphological and biochemical features of resected pancreatic cystic lesions and predictive power of these features in relation to biological behaviour and final histology. **Methods** We reviewed the literature systematically to identify relevant variables that are in use to predict the biological nature of pancreatic cystic lesions and aid therapeutic planning. We designed a template encompassing all used variables to collate the available data of resected pancreatic cystic lesions from two centres. The collated data included clinico-pathological and biochemical data, pre-operative computed tomography, magnetic resonance imaging, Endoscopic ultrasound, positron emission tomography–computed tomography, Fine-needle aspiration analysis whenever available and correlated with the final post-operative histology. Pooled data was analysed using statistics and data 14 statistical software. **Results** Sixty-four patients with pre-operative diagnosis of pancreatic cystic lesions were identified. Twenty seven cases underwent endoscopic ultra sound - fine-needle aspiration as an adjunct to the radiological assessment to evaluate the nature of these noted PCLs and both cytological and biochemical analysis were carried out on the intra-cystic aspirate. The intra cystic carcinoembryonic antigen levels recorded a mean of 667.97 in the tested group with a standard deviation of 1934.38. **Conclusion** No single test is able to predict the nature or behaviour of pancreatic cystic lesions. The differences noted on specialist imaging can be very subtle and demand specialist interpretive skills and hence a panel of pre-operative testing with review at specialist multidisciplinary meeting is mandatory for all such cases.

INTRODUCTION

Cystic lesions of pancreas may be asymptomatic or present with epigastric pain, nausea, steatorrhea, abdominal discomfort, weight loss, vomiting, jaundice, backache or diarrhoea.

Pancreatic resection continues to carry high morbidity (69%) for total pancreatectomy [1] and (20%) risk of severe complications following pancreaticoduodenectomy [2] and although mortality improved over time from 8% during 1990-1999 era to 2% during 2000- 2007 era [1], the high associated morbidity underscores the importance of a robust pre-operative evaluation prior to considering definitive surgical therapy.

We reviewed the literature to identify all reported pre-operative worrisome features and markers of malignancy in PCL and studied the pre-operative imaging in our small cohort in relation to the following features:

- Presence or absence of Septations
- Main pancreatic duct features (Dilatation of pancreatic duct)
- Size of PCL (>3 cm)
- Proximal or distal location of the cyst (i.e. Head, body or tail)
- Solid components (present or absent)

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Abbreviations CT computed tomography; CEA carcinoembryonic antigen; DAC: Ductal adenocarcinoma; EUSCFA endoscopic ultra sound guided cyst fluid aspiration; FNA fine needle aspiration; IPMN intraductal papillary mucinous neoplasm; MCN mucinous cystic neoplasm; MPD main pancreatic duct; MRI magnetic resonance imaging; PC psuedocyst; ScyA serous cyst adenoma; STATA statistics and data; VHL Von Hippel-Lindau Syndrome
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- Shape/Border (Oval, round, branching or single)
- Calcification
- Signal intensity (T1 or T2 attenuated lesion, High or Low signal intensity)
- Biliary tract involvement
- Solitary, unilocular or multilocular
- Wall Worrying features (thick or thin, regular or irregular, presence or absence of mural nodules)
- Intra-cyst fluid CEA, CA19-9 and amylase levels

METHODS

We carried out a systematic literature review to identify the relevant variables that are utilized to predict the nature of pancreatic cystic lesions (PCL) and aid therapeutic planning. This was followed by designing a template to capture all these variables for the resected lesions from two centres. We collated clinico-pathological, biochemical data, pre-operative CT, MRI, EUS, PET CT, FNA analysis whenever they are performed and correlated with the post-operative histology result. We identified 64 patients from medical records who were evaluated to a variable degree for the presence of the PCL; 27 of those underwent EUS-FNA as part of the pre-operative evaluation of the nature of the cyst as an adjunct to the other radiological investigations and 15 underwent surgical resection. Pooled data was analysed using STATA 14.

RESULTS

Sixty-four patients with pre-operative diagnosis of pancreatic cystic lesions were identified. Fifteen patients underwent surgical intervention. The final histology of these cysts was compared with preoperative predicted nature based on the various investigation modalities **(Table 1).**

Of the fifteen resected cases, 2 turned out to be serous and one confirmed to be mucinous cyst adenoma; two had IPMN (Intraductal Papillary mucinous neoplasm) while one case was VHL (Von Hippel – Lindau syndrome). Cystadenocarcinoma's was found in 5 cases, endocrine neoplasm in 1, pseudocyst in 2 of the resected cases and histology result of one of the resected cases could not be found.

Morphological characteristics of the 15 patients **(Table 2)** suggests that the majority of these lesions were either multicystic and or multilocular; with or without thickening of wall and with or without septations.

We noted calcification in two cases and duct dilatation in 7 others; and it was interesting to note that most of our small resected cohort did not have any cyst related solid components despite the malignant nature of some of them. Various modalities were utilized in the pre-operative evaluation of the 15 resected cases **(Table 3)** noting the tendency towards combining modalities.

Twenty-seven cases underwent EUS- FNA as an adjunct to the radiological assessment to evaluate the nature of these PCLs; and both cytological and biochemical analyses were carried out on the intra-cystic aspirate (**Table 4**). The intra-cystic CEA levels recorded a mean of 667.97 in the tested group with a wide standard deviation of 1934.38 (results from STATA 14 are attached as a supplement).

The small size of our retrospective cohort and lack of homogeneity for the various modalities of investigations utilized for evaluation of such diverse pathology (cystic lesions of pancreas) precluded any meaningful analysis of the diagnostic accuracy of each individual modality.

DISCUSSION

Distinguishing benign from malignant or pre-malignant PCL is essential when formulating the surgical

Table 1. Data of the patients who had biopsy proven final histology for cystic lesions of pancreas.

	Age	SEX	USS	EUS and FNAC	CT	MRI	Nature of the cyst prior to surgery	Nature of the cyst proven after Surgery	Nature of the cyst assumed prior to surgery	Nature of the cyst proven after surgery
1	61	M	Y	Y	N	N	PM	PM	IPMN	IPMN
2	57	M	N	Y	Y	N	M	M	DAC	DAC
3	58	M	N	Y	Y	N	M	M	DAC	DAC
4	55	F	Y	N	N	N	M	M	DAC	DAC
5	50	M	N	N	Y	N	M	M	DAC	DAC
6	36	F	N	N	Y	N	PM	PM	MCN	MCN
7	36	M	N	N	Y	N	B		Benign	Data missing
8	59	M	N	Y	N	Y	M	M	DAC	DAC
9	70	F	N	Y	Y	N	M	M	Neuroendocrine tumour	Neuroendocrine tumour
10	69	M	N	N	Y	Y	M	B	? Malignant	Benign
11	91	M	Y	N	N	N	B	B	Serous	Serous
12	49	M	Y	N	N	N	M	PM	? Malignant	VHL
13	54	F	Y	N	N	N	B	B	Serous	Serous
14	30	F	N	N	Y	N	B	B	Benign	Benign
15	77	M	N	Y	Y	Y	PM	PM	IPMN	IPMN

Table 2. Histology versus Morphological features observed.

SEX	Histology	Location of the cyst	MPD	Size	Complexity	Wall/Worrying features (Thick/Thin, regular/ irregular, mural nodules)	Calcification	Solid components (present/ absent)
M	IPMN	Head	Dilated and cyst is in communication with PD	Not mentioned	Complex mass	Septations	Not Mentioned	No comment
M	Cystadenocarcinoma	Tail	Not mentioned	Not mentioned	Complex mass	Adhered to splenic hilum	Not Mentioned	No comment
M	Cystadenocarcinoma	Head	Dilated	Not mentioned	Solitory	Not mentioned	No	No comment
F	Cystadenocarcinoma	Head & Body	Not commented	5.3X5.8cm	Irregular	Not mentioned	Yes	Absent
M	Cystadenocarcinoma	Head & Uncinate process	Dilated in Neck and body	5.8x5.3cm	Multilocular cystic mass	Not mentioned	No	Absent
F	MCN	Tail	No	10x9.5x8cm	Multicystic locular	thick enhancing wall with septations	No	Absent
M	Data Missing	Tail	No	Not mentioned	Multilocular	No	No	Absent
M	Cystadenocarcinoma	Head	Dilated & Irregular	3x2.6x2.4 cm	Multilocular cyst	T1-hypo intense, T2-hyper intense	No	Absent
F	Nueroendocrine tumour	Body & Tail	Normal	4.2x3.2 cm	Multiloculated	Not mentioned	No	No comment
M	Benign	Body & Tail	Dilated and Irregular	Not mentioned	Multilocular	thick enhancing wall	No	Absent
M	Serous cyst	Body & Tail	Not involved	5.1 X 2.7 cm	Single Multilocular	thin walled	No	Absent
M	VHL	Body & Tail	Dilated (0.8 cm)	5.2 cm x 4.5 cm	Multiple lobulated	Not mentioned	Yes	Absent
F	Serous cyst	Head	No Dilatation	7cm x 6 cm	Simple cyst	Not mentioned	No	Absent
F	Serous cyst	Body	No Dilatation	2.7x2.9x1.8 cm	Multi cystic lobulated	well circumscribed enhancing wall with septation	No	Absent
M	IPMN	Head & Body	Irregularly dilated	Not mentioned	Diffuse	Not mentioned	No	No comment

therapeutic strategy and lack of well-defined pre-operative predictability criteria makes therapeutic planning challenging. Pancreatic cystic lesions can generally be divided into 4 main categories:

I. Benign cystic lesions: This includes pseudocyst, serous cyst, retention cysts, parasitic cysts and pancreatic abscess.

II. Premalignant conditions: This includes intra-ductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN).

Intra-Ductal Papillary Mucinous Neoplasm

There are no reliable predictors of malignancy for patients with main duct MD-IPMN, although several studies have described clinical and radiological features that are more common in MD-IPMN carcinoma such as jaundice, recent onset or deterioration of diabetes mellitus (Saliva *et al*. 2004). Other common symptoms include weight loss, abdominal pain and steatorrhea. Radiological suspicious findings for malignant transformation in MD-IPMN are mural nodules or associated mass, enhancing cyst wall and a maximum main duct of >10 mm (Manfredi *et al.* 2009, Sahani *et al*. 2006). On the other hand, branch duct BD-IPMN without mural nodules (MNs) have a low risk of progression and malignant transformation and hence the suitability of this group for non-surgical management and safety of medium to long interval surveillance. Although a cyst size >3 cm was previously thought to be one of the

Table 3. Investigation Reports.

	Age	SEX	USS	EUS	FNAC & Biochemical Analysis	CT	MRI/MRCP	Histology
1	61	M	Bulky head of the pancreas with an echoic area and dilated Pancreatic duct	Complex lesion in the head of the pancreas communicating with Pancreatic duct				IPMN
2	57	M		Complex mass arising from tail of pancreas infiltrating spleen	Positive malignant cells	Hypodense area adhered to splenic hilum		DAC
3	58	M		Periampullary growth	CA 19-9-2280 µ/mL	Periampullary growth		DAC
4	55	F	Ill defined hypoechoic lesion					DAC
5	50	M				Multilocular cystic mass arising from the head of the pancreas		DAC
6	36	F				Multi cystic thick enhancing wall with septations in the tail of pancreas		MCN
7	36	M				Multilocular cystic lesion in tail of pancreas		Data Missing
8	59	M			CA 19-9-61.47 µ/mL		Multilocular cystic lesion	DAC
9	70	F		Likely tumour	Neuroendocrine tumour, CA 19-9 -23.8 µ/mL, CEA-0.71 µg/mL	Lobulated illdefined cystic lesion in body & proximal tail of the pancreas		Neuroendocrine tumour
10	69	M				Multiple cystic lesions in the body and tail of pancreas	Multiple cystic lesions in the body and tail of pancreas	Benign
11	91	M	Multilobulated cyst in the body and tail of pancreas					Serous cyst
12	49	M	Pancreas is heterogenous with few cystic areas in the body and tail of pancreas					VHL
13	54	F	Large cyst in the head of pancreas					Serous cyst
14	30	F				Multicystic lobulated cyst in the body of the pancreas		Serous cyst
15	77	M		IPMN	Brush cytology - No malignant cells	Diffusely enlarged pancreas	Diffusely enlarged pancreas	IPMN

predictors of malignancy and hence the recommendation for resection in the first consensus guidelines (Tanaka *et al.* 2006); the 2012 revised guidelines are more reserved and suggests that BD-IPMN >3 cm without any signs of other risk factors (i.e. mural nodules) may be observed without immediate resection. We retrospectively studied the radiological features in our cohort to test the correlation between them and the final histology as proof-of-principle exercise aiming at highlighting the high risk lesions based on the pre-operative features. Three of the 15 resected cases in our cohort who were evaluated using combined assessment were accurately identified and predicted as IPMN; two of them underwent curative resection confirming the final histology to be IPMN in both while the third patient declined surgery but was confirmed by FNA.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCN) are pre-cancerous and almost always located in the pancreatic body/tail (99.4%) in female patients (98.1%) Yamao *et al.* 2011).. In our study we encountered one case of MCN, which was identified correctly by combined assessment, and patient had a curative resection for this lesion.

III: Malignant Pancreatic Conditions: This includes ductal adenocarcinoma and malignant mucinous cystic neoplasm.

IV: Others (neuroendocrine tumor & VHL)

Predictive Abilities of Different Imaging Modalities

A. MDCT (Multi-Detector Computed Tomography)

According to Chalian *et al*. [6], the presence of thickened irregular walls/septa on MDCT correlated well with malignancy. In contrast, presence of thickened irregular walls/septa on MRCP and intramural nodules on EUS reported no correlation with malignancy. Furthermore,

Table 4. EUS-FNA Results.

Sex	Age	EUS report	Biochemical Analysis	Cytology Results
M	35	Cyst in the head of pancreas. Chronic pancreatitis	CEA= 13.3 Amylase = 62	Inflammatory cells
M	77	Cystic dilation of pancreatic duct, prominent papillae, Duodenal fistulae (? With Pancreatic duct)	CEA = 8490 Amylase= 120	No Malignant cells
M	77	Mass lesion in the head of the pancreas, Post Gastrojejunostomy	CEA=1.71 Amylase=27	Inflammation with ill-defined granulomas
F	37	Well defined mucosal echogenic lesion adjacent to head of the pancreas	CEA=3.54 Amylase=83	No Malignant cells
F	37	Multiple pancreatic cysts	CEA=1.65 Amylase=5	No Malignant cells
F	80	Multi septated cyst in the head of pancreas	CEA=50.4 Amylase=30	Oligocellular smear with possibility of benign cyst lesion
M	78	Multi sepated cyst in the head of the pancreas	CEA=1310 Amylase=1990 TGL=360	Acellular smear
M	37	Complex cyst in the uncinate process of pancreas	CEA=6.52 Amylase= 75 TGL=7805	Achylous lymph cyst
M	73	Cyst of the pancreas and Diverticulum of oesophagus	CEA=3.08 Amylase=398	No Malignant cells
F	52	Complex cyst in the head of pancreas	CEA=0.6 Amylase=280	No Malignant cells
F	45	Pancreatic abscess	CEA=19.3 Amylase=145	Acute inflamatory cells
M	64	Multiseptated cyst in the pancreas	CEA=4740 Amylase=825	Positive for Malignant cells
F	58	Cyst in the head of pancreas, Oesophageal varices	CEA=2.45 Amylase=58 CA19-9 =154	Negative for malignant cells
M	23	Psuedocyst of the pancreas	CEA=44.78 Amylase=10278	Psuedocyst
M	38	Cyst in the head of the pancreas communicating with pancreatic duct	Amylase=1897	Psuedocyst
M	15	Chronic pancreatitis,Psuedocyst	CEA=7.27 Amylase=60300	Psuedocyst
M	38	Complex cyst of pancreas, Chronic pancreatitis	Amylase=43920	Negative for malignant cells
M	36	Cyst in the head of the pancreas	CEA= 186 Amylase=1,21300	Inflammatory cells
F	19	Cyst in the tail of pancreas, chronic pancreatitis	CEA=36.3 Amylase=1230	Negative for malignant cells
F	34	Psuedocyst in the body of the pancreas	Amylase=2470	Psuedocyst
M	53	Cyst Gastric wall communicating with head of the pancreas	CEA=27.4 Amylase=55	Inflammatory cells
M	44	Cyst in the uncinate process of pancreas	CEA=62.5 Amylase=6000	Benign lesion, Giardiasis
M	44	Chronic calcific pancreatitis, Cyst in the head of the pancreas	CEA=61.1 Amylase=59300	Negative for malignant cells
M	48	Mixed echogenic lesion in distal body and tail of pancreas	CEA=472 Amylase=62000	Inflammatory cells
M	47	Complex lesion in the head of the pancreas	CEA=6.6 Amylase=53100 Lipase=124600	Psuedocyst
M	49	Cyst in the head of pancreas, Chronic calcific pancreatitis	CEA=484 Amylase=24330	Inflammatory cells
F	70	Lobulated illdefined cystic lesion in the body and tail of pancreas	CEA=0.71 CA19-9=23.8	Neuroendocrine tumour

attenuation measurement may occasionally help in differentiating pseudocysts from unilocular mucin-containing simple cysts of the pancreas on CT images. Attenuation in pseudo cyst was reported as 18.9 HU (95% CI: 15-22.7 HU), MCN as 13 HU (95% CI: 10.6-15.5 HU) and IPMN as 11.4 HU (95% CI: 8.8-14.1 HU) [6].

In a prospective study conducted by Sahani *et al*. in 2011 relating to inter-reporter variation in description of MDCT features, the radiological accuracy (reader 1 and reader 2) for stratifying lesions into mucinous and non-mucinous subtypes was reported to be 85% and 82%; and for recognizing cysts with aggressive biology was reported

to be 86% and 85%, respectively. The predictive power of MDCT was reported as superior for lesions >30 mm and for non-mucinous lesions. Features favoring aggressive biology were reported as main pancreatic duct dilation >10 mm (P<0.0001), mural nodule (P<0.0001), main-duct intraductal papillary mucinous neoplasm (P<0.0001), and advanced age (P=0.0001). Sensitivity of detecting morphologic features was reported as higher with the dual-phase pancreatic protocol CT [7].

In our study CT was done in 41 patients 7 were reported as suspicious for malignancy and 3 were thought to be cystic degeneration of solid tumors.

B. DWI/MRI (Diffusion Weighted Imaging)

Apparent diffusion coefficient (ADC) measurements from diffusion-weighted imaging (DWI) can characterize and may predict the malignant potential of cystic pancreatic lesions. ADC values may be helpful in deciding

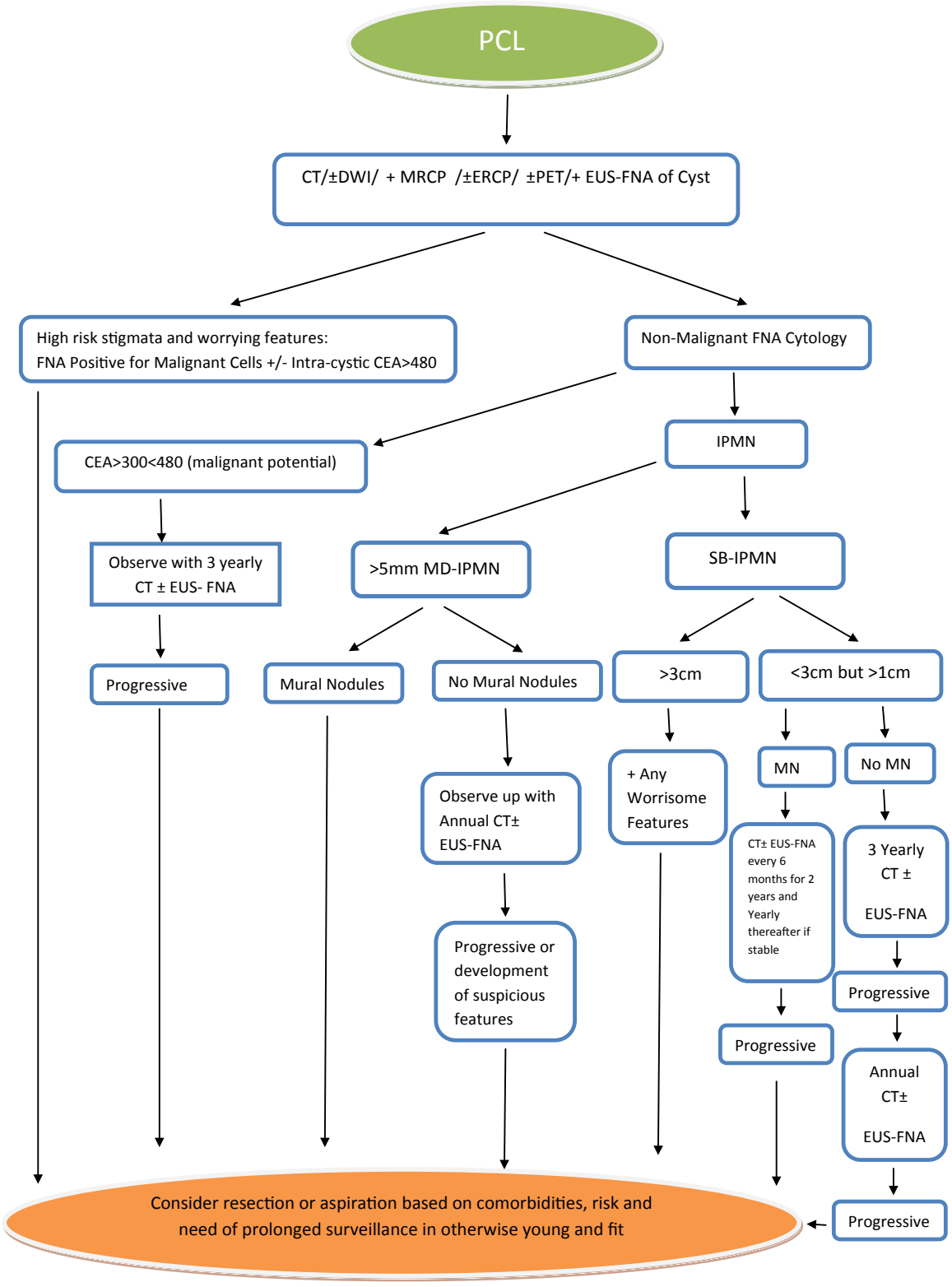

Figure 1. Flow chart to guide the management of pancreatic cystic lesions.

the malignant potential of IPMN. However, they are not useful in differentiating malignant from benign lesions or for characterizing PCL [8].

In our study MRI was done in 8 patients; 3 were suspicious for malignancy (1 was not picked up by CT) and 1 was cystic degeneration of solid tumor.

C. EUS (Endoscopic Ultrasonography)

Cyst size over 30 mm, mural nodule over 6 mm, irregular thick septa, dilatation of the MPD, and the presence of soft tissue mass may be helpful factors in predicting malignancy [10].

A forward-viewing echo endoscope that allows target sites to be punctured more perpendicularly with minimal effort, can be used for diagnostic EUS-FNA and this may be advantageous, depending on the site of target lesions [11] .

The incidence of infectious complications after EUS-FNA of pancreatic cystic lesions, with or without antibiotic prophylaxis, appears very low [12].

EUS with cyst fluid analysis can be successfully used to rule out pancreatic neoplasms and to follow-up incidentally discovered PCL [13]. Age and EUS appearance independently predict surgery in patients with pancreatic cysts referred for EUS. The "perceived need for EUS-CFA (cyst fluid analysis) also predicts surgery, but not the EUS-CFA results. The clinical value of EUS-CFA requires further research [14].

Biochemical Analysis of the Cyst Aspirate and Fine Needle Aspiration Cytology

The cytological diagnoses were correlated with cyst fluid carcinoembryonic antigen (CEA) level and subsequent histologic diagnoses [15].

In our study EUS was performed in 38 patients; 8 were suspected to be malignant based on EUS morphological criteria (2 were not picked up by CT). Three of 8 patients had neoplastic cells on FNAC; 2 had FNAC results suspicious for neoplasm, and 31 were reported to have benign FNAC.

Cyst fluid can be further analysed after aspiration for cytology, viscosity, extracellular mucin, other tumour markers (CEA, CA 19-9,CA 15-3, CA 72-4, etc.), enzymes (amylase, lipase), as well as DNA analysis of DNA quality/ content or mutational analysis to study allelic imbalance/ LOH (loss of heterozygosity) and K-*Ras* mutations [14].

Review of the literature suggests that CA 72-4 cyst fluid levels were found to be significantly higher in mucinous cystic tumors (P<0.005), with 80% sensitivity and 95% specificity in detecting mucinous or malignant cysts. A subsequent study found that a CA 72-4 level over 40 U/mL had a 63% sensitivity and 98% specificity for distinguishing mucinous cyst adenomas and cyst adenocarcinomas from serous cyst adenomas and pseudocysts. Intra-cystic CEA level of >400 ng/mL is reported to have 57% sensitivity and 100% specificity for distinguishing mucinous tumours and cyst adenocarcinomas from pseudocyst, (Bhutani *et al*. 2011). Cytological identification of extracellular mucin and CEA are thus considered predictors of MCN and malignant MCN, as recently proven by a multivariate analysis in 43 patients, which suggested CEA threshold levels >300 ng/ mL (P=0.0007) and identification of mucin (P<0.001) as reliable predictors [14]. It is also noted that CEA >=6000 ng/mL differentiates malignant from benign MCN.

In a study by Frossard *et al*. a CA 19-9 value greater than 50,000 U/mL in the cyst fluid had 15% sensitivity and 81% specificity to distinguish mucinous cysts from other cystic lesions.

In our study we noticed elevation of intra-cystic CEA levels to >300 ng/mL in 10 cases and CA 19-9 results of >2000 IU/mL in 4.

Limitations of Current Conventional Morphological Diagnostic Criteria and Future Directions

None of the available pre-operative diagnostic modalities can reliably predict the nature of non-metastatic pancreatic cystic lesions and it is our view that further research to evaluate the utility of the following diagnostic adjuncts are necessary:

1) Proteomic profiling of pancreatic cystic lesions [16], (Various mucin proteins expression in the cyst fluid such as MUC 1, MUC2, MUC 5 & MUC 7).
2) GNAS mutations were reported to be present in 66% of IPMNs and that either KRAS or GNAS mutations could be identified in 96% [17].
3) RNA can be extracted from samples obtained from EUS-FNA. MUC7 from samples could serve as a potential biological marker to identify malignant lesions, especially pancreatic adenocarcinoma [18].

CONCLUSIONS

No single test is able to predict the nature or behavior of pancreatic cystic lesions. The differences noted on specialist imaging can be very subtle and demand specialist interpretive skills. A panel of pre-operative testing and review at specialist MDT is mandatory for all such cases. Study of our cohort highlights the importance of the pre-operative combined clinical, radiological (CT/PET/MRI/ EUS) and the necessity of FNAC and biochemical analysis prior to therapeutic planning. Sensitivity and specificity may be increased by genetic testing of the cyst aspirate material. MRI/MRCP is superior to MDCT in the detection and characterisation of IPMN. Branch duct IPMN (BD-IPMN) is relatively common, image findings of BD-IPMN may overlap those of other pancreatic cysts and when MDCT or MRI/MRCP fail to demonstrate communication with the main pancreatic duct (MPD), the differential diagnosis between BD-IPMN and oligocystic serous cystic neoplasm (SCN) may be difficult. MDCT can compensate for MRI in cases where the image quality is degraded, is

a reliable modality in evaluating preoperative vascular anatomy and curved planar reformation images can also be created along the course of the MPD making it visually demonstrable. MRI/MRCP however remains to be the preferred modality for follow-up imaging as it lacks ionizing radiation. Determining whether a pancreatic cyst is mucinous or non-mucinous, benign or malignant are the key clinical questions that drive patient management; and analysis of the pancreatic cyst fluid is a vital component of the multimodal approach for preoperative evaluation.

We are proposing a flow chart **(Figure 1)**, which reflects our experience including our interpretation of current knowledge in characterisation and management of PCL but this should be applied in the context of a specialist pancreatic MDT.

Conflicting Interest

The authors had no conflicts of interest

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