Diagnosis of PANCREATIC CANCER

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The faces of pancreatic cancer

General Facts

- 42,470 new cases in the U.S. in 2009
- 5-year survival (1999-2005) 5.7%
- 4th leading cancer killer in the U.S.
- 70-80% develop obst. jaundice; 10-20% duodenal obstruction
- Gemcitabine +/- erlotinib are only chemotherapeutic agents with proven benefits

PANCREATIC CANCER

Cooke. Surg Clinic NA 2010; Merl JOP 2010; Mortenson. AJ Surg2005

General Facts

- Surgical results:
  - Only curative modality
  - 20% considered resectable; only 2/3 of them are truly resectable
  - 92% resected patients develop recurrence
  - Node-negative resected case has a 25% 5-year survival

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Cooke/Varadarajulu. Surg Clinic NA 2010Mortenson. Am J Surg2005

Reason for poor survival

- **Symptoms are minimal at early stage**
- **Poor awareness of warning features (MD and patient)**
- **Aggressive biology of pancreatic cancer**
- **Current modalities in pancreatic cancer detection are too insensitive**

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Serum markers as screening tests

Serum marker	Sensitivity	Specificity
CA 19-9	70–90	90
CEA	16–92	49–93
CA 50	65–90	58–73
CA-72-4	—	—
CA-242	57–83	79–90
CA125	45–60	76–86
CA-195	89	73
Tissue polypeptide sp ag	50–98	22–97
TIMP-1	60–99	60–99
Span-1	50–87	50–90

Pappas. Gastro Clinics 2007

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High CA 19-9 is often benign

- 204 patients with high CA19-9
- 130 (63.7 per cent) had malignant conditions
- 74 (36.3 per cent) had benign conditions or no definite cause
- Levels were significantly lower in patients with benign reasons than those with malignant pathology

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McLaughlin. Ir J Med Sci 1999

But CA19-9 can be very high ….

- 79 yo woman presented with cholangitis and pancreatic pseudocyst. CA19-9 was 35,500 U/mL. She was adequately treated and at two months' follow-up the CA19-9 level had returned to normal

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Akdogan. Tumori. 2001

High level in benign diseases

Reports in the literature:

- 12.8% of pancreatic disease
- 38.8% of biliary tract disease
- 50% of pancreatic or biliary tract disease with obstructive jaundice
- 8.8% of pulmonary disease
- Very high level in hydronephrosis

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Suzuki. J Urol 2002

What cells are producing CA 19-9?

Epithelial cells of the

- Pancreas
- Bile duct
- Gallbladder
- Gastrointestinal tract
- Airway

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Ito. Internal Medicine. 1999

High CA 19-9: Benign conditions

- Inflammatory bowel dis
- Pancreatitis
- Cirrhosis
- Chronic hepatitis
- Cholangitis
- Bronchial cyst
- Bronchitis
- Pulmonary fibrosis
- Bronchiectasis
- Cystic fibrosis
- Endometriosis
- Benign splenic cyst
- Diabetes mellitus
- Chronic renal failure
- Thyroid disese
- Rheumatologic dis
- Hydronephrosis

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Suzuki. J Urol 2002

Cancer with high CA 19-9

- Pancreatic
- Biliary
- Hepatocellular
- Cholangiocarcinoma
- Gastric
- Colorectal
- Ovarian
- Lung
- Breast
- Uterine

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Suzuki. J Urol 2002

CA 19-9 is not a good screening test

- CA 19-9 is rarely elevated in health, but can occur in a variety of benign conditions
- Using CA 19-9 to screen for pancreatic cancer is rarely useful or reliable

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Look for Patients at Risk

- Smoking
- Old age
- Diabetes
- Peutz-Jeghers
- Panc cyst
- Hereditary pancreatitis
- Family history
- Other cancer (BRCA, HNPCC)
- Chr pancreatitis
- IPMN
- Cystic fibrosis

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Rosty. Hem/onc Clinics NA. 2002; Stolzenberg-Solomon. J NCI. 2001

Potential Warning Signs

New onset IDDM

Painless jaundice

Dull, unexplained pain

Sudden loss of appetite and weight

Recurrent pancreatitis

Unexplained delayed gastric emptying

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Barkin. Gastroenterology Clinics 1999

Pancreatic lesions linked to cancer

- Chronic pancreatitis
- Cystic lesions
  - IPMN (intraductal papillary mucinous tumor)
  - Mucinous cystadenoma
  - Mucinous cystadenocarcinoma
  - Neuroendocrine tumor
- Solid lesions
  - Neuroendocrine tumor
  - Pancreatic ductal carcinoma
  - Lymphoma
  - Metastatic cancer
  - Autoimmune pancreatitis

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Familial links to pancreatic cancer

Familial pancreatic cancer (FPC):

- ≥ 2 first-degree relatives with pancreatic ductal adenocarcinoma (in the absence of other cancers or diseases that are known to be familial)
- 1-3.5% of all ductal pancreatic cancer
- 18X (2 relatives); 57X (3 relatives)

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S Hahn. Clin Lab Med 25 (2005) 117–133

IPMN

Fish mouth papillary orifice

Early lesions are flat

Profuse mucin production

Mistaken as chronic pancreatitis

Premalignant

Indistinguishable from ductal pancreatic cancer

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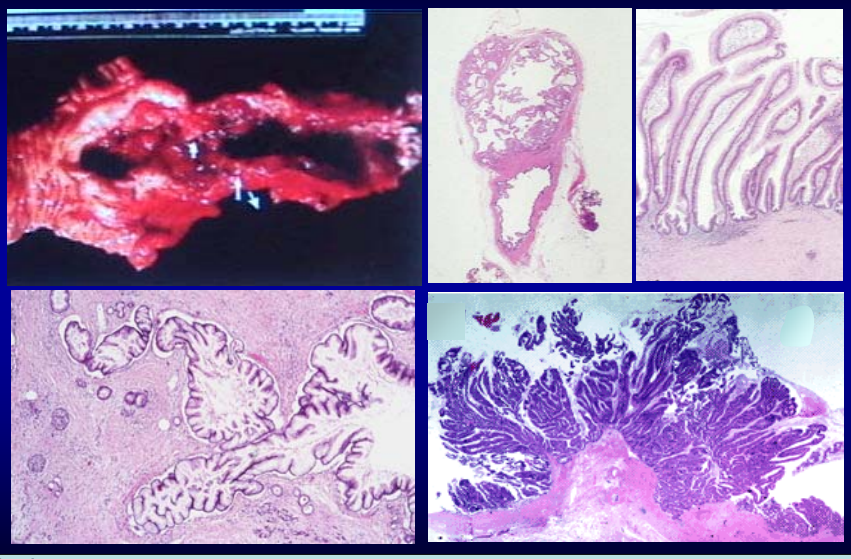
IPMN – percancerous tumor



1996

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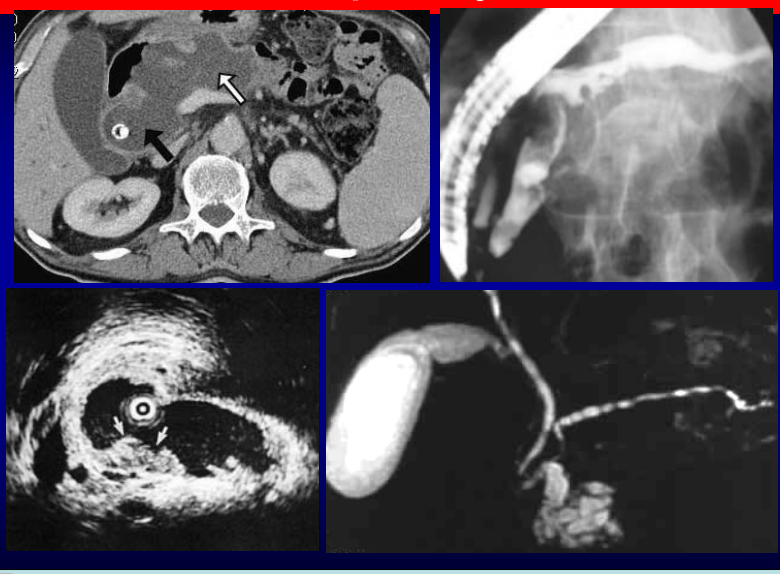
Intraductal Papillary Mucinous N



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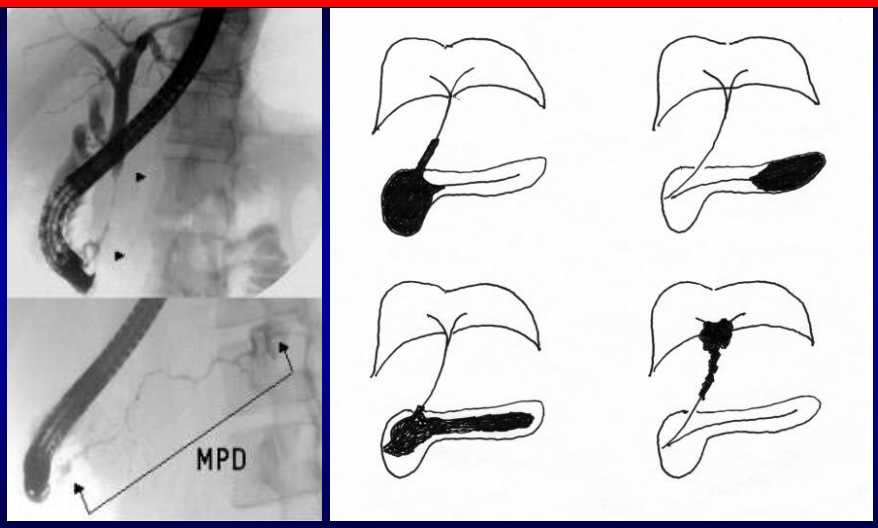
Autoimmune pancreatitis



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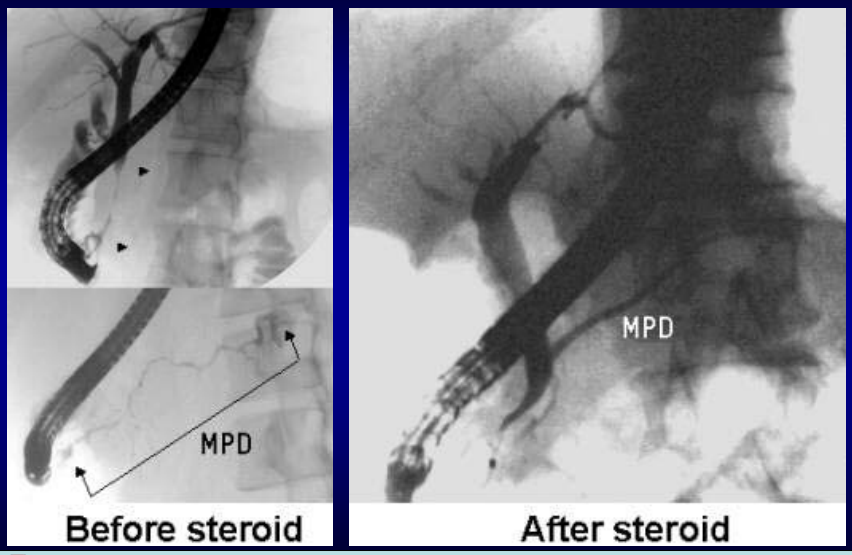
G Kloppel. J Pancreas (Online) 2005; 6(1 Suppl.):97-101.

Autoimmune pancreatitis



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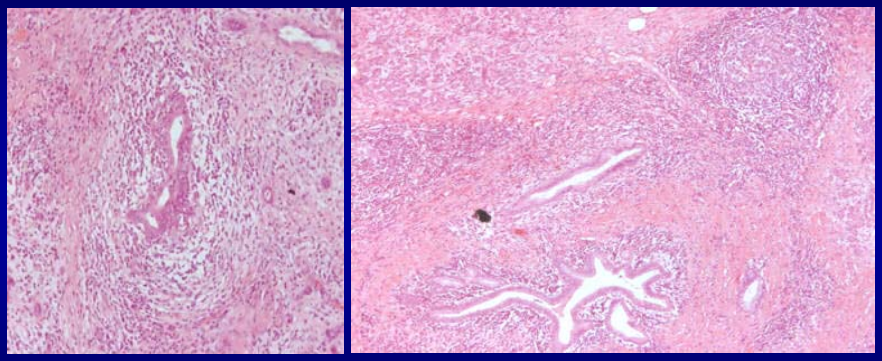
Lymphoplasmacytic infiltration



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R Pezilli. J Pancreas (Online) 2004; 5:527-530.

Familial links to pancreatic cancer

- Syndromes that shows an increased risk:
  - Familial atypical multiple mole melanoma (FAMMM) (CDKN2A)
  - Peutz-Jeghers syndrome (PJS) (36% life risk)
  - Hereditary pancreatitis (HP) (40% risk)
  - Hereditary nonpolyposis colorectal carcinoma (HNPCC) (<5% risk)
  - Familial breast and ovarian cancer (FOBC) (BRCA1, BRCA2)
  - Cystic fibrosis (CF) (CFTR)
  - Ataxia-telangiectasia (AT)
  - Familial adenomatous polyposis (FAP)

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S Hahn. Clin Lab Med 25 (2005) 117–133

Desired characteristics of imaging tests

- Early detection
- Identify those who will need surgery
- Select out those will not benefit from surgery
- Minimal invasiveness
- Simple tissue acquisition for definitive diagnosis to guide palliation or resection
- Cost-effective
- Safe
- Local availability

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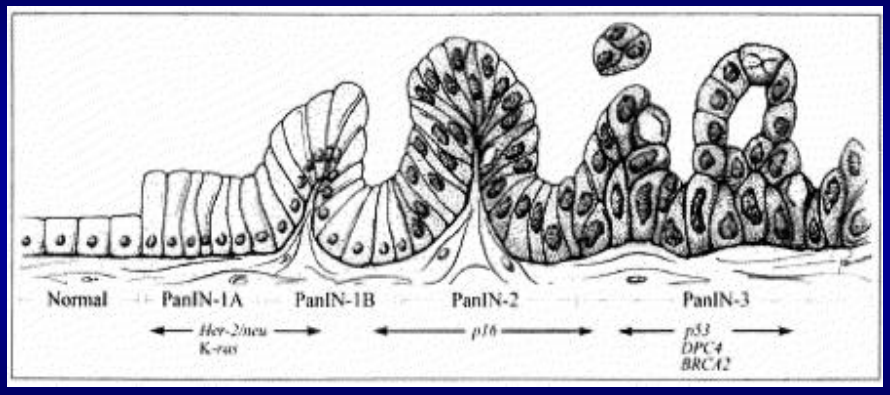
Kochman. GIE 2002

Panc CA: Dysplasia to Cancer



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Rosty. Hem/onc Clinics of NA. 2002

Pancreatic Intraepithelial Neoplasm

- **PanIN-1A:** Flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin
- **PanIN-1B:** These lesions have a micropapillary, papillary or basally pseudostratified architecture **PanIN2:** May be flat or papillary. They must have some nuclear abnormalities
- **PanIN-3 (CIS):** Papillary or micropapillary lesions. True cribriforming, budding off of clusters of cells into the lumen and luminal necroses should all suggest the diagnosis of PanIN-3

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Johns Hopkins Web site

Early Diagnosis of dysplasia/CA

- 7/14 FPC patients believed to have dysplasia on the basis of hx, EUS and ERCP were referred for resection
- All 7 had dysplasia in pancreatectomy specimens
- EUS findings were subtle and similar to those seen in chronic pancreatitis
- ERCP findings: ductal stricture, irregularities and small sacculations
- CT and serum markers had low sensitivity

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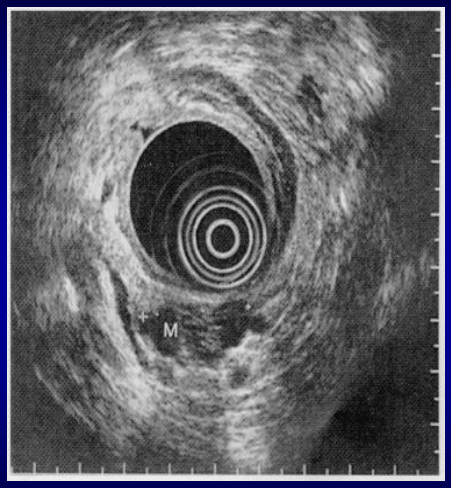
Brentnall. Ann Intern Med 1999

Early Diagnosis of dysplasia/CA



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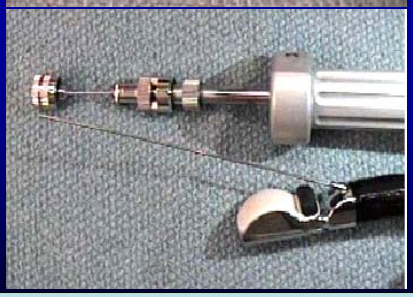
Brentnall. Ann Intern Med 1999

Endoscopic Ultrasonography (EUS)



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EUS

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How good is a normal EUS?

- 80 (medium/low cancer risk) patients
  - High CA 19-9 level alone
  - Chronic abdominal pain
  - Significant weight loss without a clear etiology
  - Indeterminate CT (‘‘enlarged head of pancreas,’’ ‘‘heterogenous appearance,’’ "mass cannot be excluded)

PANCREATIC CANCER

Catanzaro. Gastrointest Endosc 2003;58:836-40

Normal EUS = no pancreatic cancer

- Mean FU 23.9 months
- One with chronic pancreatitis changes subsequently found to have panc cancer
- No patient (n=58) with normal pancreas EUS developed pancreatic cancer or required pancreatic surgery during the follow-up period

PANCREATIC CANCER

Catanzaro. Gastrointest Endosc 2003;58:836-40

Normal EUS = no pancreatic cancer

- **Conclusions:** A normal EUS of the pancreas in the setting of subtle radiologic findings, serologic abnormalities, and/or nonspecific symptoms definitively rules out pancreatic cancer

PANCREATIC CANCER

Catanzaro. Gastrointest Endosc 2003;58:836-40

EUS is good for early detection

- EUS is the most accurate dx modality
- Both dual-phase CT and EUS had high sensitivity for pancreatic cancers >15 mm, but CT was less sensitive than EUS for cancers <15 mm (67% vs 100%)
- T and N staging by EUS has an accuracy of 85% and 70%, respectively
- EUS had sensitivity of 61% and PPV of 69% in predicting resectability vs sensitivity of 73% and PPV of 71% for MRI

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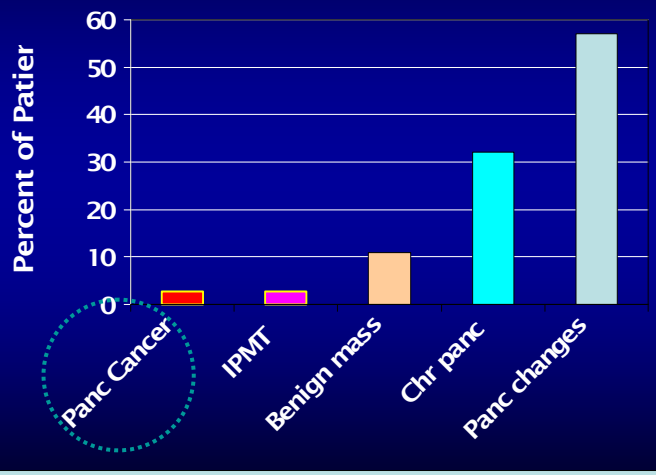
R Tamerisa. Med Clin N Am 2005; 89:139–158

EUS is good for screening & detection

EUS done on 37 FPC relatives



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Canto. Johns Hopkins. GIE Abs. 10/2002

Multi-detector CT

- Increased speed of image acquisition
- Ability to time acquisition with vascular contrast injection
- Increased resolution
- High quality 3-D reconstruction

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Nino-Murcia. Gastro Clinics 2002

3D CT Rendering

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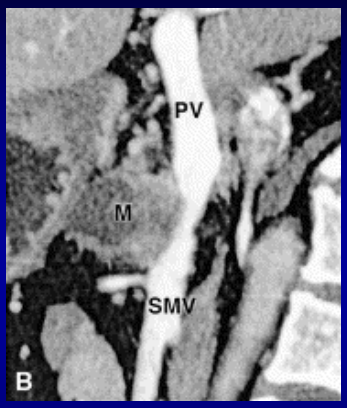
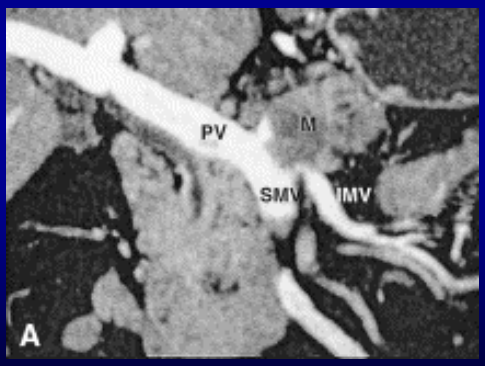
David Lu. UCLA

Multi-detector CT



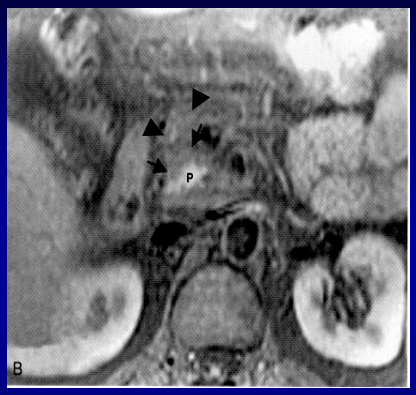
Vascular involvement can be readily identified



PANCREATIC CANCER

Nino-Murcia. Gastro Clinics 2002

MRI & MRCP



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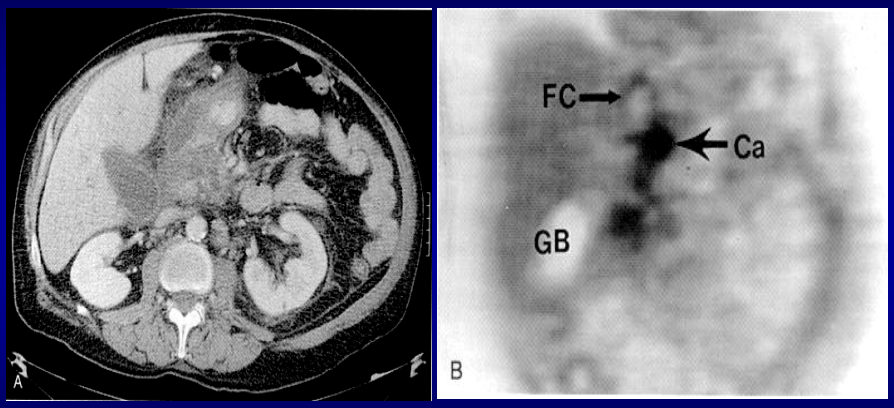
Freeny. Gastro Clinic 1999

PET Scan for Pancreatic Cancer



PANCREATIC CANCER

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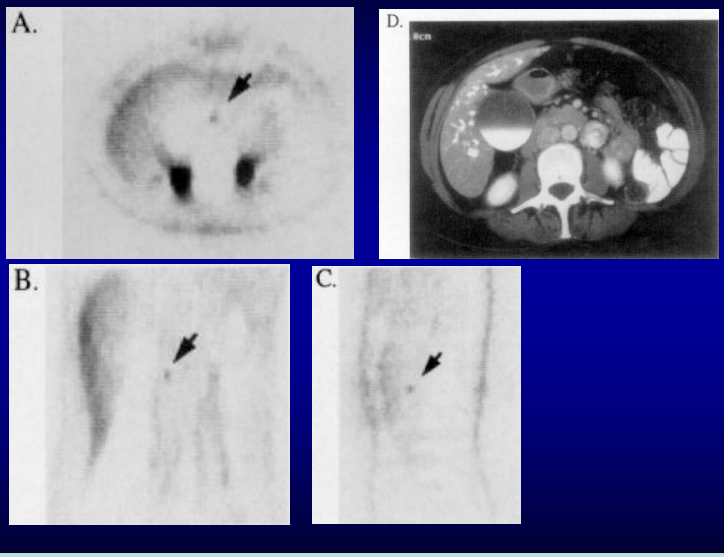

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Rose. Annals of Surg 1999

PET for Pancreatic Cancer

Author	Year	Total	Malig. (%)	Sens (%)	Spec (%)
Bares	1994	40	27 (68%)	92	85
Stollfuss	1995	73	43 (59%)	93	93
Friess	1995	80	48 (60%)	94	88
Kato	1995	24	15 (63%)	93	78
Inokuma	1995	46	35 (76%)	94	82
Ho	1996	14	8 (57%)	100	67
Zimny	1997	106	74 (70%)	85	84
Imdahl	1998	48	27 (56%)	96	100
Clark	1998	30	22 (73%)	82	75
Rose	1998	65	52 (80%)	92	85

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Rose. Annals of Surg 1999

PET vs CT for Pancreatic cancer

Sensitivity Stratified by Tumor Diameter

Tumor Diameter	n	CT	^{18} FDG-PET
2.0 cm	14	18%	100%
2.1-4.0 cm	15	76%	90%
>4.0 cm	20	100%	92%

PANCREATIC CANCER

Rose. Annals of Surg 1999

PET Scan

- Sensitivity, and even specificity, of diagnosing pancreatic cancer reported as high as 100%
- Results varied with timing of study and SUV (standardized uptake value) used as positive readings
- Not helpful in distinguishing acute pancreatitis from cancer

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Moadel. Gastro Clinic. 2002

EUS vs CT for pancreatic cancer

	Detection		Accuracy - resectability		Sens. - vas. invasion	
Series	EUS	CT	EUS	CT	EUS	CT
Legmann	27/27	25/27	20/22	19/22	6/7	7/7
Midwinter	33/34	26/34	25/30	23/30	13/16	9/16
Tierney			30/31	25/31	16/16	10/16
Mertz	29/31	16/31	16/16	13/16	6/6	3/6
Total	97%	73%	91%	83%	91%	64%
p Value*	<0.001		0.02		<0.001	

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Hunt. GIE 2002

Current status re: EUS and CT

- EUS and helical CT are complementary for staging pancreatic cancer
- EUS is a more accurate for local T staging and for predicting vascular invasion, especially in tumors <3 cm,
- Helical CT is better for the evaluation of distant metastasis and for staging larger tumors

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Varadarajulu. Surg Clinic NA 2010

CT and EUS can be used together

Criterion	*n*	*p*[a]	Sensitivity (%)	Specificity (%	PPV (%)	NPV (%)
Vascular abutment, CT	16	<0.001	94	74	44	98
Adenopathy >1 cm, CT	29	<0.001	76	74	69	80
Liver lesion, CT	10	0.06	70	60	18	94
Vascular abutment, EUS	18	0.004	72	67	42	88
Adenopathy >1 cm, EUS	13	0.03	69	64	30	90

PPV = positive predictive value, NPV = negative predictive value, RR = relative risk
[a] *p* vs resectable patients
[b] 95% CI are in parentheses

Score	# Resectable	# Unresectable
0	27/29 (93%)	2/29 (7%)
1	9/21 (43%)	12/21 (57%)
≥1	17/46 (37%)	29/46 (63%)
2	2/18 (11%)	16/18 (89%)
≥2	2/22 (9%)	20/22 (91%)
3	0/4 (0%)	4/4 (100%)

Score ≥ 2 are unresectable and should consider chemotherapy

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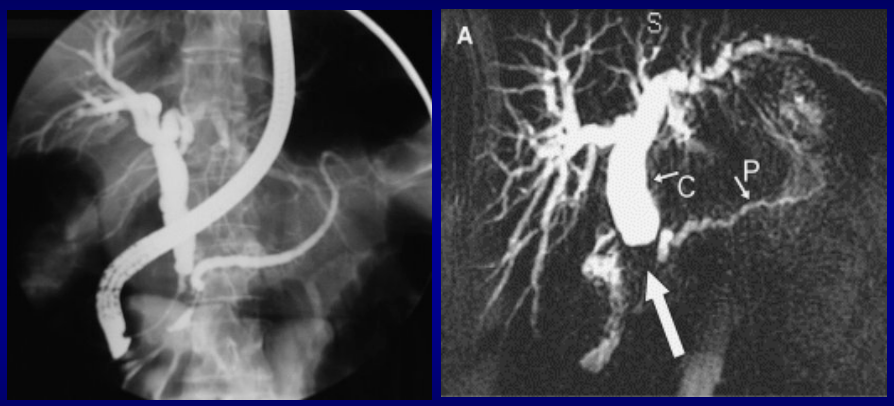
Yovino. J Gastroint Surg 2007

Double duct sign from cancer



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ERCP for Pancreatic cancer

- Reported as 95% sensitive
  (Freeny. Rad Clinic NA 1989)
- Used as a standard test for diagnosing pancreatic carcinoma when a CT is non-diagnostic
- But ERCP is invasive, can MRCP replace ERCP?

PANCREATIC CANCER

Suspected cancer: what to do?

- Start with abdominal CT. Do not use CA19-9 or CEA
- When CT is negative, EUS is the imaging modality of choice
- Perform FNA if EUS is positive
- ERCP has a limited role in diagnosing cancer because of risks of complications
- PET scan may have a small role for early cancer, but mainly for tracking the activity of known cancer

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Rosty. Hem/onc Clinics of NA. 2002

SUMMARY

- Many new and improved diagnostic modalities are now available to detect and assess pancreatic cancer
- In spite of recent advances, the overall survival of pancreatic cancer is still among the worst of solid tumors

PANCREATIC CANCER

SUMMARY

- There is the limited possibility to detect pancreatic dysplasia, thus potentially preventing cancer in the high risk populations
- Treatment options have expanded tremendously recently, along with much improved palliative modalities

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