
Pancreatic
COUNDRUMS
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Sunnybrook
ODETTE CANCER CENTRE
when it matters MOST

Objectives

CHAPTER 1
- The mysterious ***solid incidentaloma***

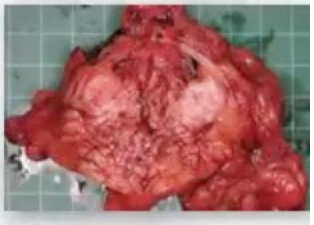
CHAPTER 2
- The mysterious ***cystic "IPM-something"***

CHAPTER 3
- It's ***cancer*** - now what?
  - evaluating for resectability
  - operative issues
  - where are we at with [neo]adjuvant therapies?

CHAPTER 1

"Incidental Solid Pancreas Lesions"

The Good
The (could be) Bad
The (clearly) Ugly



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Overview

- Getting the differential right!
- How to talk to your radiologist?
- What to ask from your lab?
- How might your friendly neighbourhood gastroenterologist help?
- Formulating a plan.

Where do they come from?

Presentation	Percent
GU/Renal	16
Elevated LFTs	13
Screening / Surveillance	13
Chest Pain	6
Cholangitis/Cholecystitis/Biliary Colic	6
Trauma / Emergency	5
Vague Abdominal Symptoms	5
Diverticulitis	4
Gastroesophageal Reflux	3
Anemia	3
Integumentary	3
All Others	3

Sachs et al. 2009

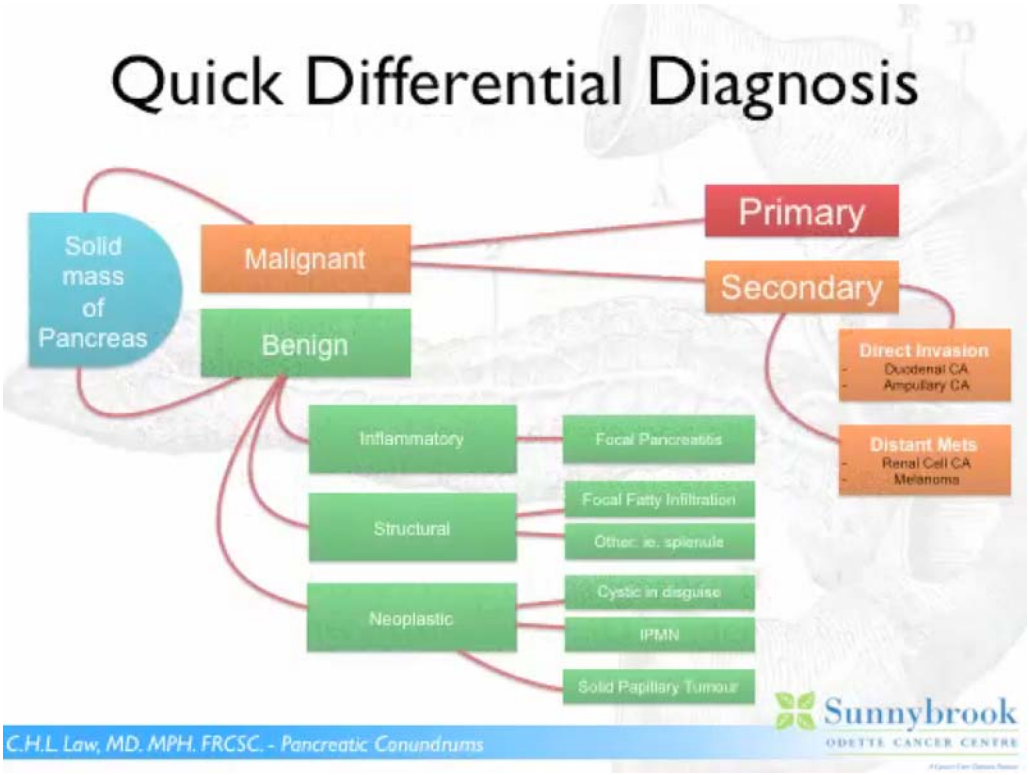
Incidental ≠ Asymptomatic

- Truly asymptomatic and truly incidental
- Symptomatic but not related and truly incidental finding
- Symptomatic related and found a pancreatic lesion

Incidental Cystic ≠ Incidental Solid

- Incidental cystic lesions of the pancreas have been well described with size criterion and consensus management strategies (Sendai Conference guidelines)
- SOLID incidental lesions have not had the attention or well described consensus strategies developed
- There is a higher rate of malignancy or at least significant neoplasm in SOLID incidental lesions.

Quick Differential Diagnosis



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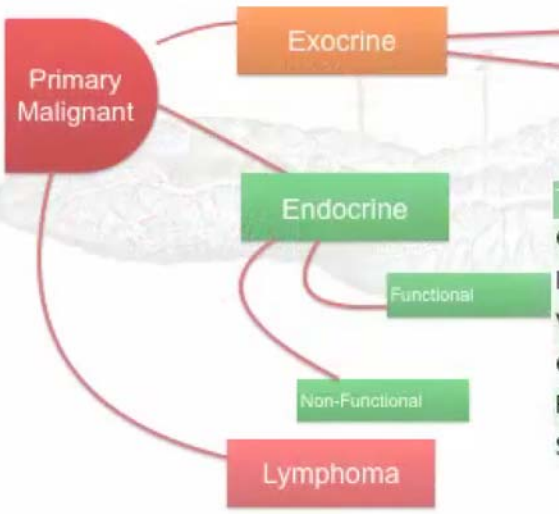
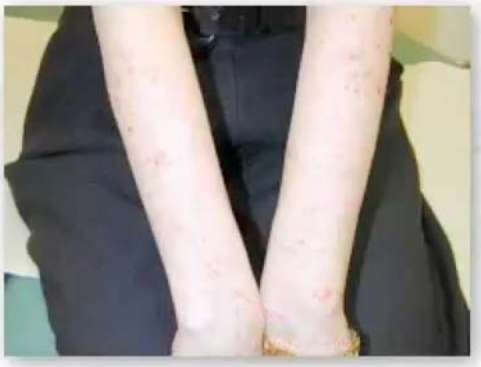
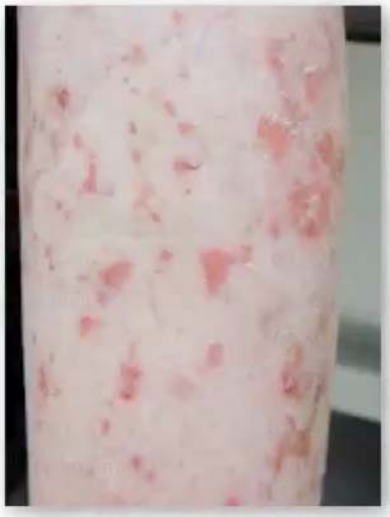
Quick Malignant Differential Diagnosis



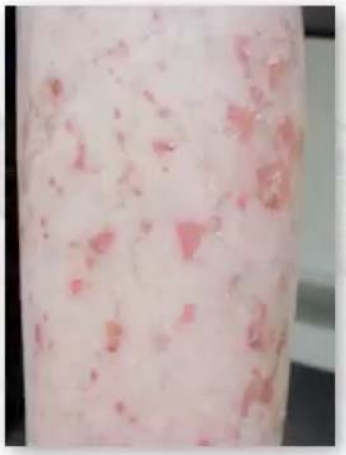
Type	% Malignant
Gastrinoma	60-90%
Insulinoma	10-15%
VIPoma	60-80%
Glucagonoma	60-70%
Ppoma	60%
Somatostatinoma	90%

Classic Rash





Rash Resolution



How to talk to your radiologist

- Give a good history
  - interpretation always in context
- Getting the right test
  - **CT Scan – "Pancreas Protocol"**
    - ALWAYS better than a standard "screening" single phase scan
    - NOT THE SAME as a standard "triphasic" scan either
  - **MRI / MRCP**
    - MRCP portion can help identify relationships to ducts
    - Interpretation aided with contrast
    - Can do correlative US that day if planned
  - Full staging investigations
    - Depends on the clinical suspicion for malignancy

How to talk to your radiologist

- What might they find?
  - 10-15% of the time – really nothing or something other than pancreatic tissue
  - Remainder of the time:
    - Suspect adenocarcinoma
    - Suspect pancreatic neuroendocrine tumour
    - The peripancreatic "haze" factor – ***itis*** versus ***oma***
    - "I can't see a thing" – which is not always the same as really nothing…..

What to ask for from the lab?

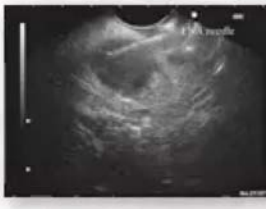
- What am I thinking about?
  - Inflammatory – any signs of pancreatitis?
  - Malignant – Exocrine
    - CA19-9
  - Malignant – Lymphoma
    - LDH, Blood Smears, etc.
  - Malignant – Endocrine
    - Ok which one?

Biochemical workup for PNETs

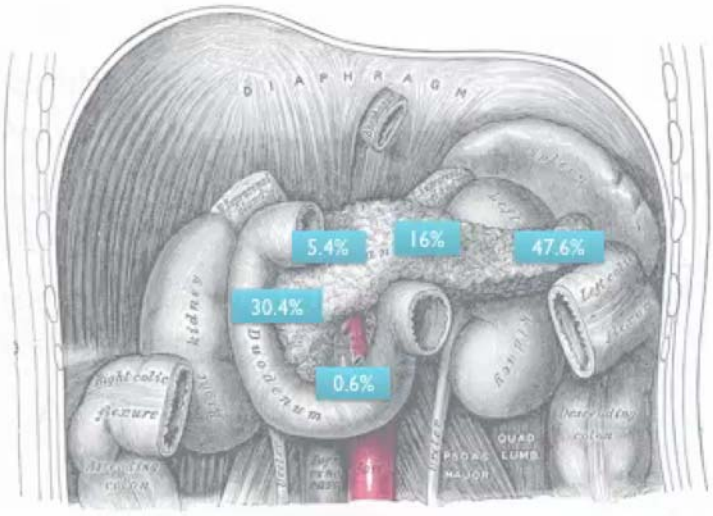
Type	Suggested Labs
Gastrinoma	(fasting) serum gastrin Secretin stimulation test (reactive serum gastrin)
Insulinoma	(fasting) serum insulin (fasting) serum pro-insulin (fasting) serum C-peptide
VIPoma	(fasting) vasointestinal polypeptide (fasting) PHM (peptide-histine-methionine) WD**HA** – watery diarrhea/**hypokalemia/achlorhydria**
Glucagonoma	(fasting) plasma glucagon (fasting) pancreatic polypeptide Hypoproteinemia Hyperglycemia
Ppoma	(fasting) plasma glucagon (fasting) pancreatic polypeptide Hypoproteinemia Hyperglycemia
Somatostatinoma	(fasting) plasma somatostatin

How EUS can help.

- Further clarification of lesional characteristics:
  - Vascular / neovascular
  - Density
  - Small lesions (especially insulinoma, or any <2 cm)
- Tissue diagnosis without disruption of an "operative plane"
  - FNA / Tru-cut possible



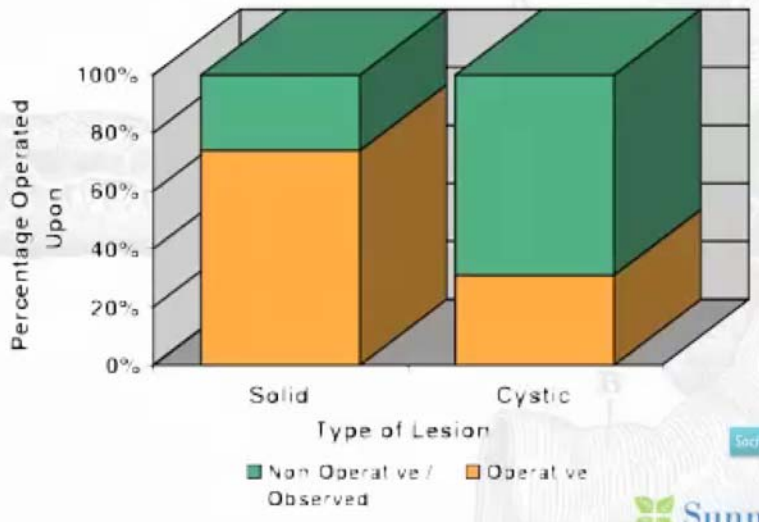
Distributions in the Pancreas



So now what do we do?

- We're going to see more due to imaging but we must demand that the imaging **tell us more** at the same time!
- Solid lesions in the pancreas are **more likely to be malignant** than cystic lesions
- Must be sharp about **differentiating incidental from asymptomatic**
- If resectable but not resected, must be **followed closely** for interval growth

What typically happens?



Sachs et al 2009

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What kind of risks are we talking about?

- Boston series:
  - 110 Asymptomatic pancreatic lesions
  - 24% malignancy rate including *in situ*
    - 17% invasive maligancy rate
    - 94% in solid lesions
  - 47% had lesions harboring potential for malignant degeneration
    - IPMN, MCA, PNET etc.
  - Total: 71% of asymptomatic solid lesions had some malignancy or risk of malignancy

The good, the bad and the ugly?

- The good:
  - Truly asymptomatic
  - Benign structural lesions like fatty replacement
- The (could be) bad:
  - Anyone with possibly related symptoms
  - Non-specific but possibly new solid lesions
  - stable lesions but have a PNETs appearance
- The (definitely) ugly:
  - Symptomatic PNETs
  - Adenocarcinoma

The good…..

- Unless 110% sure:
  - Interval follow-up at 6-12 months with imaging and clinical exam to rule out new or intervening symptomatology

The (could be) bad…

- Multidisciplinary discussion is mandatory
- Utilize all methods of further diagnosis:
  - Laboratory examination / screening
  - EUS
  - Better protocoled CT / MRI / MRCP
- Discussion with patient for consideration of surgical excision
  - Depends on location of tumour
  - Depends on patient factors
- If observation chosen, strict and mandatory follow-up
  - 3-6 month maximum repeat imaging and clinical evaluation for at least 1-2 years unless operated on, or before consideration of lengthening follow-up

The (definitely) ugly

- Immediate detailed staging with imaging and biochemistry
- Rapid decision: operative management
- If not resectable:
  - Definitive diagnosis must be sought – EUS bx, Percutaneous Bx etc.
  - Multidisciplinary management – especially involving medical oncology and radiation oncology – especially if there are symptoms.

Summary

- Careful evaluation with all modalities required:
  - Clinical, Radiological, Endoscopic, Biochemical, Multidisciplinary, Time
- Low threshold overall and over time for surgical intervention
- ***The initial workup should be the most intensive work-up!***

CHAPTER 2

The mysterious cystic "IPM-Something"

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*Is it a **wolf** in sheep's clothing?*

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Is it a wolf in sheep's clothing?

Or

Are we killing a fly with a shotgun?

Objectives

- What is "IPMT"?
- The multidisciplinary approach to IPMT
  - The radiologist – what you need to tell the team?
  - The endoscopist – maneuvers that make a difference
  - The surgeon – making intervention decisions
  - The pathologist – optimizing the diagnosis
- What follow-up do we recommend?

What is IPMT?

A Background

- An autopsy series of 300 patients showed:
  1. 50% had cystic lesions in the pancreas of which 4% had epithelial atypia
  2. prevalence increased with age

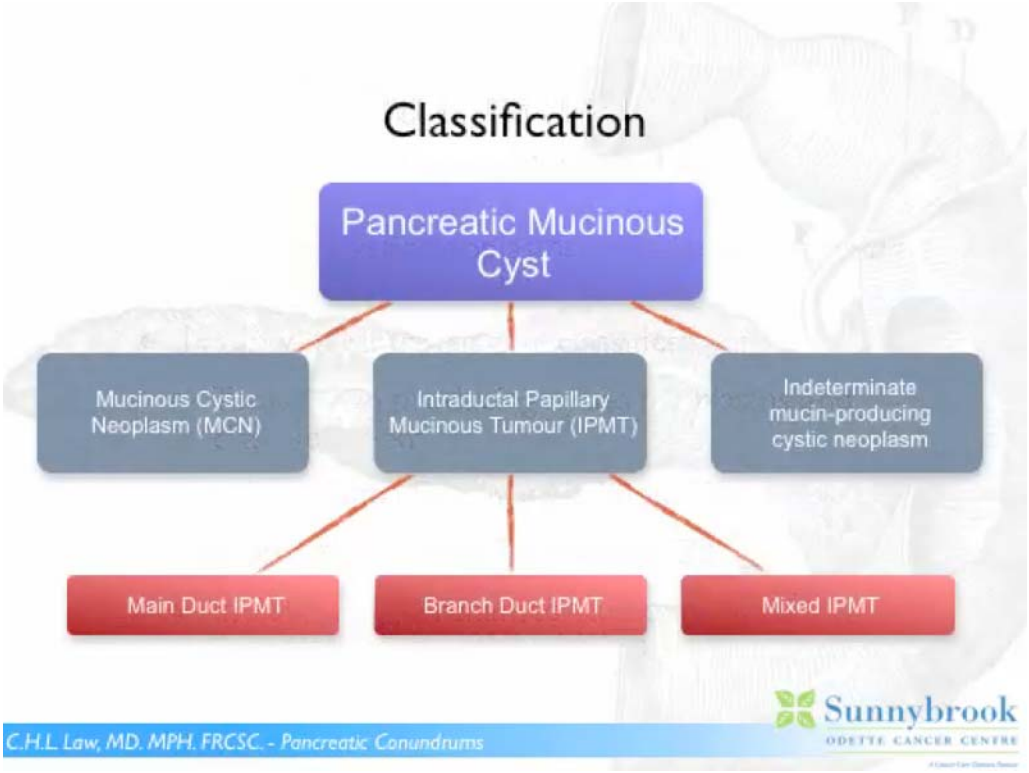
Kimura et al. Int J Pancreatol 1995

- So…if you buy *better* imaging devices and you have an *aging* population…

What is IPMT?

Some history

- Therefore cystic neoplasms were increasing being reported
- 1996: WHO introduced a classification:
  - Took mucin producing cystic neoplasms and classified them as:
    - Intraductal Papillary Mucinous Tumour (IPMT)
    - Mucinous Cystic Tumour (MCT)
  - In 2004, WHO renamed "tumour" as "neoplasms" (ie. IPMN, MCN)


Classification
Pancreatic Mucinous Cyst
Mucinous Cystic Neoplasm (MCN)
Intraductal Papillary Mucinous Tumour (IPMT)
Indeterminate mucin-producing cystic neoplasm
Main Duct IPMT
Branch Duct IPMT
Mixed IPMT
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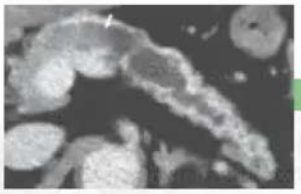
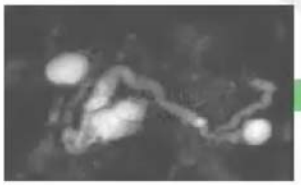
IPMTs

- Main duct IPMTs
  - associated with a dilated (<1cm) pancreatic duct
  - Have a relatively higher predilection to malignancy
- Branch Duct IPMTs
  - Often multifocal but smaller
  - Relatively lower predilection to malignancy
- Mixed IPMTs
  - Usually a branch duct IPMT that shows some changes in the main duct as well
  - No established criteria to say *"how much main duct involvement"* makes it a *"true main duct IPMT"*

Malignant risk in IPMT subtypes





Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	13	92	23
Terris [17]	2000	30	57	37
Doi [18]	2002	12	83	Not stated
Matsumoto [19]	2003	27	63	Not stated
Choi [20]	2003	34	85	Not stated
Kitagawa [21]	2003	37	65	54
Sugiyama [22]	2003	30	70	57
Sohn [23]	2004	69	Not stated	45
Salvia [24]	2004	140	60	42
Mean of all series			70	43

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	17	31	6
Terris [17]	2000	13	15	0
Doi [18]	2002	26	46	Not stated
Matsumoto [19]	2003	16	6	Not stated
Choi [20]	2003	12	25	Not stated
Kitagawa [21]	2003	26	35	31
Sugiyama [22]	2003	32	40	9
Sohn [23]	2004	60	Not stated	30
Mean of all series			25	15

Natural History of IPMT?

- No reliable data to document natural history
- Limited data from Johns Hopkins and a combined Massachusets General and University of Verona experience
  - Suggested time lag of 5-10 years from non-invasive to invasive lesions

Mucinous Cystic Neoplasms

- True MCNs have ovarian like stroma and are thought to originate from ovarian rests
  - Solitary and do not recur following resection
- Occurs much more commonly in females of child bearing age

Why differentiate MCN vs. IPMT?

- Different biological behaviours
- Different management strategies
- Different prognoses
- Different follow-up care

MCN versus Branch Duct IPMT

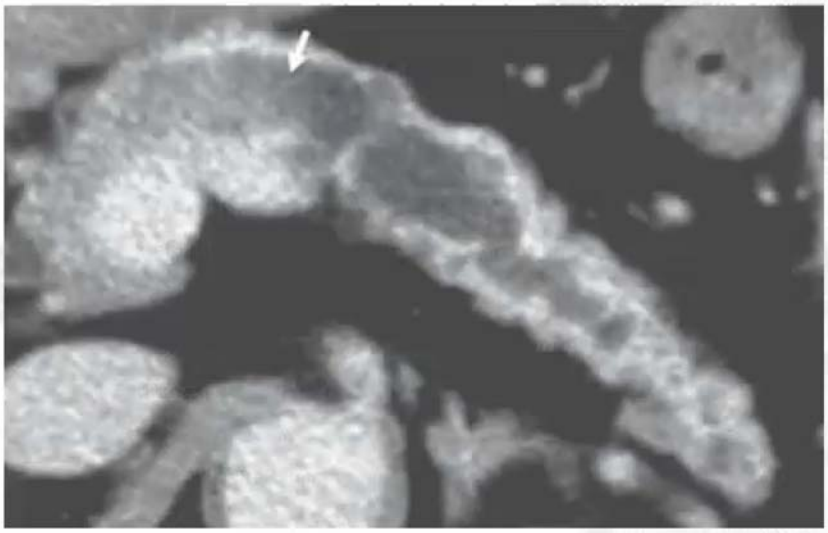
Characteristic	MCN	Branch duct IPMN
Gender (% female)	>95%	~30%
Age (decade)	4th and 5th	6th and 7th
Location (% body/tail)	95%	~30%
Common capsule	Yes	No
Calcification	Rare, curvilinear, in the wall of cyst	No
Gross appearance	Orange-like	Grape-like
Internal structure	Cysts in cyst	Cyst by cyst
Pancreatic duct communication	Infrequent	Yes (though not always demonstrable)
Main pancreatic duct	Normal or deviated	Normal, or if dilated, suggests combined type

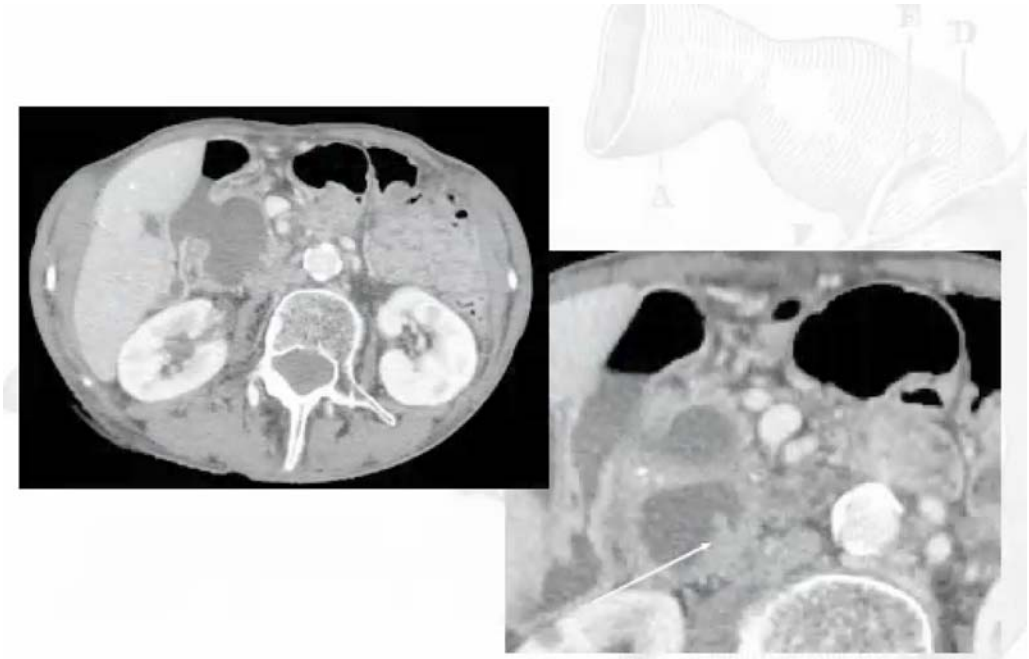
Diagnostic Imaging and IPMT

- Relevant clinical questions are:
  - What is the relationship to the pancreatic duct?
  - Is there duct dilatation or papillary formations?
  - Is it unifocal or multifocal?
  - Is this a MCN or an IPMT
  - Is this a main duct IPMT or branch duct IPMT?

Diagnostic Imaging for IPMT

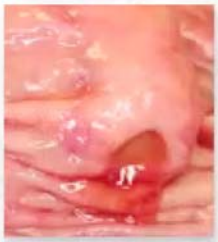
- MRI / MRCP
  - Best method to outline gross appearance
  - Helpful for demonstrating duct communication
- Criteria for malignancy
  - Main Pancreatic Duct Diameter > 15 mm
  - Branch Duct IPMT
    - Lesion > 3 cm
    - Main Duct > 7mm
  - Thick enhancing wall
  - Soft tissue nodules





Endoscopic Evaluation of IPMT

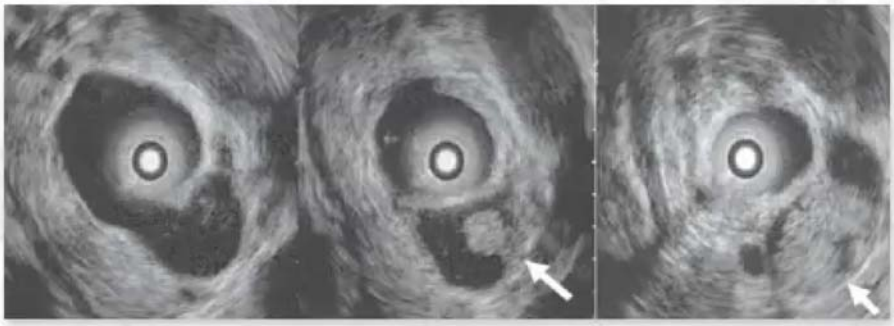
- Ductal anatomy – ERCP can be the most definitive test
- Patulous Papilla filled with mucin



- Pancreatoscopy
  - "fish egg" appearance

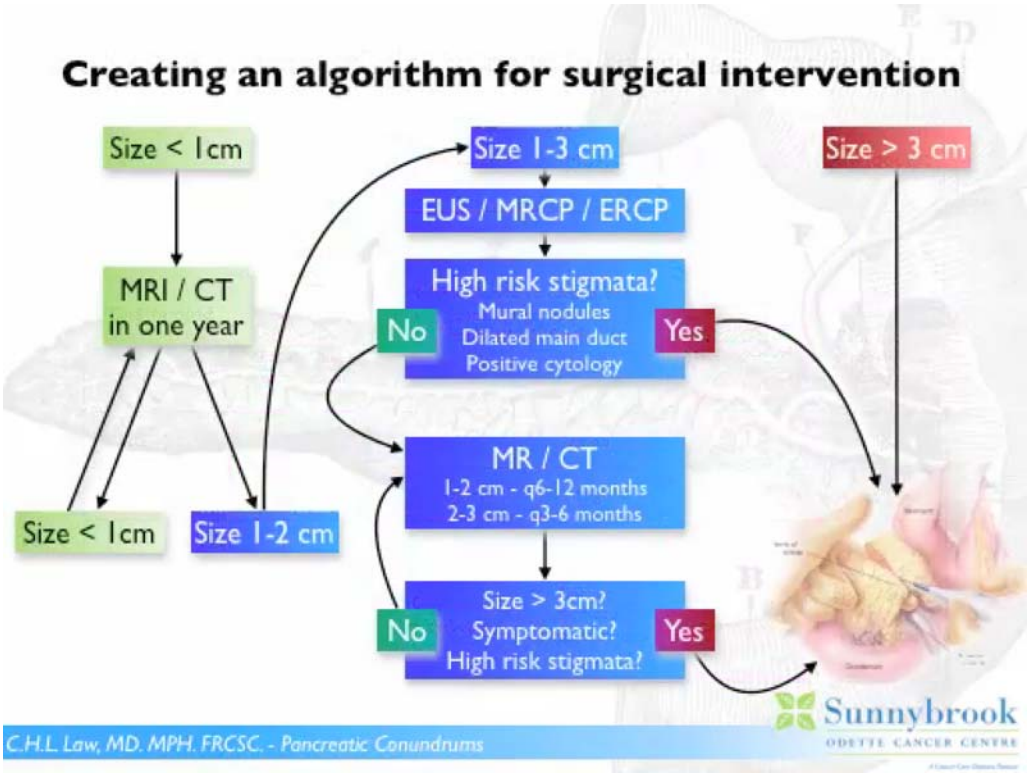
Endoscopic US

- Can give very detailed imaging within cystic neoplasms
- Can perform FNA to allow for cytological and biochemical evaluation
- May assist in deciding on major pancreatic resection versus observation especially where imaging is equivocal



EUS FNA characteristics of certain pancreatic cystic lesions

	SCA	MCA	MCAC	IPMN	Pseudocyst
EUS finding	Multiple small microcysts, dense fibrous septations, honeycomb pattern. Central calcification	Multiple fluid filled cavities, thin septations. Larger than SCA. Peripheral calcification		Dilated pancreatic duct (s). Connection to duct. Multilocular. No septations.	Internal echoes representing debris. Unilocular. Pancreatitis parenchymal change.
Amylase	Variable	Variable	Variable	High	High
CEA	Low	High	High	Variable	Low
Cytology	No mucin. Glycogen. Flattened epithelium Low cellularity	Mucin Columnar epithelieum	Mucin Columnar epithelium Atypical nuclei.	Mucin Columnar epithelium	No mucin No epithelial lining Histiocytes


Creating an algorithm for surgical intervention
Size < 1cm
MRI / CT
in one year
Size < 1cm
Size 1-2 cm
Size 1-3 cm
EUS / MRCP / ERCP
High risk stigmata?
Mural nodules
Dilated main duct
Positive cytology
No
Yes
MR / CT
1-2 cm - q6-12 months
2-3 cm - q3-6 months
Size > 3cm?
Symptomatic?
High risk stigmata?
No
Yes
Size > 3 cm
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Surgical Issues in IPMT

- Indications for resection
  - Main Duct IPMT
  - Branch Duct IPMT
- Methods of resection
  - Partial versus Total versus Segmental Pancreatectomy
  - Lymphadenectomy

Main Duct IPMT

Indications for Surgical Resection

- Symptoms
  - Pain, jaundice, worsening diabetes
- Criteria for Malignancy
  - > 15mm duct diameter
  - Intraductal papilla or nodules
- Risk of malignancy >60%
- Practical: treat mixed as main duct

Branch Duct IPMT

Indications for surgical resection

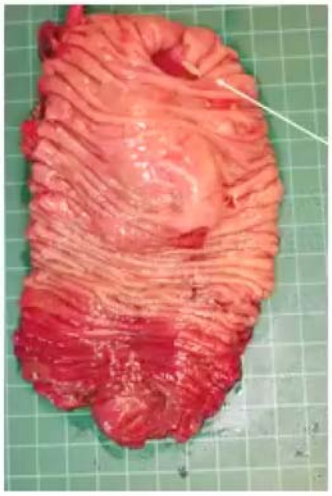
- Risks of surgery are more balanced with risk of malignancy since it is lower (estimated < 25%)
- Criteria for higher risk lesions:
  - > 30mm lesion
  - Intraductal papilla or nodules
  - Associated duct dilatation > 7mm

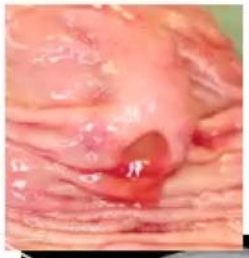
Branch Duct IPMT

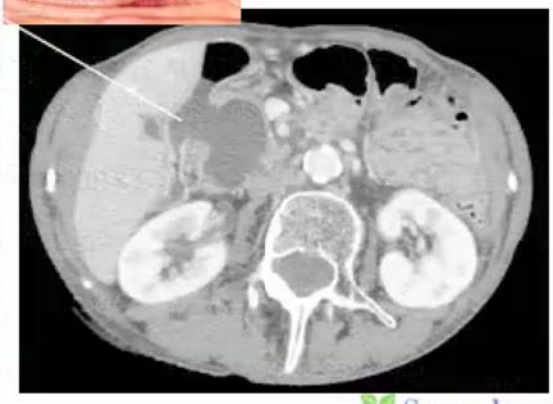
- Japanese studies:
  - Branch IPMT <30mm and no mural nodules have no association with invasive cancer and low association with in situ disease
- Controversy:
  - >30mm without symptoms or mural nodules

Method of Pancreatectomy

- Surgery determined by extent of tumour
- If pre-operative investigations suspect malignancy, a standard oncologic resection applies
- Multifocality of IPMT balanced by:
  - Relatively indolent tumour
  - Ability to image in follow-up
  - Limited data showing superiority of total pancreatectomy







Histology Issues

- The dreaded frozen section
- Caveats of FS:
  - Difficulty confirming negative margin
  - Does not account for skip lesions
  - Careful handling required as to not denude the epithelial layer

The positive margin

- Adenoma
  - Continued follow-up
  - Data indicates minimal risk of progression
- Borderline Atypia
  - Poorly defined category
  - Florid papillary nodules at the margin or presence of high grade dysplasia anywhere in the specimen may be criteria for further resection
- CIS or Invasion
  - Further resection balanced with patient factors

Follow-Up Post Resection

- MCNs are usually cured completely
- No studies to define a guideline
- Prognosis: Invasive Ca identified with IPMT still associated with 60% 5 year OS
- General:
  - 6-12 month follow-up with imaging
  - Continue for 5-10 years
  - No value in doing serum markers