Pancreatic cancer: Etiology, Risk factors, Diagnosis and Investigations

Mr Somaiah Aroori
Mr Chris Briggs
Dr Mark Puckett

Pancreatic cancer study day 5 July 2021

Introduction

- 14th most common cancer in the World
- 7th highest cause of cancer related deaths in the World
- Mortality rates have not changed and 5-year survival rate for PC is approximately 6% (2% to 9%)
- The incidence is on the rise in across the World, especially in the developed World
- According to **SEER** data- from 1973 to 2014- PC increased by 1.03% every year
- By 2030, it is expected to become the 2nd most common cancer

Incidence/Risk

- Life-time risk is <1%
- Higher male to female incidence ratio
- Highest age standardized incidence is in Europe and North America
- 90% of newly diagnosed patients are over 55 years of age (majority in their 7th and 8th decade of life)

Risk factors

Modifiable

- Smoking
- Alcohol/Chronic pancreatitis
- Obesity
- Dietary factors
- Helicobacter Pylori
- Periodontal disease
- Vitamin D
- Certain chemicals:
  - Heavy metals, Beta-naphthylamine, benzidine, pesticides, chlorinated hydrocarbons

Non-modifiable

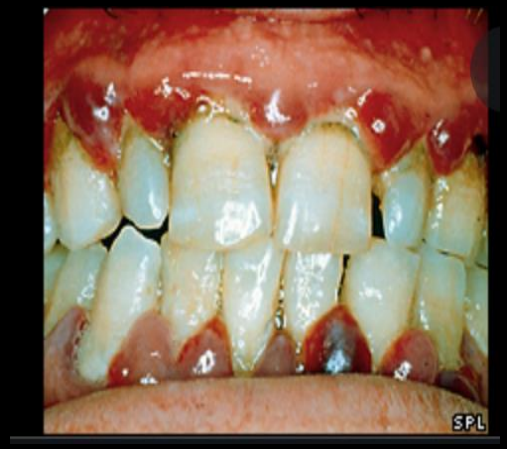
- Age
- Sex
- Ethnicity
- Genetic /familial risk

- **Word of caution** – due to low incidence and high mortality most of the evidence for the risk factors comes from case control studies

Modifiable Risk factors

- 74% increased risk in current (OR: 1.74, 95%CI: 1.61-1.87)
- 20% increased risk in former smokers
- The risk remains for at least 10 years
- The risk increased with both duration of smoking (> 50 years) and number of cigarettes smoked (> 30 cigarettes/d)

McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; 24(43): 4846-4861 [PMID: 30487695 DOI: 10.3748/wjg.v24.i43.4846]



- The RR for periodontitis and PC was 1.74 [95% CI 1.41-2.15]
- For Edentulism RR-1.54 (95% CI 1.16-2.05).

Modifiable risk factors

- **Alcohol:** 15-43% increased risk
  - This increased risk was strongest in heavy male drinkers and heavy drinkers of spirits.
  - Excessive alcohol consumption is also the main cause of chronic pancreatitis
- **Red meat:** variable association. 17% increased risk 50g/d vs 20g/d meat – further research needed
- **Vitamin D:** contradictory
- **Obesity:** positive association, for every 5 units of excess BMI- 10% increased risk
- **Helicobacter pylori-** negative association

McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; 24(43): 4846-4861 [PMID: 30487695 DOI: 10.3748/wjg.v24.i43.4846]

Modifiable risk factors

- Type II diabetics –risk is twice higher than normal
- 1% of diabetics >50 years or younger within 3 years of diagnosis
- For every 0.56mmol/l increase in FBS - 14% increased risk of PC
- Insulin/sulfonylureas increases/Metformin lower risk
- Metformin use improved 2-year survival (30.1% vs 15.4%) OS- 15.2m vs 11.1 m)
- Diabetics with PC vs Non-diabetics with PC 14.4 m vs 21.7 m

- **Diagnosis of diabetes in 50s with no risk factors- think about PC**
- **Diabetics with erratic blood sugars with no other cause-think about PC**

Non-modifiable risk factors

- **Age :**
  - PC is typically a disease of the elderly.
  - Rare for patients to be diagnosed before the age of 30
  - 90% of newly diagnosed patients are over 55 years of age (majority in their 7th and 8th decade of life)

- **Gender:**
  - **M**ales > females (Age-standardised rate 5.5 in males To 4.0 in females)

- **Ethnicity:** In USA - 50%-90% increased risk of PC in African-Americans

- **Blood group:** patients with blood group O < A < AB < B

Non-modifiable risk factors

Family history and genetic disorders

- 10% familial
- 80% familial - have no inherited genetic disorder

Family h/o/ & Syndrome	Risk	Gene
One 1st-degree relative	4.6-fold increase	
Two 1st degree relatives	6.6-fold increase	
Lynch syndrome	9 to 11-fold	MMR
Malignant-melanoma syndrome	20 to 47-fold	CDKN 2A
Breast-ovarian cancer syndrome	2to 6-fold	BRCA1/2
ATM	4% with PC	
Peutz-Jeghers syndrome	132-fold	STK11
Hereditary pancreatitis	26-to-87-fold	SPINK1, CFTR, PRSS1

Genetic counselling/screening

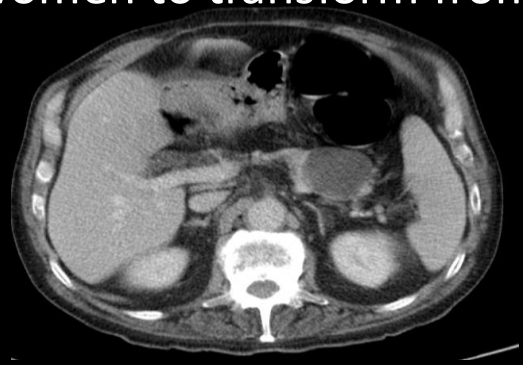
- **Routine screening is not indicated**
- **Screening**
  - Familial h/o pancreatic cancers
  - Young
  - Ancestral h/o- Ashkenzi Jewish family
- Screening methods
  - EUS and MRI/MRCP
  - CA19.9- may be elevated up to 2 years

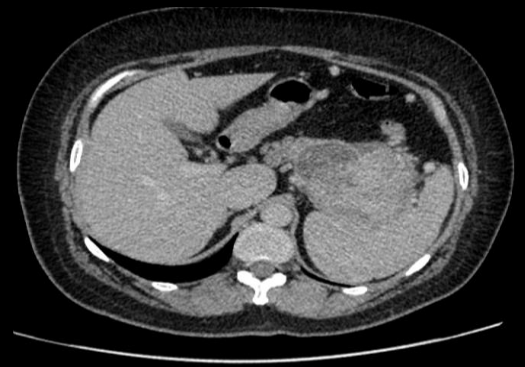
Pathology

- 90% ductal adenocarcinomas
- 60-70% in the head, rest body and tail
- 20% resectable
- **Variants:**
  - Signet ring
  - Acinar
  - Adenosquamous
  - Mucinous
  - Medullary, and hepatoid

Pathogenesis/Pre-malignant tumours

- Normal ducts to Low grade PanIN to high grade PanIN
- It will take 11.3 years for men and 12.3 years for women to transform from PanIN 3 to pancreatic adenocarcinoma
- **Pre-malignant lesions**
  - IPMN
  - MCN
- **Mucinous cystic neoplasms (MCN)**
  - 10-17.5% risk of malignancy
  - More common in females
  - Account for 25% cystic lesions going for resection



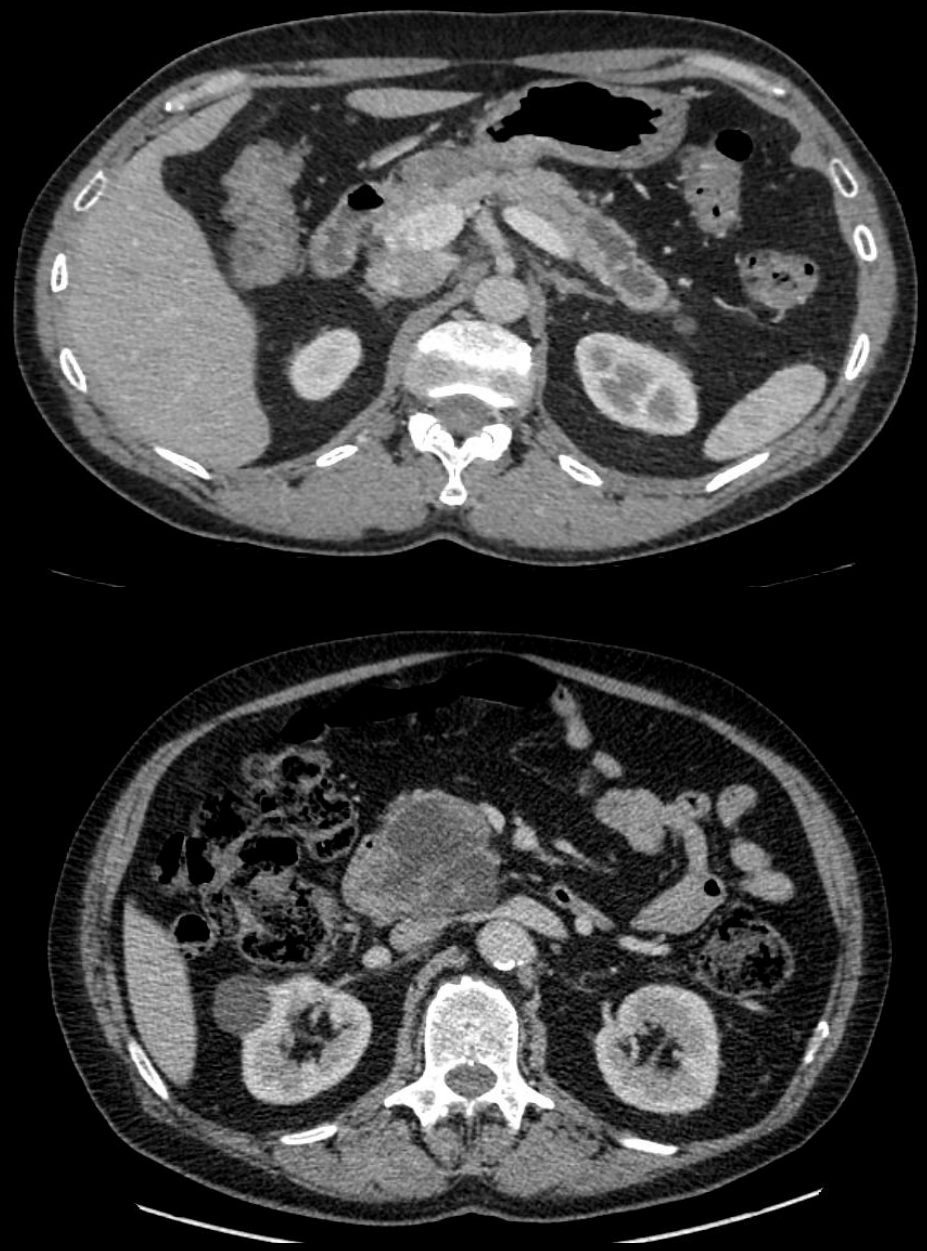


- McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; 24(43): 4846-4861 [PMID: 30487695 DOI: 10.3748/wjg.v24.i43.4846]

Pre-malignant lesions

- **IPMN:**
  - Sid branch/Main duct/Mixed
  - Can present with recurrent pancreatitis
  - Jaundice
  - Incidental

  - **High risk group:**
    - **Main duct type: >10mm PD – 60% chance of having underlying malignancy**
    - **Mixed duct**
    - **Side duct with mural nodules in the head of pancreas**
    - **h/o jaundice**



Diagnosis

- Often present late- multifactorial
- Only 20% resectable disease
- Low life-time risk (<1%)
- Routine Screening is not recommended
- High-risk groups should be offered screening

- Many people who were ultimately diagnosed with PC were falsely reassured by the intermittent nature of their symptoms over the preceding months.

- That many primary care physicians will only see a case every few years on average.

- One study found that - in primary care patients sought medical attention 18 times on average in the period preceding their pancreatic cancer diagnosis

Presentation

- Non-specific symptoms
- Weight loss, obstructive jaundice, steatorrhea
- **Recent onset of diabetes**
  - 50 years and above
  - No family h/o- diabetes
  - No risk factors for diabetes
  - Diabetics with erratic blood sugars/abdominal symptoms/steatorrhea/weight loss
- Chronic pancreatitis with ongoing pain /weight loss
- Iron deficiency anaemia
- Incidental
- **Gastric outlet obstruction**
- **Back pain**

Bio/Tumour markers

CEA/CA19.9/PAA/CA125/S100

CA19.9

- Blood group Lewis A antigen
- Best and most validated marker
- May be elevated in up to 2 years prior to diagnosis
- Shed by pancreatic and hepatobiliary malignant cells
- Non-specific
- Elevated in jaundice
- Useful as surveillance, prognostic, and treatment marker
- In Symptomatic patients -sensitivity 70 to 80% /specificity – 70 to 90%
- Low PPV- not a good screening tool

Differential diagnosis

- 50% peri-ampullary tumours are not pancreatic cancers
- Autoimmune pancreatitis
- Benign strictures from stone disease

Investigations

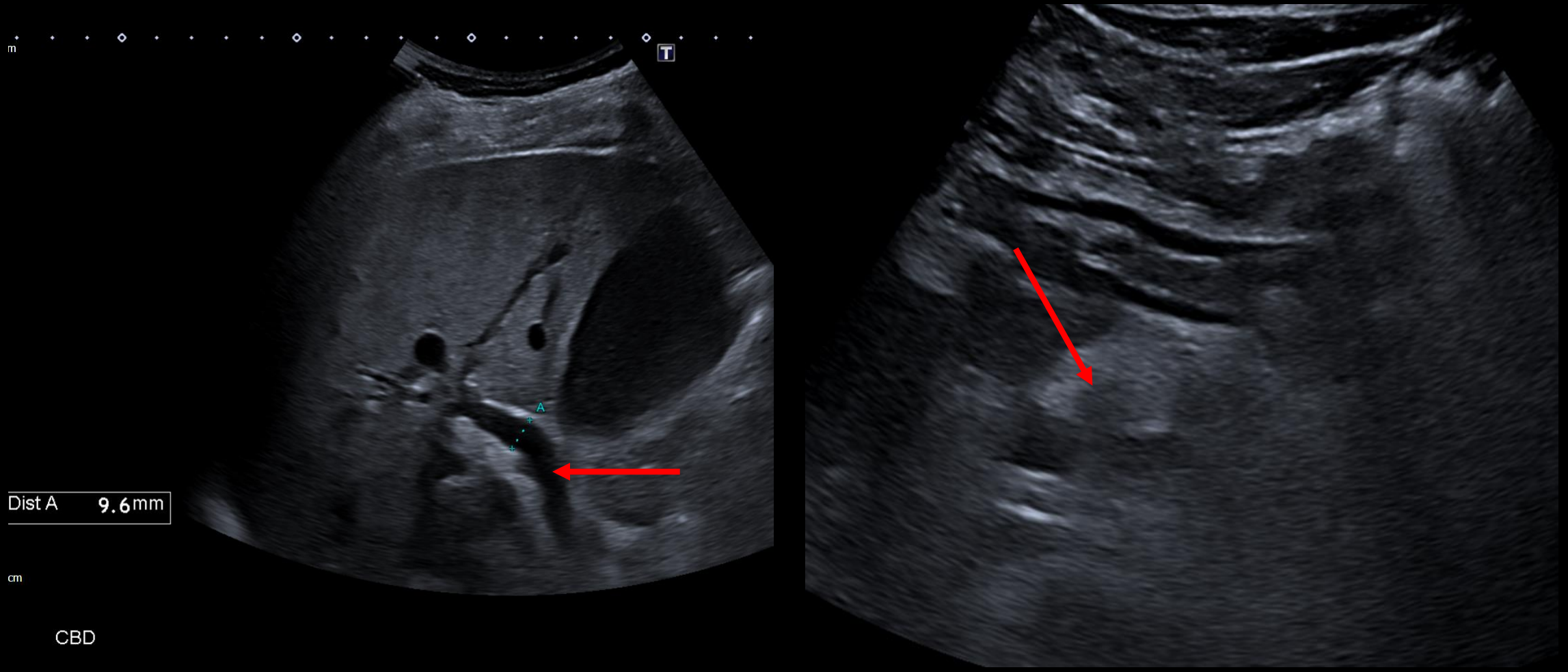
- Blood tests
- Tumour markers
- CT TAP with pancreatic protocol
- MRI
- EUS
- PET-CT
- Laparoscopy
- **Biopsy**

Imaging Journey. Patient X

- Patient referred via Primary or secondary care.

 - Painless Jaundice, deranged LFT's, upper abdominal pain, new onset DM, etc

- Primary care – first test USS.
- Secondary care – first test USS, "standard CT", or dedicated CT pancreatic protocol


m
T
A
Dist A 9.6mm
cm
CBD

- First test – USS ✓
- Next investigation – CT pancreatic protocol

CT pancreatic Protocol –

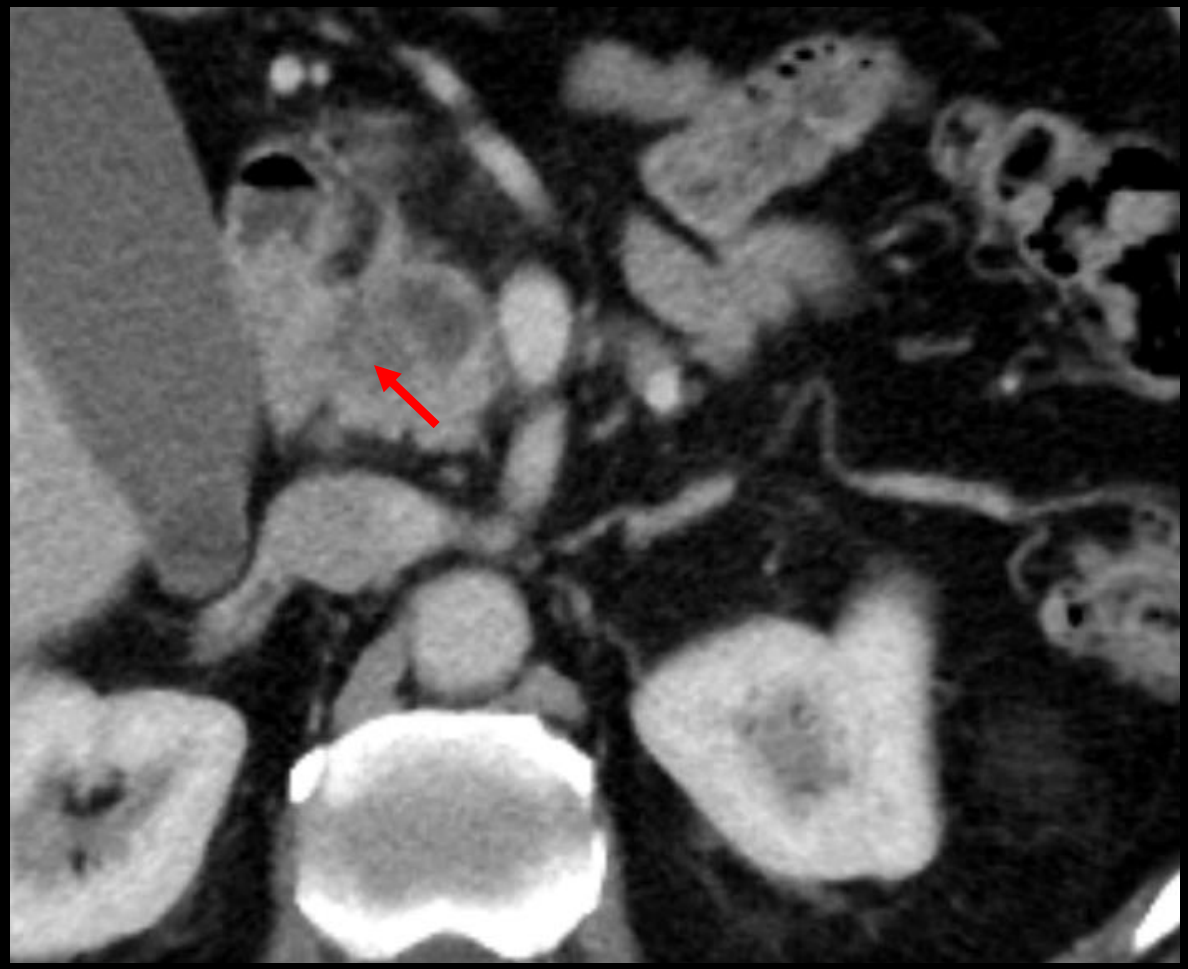
1000ml Water Oral Preparation

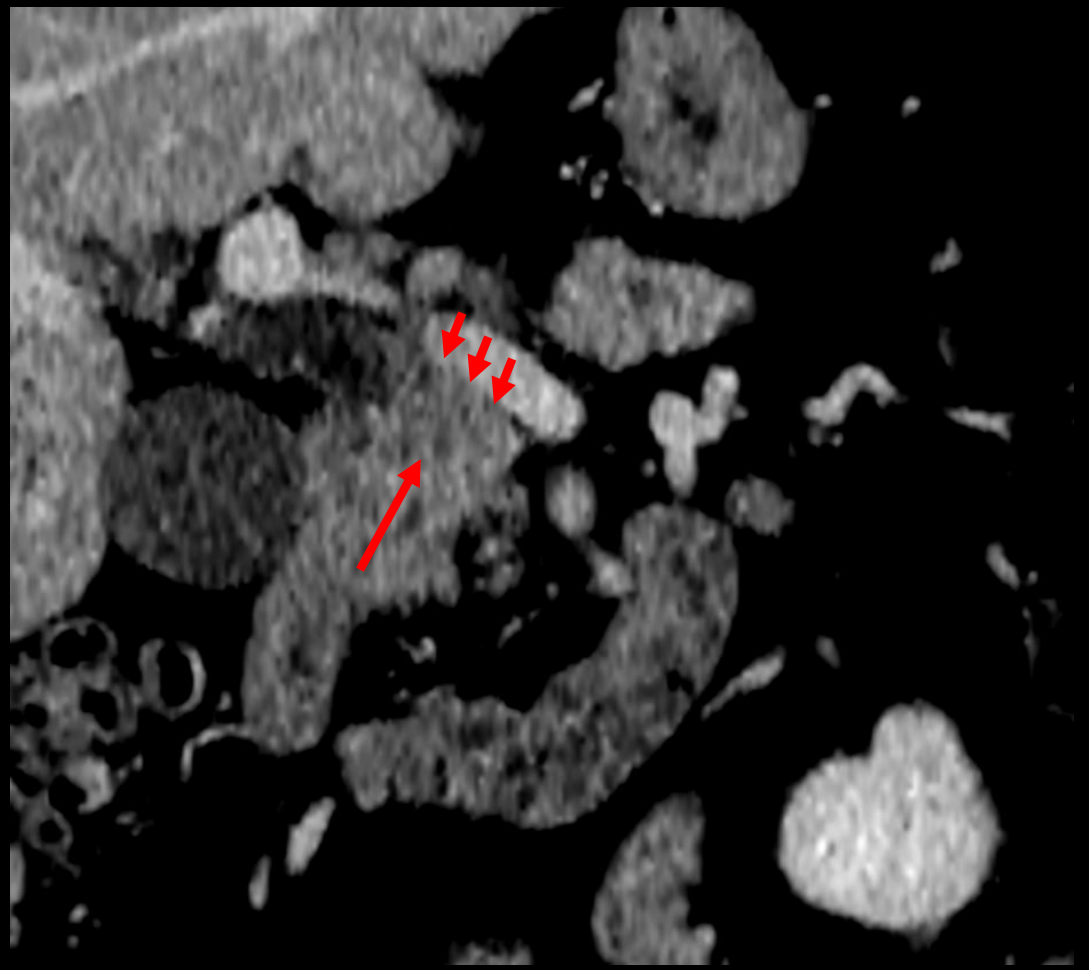
CT chest/abdomen – iv contrast 125ml 350 at 3.5ml/sec

- images obtained at 40 secs, slice thickness 1.25mm

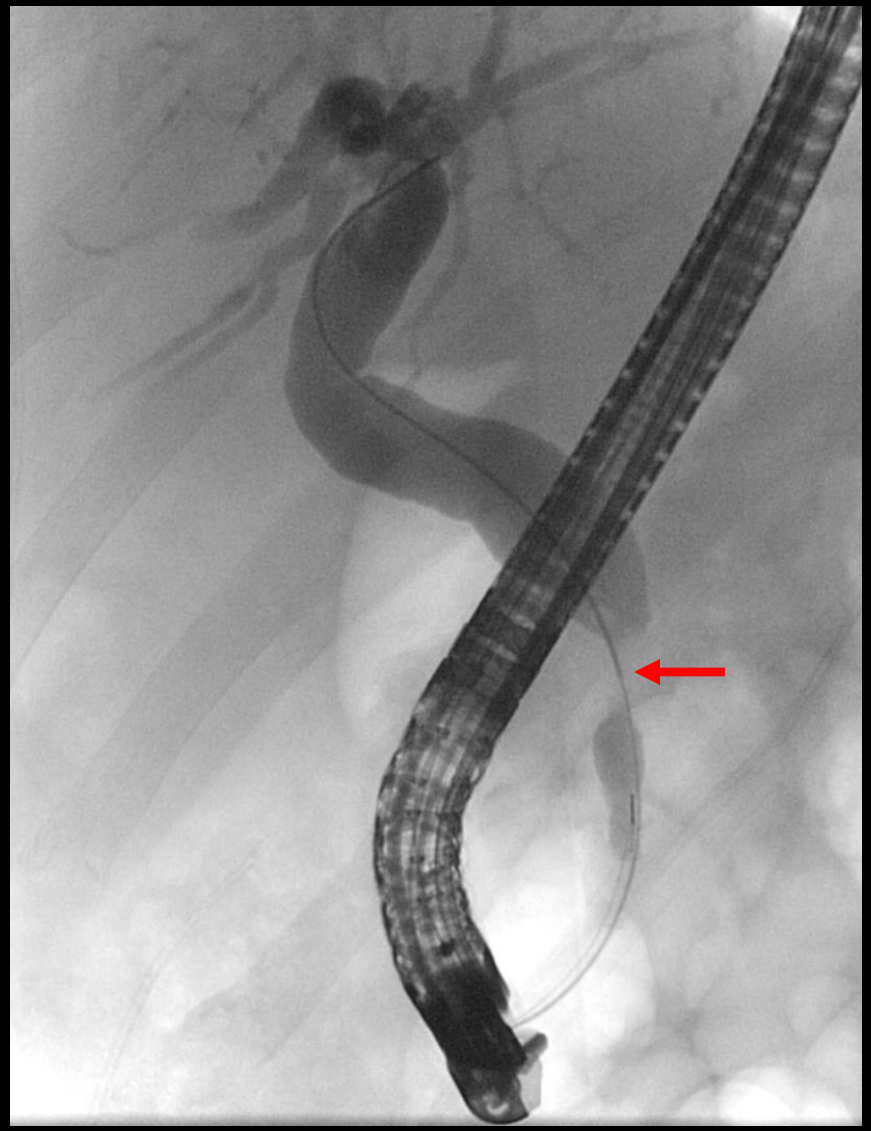
CT Abdomen/pelvis –

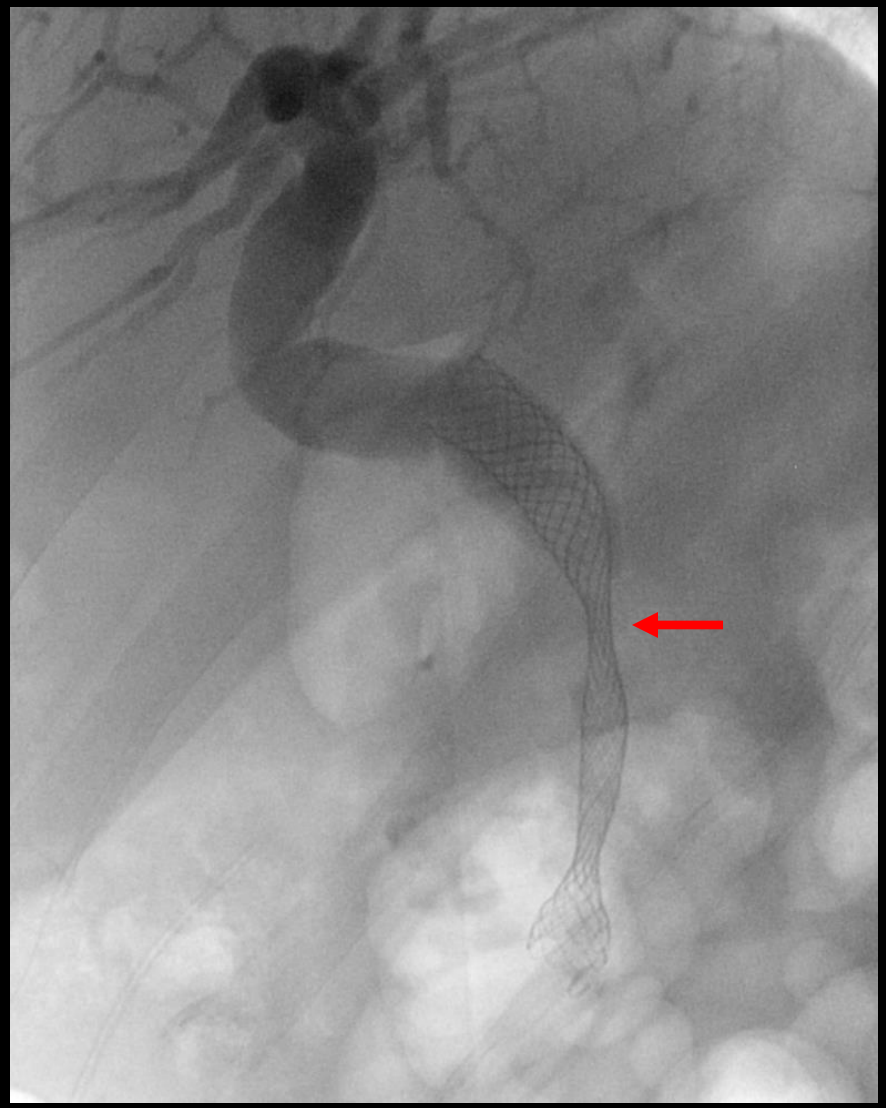
- images obtained at 70 secs, slice thickness 1.25mm

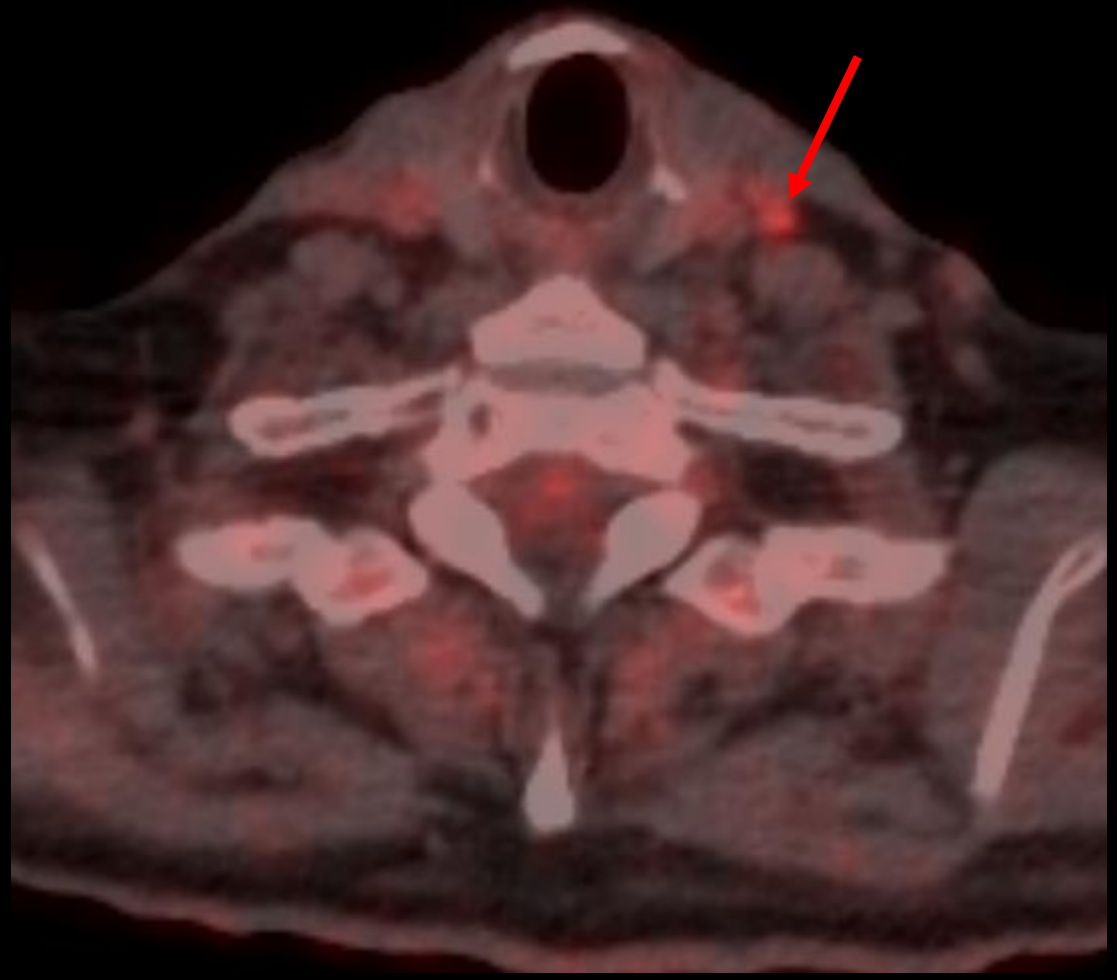


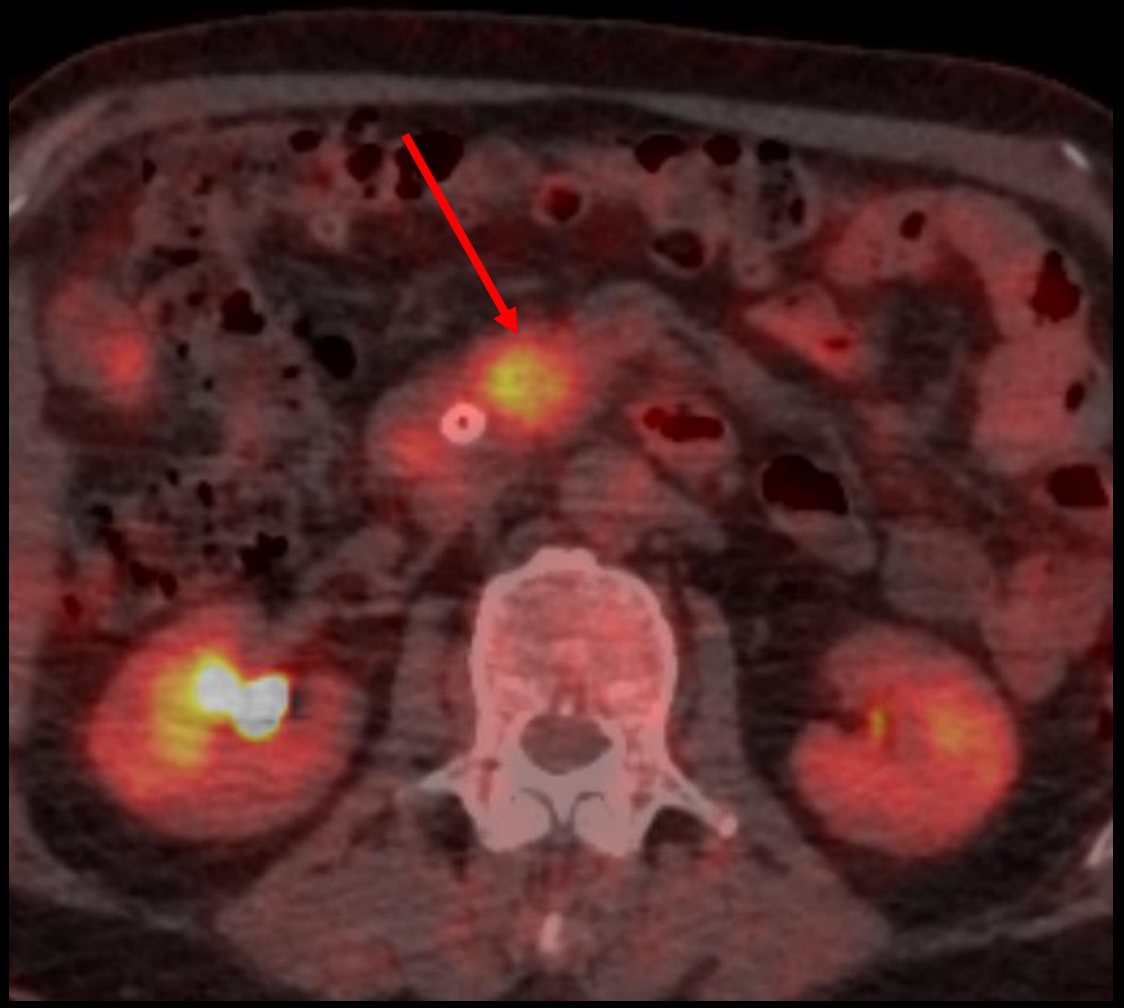


- First test – USS ✓
- Second test – CT pancreatic protocol ✓
- Third test – suspecting pancreatic cancer – need to make confirmatory diagnosis and relieve jaundice
    - ERCP – for relief of jaundice & histology
    - PET CT – for staging





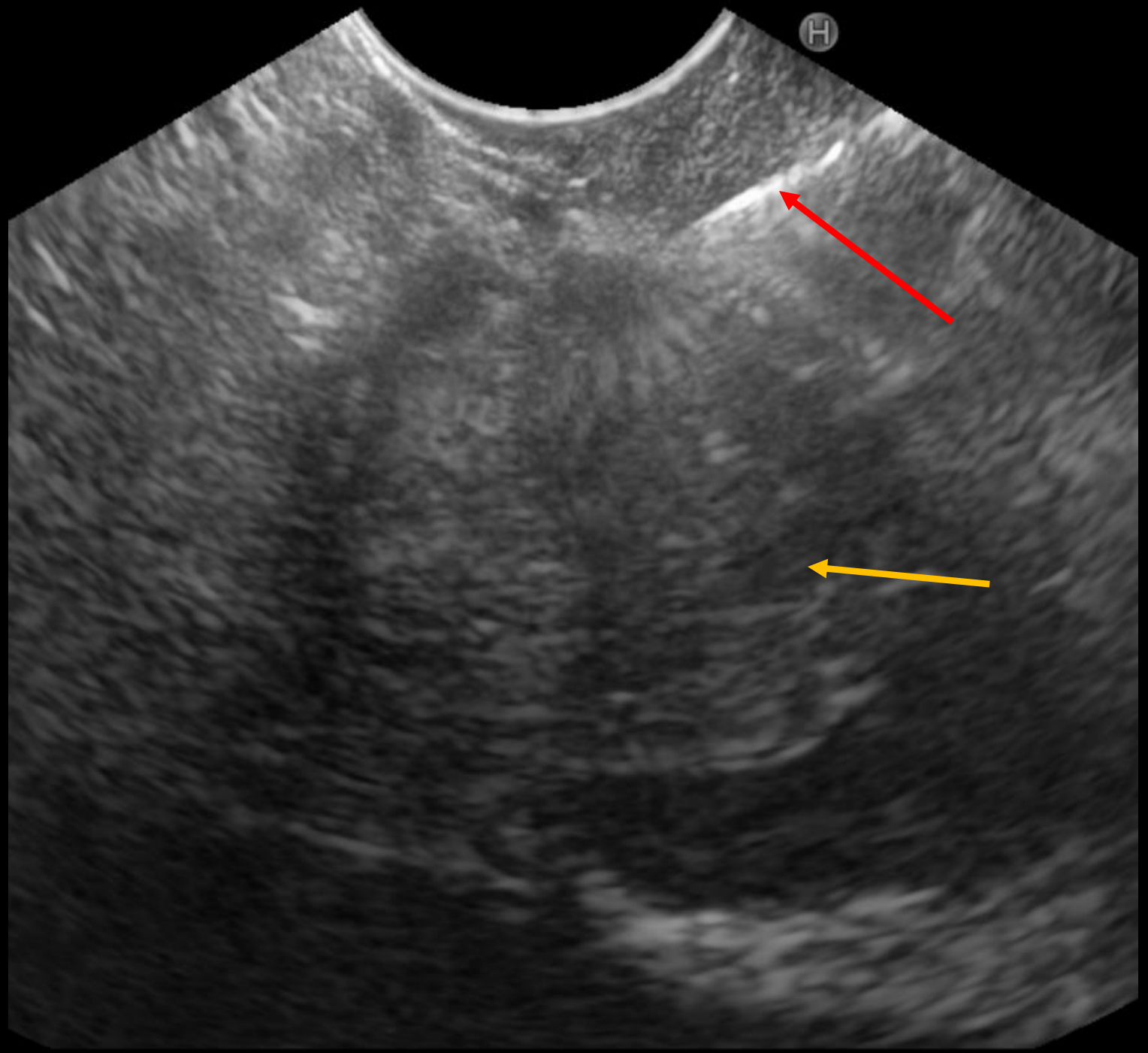




- First test – USS ✓
- Second test – CT pancreatic protocol ✓
- Third test(s) - ERCP – (jaundice relieved) ✓
  - PET CT ✓

ERCP brushings negative

- Fourth test(s) – USS FNA left supraclavicular lymph node
  - EUS FNA of pancreatic mass



- First test – USS ✓
- Second test – CT pancreatic protocol ✓
- Third test(s) - ERCP – (jaundice relieved) ✓
  - PET CT ✓

ERCP brushings negative

- Fourth test(s) – USS FNA left supraclavicular lymph node ✓
  - EUS FNA of pancreatic mass ✓

Histology from Left supraclavicular lymph node – negative
Histology from pancreatic mass – positive

Diagnosis ✓

Requires staging -

Staging: Pancreatic Adenocarcinoma

- AJCC 2017 8th edition
- Size based for the tumour. Staged with CT and PET
- Resectability controversial

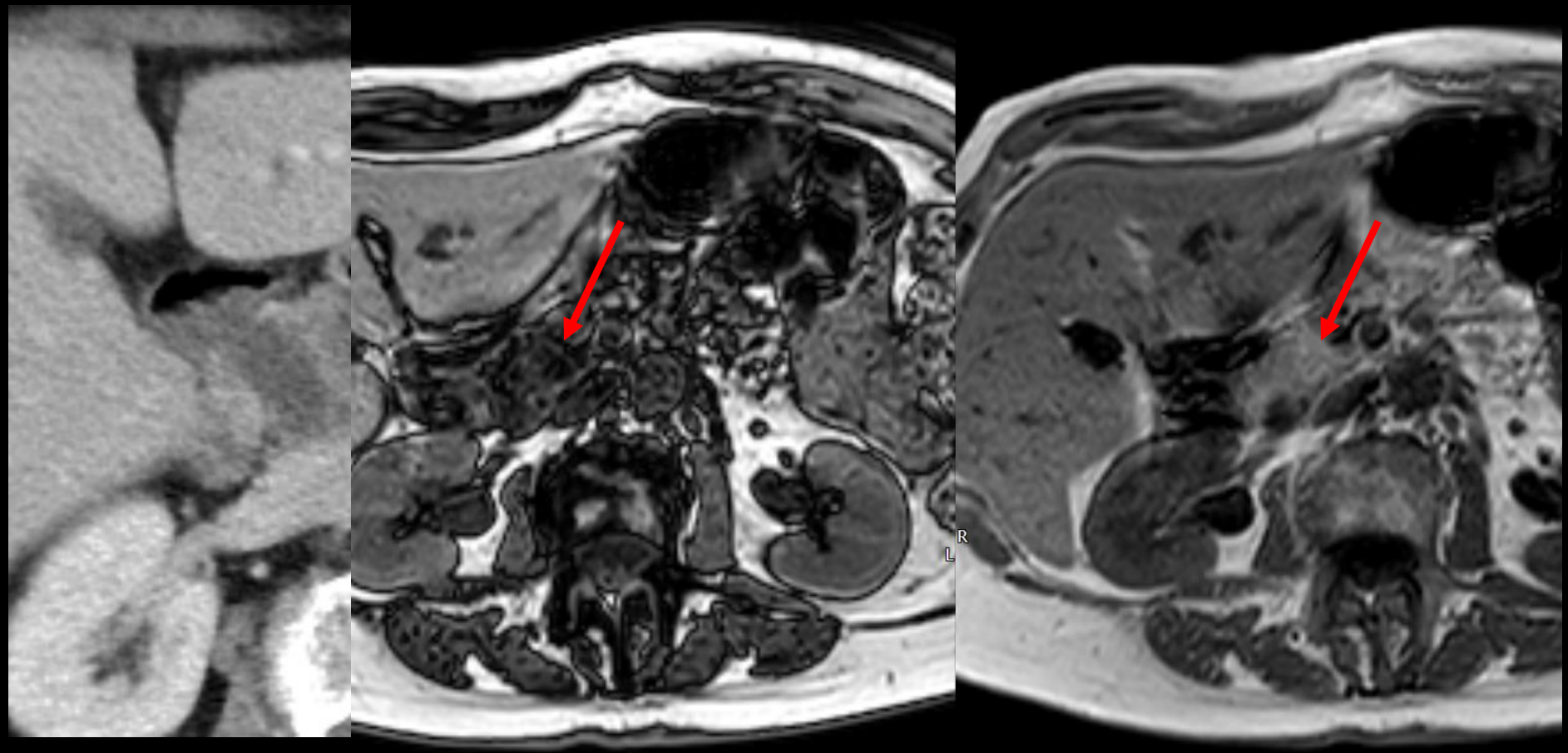
T1: Tumour <2cm (greatest diameter)
T2: Tumour >2cm (greatest diameter) but less than 4cm
T3: Tumour >4cm (greatest diameter)
T4: involvement of superior mesenteric artery or coeliac axis

N0: No nodes
N1: 1-3 regional nodes present
N2: 4 or more nodes present

M0: No metastases
M1: Distant metastases

So patient X – Staging T2 N0 M0
(but is it resectable??)

Role of MR in staging – currently none.
- main use is problem solving in making diagnosis



Questions ?

Summary

- The incidence of PC is on the rise
- Early diagnosis and treatment are the best ways to improve survival
- New onset of diabetes in >50yrs with no risk factors –think about PC
- Vague abdominal symptoms with weight loss- think about PC
- Think about modifiable risk factors to reduce/prevent PC
- High risk groups should be offered screening