GEP NETs: ENDOSCOPIA NELLA DIAGNOSI E NEL TRATTAMENTO

(SIMPOSIO: **I NETs**, a che punto siamo?
Milano, 20 giugno 2008
Jolly Hotel Touring)

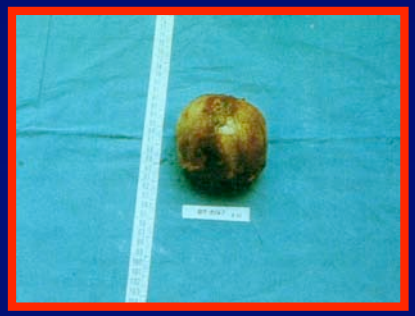
Claudio G. De Angelis

Turin

GEP (NEURO)-ENDOCRINE TUMORS:

" A COMPLEX DILEMMA FOR DIAGNOSTIC IMAGING"

- Small sizes:



< 2 cm in 55-70% of insulinomas
< 1 cm in 38% of gastrinomas
< 1.5 cm (often) GI carcinoids
(< 1 cm: 80% of rectal carcinoids)

- Profound site in the retroperitoneum, multiple and extrapancreatic locations

- Sometimes only submucosal location in the GI tract (e.g. gastrinomas)

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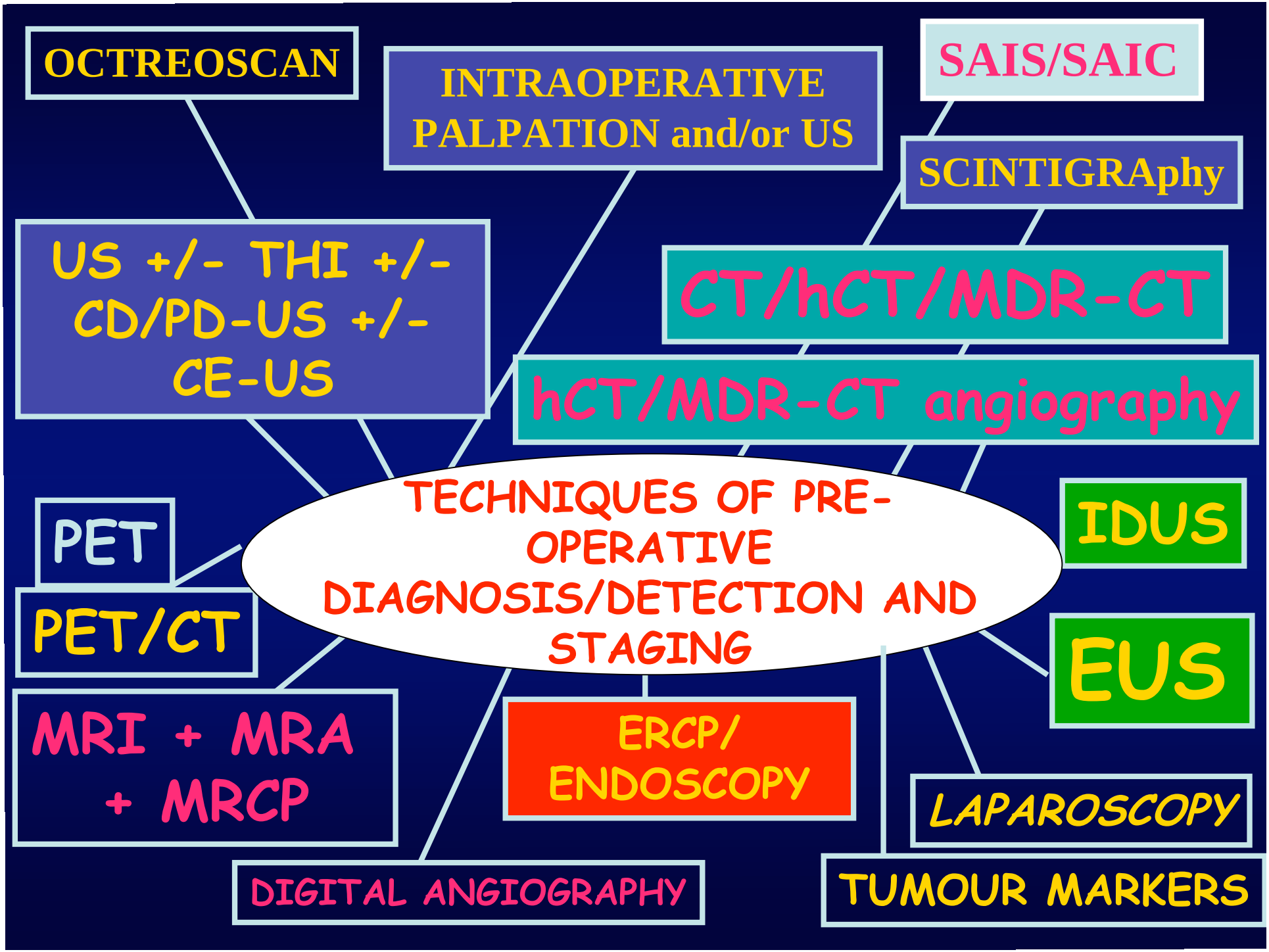
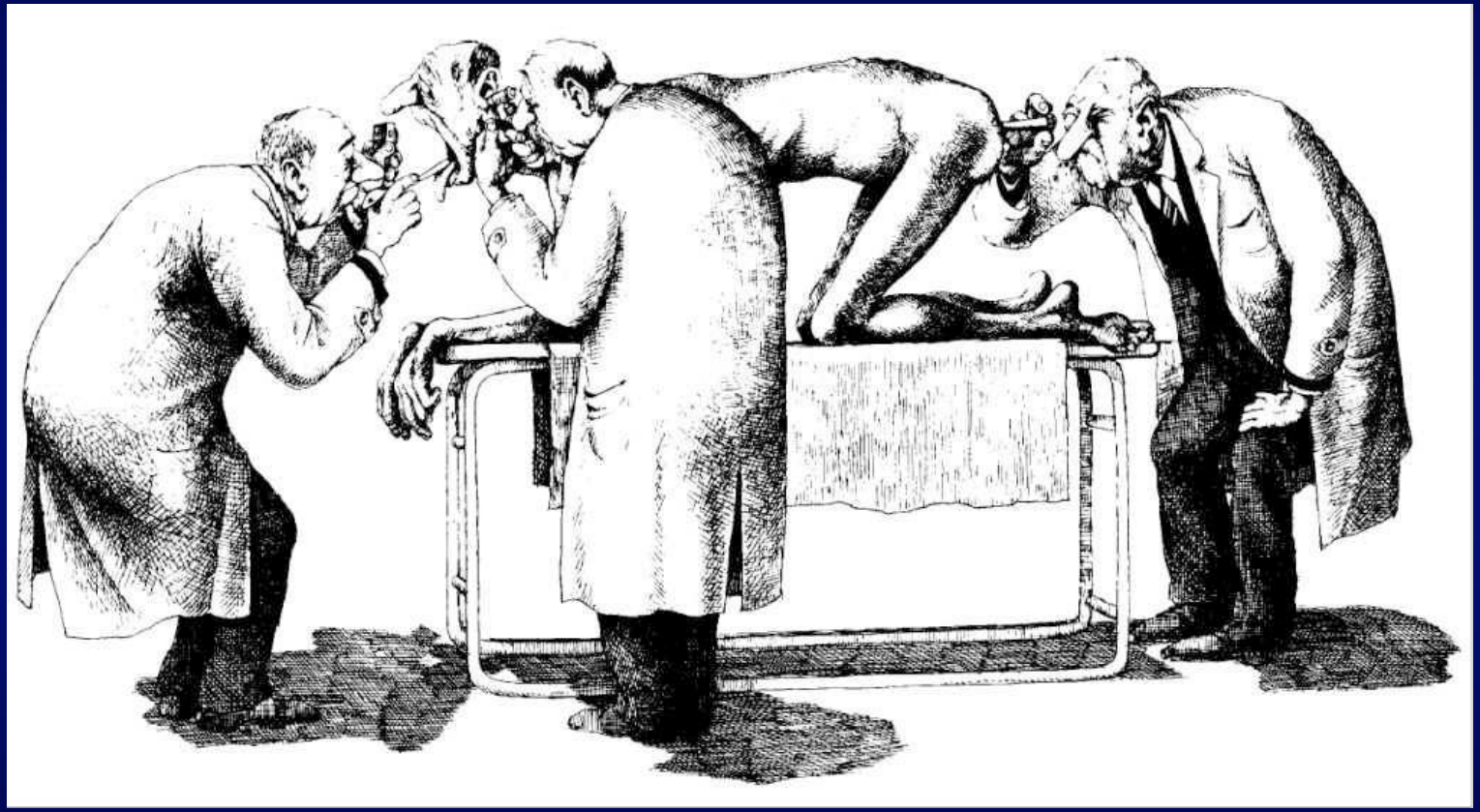

OCTREOSCAN
INTRAOPERATIVE PALPATION and/or US
SAIS/SAIC
SCINTIGRAphy
US +/- THI +/- CD/PD-US +/- CE-US
CT/hCT/MDR-CT
hCT/MDR-CT angiography
TECHNIQUES OF PRE-OPERATIVE DIAGNOSIS/DETECTION AND STAGING
IDUS
PET
PET/CT
EUS
MRI + MRA + MRCP
ERCP/ ENDOSCOPY
LAPAROSCOPY
DIGITAL ANGIOGRAPHY
TUMOUR MARKERS

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

NEUROENDOCRINE PANCREATIC TUMORS AND THE ENDOSCOPIST:



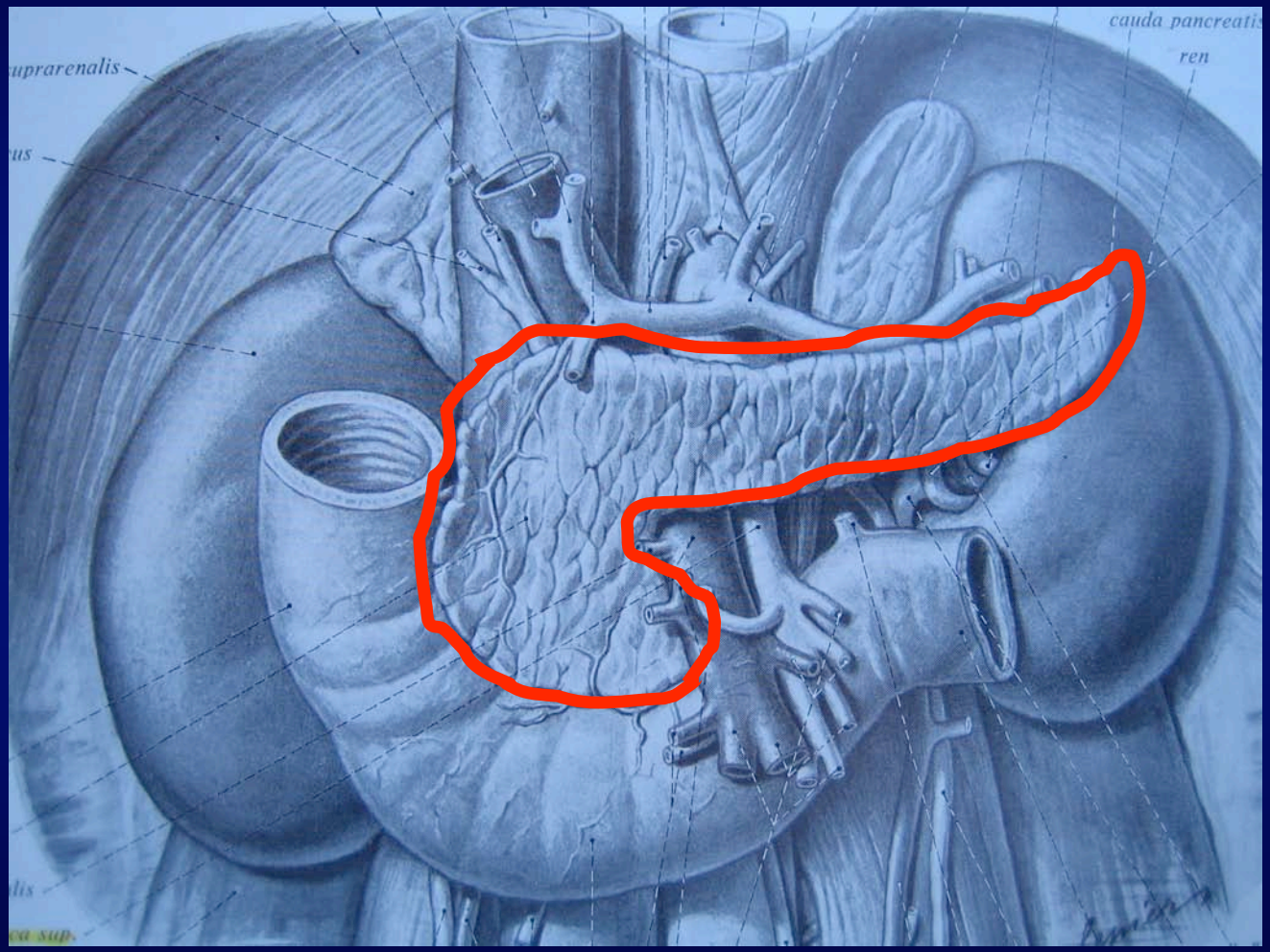
or "SEARCHING THE NEEDLE IN THE HAYSTACK"

THE ENDOSCOPIST'S SHOP

WHAT YOU CAN ASK TO THE ENDOSCOPIST ?

- To identify/ detect the lesion (DIAGNOSIS AND LOCALIZATION)
- To stage the lesion (prognostic evaluation) (STAGING)
- To treat the lesion (?) (THERAPY)

PANCREAS and NETs



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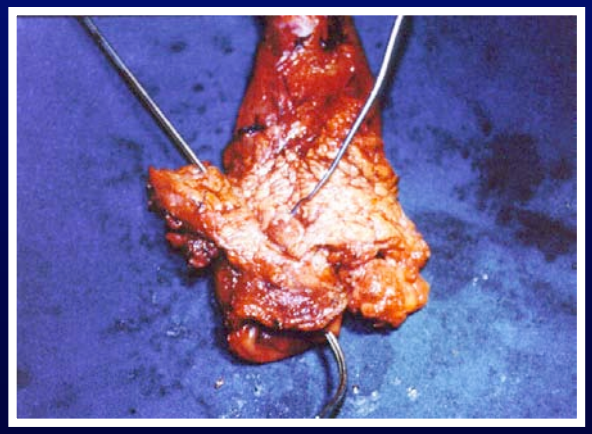
EUS
ITALIAN CLUB

ENDOSCOPY AND ENDOSONOGRAPHY IN PRE-OPERATIVE DETECTION OF PANCREATIC NETs

- A correct pre-operative localization and staging are MANDATORY in order to select the right therapeutic options, optimize surgical treatment, reducing times and complexity of surgery:
  - IMPROVING RESULTS AND OUTCOMES



PANCREATIC NETs: THE ROLE OF ENDOSCOPIC TECHNIQUES

ERCP

Bile ducts

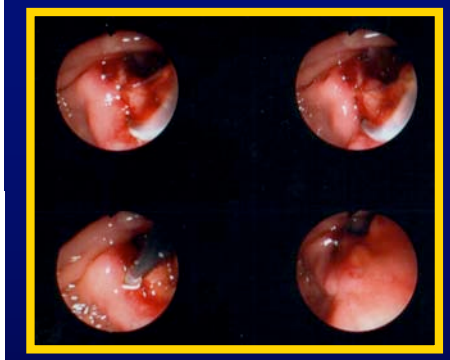
- **Carcinoids (0.3%)**
- **Somatostatinomas (1.2%)**

Ar ull

- **matostatinomas (9.3%)**

P ncreas*

- **In linomas (99%)**
- **G trinomas (33-79%)**
- **rcinoids (0.46%)**
- **Glucagonomas (ca.100%)**
- **Vipomas (90%)**
- **Somatostatinomas (37.9%)**
- **PPomas (92%)**
- **Non-functioning (15-52%)**

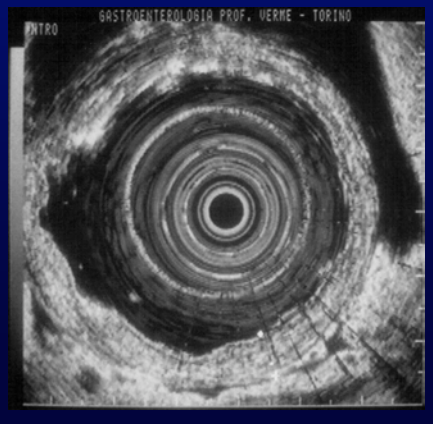


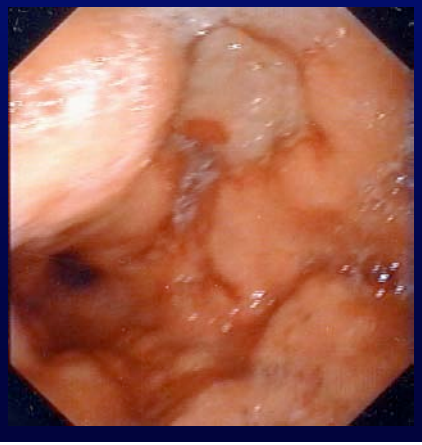
*Ogawa Y et al. Islet cell tumors of the pancreas: the diagnostic value of ERCP. Int J Pancreatol 6,1990

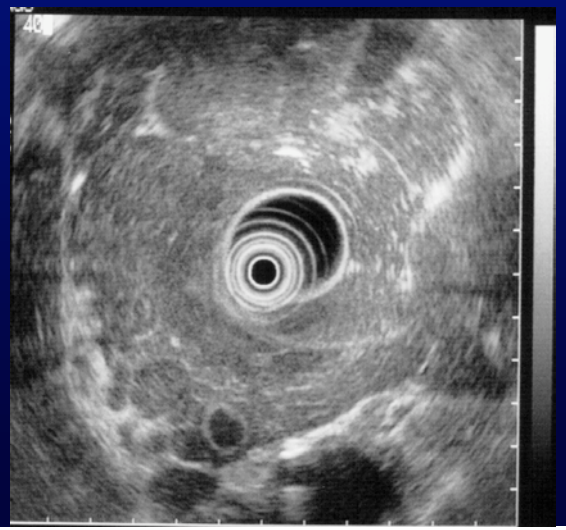
THE CHALLENGE OF EUS

- EUS is the most important of the many innovations that have occurred in GI endoscopy during the last 25 yrs

- EUS has extended the range of possibilities for endoscopic diagnosis endowing the endoscopist with the matchless ability to see within and beyond the wall of the gut





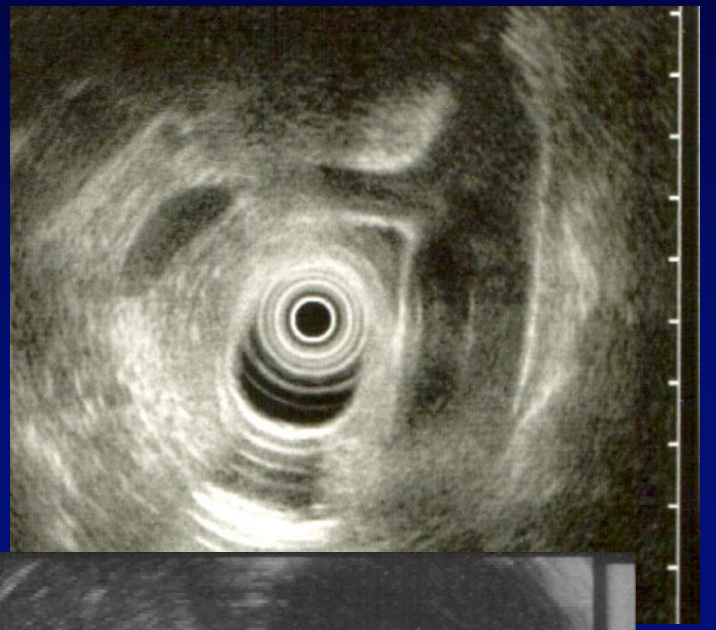


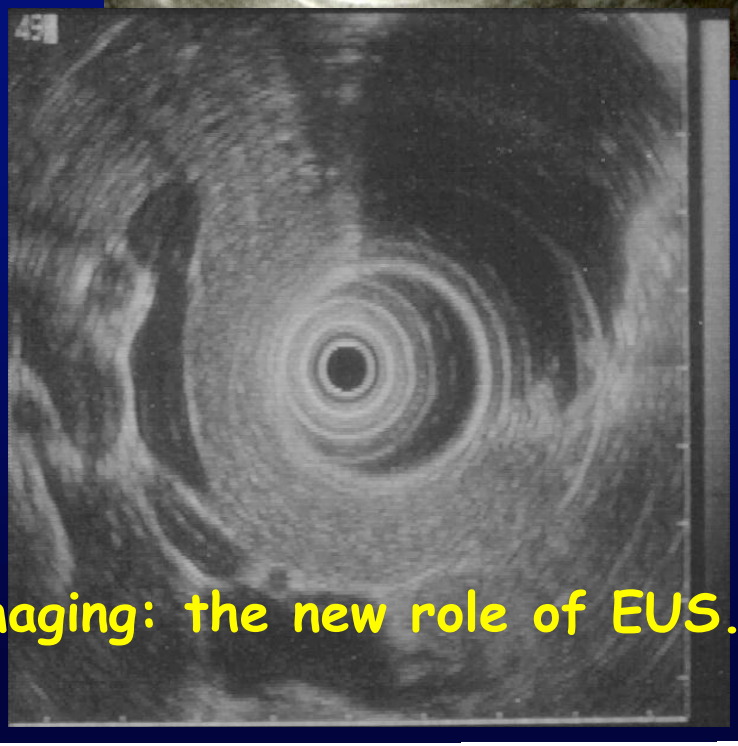
ENDOSCOPIC ULTRASOUND (EUS)

THE BEST CURRENTLY AVAILABLE TECNIQUE FOR IMAGING THE PANCREAS

HIGH RESOLUTION IMAGES OF THE MAIN PANCREATIC DUCT AND SURROUNDING PARENCHYMA

STRUCTURES AS SMALL AS 2-3 MM CAN BE DISTINGUISHED





De Angelis C et al. Pancreatic cancer imaging: the new role of EUS.
JOP J Pancreas (online) 2007;8 (1)

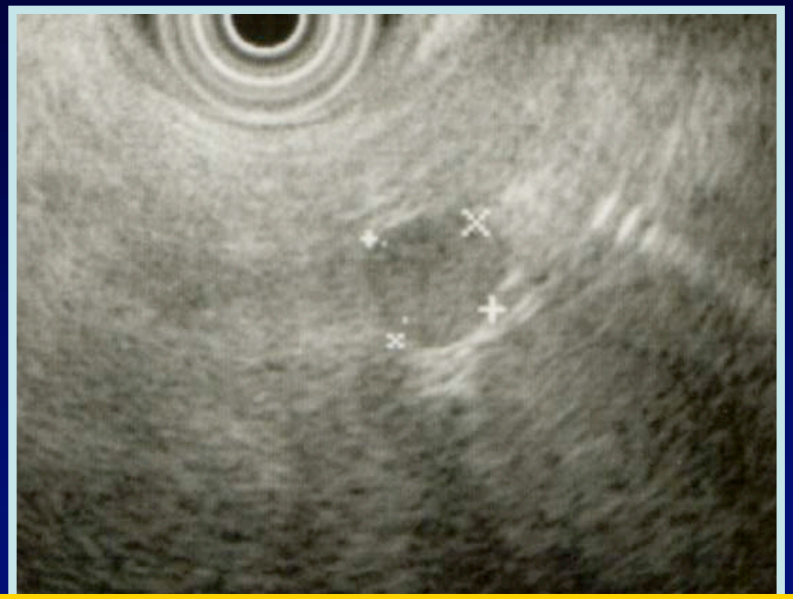
EUS FEATURES OF THE NETs OF THE PANCREAS

Echopattern as to the rest of the gland

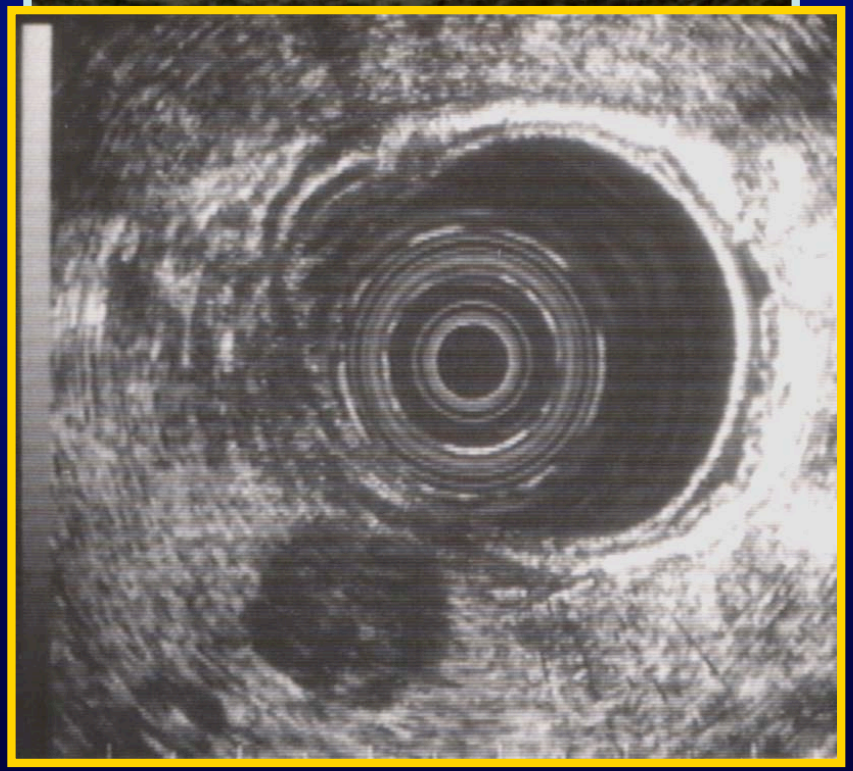
Homogeneous	81%
Hypoechoic	69%
Hyperechoic	6%
Isoechoic	6%
Inhomogeneous	19%
Cystic spaces	9%
Calcifications	6%

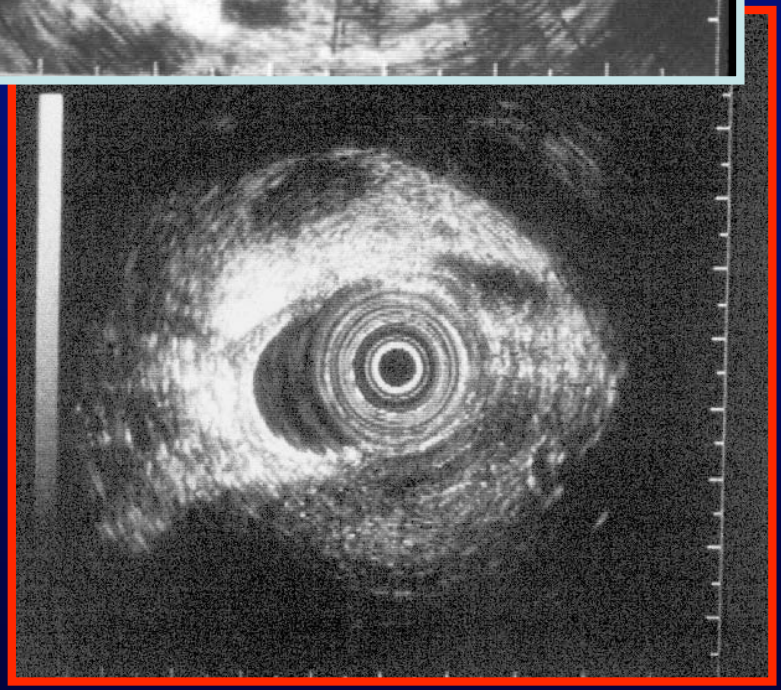
Margins

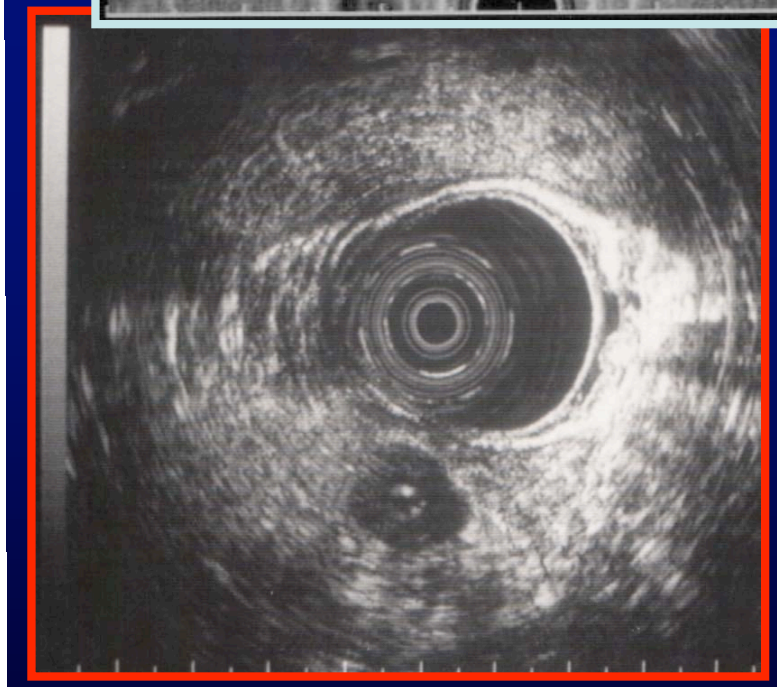
Sharp	84%
Irregular/indistinct	16%
Hypoechoic border	6%




GASTROENTEROLOGIA PROF. VERME - TORINO








EDALE MOLINETTE TO :BARO ROS
GASTROEPATOLOGIA :ENDOCR
168

Endoscopic UltraSound (EUS)

- In several studies EUS demonstrated high sensitivity and specificity in detecting NETs of the pancreatico-duodenal area

Loc.%	n. les.	Corr.
• Palazzo et al. 1992 (multicentric)	23	78
• Rosch et al. 1992 (multicentric)	39	82
• Thomson et al. 1994	10	70
• Zimmer et al. 1994	18	88
• Ruszniewski et al. 1995 (2 centers)	19	89
• Schumacher et al. 1996	14	57 (H83/T37)
• De Angelis et al. 1999	42	79
• Anderson et al. 2000	54 (pts)	93

EUS: SUMMARY OF LITERATURE DATA

Sensitivity	Specificity	Complication rate	Availability	Costs
%	%	%		
57 - 100	88 - 95	0.05 - 0.3	Few centers	Medium/ High (n° of exams)

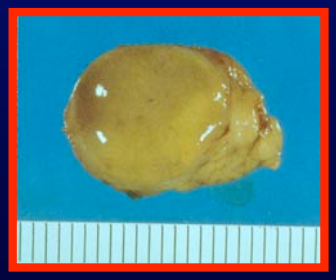
"Endosonography in decision making and management of gastrointestinal endocrine tumors"

De Angelis C et al. Eur J Ultrasound 1999;10:139

42 lesions

Pancreas	**23**
Duodenal wall	**8**
Peripancreatic LN	**10**
Paraduodenal solitary LN	**1**

7-35 mm



< 20 mm: 83%
< 15 mm: 67%

EUS AND PANCREATIC NETs

Pre-operative detection of NETs in the pancreas: comparison of EUS vs Other imaging techniques

Technique	N. of pts	Detection rate	
		lesions	%
EUS	**19**	**20/23**	**86.7%**
US	19	4/23	17.4%
CT	19	7/23	30.4%
MRI	8	3/12	25%
Angiography	11	4/15	26.6%
SRS	9	2/13	15.4%

De Angelis C et al. 1999

CLINICAL IMPACT OF EUS ON DECISION-MAKING AND MANAGEMENT OF PATIENTS WITH PANCREATIC NETs

- All considered EUS alone gave us more information than all other imaging techniques together
- It changed treatment plans in 17/39 (44%) of pts with NETs
- No other procedure, even more invasive than EUS, has been able to visualize the 3 pancreatic tumors and the 5 duodenal gastrinomas that EUS could not detect

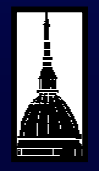
De Angelis C et al. 1999

CLINICAL IMPACT OF EUS ON DECISION-MAKING AND MANAGEMENT OF PATIENTS WITH PANCREATIC NETs

- Using EUS as first-line method for the detection of our NETs should have allowed a significant costs saving in **15/23 (65.2%) of** patients, avoiding both multiple and more invasive (like angiography in 50% of cases) and more expensive (like SRS in 45% or MRI in 32% of cases) diagnostic procedures

- Finally **6/39 patients (15.4%)** did not undergo a major surgical intervention based on the negative results of EUS examination

De Angelis C et al. 1999



furthermore….

- EUS sensitivity was significantly reduced (30%) for the NETs of the duodenal wall (gastrinomas)
- **Intra-operative endoscopic transillumination** of the duodenum remains today the best technique for the detection of duodenal wall gastrinomas (sensitivity: 83%)
- L'EUS remains a highly operator-dependent technique

De Angelis C et al. 1999

CONCLUSIONS

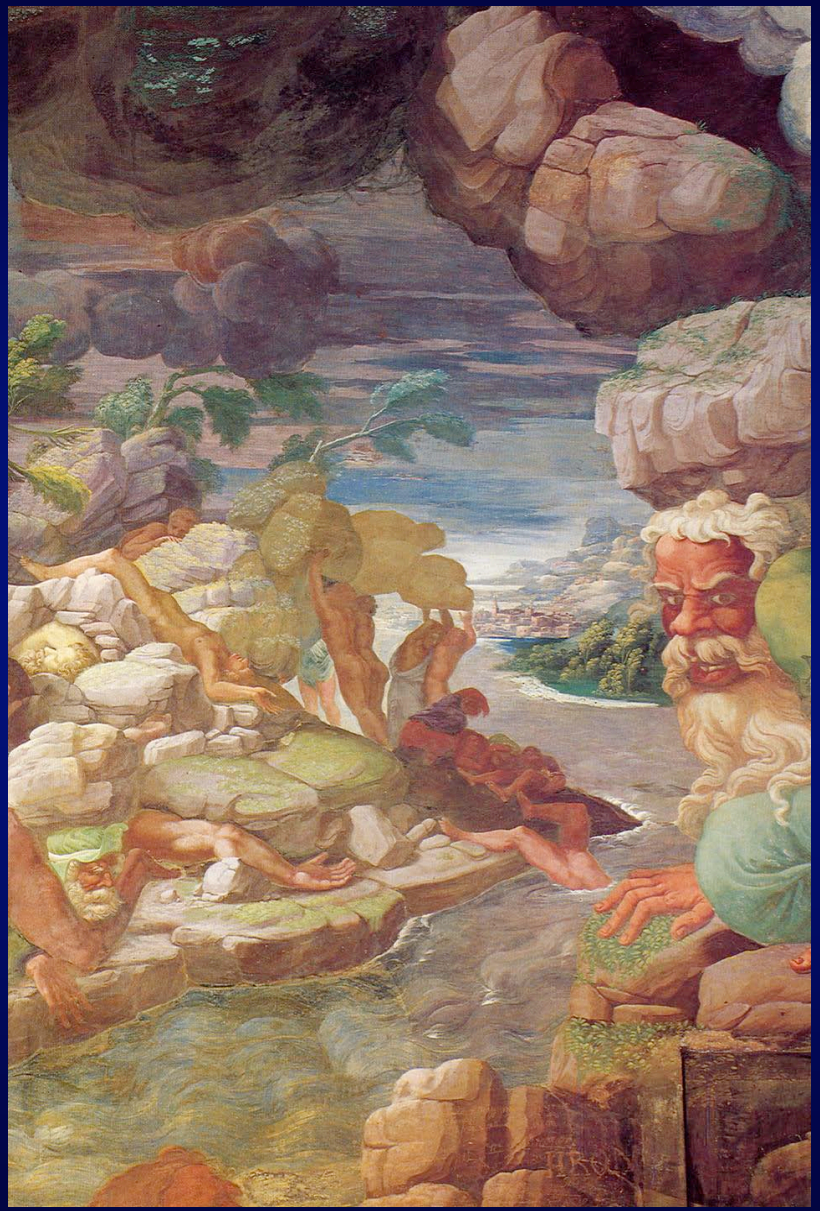
- Notwithstanding these problems, EUS has imposed itself as an accurate method of preoperative detection of pancreatic NETs and can be considered the imaging modality of first choice in this clinical setting.
- It is the single detection and staging technique more sensitive and should be used at an early stage in the diagnostic work up, if possibile straight after an US or a spiral CT to exclude hepatic metastases.
- EUS seems to be cost-effective: reducing costs, saving times and lowering morbidity due to more invasive tests

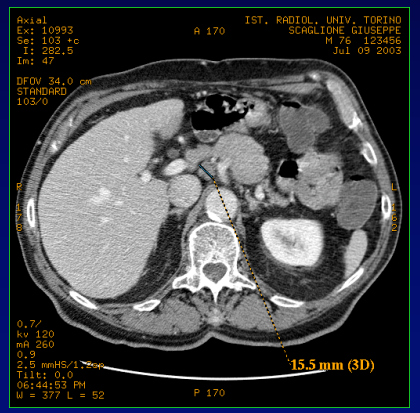
De Angelis C et al. 1999

EUS

+/-

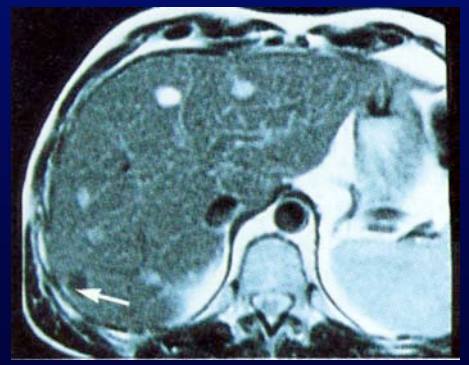
FNA

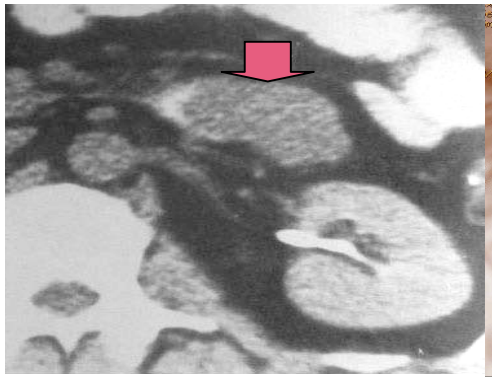


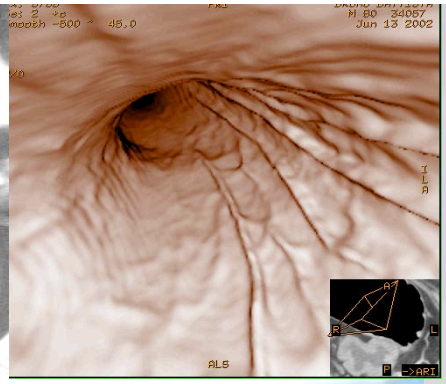


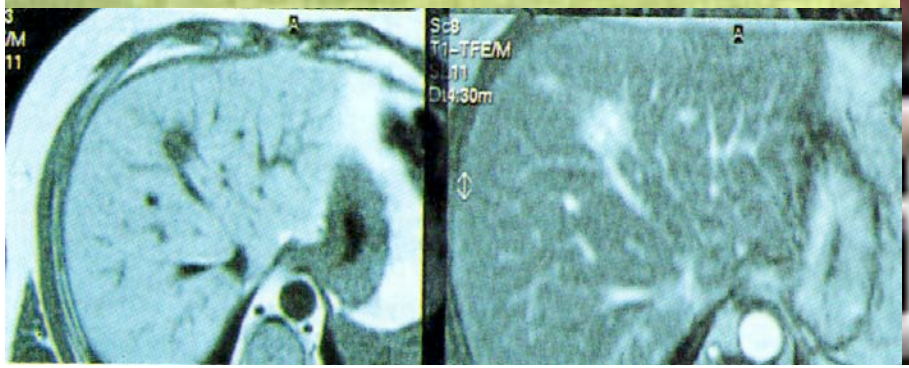
CT/MRI

PET/CT






Jun 13 2002
ALS


T1-TFEM

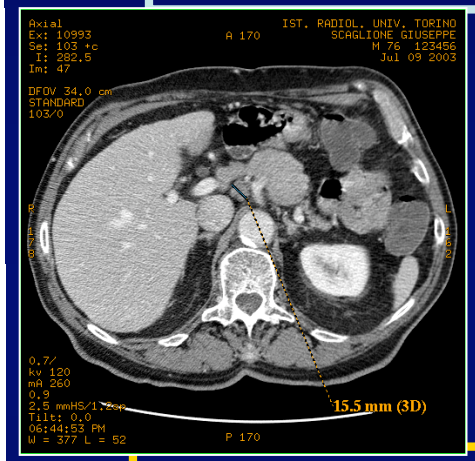

JUMP!
Horse Sports

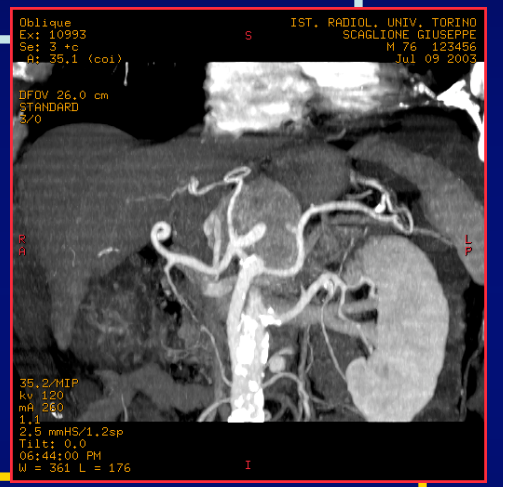
Comparison of EUS and CT for the preoperative evaluation of pancreatic cancer: a systematic review.

.....(DeWitt J et al. Clin Gastroenterol Hepatol 2006)

- *Literature is heterogeneous in: study design, quality and results. Methodologic limitations that potentially affects results.*
- *Overall EUS is > to CT for detection of PC, for T staging and for vascular invasion of the splenoportal confluence.*
- *The 2 tests appear to be equivalent for N staging, overall vascular invasion and assessment of tumor resectability.*

.... however EUS can not define distant metastatc disease, is still not universally available and is to a high degree operator dependent





Spiral CT or multislice CT must be the initial study of choice in pts with suspected pancreatic tumors

De Angelis C et al. Pancreatic cancer imaging: the new role of EUS. JOP J Pancreas (online) 2007;8 (1)

INSULINOMA

Table 1. Insulinoma—sensitivity of localisation by EUS and CT.

Study/date	Number patient (tumour)	Size (mm)	EUS (%) All areas	EUS (%) Head	EUS (%) Tail	CT (%)
Glover 1992	16	6–40	79			25
Rosch 1992	31	5–25	82			0
Pitre 1996	18	18 (mean)	90			38
Schumacher 1996	14	16 (mean)	57	83	37	
Ardnengh 2000	12	7–42	83	100	50	17
Anderson 2000	38 pt (29 tu)	15 (mean)	88			
Zimmer 2000 (meta analysis)			75 mean (range 57–92)			32 mean (range 0–73)
Gouya 2003	32	19.6 (mean)	94			57 (dual phase) 94 (thin section)

Refs. [1,2,10–15].

Best Practice & Research Clinical Endocrinology & Metabolism 2005; 19:177–93

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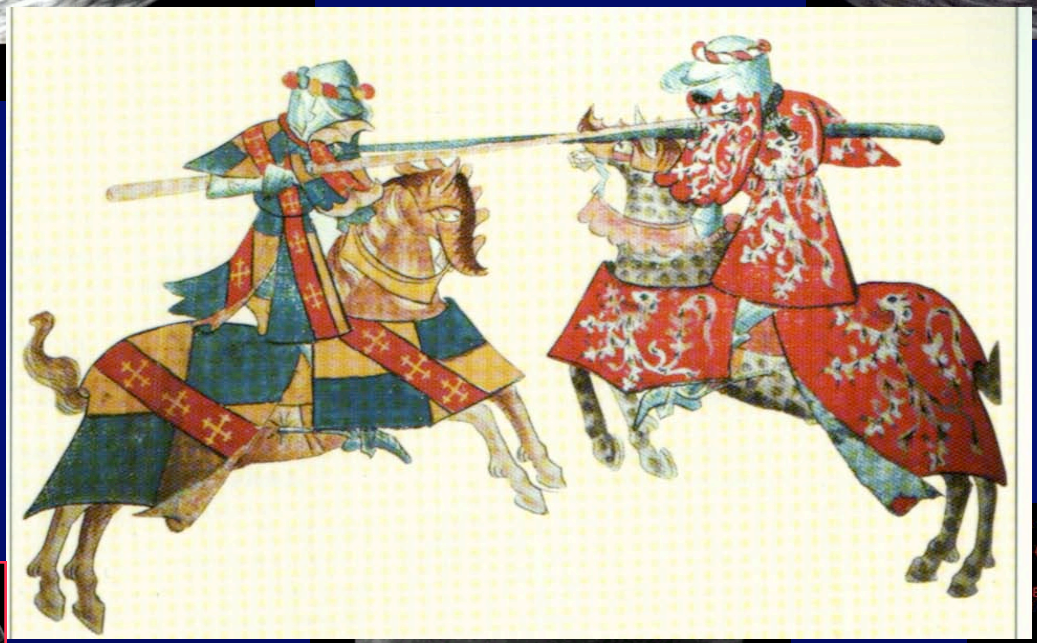
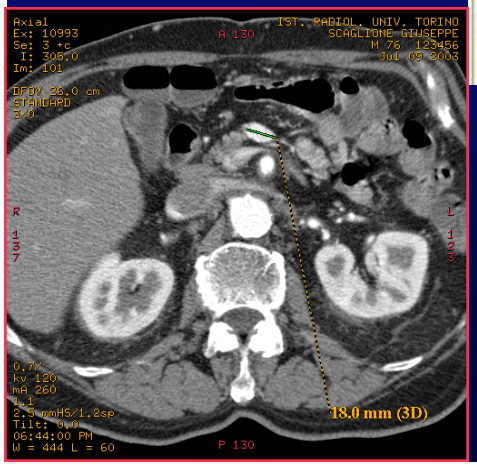
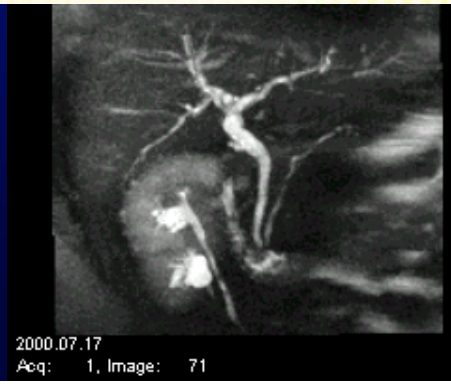
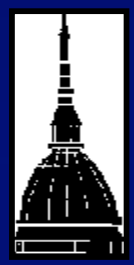
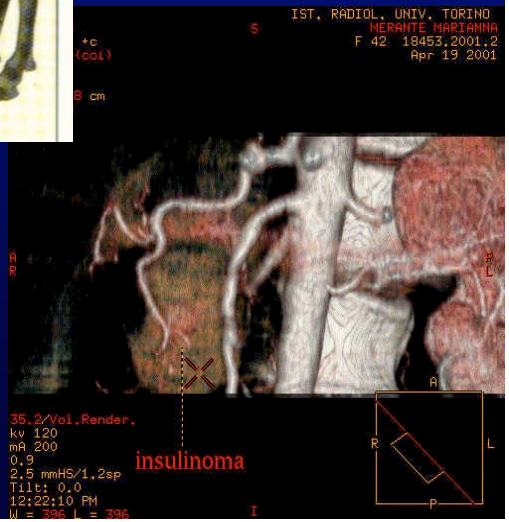
EGEUS
European Group for Endoscopic Ultrasonography











INSULINOMA

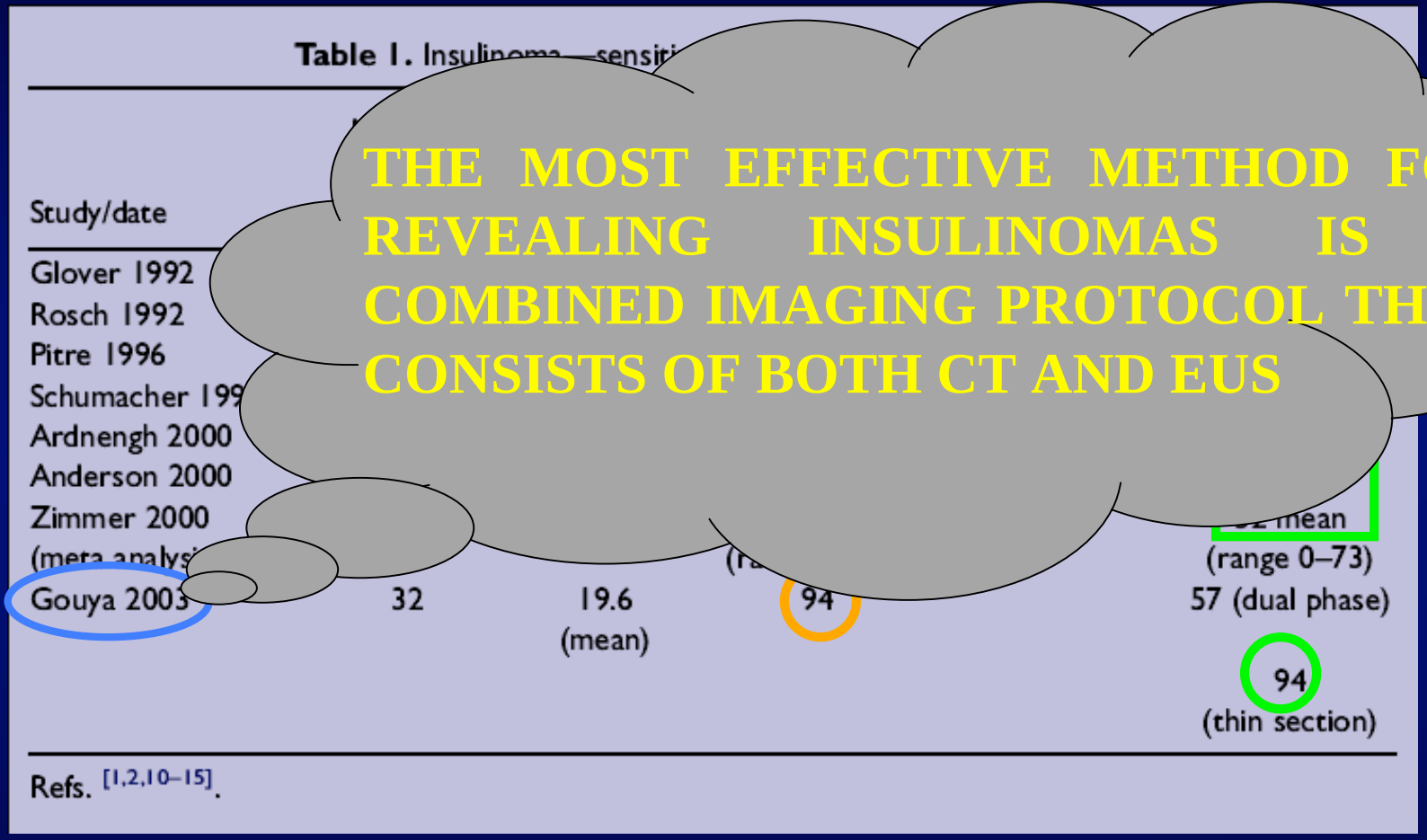


Table 1. Insulinoma—sensiti

Study/date				
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Zimmer 2000				
(meta analys			(r	mean (range 0–73)
Gouya 2003	32	19.6 (mean)	94	57 (dual phase)
				94 (thin section)

Refs. [1,2,10–15].

THE MOST EFFECTIVE METHOD FOR REVEALING INSULINOMAS IS A COMBINED IMAGING PROTOCOL THAT CONSISTS OF BOTH CT AND EUS

Best Practice & Research Clinical Endocrinology & Metabolism 2005; 19:177–93

GASTRINOMA: problems

- the location: 50% extra-pancreatic

- lesions in the duodenal wall are smaller than the pancreatic ones (9.6 mm vs 28.7 mm)

O Kisker et al. World J Surg 1998; 22: 651-7

- EUS sensitivity for pancreatic lesions: about 93%, it falls to 50% for extra-pancreatic lesions.

T Zimmer et al. Digestion 2000; 62: 45-50

- usefulness of intraoperative endoscopic transillumination (diagnostic improvement: + 20%) and duodenotomy (+15%)

Best Practice & Research Clinical Gastroenterology 2005; 19: 753–781

MEN-I

- many tumors are small (mean 1.1 cm)

EJ Wamsteker et al. Gastrointest Endosc 2003; 58: 531-5

- very often tumors are multiple (mean 3.3 tumors/pt)
- Screening with EUS in MEN-I asymptomatic pts can be recommended

EJ Wamsteker et al. Gastrointest Endosc 2003; 58: 531-5

EGEUS European Group for Endoscopic Ultrasonography

EUS ITALIAN CLUB

MEN-I

- many tumors are small (mean 1.1 cm)

  EJ Wamsteker et al. Gastrointest Endosc 2003; 58: 531-5

- spesso i [illegible] 3.3 tumori/p.te)

- r[illegible]asintomatici

In 13 MEN I asymptomatic pts, an EUS follow up of 13 yrs demonstrated the appearance of pancreatic tumors in 11

Aggressive early surgical treatment may improve the prognosis for these pts.

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MEN-I

However several papers subsequently demonstrated EUS effectiveness in detecting and following small pancreatic NETs in asymptomatic patients with MEN I sindrome

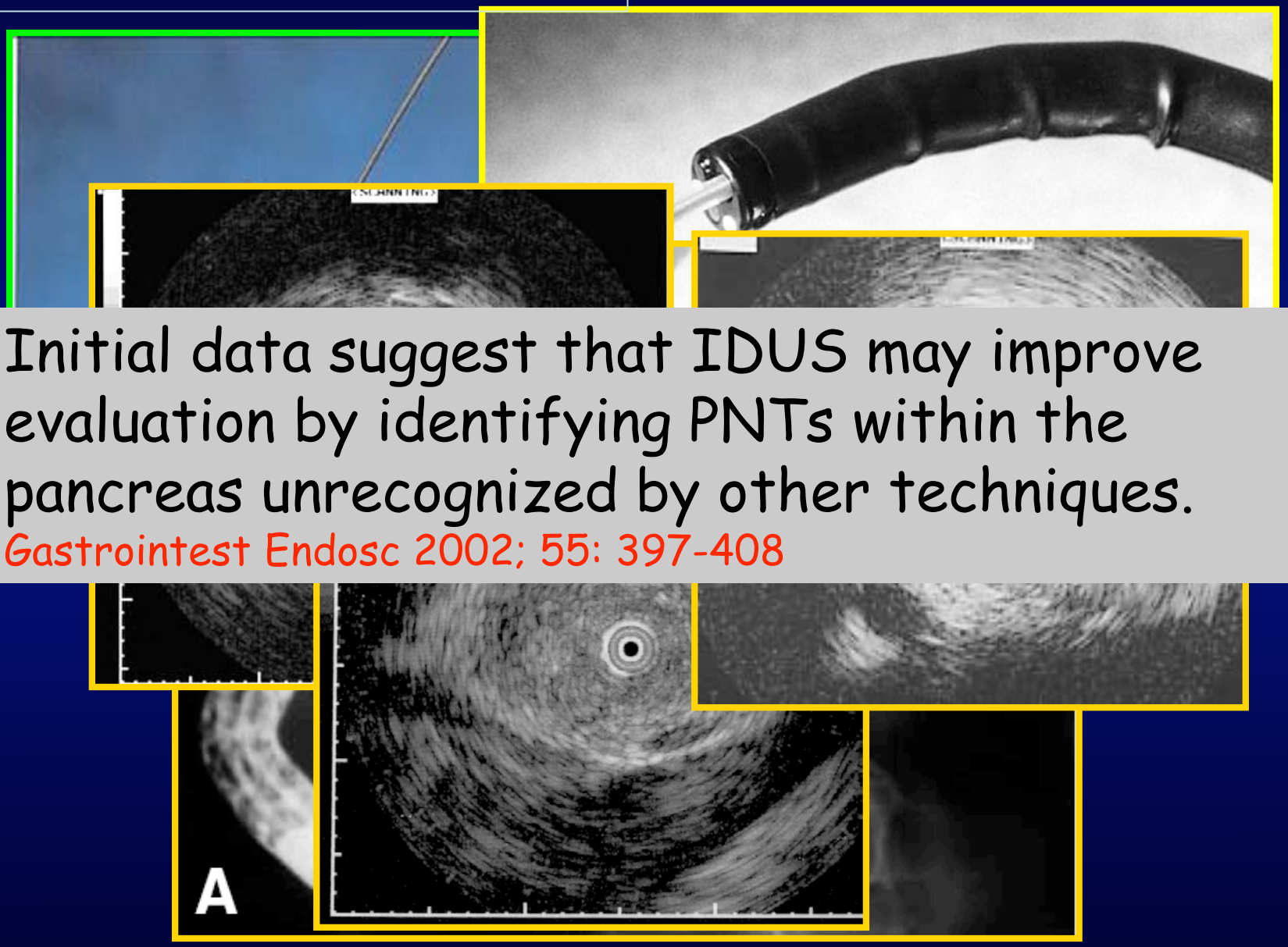
Gauger PG et al. Br J Surg. 2003;90(6):748-54.
Langer P et al. World J Surg. 2004;28(12):1317-22
Hellman P et al. Br J Surg. 2005;92(12):1508-12.
Thomas-Marques L et al. Am J Gastroenterol. 2006;101(2):266-73.
Kann PH et al. Endocr Relat Cancer. 2006;13(4):1195-202

EUS ITALIAN CLUB

EUS: REMARKS

Diagnostic EUS seems to be near to its TOP, but some new technologies (IDUS, CD-EUS, CE-EUS, THI-EUS) and interventional EUS are only at the beginning both as indications and instrumentation

MINIPROBES



Initial data suggest that IDUS may improve evaluation by identifying PNTs within the pancreas unrecognized by other techniques.

Gastrointest Endosc 2002; 55: 397-408

ELECTRONIC INSTRUMENTS WITH LINEAR SCANNING ALLOW:

1. EUS-GUIDED BIOPSIES (EUS-FNA)

a) ↑ SPECIFICITY FOR THE DIAGNOSIS OF PANCREATIC CANCER AND LYMPH NODES INVOLVEMENT

b) "Usefulness of EUS-guided fine needle aspiration (EUS-FNA) in the diagnosis of functioning neuroendocrine tumors"

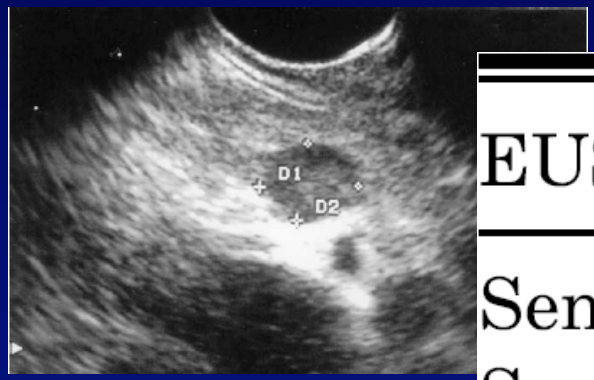
Ginès A et al. Gastrointest Endosc 2002;56:291

EUS-FNA safely provides cytologic confirmation with high accuracy in these patients.

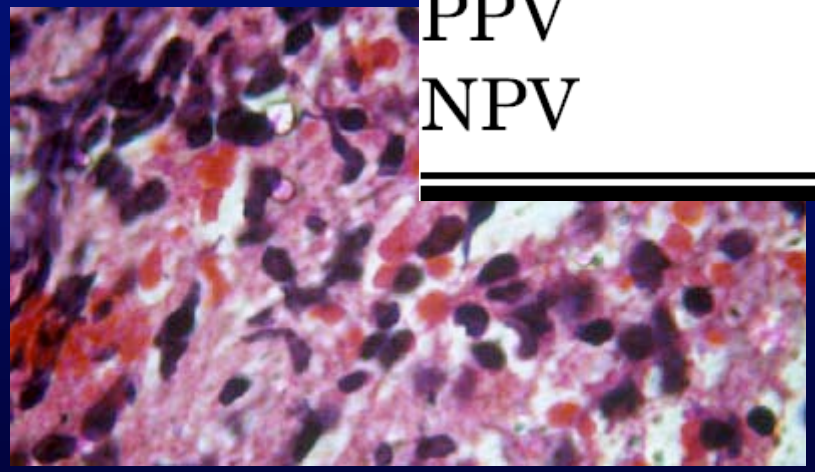
2) COLOR-DOPPLER APPLICATION

EUS-guided FNA in the diagnosis of pancreatic neuroendocrine tumors before surgery

José Celso Ardengh, MD, Gustavo Andrade de Paulo, MD, Angelo Paulo Ferrari, MD



EUS-FNA	n = 30	%	95% CI
Sensitivity	19/23	82.6	60.5, 94.3
Specificity	6/7	85.7	42.0, 99.0
Accuracy	25/30	83.3	64.5, 93.7
PPV	19/20	95.0	73.1, 99.7
NPV	6/10	60.0	27.9, 86.9



Gastrointest Endosc 2004;60: 378-84

EUS-FNA in the diagnosis of pancreatic NETs

- Other papers confirmed usefulness and effectiveness of EUS-FNA in the diagnosis of pancreatic NETs, both functioning and non-functioning.

- It is possible to reduce false positive results of only morphological EUS due to peri-and intra-pancreatic lymph nodes or splenosis nodules

Voss M et al. Gut. 2000;46(2):244-9
Gu M et al.Diagn Cytopathol. 2005;32(4):204-10.
Chang F et al. Cytopathology. 2006;17(1):10-7.
Jani N et al.Gastrointest Endosc. 2008;67(1):44-50.

EUS-FNA in the diagnosis of pancreatic NETs

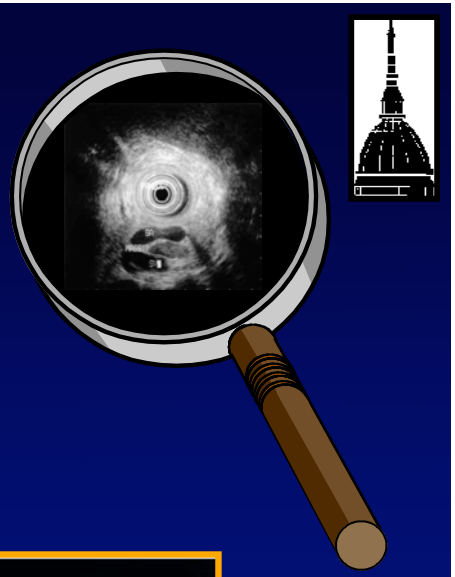
- **EUS-FNA works better than CT-FNA**

  Jhala D et al. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. Ann Diagn Pathol. 2002;6(2):106-12.

- **Possibility of predicting biological behaviour and outcome of the NET applying molecular biology techniques to the cell specimens obtained wth EUS-FNA .**

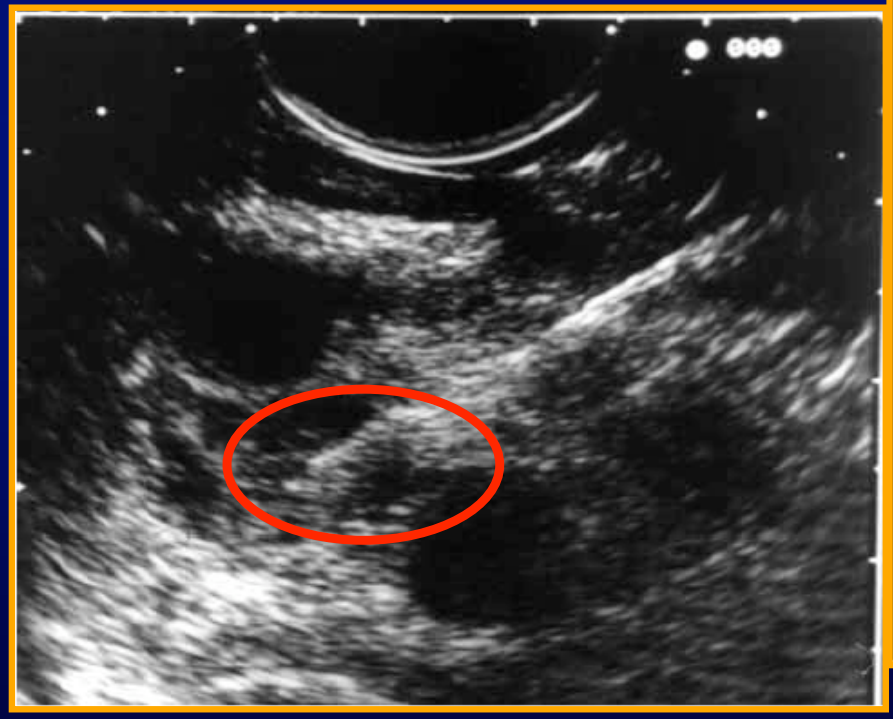
  Nodit L et al. Endoscopic ultrasound-guided fine needle aspirate microsatellite loss analysis and pancreatic endocrine tumor outcome. Clin Gastroenterol Hepatol. 2006;4(12):1474-8.

EUS allows identification of tiny lesions difficult to find by palpation during surgery



Preoperative localization of a neuro-endocrine tumor of the pancreas with EUS-guided fine needle tattooing

Frank G. Gress, MD, Mohammed Barawi, MD, Dong Kim, MD, James H. Grendell, MD



Gastrointestinal Endoscopy 2002; 55:594-7

Zografos GN et al. Hormones (Athens). 2005;4(2):111-6.

WHEN DO WE NEED A TISSUE DIAGNOSIS ?

WHEN THE RESULTS CAN ALTER PATIENT MANAGEMENT !!!

I.E....

- Differential diagnosis between benign and malignant lesion

- When there is the suspicion that the pancreatic lesion visualized by EUS or other imaging modalities could be a peri- or intra-pancreatic lymph node or a splenosis nodule or another type of lesion amenable of different therapeutic approaches (lymphoma, metastasis etc)

- Patient or lesion not fit for surgery and there is indication for CT

- **reluctance of the patient or the surgeon to perform a major surgical intervention, without a tissue diagnosis**

ELECTRONIC INSTRUMENTS WITH LINEAR SCANNING ALLOW:

1) EUS-GUIDED BIOPSIES (EUS-FNA)

2) COLOR-DOPPLER application:

"Utility of Endoscopic Ultrasonography with Color Doppler Function for the diagnosis of islet cell tumor"

Ueno N. et al. AJG 1996

EUS: NEW PROSPECTS

- *"Contrast-enhanced EUS" could improved the already high accuracy of EUS in visualizing small pancreatic NETs and in differential diagnosis of pancreatic lesions*