PANCREATIC INCIDENTALOMA

TAKE it or LEAVE it?

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“Asymptomatic lesion detected incidentally by an imaging or other diagnostic test”

INTRODUCTION

- First report of pancreatic incidentaloma (PI) was published in 2001 by Kostiuk
- Increasing in number, increasing use of imaging
- Comprise between 6-23% of all pancreatic surgical resections

Kostiuk TS, Klin Khir 2001;9:62-63
Kent TS, World J Gastrointest Surg 2010;27:319-323

- Incidentally found during the evaluation of
  - Genitourinary and renal symptoms (61%)
  - Asymptomatic abnormal liver function tests (13%)
  - Screening or surveillance (7%)

Sachs T, J Gastrointest Surg 2009;13:405-415

- Equal distribution of solid to cystic lesions (48% vs 52%)
- Located in the distal pancreas 56% and in the head 44%
- Nearly 12% had no pancreatic lesions

Lahat G, J Am Coll Surg 2009;209:313-319
Sachs T, J Gastrointest Surg 2009;13:405-415

Solid mass	Cystic mass
Exocrine	Inflammatory
Ductal adenocarcinoma	Pseudocyst
Serous cystic tumor	Retention cyst secondary to chronic pancreatitis or trauma
Mucinous cystic tumor	Congenital/hereditary
Solid pseudopapillary mucinous tumor	Simple or solitary true cyst
Acinar cell carcinoma	Polycystic disease
Anaplastic carcinoma	Infection
Pancreatoblastoma	Tuberculosis
Endocrine	Neoplastic
Insulinoma	Inherently cystic
Gastrinoma	Serous cystadenoma
Glucagonoma	Mucinous cystic neoplasm
VIPoma	Solid neoplasm with cystic degeneration
Somastatinoma	Solid pseudo-papillary tumor
Non-hyperfunctioning tumor	Cystic pancreatic endocrine tumor
Non-epithelial tumor	Intraductal neoplasm
Lymphoma	Intraductal papillary mucinous neoplasm
Teratoma	Miscellaneous
Lymphangioma	Lymphoepithelial cyst of the pancreas
Lipoma	
Neural tumor	
Ectopic spleen	
Secondary tumors	
Autoimmune or groove pancreatitis	
Metastasis	

Conrad C, J Surg Oncol 2013;107:23-32

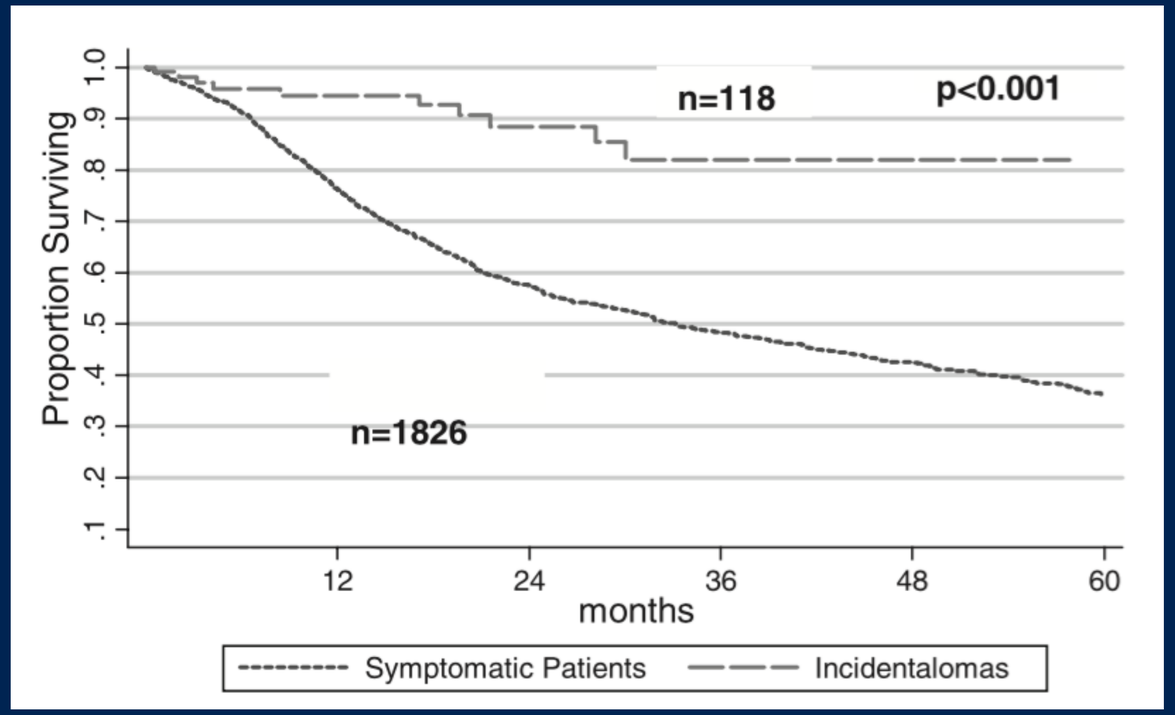
Periampullary and Pancreatic Incidentaloma

A Single Institution's Experience With an Increasingly Common Diagnosis

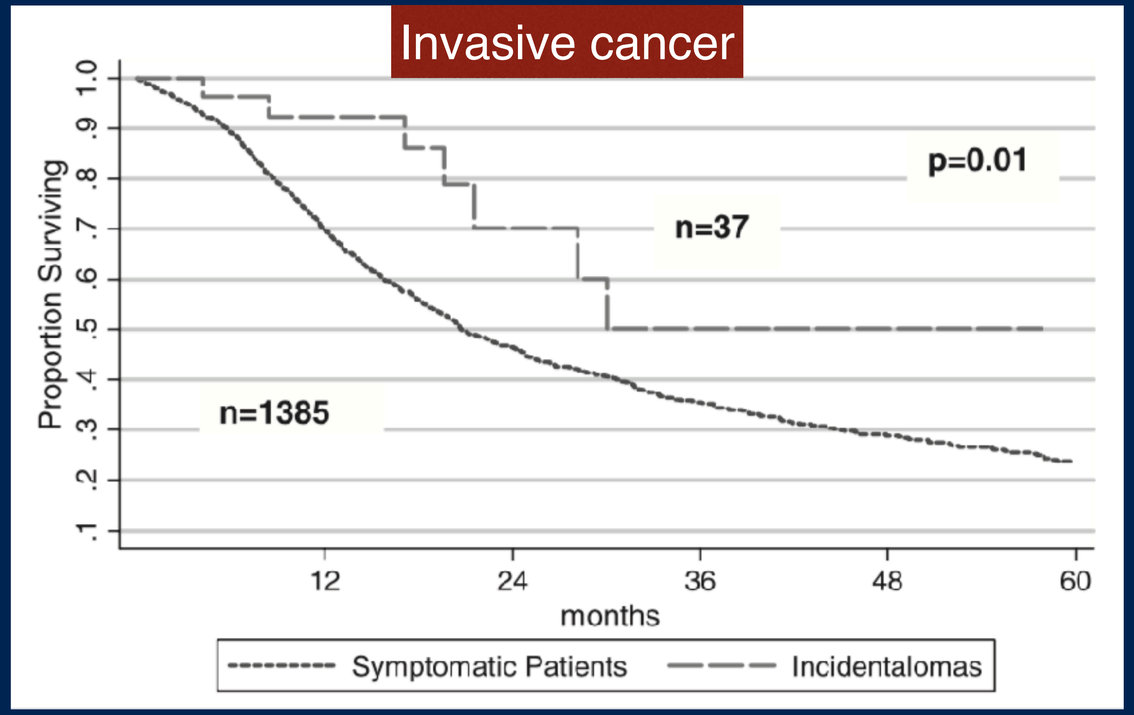
Jordan M. Winter, MD, John L. Cameron, MD,* Keith D. Lillemoe, MD,‖ Kurtis A. Campbell, MD,* David Chang, PhD,* Taylor S. Riall, MD,§ JoAnn Coleman, CRNP,* Patricia K. Sauter, CRNP,¶ Marcia Canto, MD,† Ralph H. Hruban, MD,‡ Richard D. Schulick, MD,* Michael A. Choti, MD,* and Charles J. Yeo, MD¶*

- Review of 1,944 PD (118 patients are PI)
- 31% were malignant and 47% were premalignant
- 30% IPMN, 17% MCN, 10% PDAC
- Surgery improved survival, compare with patients with symptomatic disease

Winter JM, Ann Surg 2006;243:673-683



1, 2, and 5-year survival rate
PI group were 95%, 88% and 68%
NI group were 76%, 56% and 36%



1, 2, and 5-year survival rate
PI group were 93%, 70% and 50%
NI group were 70%, 46% and 23%

Winter JM, Ann Surg 2006;243:673-683

Pancreatic Incidentalomas: High Rate of Potentially Malignant Tumors

Guy Lahat, MD, Mendy Ben Haim, MD, Ido Nachmany, MD, Ronen Sever, MD, Arye Blachar, MD, Richard Nakache, MD, Josef M Klausner, MD

- Retrospective study of 475 pancreatectomies, 64 PI
- 34% were malignant and 60% were premalignant
- IPMN was the most common
- Resection of these early tumours is associated with improved survival, as compared with symptomatic patients

Lahat G, J Am Coll Surg 2009;209:313-319

The Incidental Asymptomatic Pancreatic Lesion: Nuisance or Threat?

Teviah Sachs · Wande B. Pratt · Mark P. Callery · Charles M. Vollmer Jr.

- Premalignant lesions 47%

- Malignancy 24%

Sachs T, J Gastrointest Surg 2009;13:405-415

- Majority have at least premalignant
- Surgical resection is required
- Early treatment achieve a higher cure rate and prolonged survival
- Chronic pancreatitis accounts for almost 70% of the benign lesions

INVESTIGATIONS

BIOMARKERS

RADIOLOGY

ENDOSCOPY

INVESTIGATIONS

BIOMARKERS

RADIOLOGY

ENDOSCOPY

CARBOHYDRATE ANTIGEN 19-9 (CA19-9)

- Sensitivity 70%, specificity 87%
- Should be interpreted after biliary decompression
- Measurement of recurrent after resection
- Lack of CA 19-9 response to chemotherapy was the strong negative predictor of survival

Fong ZV, Cancer J 2012;18:530-538

CHROMOGRANIN A

- Assist in the diagnosis of a neuroendocrine tumour
- Secreted by either function or non-function tumours
- False-positive can result from decreased renal function, treatment with PPIs and essential hypertension

Nobels FR, Eur J Clin Invest 1998;28:431-440

IMMUNGLOBULIN G4 (IgG4)

- Marker for autoimmune pancreatitis (AIP)
- IgG4 found 95% in AIP and 10% in PDAC
- Useful as a marker of efficacy of steroid treatment

Frulloni L, N Engl J Med 2009;361:2135-42

NOVEL SERUM MARKER

- Distinguish a malignant lesion from benign
- Greater sensitivity and specificity than CA19-9
- Combined biomarker panels could maximise diagnostic sensitivity and specificity

Biomarkers in Pancreatic Cancer

Biomarker Category	Subfocus	Examples
Diagnostic	Gene expression	KRAS, FANCI, CASP8, S100P
	Proteomics	CA-19-9, CA-125, CEA, intercellular adhesion molecule 1, OPG, TIMP-1
	Micro-RNAs	MiR-21, MiR-210, MiR-155, MiR-196a, MiR-100a
Prognostic	Gene expression	MUC 1, MSLN, FOSB, KLP6, NFKB12, ATP4A, GSG1, SIGLEC11, SMAD4
	Circulating tumor cells	CEA-mRNA
Predictive	Gemcitabine	HuR, HENT1, RRM1, ERCC1
	nab-Paclitaxel	SPARC
	PARP inhibitors	BRCA2, PALB4, FANCC, FANCG
	Mitoxantrone	USP-11

Fong ZV, Cancer J 2012;18:530-538

CIRCULATING TUMOUR CELLS (CTCs)

- Exist in the peripheral blood of cancer patients
- Can be present as low as one per 10 million normal blood cells
- Methods with sufficient sensitivity are not currently available

Liang JJ, Int J Clin Exp Pathol 2009;2:1-10

INVESTIGATIONS

BIOMARKERS

RADIOLOGY

ENDOSCOPY

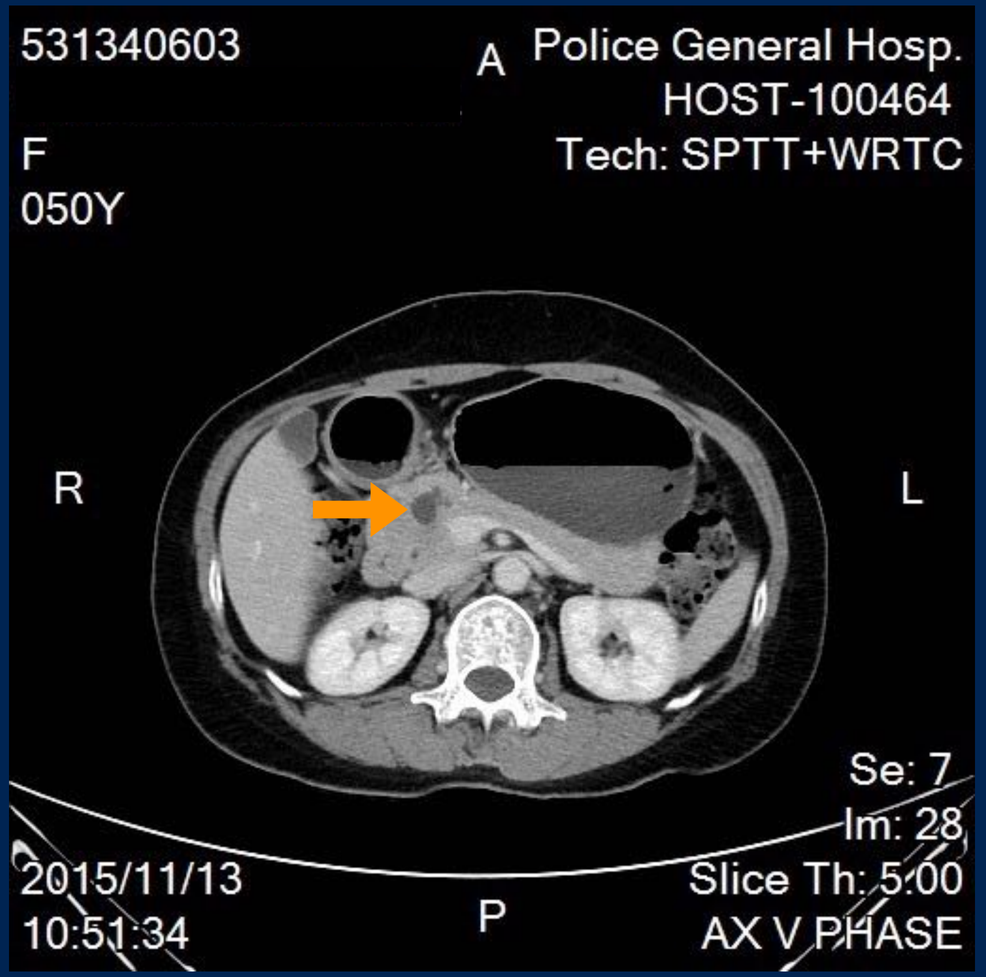
ULTRASONOGRAPHY

- Initial diagnostic tool, non-invasive, cost-effective
- Highly operator dependent
- Typical characteristics for PDAC
  - Hypoechoic mass
  - Dilatation of the pancreatic duct or bile duct

Lee ES, World J Gastroenterol 2014;20(24):7864-7877

COMPUTER TOMOGRAPHY (CT)

- Gold standard for pancreatic parenchymal imaging
- Pancreatic protocol: arterial and venous phases in 1 mm slice thickness
- Equivocal between inflammatory and neoplastic characteristics in lesions <2 cm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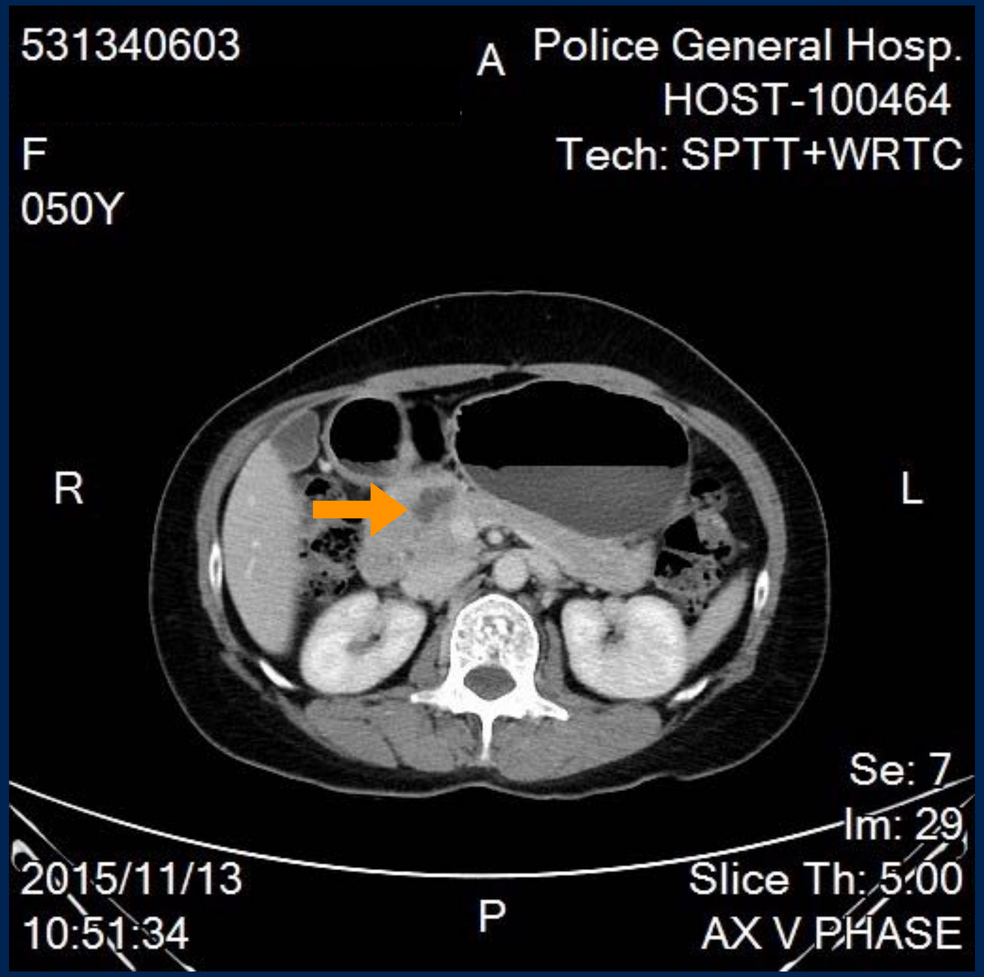
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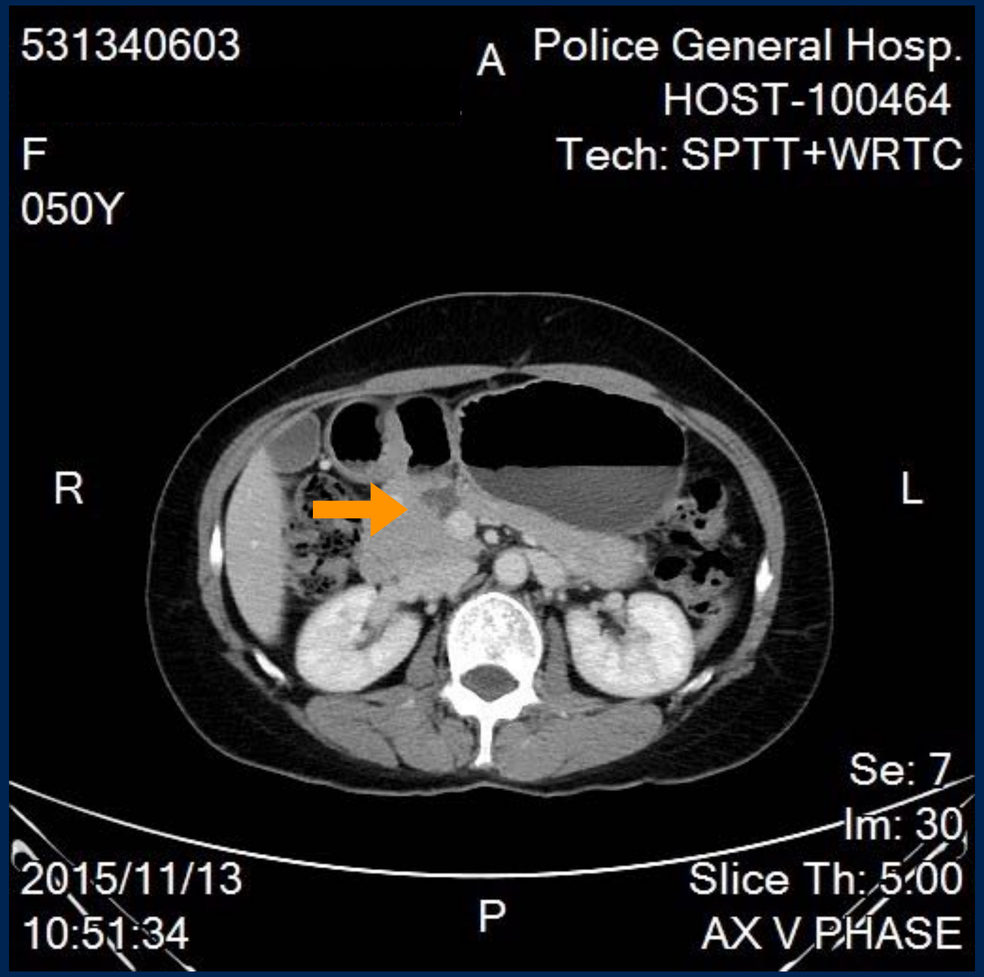
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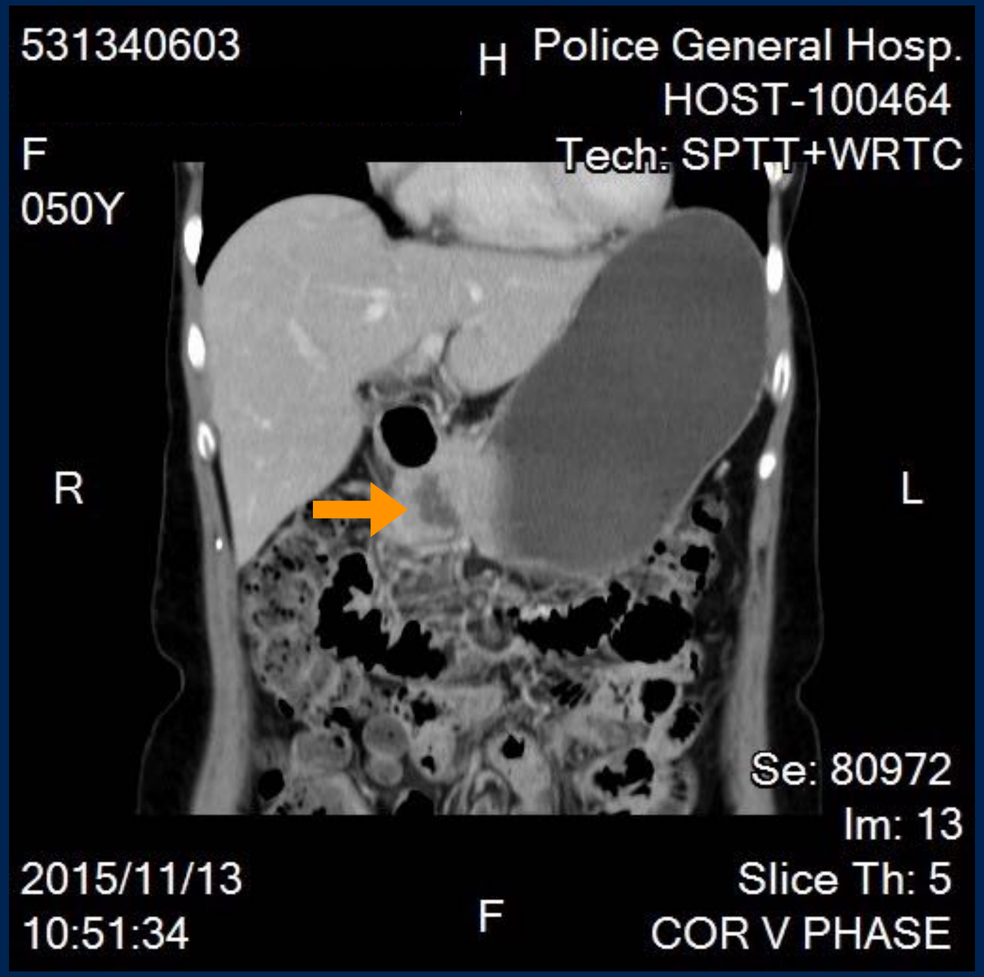
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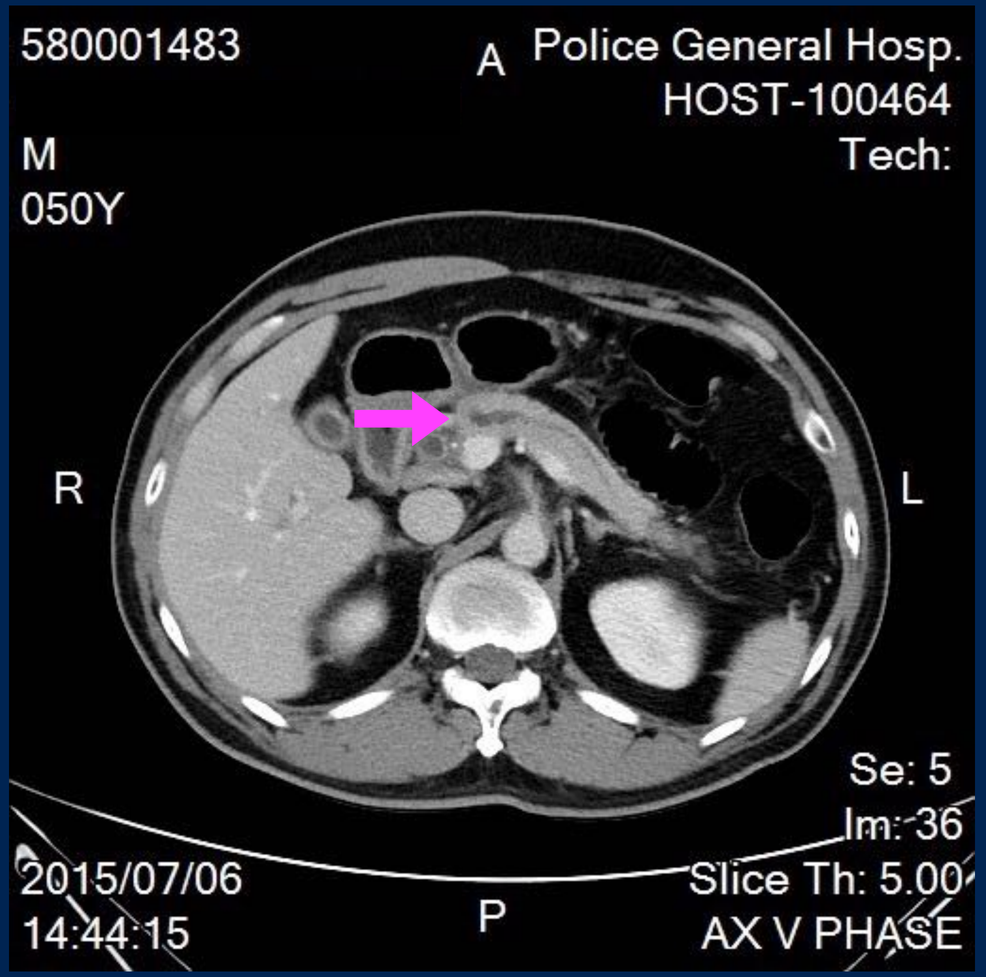
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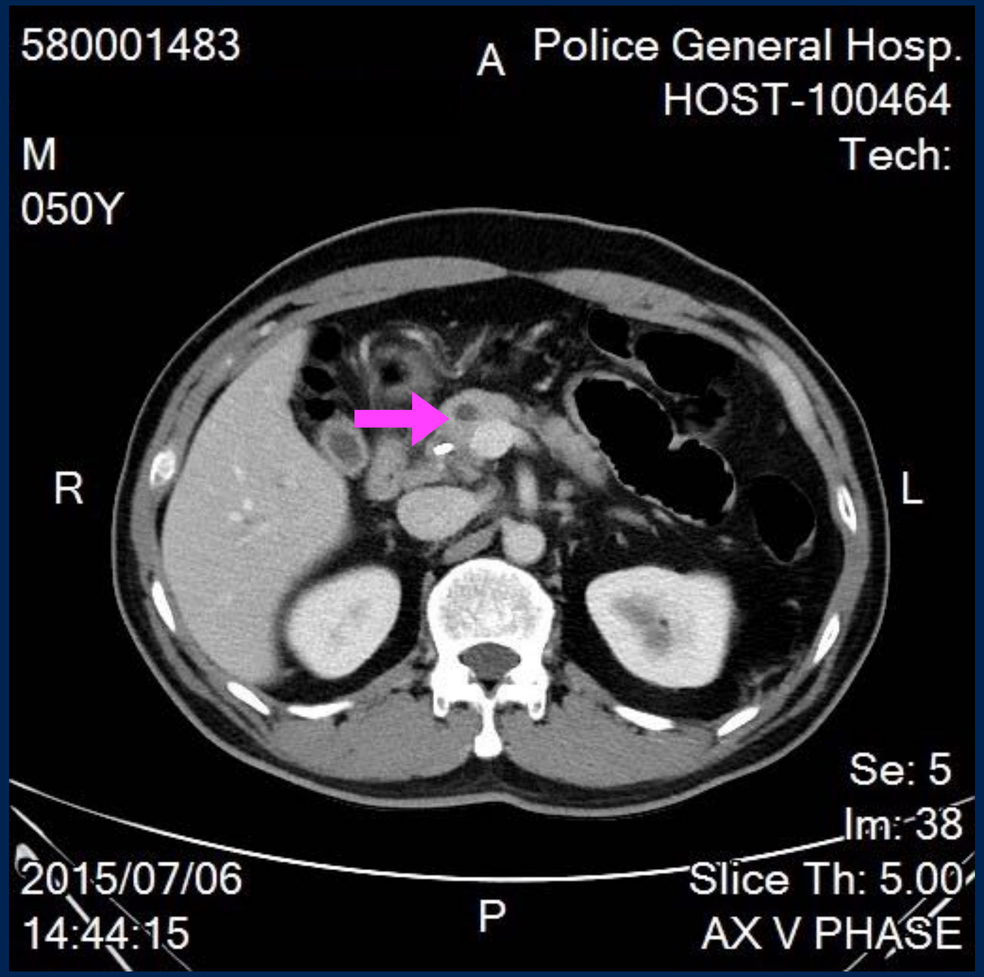
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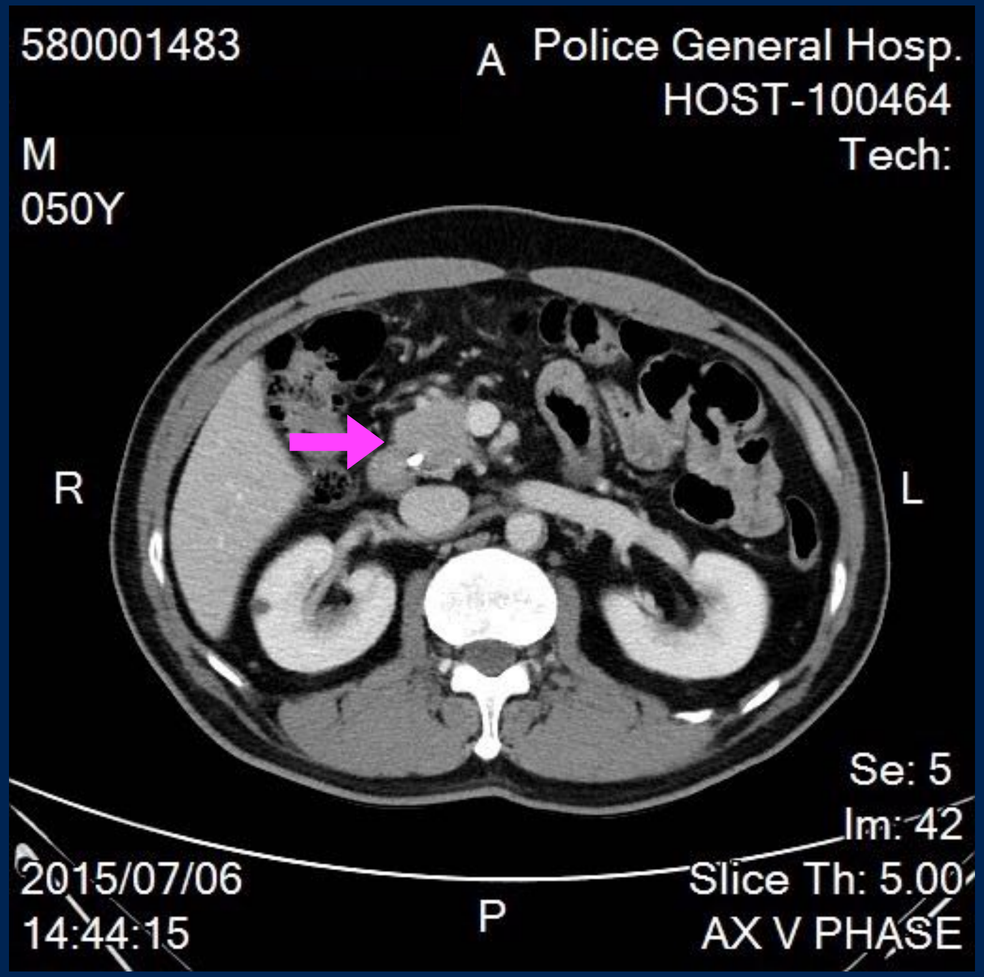
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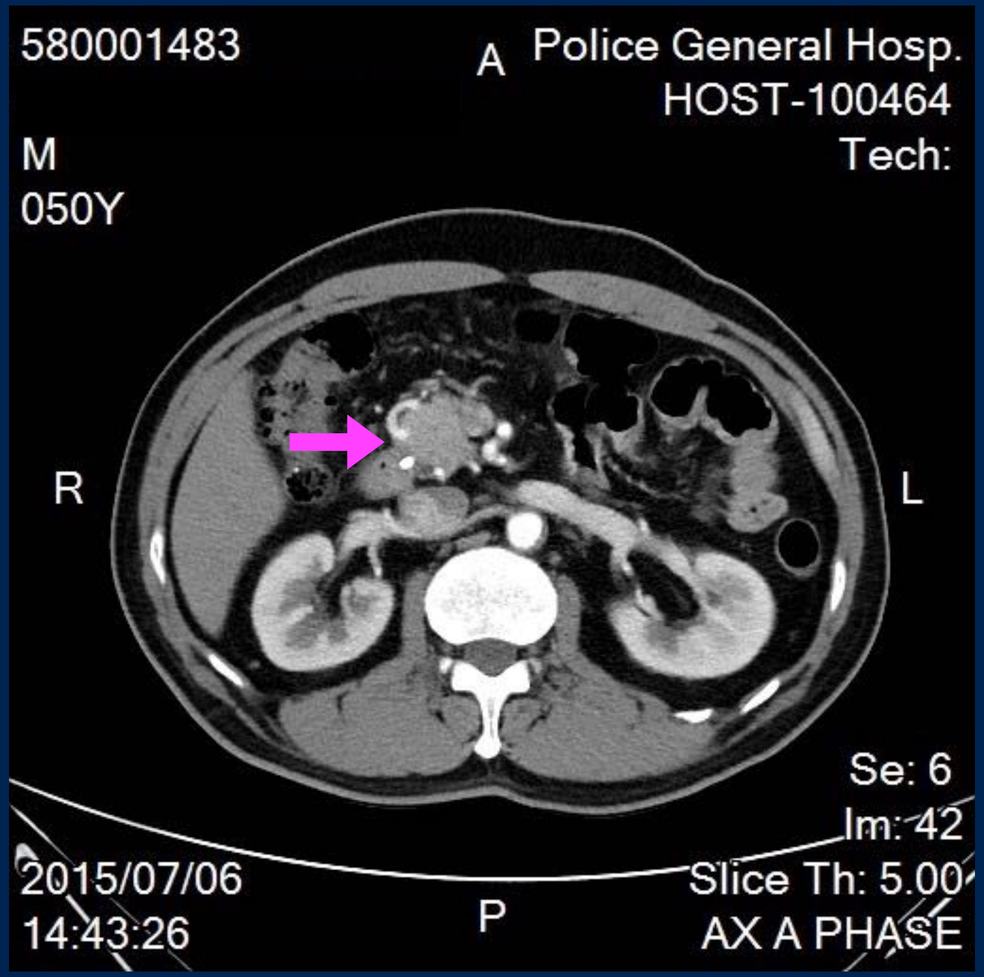
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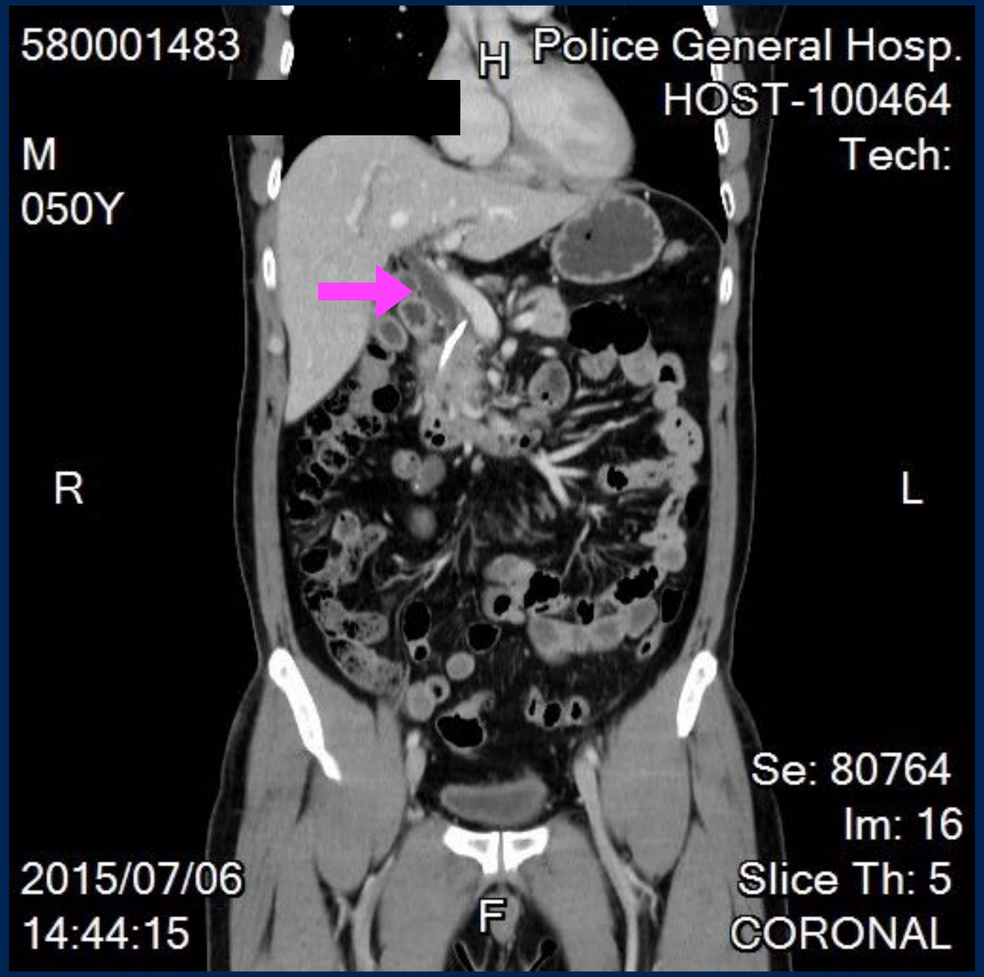
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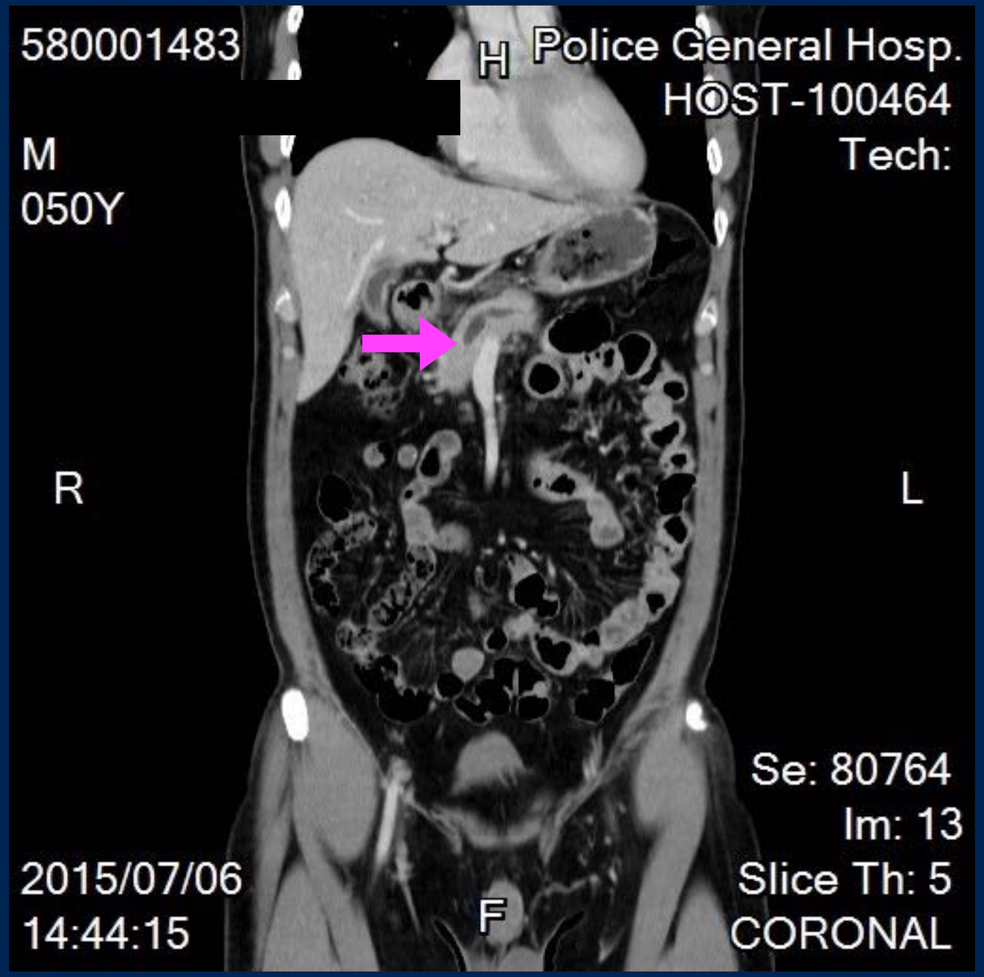
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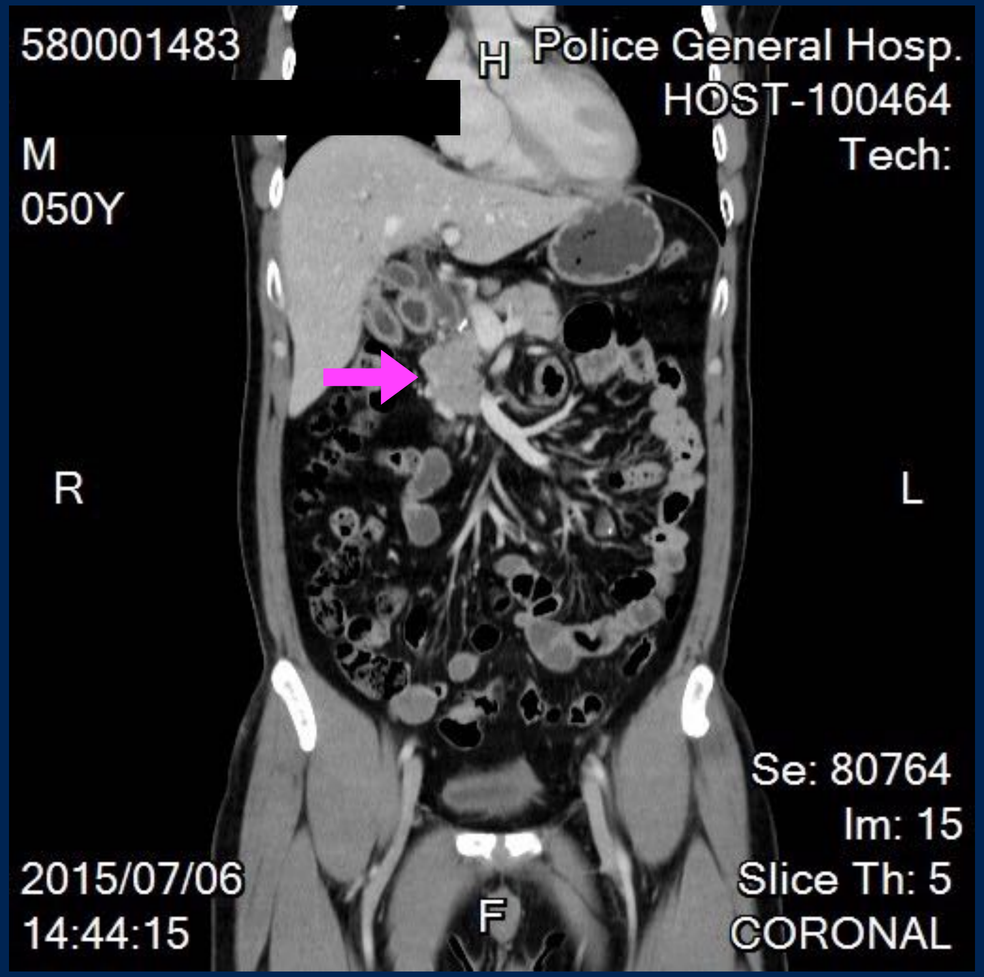
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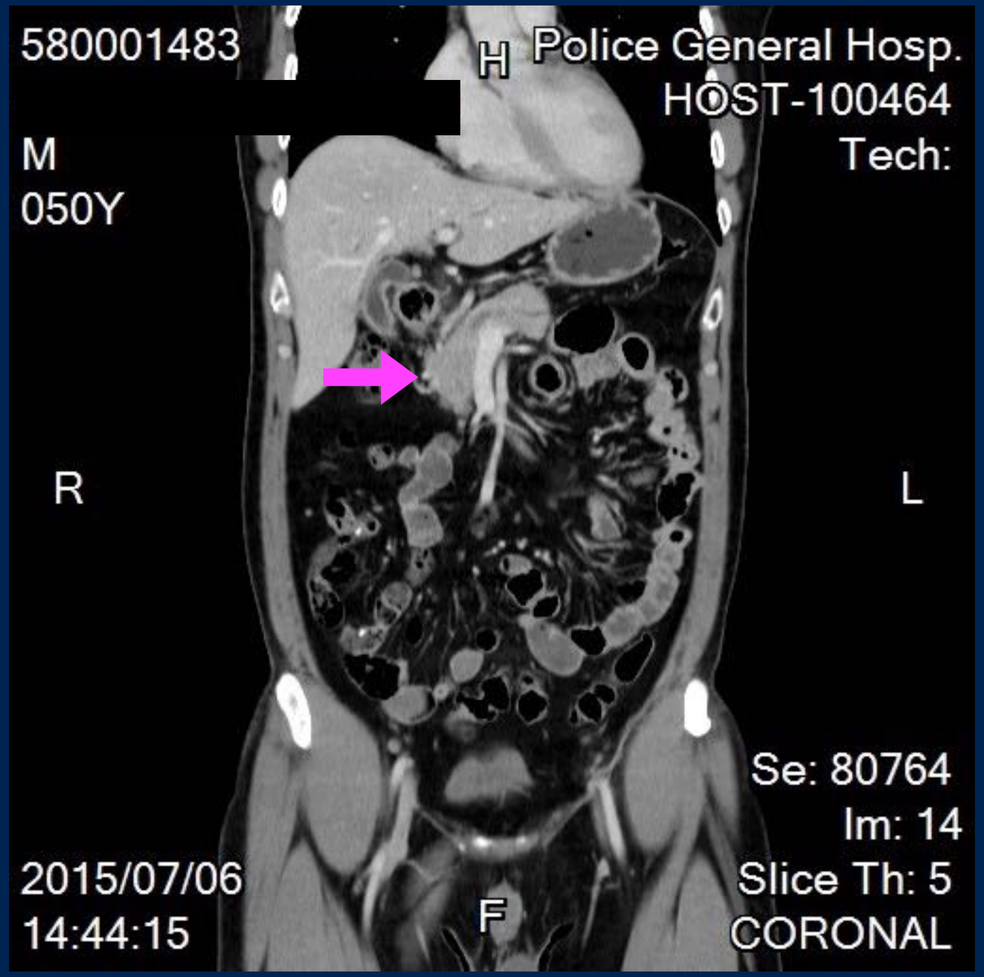
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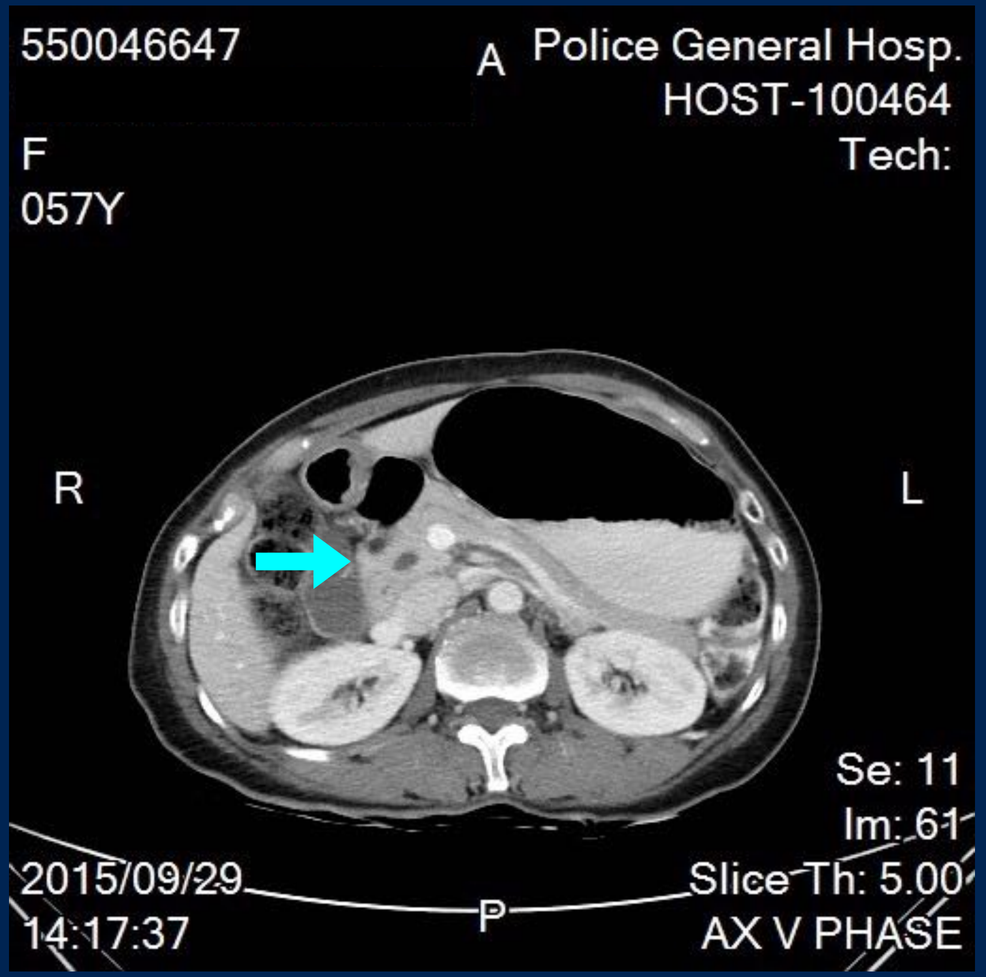
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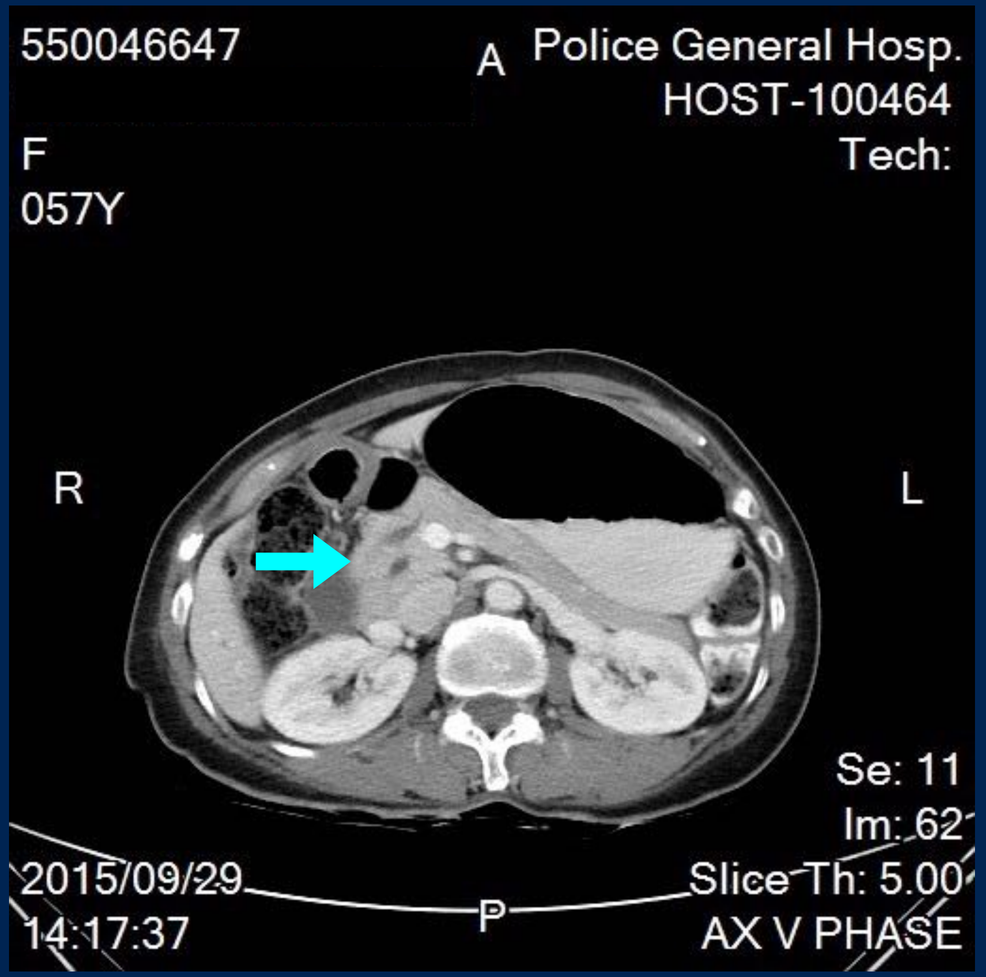
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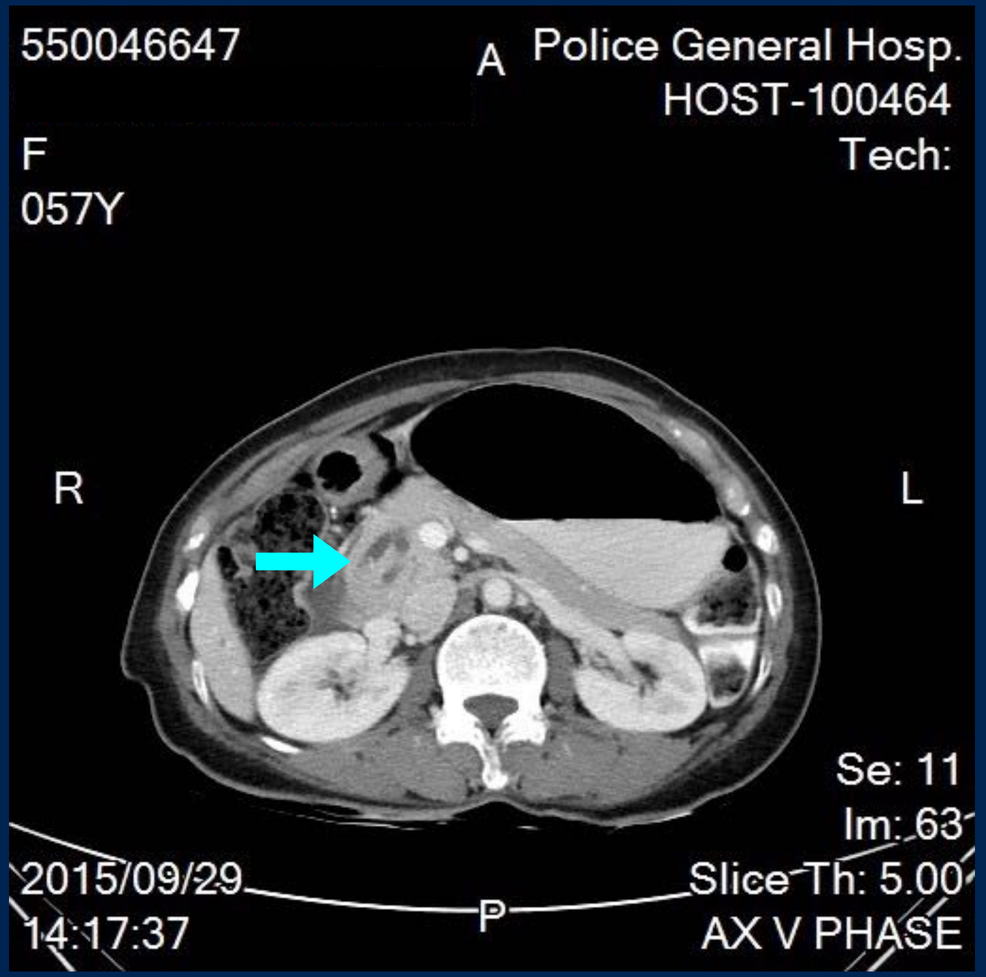
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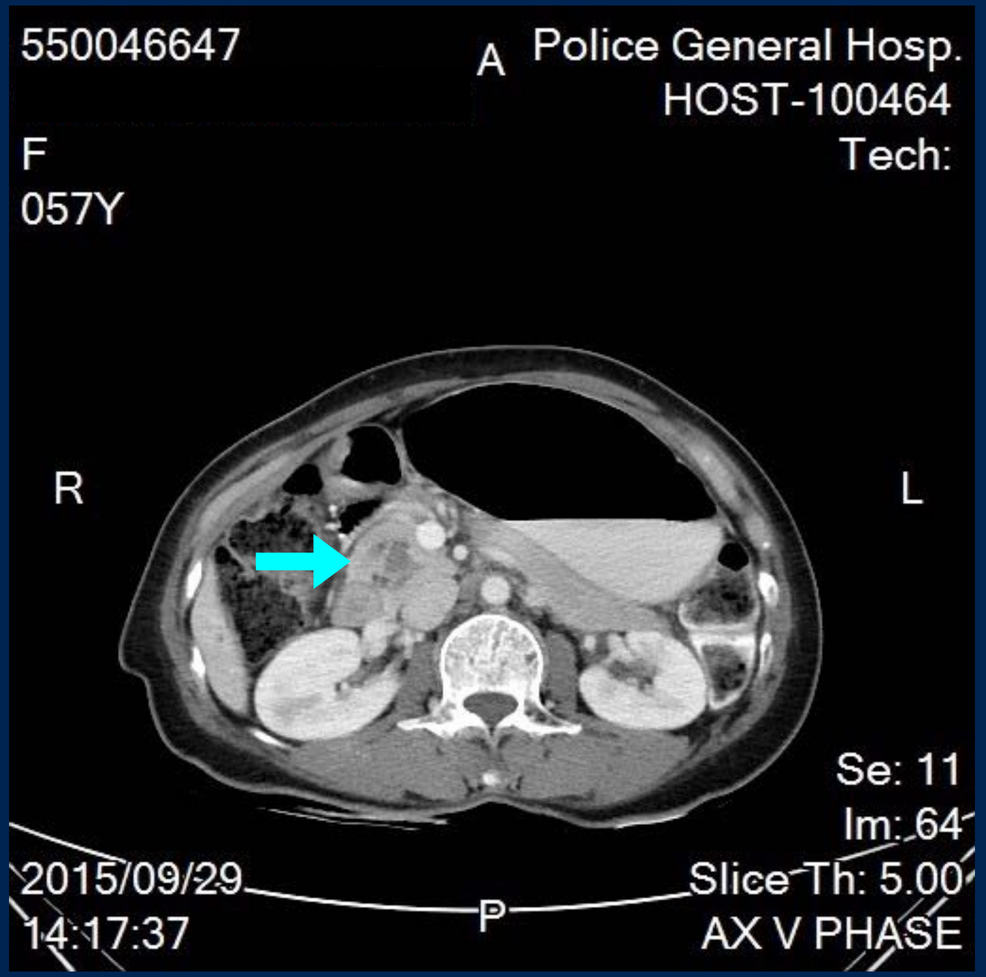
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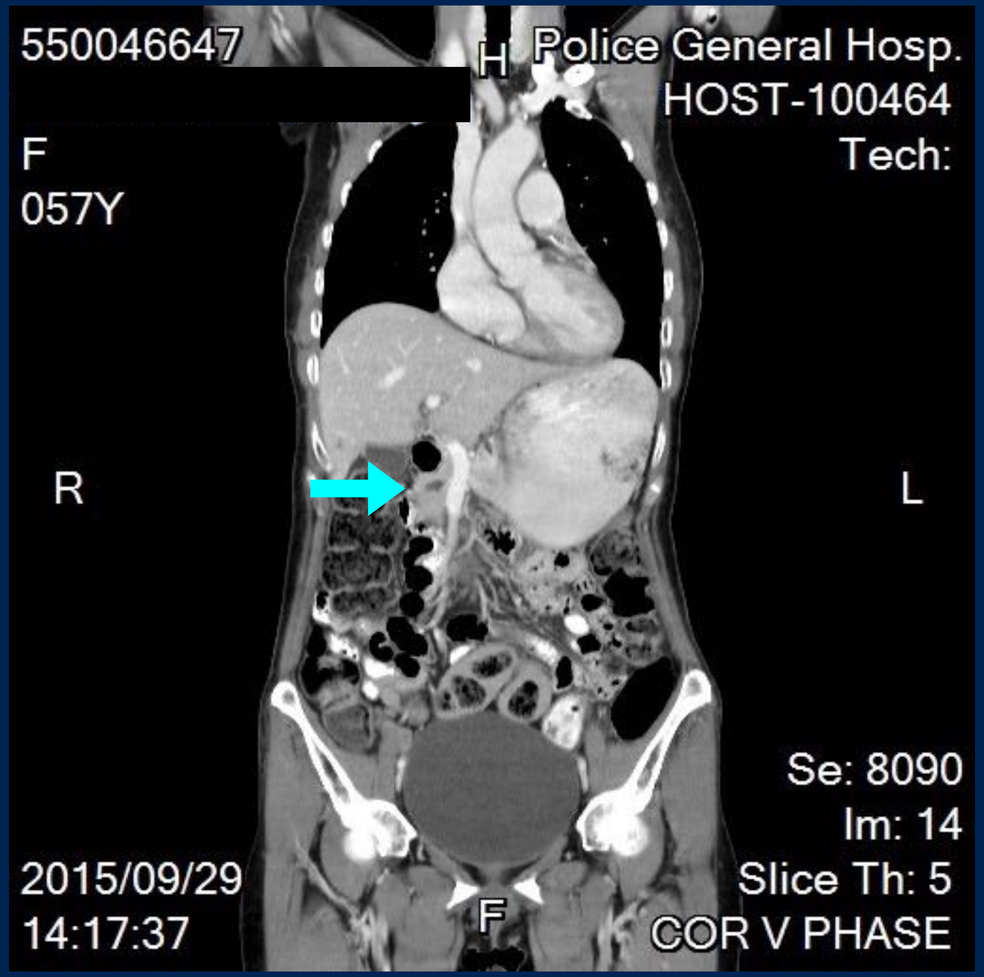
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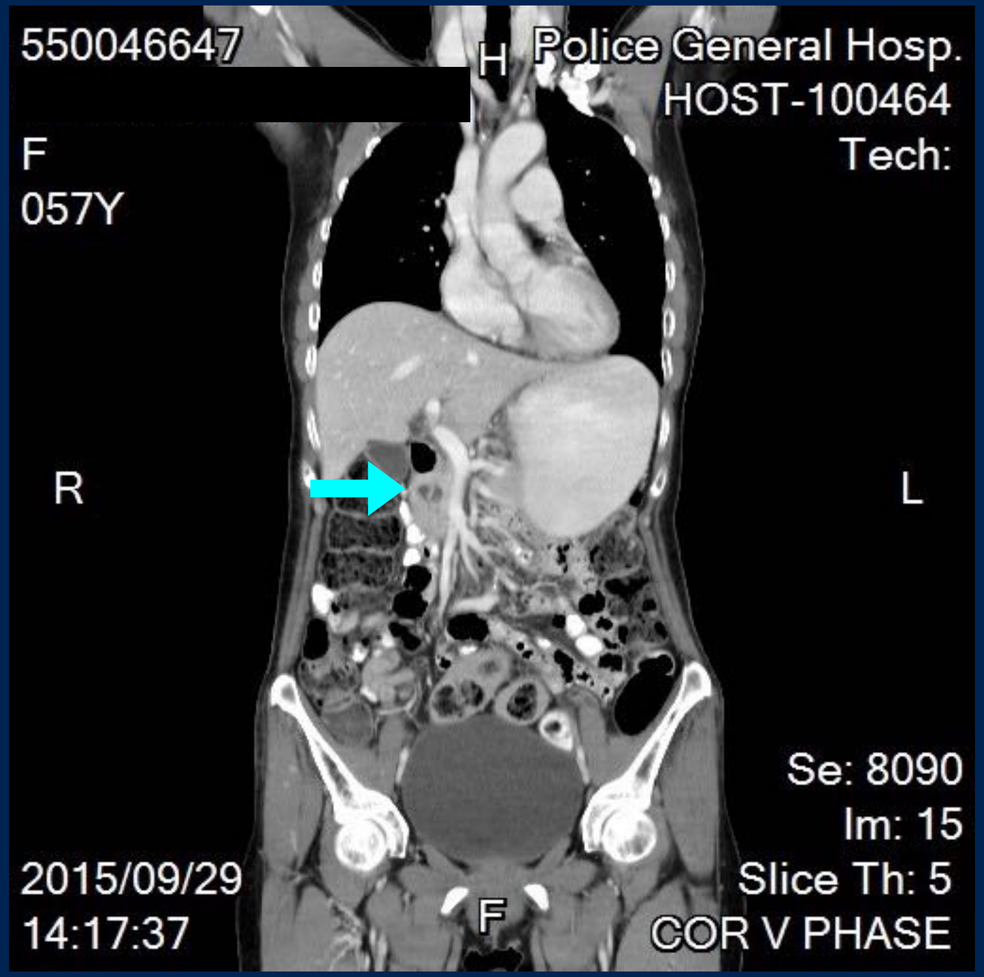
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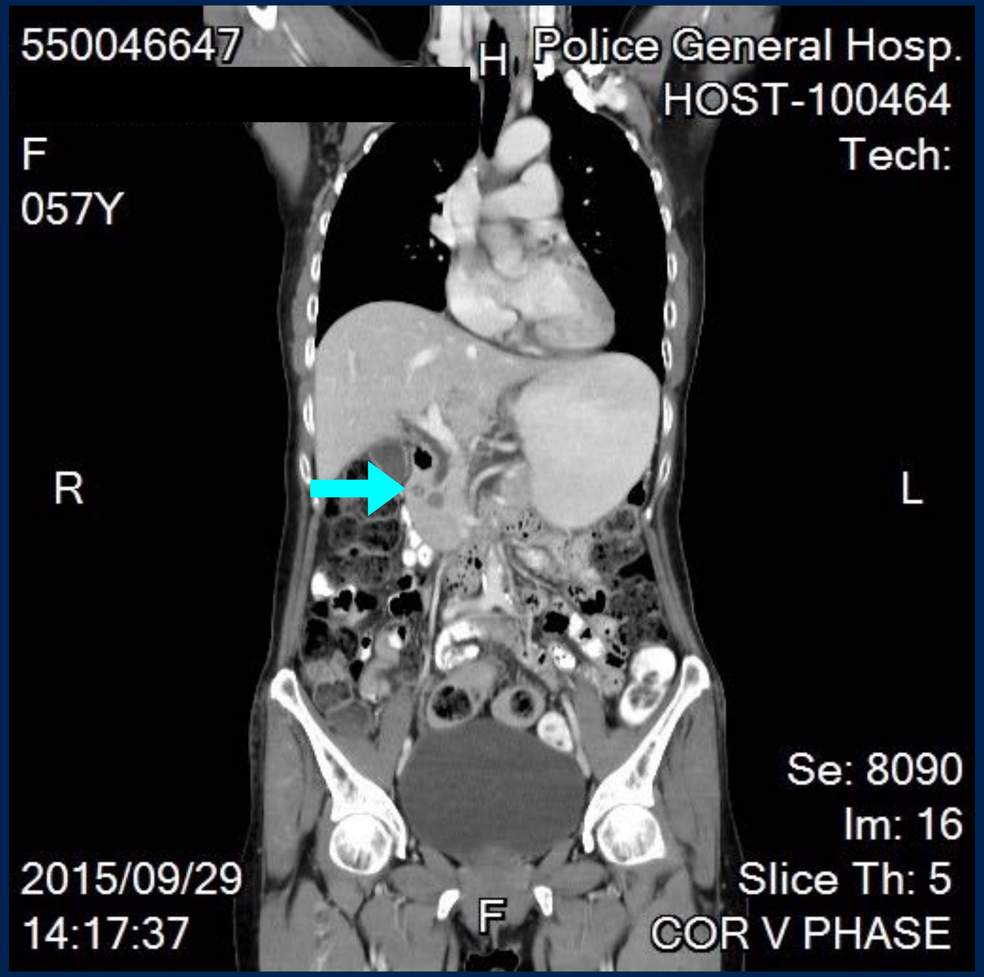
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MAGNETIC RESONANCE IMAGING (MRI)

- Provides information similar to a contrast enhanced CT
- MRCP is better in delineating biliary and pancreatic duct anatomy
- Double duct sign can be found in 75% of pancreatic cancer patients

Griffin N, Insights Imaging 2012;3:11-21

Double duct sign

INVESTIGATIONS

BIOMARKERS

RADIOLOGY

ENDOSCOPY

ENDOSCOPIC ULTRASONOGRAPHY (EUS)

- Useful in detecting small pancreatic lesions
- Assess vascular and local invasion better
- Combine with other techniques like FNA, elastography or contrast enhancement (CE)

Wiersema MJ. Pancreatology 2001;1:625-632

- EUS-FNAB performed for pancreatic mass lesions
  - Decreased sensitivity in chronic pancreatitis from 91.3% to 73.9%
  - Avoid peritoneal seeding
  - Sensitivity 75–90%, specificity 100% for solid pancreatic lesions

Varadarajulu S, Gastrointest Endosc 2005;62:728-736
Helmstaedter L, Langenbecks Arch Surg 2008;393:923–927

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB): past, present, and future

Kenji Yamao[1], Akira Sawaki[1], Nobumasa Mizuno[1], Yasuhiro Shimizu[2], Yasushi Yatabe[3], and Takashi Koshikawa[4]

INDICATION

- Make diagnosis and decide to go on surgery
- Unresectable cancer requiring chemotherapy or radiation
- Exclusion of other cancers that may require a different management

CONTRAINDICATION

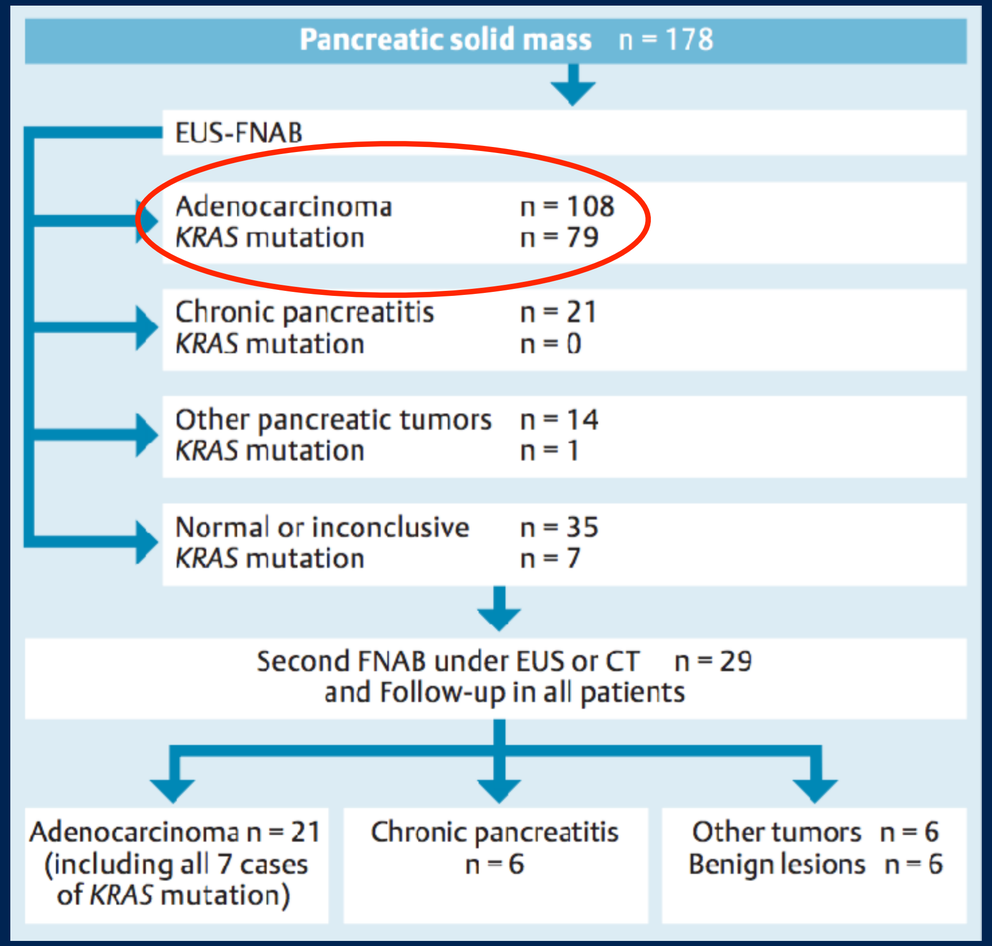
- Result cannot affect management
- Inability to visualize a lesion
- Involved vessel is situated between the gut and the target

Yamao K, J Gastroenterol 2005;40:1013-1023

Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with *KRAS* mutation assay to distinguish pancreatic cancer from pseudotumoral chronic pancreatitis

- Prospective multicentre study
- 178 patients with solid pancreatic mass
- KRAS mutation is present in 75 % to 95 % of PDAC

Bournet B, Endoscopy 2009;41:552-557



- Additional KRAS mutation help distinguishing PDAC from chronic pancreatitis
- When the cytopathology is inconclusive or inadequate

Bournet B, Endoscopy 2009;41:552-557

Contrast-enhanced endoscopic ultrasonography: advance and current status

- Sensitivity 94%, Specificity 89%
- Improving the diagnostic yield and adequate sampling
- Shows the microvasculature of a pancreatic lesion and adjacent organs

Contrast agents	Composition	Manufacturer
First generation		
Albunex	5% Sonicated serum albumin with stabilized microbubbles	Mallinckrodt Pharmaceuticals (Hazelwood, MO, USA)
Echovist (SHU 454)	Standardized microbubbles with galactose shell	Schering (Bergkamen, Germany)
Levovist (SHU 508)	Stabilized, standardized microbubbles with galactose, 0.1% palmitic acid shell	Schering
Myomap	Albumin shell	Quadrant (Nottingham, UK)
Qantison	Albumin shell	Quadrant
Sonavist	Cyanoacrylate shell	Schering
Second generation		
Definity/luminity	C_3F_8 with lipid stabilizer shell	Bristol-Myers Squibb Medical Imaging (N. Billerica, MA, USA)
Sonazoid	C_4F_{10} with lipid stabilizer shell	GE Healthcare (Little Chalfont, UK)
Imagent-imavist	C_6F_{14} with lipid stabilizer shell	Alliance (San Diego, CA, USA)
Optison	C_3F_8 with denatured human albumin shell	GE Healthcare
Bisphere/ cardiosphere	Polylactide-coglycolide shell with albumin overcoat	Commercially unavailable
SonoVue	SF_6 gas with lipid stabilizer shell	Bracco (Milan, Italy)
AI700/imagify	C_4F_{10} gas core stabilized with polymer shell	Acusphere (Lexington, KY, USA)
Third generation		
Echogen	Dodecafluoropentane liquid in phase shift colloid emulsion	Sonus Pharmaceuticals (Washington, DC, USA)

Jang SI, Ultrasonography 2014;33:161-169

- EUS elastography has been proposed to evaluate tissue elasticity
- Distinction between chronic pancreatitis and hard tumors still appears to be difficult
- Help to select a site where FNA can be performed with improved accuracy

Arcidiacono PG. Endoscopy 2012;8(1):48-67

- Cyst fluid analysis is used for distinguishing between mucinous and nonmucinous cysts
- Tumour markers: CEA, CA 72-4, CA 125, CA 19-9 and CA 15-3
- CEA level is the most accurate tumour marker to diagnose a mucinous lesion

Rockacy M, Ann Gastroenterol 2013;26(2):122-127

- Cytology analysis
  - MUC-containing cells
  - Malignant cells
  - Glycogen-rich cuboidal cells
  - Branching papillae with myxoid stroma
  - Abundant anucleate squamous cells and debris

Rockacy M, Ann Gastroenterol 2013;26(2):122-127

- Amylase is indicator of pancreatic duct communication
- *KRAS* mutation is the molecular marker used for the diagnosis of IPMN and MCN
- We currently use cyst fluid cytology and CEA level in our clinical practice

MANAGEMENT

Risk of surgical resection

VS

Risk of untreated pancreatic cancer

- Clinical presentations
  - Jaundice
  - Anorexia
  - Previous pancreatitis
  - New onset of diabetes mellitus
  - Decreasing BMI

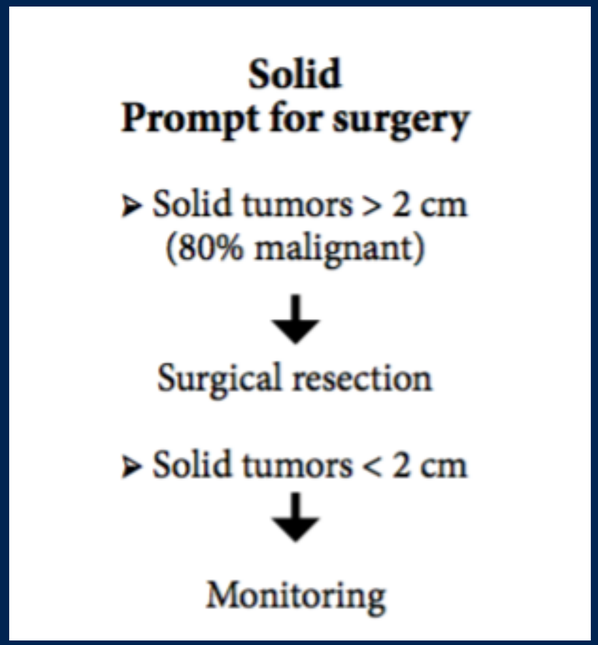
Clinical presentation

CA 19-9
Chromogranin A, IgG4

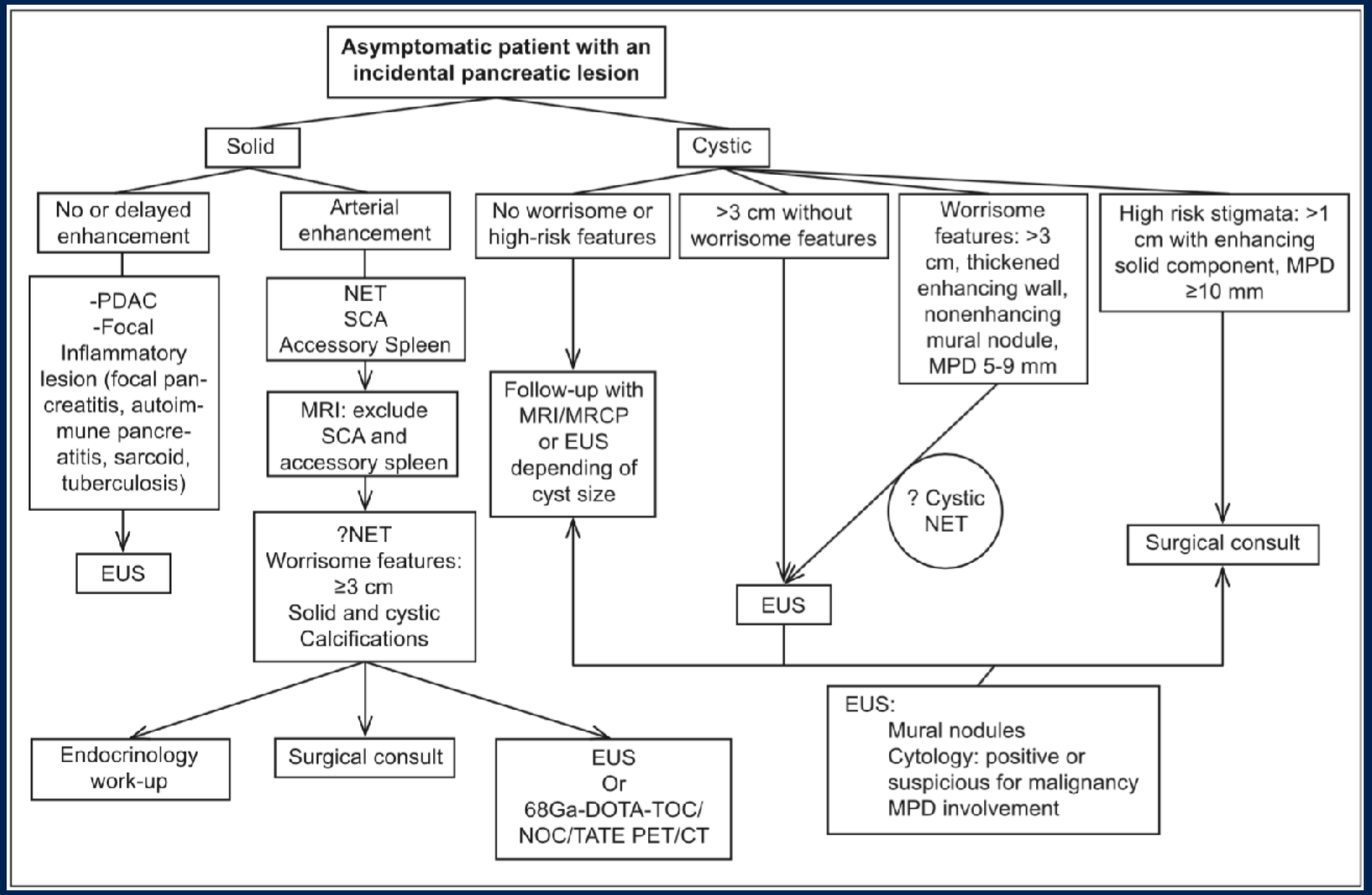
CT scan
MRI

EUS-FNAB
Cyst fluid analysis

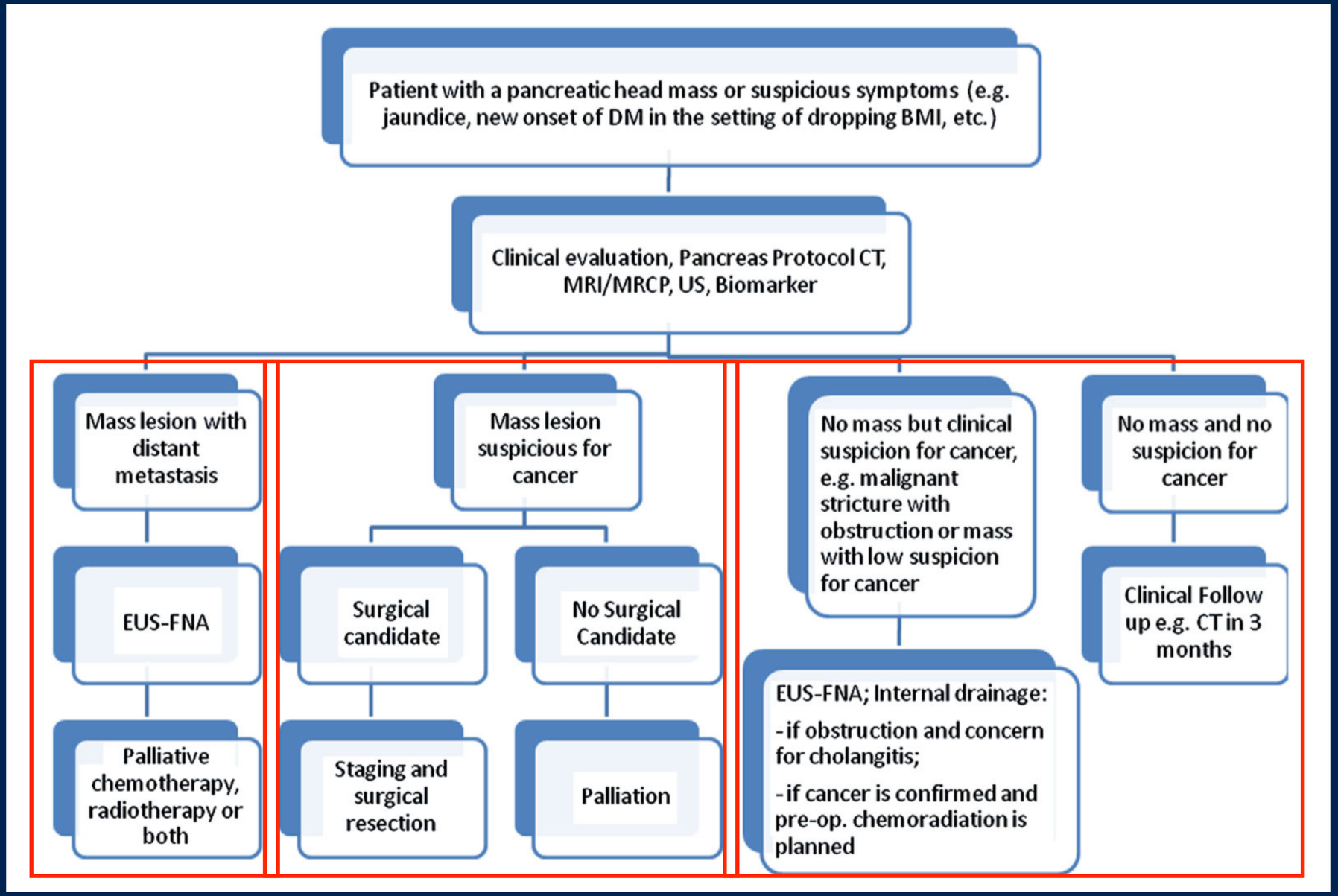
Most series agree that 80% of patients who had solid tumours > 2 cm had a malignancy



Karatzas T, J Boun 2013;18(1):17-24



Herrera MF, Endocr Pract 2015;21:546-553



Conrad C, J Surg Oncol 2013;107:23-32

CONCLUSION

- Clinical presentation is usually the key to diagnosis
- Biomarkers provide a helpful information but cannot be used for making a definitive diagnosis
- Preoperative diagnosis and treatment stratification rely mainly on radiologic imaging
- EUS is useful with additional imaging and biopsy when necessary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