Role of EUS in Cystic Pancreatic Lesions

The 10th Nottingham Endoscopy Masterclass
3rd November 2017

Manu Nayar
Consultant Pancreaticobiliary Physician
President – UK & Ireland EUS Society
HPB Unit
Freeman Hospital Newcastle upon Tyne
Speaker Declarations

This presenter has the following declarations of relationship with industry

• Personal payments/honoraria/fees
• Research grants
• Educational grants
• Travel grant or fellowship
• Equipment grant
• Sponsorship of fellow within department
• NONE
Pancreatic Cystic Lesions - PCL

- Background
- Role of EUS – Diagnostic
- Role of EUS - Interventional
- Current management protocols

- Where does EUS sit in the management algorithm
Background

- The increasing use of cross-sectional imaging has led to the increased diagnosis of pancreatic cysts
  - prevalence 2.4% to 14%
- The majority of cystic neoplasms are
  - Mucinous cystadenomas (MCA)
  - Serous cyst adenomas (SCA)
  - Intraductal papillary mucinous neoplasms (IPMN)
- Important differentiation is between mucinous (MCA & IPMN) and non-mucinous (SCA & Pseudocysts)
- Non-mucinous however not synonymous with benign
  - Solid pseudopapillary tumour (SPT), cystic neuroendocrine tumours and ductal adenocarcinoma with cystic degeneration are important diagnosis
### Classification of Cystic Neoplasms of the Pancreas

**Epithelial neoplasms**

1. Serous cystadenoma*
2. Mucinous cyst neoplasm (MCN) and MCN-associated carcinoma*
3. Intraductal papillary mucinous neoplasm (IPMN) and IPMN-associated carcinoma*
4. Solid pseudopapillary neoplasm*
5. Pancreatic ductal adenocarcinoma with cystic degeneration*
6. Cystic pancreatic endocrine neoplasm (CPEN)*
7. Acinar cystadenoma and cystadenocarcinoma
8. Dermoid cyst (cystic teratoma)

**Nonepithelial**

1. Lymphangioma
2. Epidermoid cyst in intrapancreatic spleen
3. Cystic pancreatic hamartoma
4. Mesothelial cyst

**Lesions resembling pancreatic cystic neoplasms**

- Pseudocyst*
- Lymphoepithelial cyst (epidermoid cyst)
- Mucinous nonneoplastic cyst
- Enteric duplication cysts
- Endometrial cyst
- Hydatid cyst
- Retention cyst
- Accessory splenic cyst
- Cystic pheochromocytoma
- Cystic gastrointestinal stromal tumor
- Retention cyst
- Squamoid cyst

*Clinically common and important diseases.*
Guidelines/Guidance for management of incidental & asymptomatic pancreatic cysts

- International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas
  
  Tanaka M et al 2006

- International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas
  
  Tanaka M et al 2012

- European experts consensus statement on cystic tumours of the pancreas
  
  Del Chiara M et al 2013

- Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms
  
  Italian Association for the Study of the Pancreas, AISP 2013

- American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts
  
  Santhi Swaroop Vege et al 2015
Role of EUS in PCL

- **Endoscopic ultrasound**
  - High resolution imaging
  - Identify morphological differences

- **EUS-FNA**
  - Cytology
  - Fluid tumour markers
  - Fluid amylase
  - Fluid viscosity
  - Fluid Mucin
  - Molecular analysis
EUS - Advantages

- Assessing & sampling cysts especially < 1cm
- Detecting focal nodules
- Detecting duct communication with MPD
EUS-FNA of PCLs

- **Technique**
  - IV antibiotics prior
  - Needle type - (22g/19g) to a minimum
  - Aspirate to dryness

- **Fluid**
  - Cytology
  - CEA, CA19-9, Amylase
  - Visual assessment of viscosity
## Cyst Characteristics

<table>
<thead>
<tr>
<th>EUS Morphology</th>
<th>Pseudocyst</th>
<th>SCA (32-39%)</th>
<th>MCA (10-45%)</th>
<th>IPMN (21-33%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anechoic, thick walled, debris, parenchymal changes</td>
<td>Microcystic (&lt;3mm) honeycomb, macrocysts, central scar</td>
<td>Macrocystic, septated, mural calcification. Mural mass</td>
<td>Dilated PD or side branches, communicating with cyst, solid components</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluid appearance</th>
<th>Thin, dark</th>
<th>Thin, straw coloured/clear</th>
<th>Viscid, clear</th>
<th>Viscid, clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid markers</td>
<td>Elevated amylase</td>
<td>Low CEA</td>
<td>Elevated CEA</td>
<td>Elevated CEA Elevated Amylase</td>
</tr>
<tr>
<td>Cytology</td>
<td>Neutrophils, macrophages, histiocytes</td>
<td>Stains for glycogen, cuboidal epithelium</td>
<td>Mucinous columnar epithelium, mucin staining</td>
<td>Mucinous columnar epithelium, mucin staining</td>
</tr>
</tbody>
</table>

| Malignant potential | None | Rare case reports | Yes | > 3cm Presence of nodule |
54 year old lady, non specific abdominal discomfort

2cm cystic lesion in uncinate process

**Fluid Analysis**
- Appearance: Straw coloured & thin
- Cytology: no epithelial cells, equivocal mucin stain
- Amylase 296 U/L
- CEA < 1µg/L

**EUS-FNA diagnosis** = Macro cystic serous cystadenoma
62 yr female
Incidental finding 33mm thin walled cyst in HOP – Single septum

**EUS performed**
- Communicates with PD
- Mucoid aspirate
- SB-IPMN on EUS

- Closely monitored
- Slight increase in size 7m later
- Whipples - **34mm IPMN adenoma**
EUS in PCL - Studies

- **Brugge WR et al** Gastroenterology 2004
  - Multi centre (17 Collaborators)
  - 341 patients
  - Aim to differentiate mucinous (malignant/premalignant) from serous (benign)

Analysis restricted to 112 patients with Histology

- EUS morphology
  - Accuracy 51%

- Cytology
  - Overall accuracy 59%

- Cyst fluid tumour markers
  - CEA optimal cut-off 192 ng/ml
  - Accuracy 79.2%
Consecutive patients who underwent EUS with FNA at 3 tertiary care centers were identified.

Patients with histologic confirmation included in the analysis

CEA levels was 0.77 (95% confidence interval, 0.71-0.84, P < .01)

Cutoff of 105 ng/mL, demonstrating a sensitivity and specificity of 70% and 63%, respectively. The cutoff value of 192 ng/mL yielded a sensitivity of 61% and a specificity of 77% and would misdiagnose 39% of MCN cases

Cyst fluid CEA levels have a clinically suboptimal accuracy level in differentiating MCNs from NMCNs.
<table>
<thead>
<tr>
<th>Test</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tests (n=93)</td>
<td>65%</td>
<td>73%</td>
<td>42%</td>
<td>77%</td>
<td>38%</td>
</tr>
<tr>
<td>Recorded EUS diagnosis (n=75)</td>
<td>80%</td>
<td>86%</td>
<td>61%</td>
<td>88%</td>
<td>58%</td>
</tr>
<tr>
<td>FNA Cytology (N=92)</td>
<td>66%</td>
<td>56%</td>
<td>96%</td>
<td>97%</td>
<td>43%</td>
</tr>
<tr>
<td>Fluid appearance (N=78)</td>
<td>68%</td>
<td>64%</td>
<td>68%</td>
<td>81%</td>
<td>47%</td>
</tr>
<tr>
<td>CEA &gt;159ng/ml (N=54)</td>
<td>67%</td>
<td>51%</td>
<td>95%</td>
<td>95%</td>
<td>51%</td>
</tr>
<tr>
<td>Combination of tests*</td>
<td>82%</td>
<td>90%</td>
<td>62%</td>
<td>86%</td>
<td>70%</td>
</tr>
</tbody>
</table>

*combination of tests was significantly better than any individual test p<0.05*

EUS and EUS-FNA diagnosis of suspected pancreatic cystic neoplasms: Is the sum of the parts greater than the CEA?

Other techniques

Elastography

Contrast enhanced EUS

Serrani M et al. Endosc Ultrasound 2017

Probe based Confocal Laser Endomicroscopy

**Cellvizio®**

probe based Confocal Laser Endomicroscopy (pCLE)

**nCLE CASES REPORT**

**Case 1 IPMN**

- Papillary projection

**Case 2 Serous cystadenoma**

- Superficial Vascular Network

_Napoléon B et al. Endoscopy 2015_

_Krishna SG et al. Gastrointest Endosc. 2017_
Role of Interventional EUS in PCL – Ethanol Ablation

- 91 patients with median follow-up of 40 months
- Success rate was significantly different according to cystic fluid analysis (SCA = 58%; MCN = 50%; IPMN = 11%; uncategorized cysts, 39%; P < 0.0001)

- 3 patients with mild pancreatitis after the treatment
- EUS-guided ethanol ablation therapy seems to be a safe treatment modality = only effective in 11% of IPMNs.
- Clinical application should be very limited for certain patients who could not tolerate the surgical treatment.

Role of Interventional EUS in PCL

Radiofrequency Ablation

■ Six had a pancreatic cystic neoplasm (4 =MCN, 1 = IPMN and 1 -SCA)
■ 3-6 months showed complete resolution of the cysts in 2 cases
■ In 3 cases there was a 48.4% reduction [mean pre RF 38.8 mm (SD ± 21.7 mm) vs mean post RF 20 mm (SD ± 17.1 mm)] in size
■ Safe, feasible - no long term follow up
■ Radiocyst 1 - *Phase II multicentre trial of endoscopic ultrasound guided radiofrequency ablation of cystic tumors of the pancreas*

Pai M et al. World J Gastrointest Surg. 2015
Role of Interventional EUS in PCL – Drainage of pancreatic cysts

Law R, Baron TH. Gastrointest Endosc Clin N Am. 2017


videos
Safety of EUS FNA

Post FNA pancreatitis

? Mixed type IPMN – 16mm; No worrying features; Serous fluid

Cytology – Inconclusive

Fluid Amylase = >1000

**Likely pseudocyst**
Where does EUS sit in the management algorithm?
Majority of pancreatic cysts now referred to tertiary centres are asymptomatic
- Knowledge of natural history incomplete
- Concern that some may be precursors of cancer

Ideal management algorithm would swiftly discriminate between those with malignant potential and those without
- Surgery for high risk lesions
- Surveillance for low to intermediate risk
- Low risk lesions excluded from further assessment
Fukouka criteria

1. Classification
1a. The threshold of MPD dilation, segmental or diffuse, for characterization of MD-IPMN has been lowered to >5 mm without other causes of obstruction, thereby increasing the sensitivity for radiologic diagnosis without losing specificity. MPD dilation of 5–9 mm is considered a “worrisome feature”, while an MPD diameter of >10 mm is one of the “high-risk stigmata”.  
1b. The definition of “malignancy” of IPMNs and MCNs has been variable, hampering comparisons of data. We recommend abandoning the term carcinoma in situ in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification.

2. Investigation
2a. CT or MRI with MRCP is recommended for a cyst of ≥1 cm to check for “high-risk stigmata”, including enhanced solid component and MPD size of ≥10 mm, or “worrisome features”, including cyst of ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5–9 mm, and pericystic lymphadenopathy. All cysts with “worrisome features” and cysts of >3 cm without “worrisome features” should undergo EUS, and all cysts with “high-risk stigmata” should be resected. If no “worrisome features” are present, no further initial work-up is recommended, although surveillance is still required.
2b. MDCT and MRCP are most useful for distinguishing BD-IPMN from other cysts by showing multiplicity and a connection to the MPD.
2c. Cyst fluid analysis is still investigational, but is recommended for evaluation of small BD-IPMNs without “worrisome features” in centers with expertise in EUS-PNA and cytological interpretation.
2d. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be in the context of research.
2e. Distinction of BD-IPMN from a small oligocytic SCN is challenging and may require the use of serum markers.

3. Indications for Resection
3a. Resection is recommended in all surgically fit patients with MD-IPMN. If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia.
3b. The indications for resection of BD-IPMN are more conservative. “Worrisome features” as well as “high-risk stigmata” are proposed. A BD-IPMN of >3 cm without “high-risk stigmata” can be observed without immediate resection.
3c. Surgical resection is recommended for all surgically fit patients with MCN. For MCNs of <4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation should be considered.

Moderate-grade or low-grade dysplasia may not require any further therapy. 5c. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN, being careful to identify the MPD as precisely as possible when processing the specimen.
5f. A distinction between PDAC derived from an IPMN and PDAC comitant with an IPMN is proposed with regard to the topological relationship and histological transition, although the distinction sometimes remains undetermined.

6. Methods of follow-up
6a. Patients without “high-risk stigmata” should undergo MRI/MRCP (or CT) after a short interval (3–6 months) to establish the stability, and then annual history/physical examination, MRI/MRCP (or CT) and serologic marker surveillance. Short interval surveillance (3–9 months) should be considered for patients whose IPMN progresses toward “high-risk stigmata” and patients with a family history of hereditary PDAC. Some investigators continue surveillance at short intervals owing to concern over the development of distinct PDAC.
6b. Non-invasive MCNs require no surveillance after resection. IPMNs need surveillance based on the resection margin status. If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable. The aspect of whether a margin with moderate-grade dysplasia increases recurrence is unknown. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice a year. The follow-up strategy of invasive IPMN should be identical to that for PDAC.
6c. In patients with two or more affected first-degree relatives, the risk rapidly escalates and merits aggressive surveillance by MRI/MRCP (or CT) and EUS. “Worrisome features” are of more concern. If present, patients should be considered for resection if they are surgically fit. If absent, patients should be followed by MRI/MRCP (or CT) at 3-month intervals and EUS annually for the first 2 years. Patients with a rapidly growing BD-IPMN and patients who develop “worrisome features” should be strongly considered for resection. The interval of surveillance after 2 years of no change can be lengthened to 6 months, but no longer in view of the relatively high incidence of PDAC reported for BD-IPMN.
6d. There are no screening recommendations for detecting extrapancreatic malignancies in patients with IPMN on surveillance and after resection, but consideration of extrapancreatic neoplasms should be made based on the frequency of these malignancies in the general population of the country or region.

### Guideline performance for referral to EUS

<table>
<thead>
<tr>
<th></th>
<th>AGA 2015</th>
<th>Fukuoka 2012</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>17.6%</td>
<td>35.3%</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>94.5%</td>
<td>66.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>50.0%</td>
<td>24.5%</td>
<td>0.154</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>78.6%</td>
<td>76.6%</td>
<td>0.747</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>76.2%</td>
<td>58.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

For referral to surgery, both guidelines have modest sensitivity and specificity and miss a similar percentage of malignant lesions.
Practicality of guidelines in the NHS

- Evidence base is poor
- CT widely available but most trusts in the UK would struggle to provide MR for diagnosis/surveillance
- Most patients may not be fit for further intervention - who makes that decision i.e. referral centre or the local HPB centre
- Initial characterisation of cysts may not be accurate especially if reported by a non HPB radiologist
- Follow up of patients with incidental cysts is variable –some of the guidelines can be challenging to follow due to lack of resources/patient factors

Hol L et al Pancreatology 2016
MANAGEMENT OF SUSPECTED NEOPLASTIC PANCREATIC CYSTIC LESIONS

Pancreatic protocol CT + Fitness score (METS)
Refer to Freeman HPB MDT

MDT review to identify worrisome or high risk features – see below

- No
- High risk

Worrisome features

- Repeat imaging at 1 year and then biennially to 5 years (d/w patient)
  - MRI < 70 yrs; CT > 70 yrs – to be done by referring hospital
  - Positive features or enlargement during surveillance
    - No
    - Yes

High risk

Worrying/high risk features +/- cytology

Consider EUS +/- FNA

Consider surgery

Stop criteria
1. Unfit for intervention
2. No worrisome features and cyst unchanged > 5 years

Worrisome features
- Pancreatic duct 5 – 10 mm
- Non enhancing nodules
- Size >30mm
- Pancreatitis
- Abrupt change in PD calibre

High risk features
- Obstructive jaundice
- Enhancing nodule
- PD >10 mm

Manu Nayar, Kofi Oppong, John Scott, Kirsty Anderson, Richard Charnley on behalf of the NUTH HPB MDT

The Newcastle upon Tyne Hospitals NHS Foundation Trust
Conclusion - 1

- EUS plays an adjunctive role in the investigation and management of PCLs
- EUS morphology alone not accurate enough to be solely relied on to differentiate mucinous from non-mucinous cysts
- EUS-FNA with Cytology, CEA, Amylase adds valuable information - Combining the test results potentially gives the best performance
- Newer techniques – elastography, CEEUS & nCLE can provide useful information
Conclusion - 2

- Incidental pancreatic cysts is commonly detected on cross sectional imaging - ~ 15% ; a small proportion are pre malignant – majority of them can be followed up

- EUS FNA does carry a small risk of complications but would be significant in an asymptomatic patient

- Therefore the decision regarding the use of EUS-FNA should be made at the HPB MDT

- Decision should be dependent on local experience and audited results

- Interventional techniques e.g. RFA could be considered as an option in a select group of patients