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POINT OF VIEW

Diagnostic protocol for pancreatic neuroendocrine tumors (PNETs)

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ABBREVIATIONS

A: angiography; US: ultrasonography; EUS: endoscopic ultrasonography; IUS: intraoperative ultrasonography; EUS-FNA: endoscopic ultrasonography-guided fine-needle aspiration; MRI: magnetic resonance imaging; SRS: octreoscan; CT: computerized tomography; MDCT: multidetector computerized tomography; PET: positron emission tomography; PET-CT: PET with computerized tomography; ICC: immunocytochemistry; I: insulinoma; G: gastrinomas; PNET: pancreatic neuroendocrine tumor or apudoma; NF-PNET: non-functioning PNET; MEN: multiple endocrine neoplasia; VHL: von Hippel-Lindau disease; R: review; C: cystic; CE: contrast-enhanced.

INTRODUCTION

The advent of endoscopic ultrasonography (EUS) or echoendoscopy (EE) represented a breaking point in the localization and diagnosis of PNETs (1-4) (insulinomas, gastrinomas, glucagonomas, non-functioning, etc.) as it provided a high yield (sensitivity around 90%, specificity at 98%) (5-10) only second to EUS-FNA (almost 100%) (10-15).

New EUS-related technologies such as contrast media and elastography have also improved PNET localization (16-22) with percentages matching those obtained with EUS-FNA.

A recent paper states that contrast agents (S: 95%) substantially improve conventional EUS findings (21).

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Therefore, diagnostic EUS should be now considered seriously for PNET assessment (10) in addition to elastography, contrast media, both things, or even FNA (22).

Furthermore, novel imaging techniques other than US (23), CT (24,25), and MRI (25,26), including PET (FDG & DOPA) and PET-CT, may be used for the localization and staging of PNETs, particularly when no primary tumor has been found (27-32) (Table I).

When CT will not find a PNET, EUS does so in 91% of cases (34). According to several papers EUS is superior to MDCT (Multiple Detector Computerized Tomography) (8,21,33,34).

PET-CT may be a match for Octreoscan (31) for tumors other than insulinomas, and only PET-CT is superior to Octreoscan when tumors with a high Ki-67 proliferation index are considered (32), with sensitivity approaching 100% when it comes to finding a primary tumor and its related metastases (35-38).

Once a tumor is precisely located its staging must ensue in order to decide on its appropriate management (surgical or otherwise) and to define a prognosis according to histopathology (Figs. 1 and 2) (39).

We have moved from the classical TNM system to the WHO histological classification (40):

- *Well differentiated:* benign, smaller than 2 cm, confined to the pancreas, fewer than 2 mitoses per 10 HPFs, Ki-67 below 2%, and chromogranin A +. No vascular invasion.
- *Uncertain behavior:* confined to the pancreas and one or more of the following: a) larger than 2 cm; b) 2-10 mitoses; c) Ki-67 above 2%; and d) vascular invasion and perineural permeation.

Table I. A comparison of PNET detection rates with several imaging techniques

Author	Year	N.º	% Insulinoma	Size	CT	EUS	MR	SRS	US	A	PET
Zimmer	1994	18				88		52			
Ueno	1996 (5)	7	71%		57	100			86	100	
Proye	1998	7				77					
Anderson	2000 (6)	54	58%	15 mm		93				44	
Thoeni	2000						80				
Rickes	2003 (23)	29						54	94 US-CE		
Gouya	2003 (24)	30	100%	20 mm	72	94					
Rappeport	2006 (8)	20	10%	18 mm	80	100					
Koopmans	2008 (29)	23			87			78			89
Alsohaibani	2008 (9)	14		4-25 mm	77	100 90 USE-PAAF	67	50			
Malagò	2009 (42)	38	0%						81.5 US-CE		
An	2010 (43)	31	100%						89 US-CE		
Ishikawa	2010 (21)	41			81	95			45		
Suzuki	2010 (15)	34		30 mm	62	65 90 USE-PAAF			32		
Druce	2010 (26)	30	100%		64	65	75	50			
Versari	2010 (33)	19			91	100					92
Khashab	2011 (34)	60	32%	32.7 mm	63	92					
Gornals	2011 (14)	9 y 16 casos	33%	19 mm		100 USEPAAF					
Varas	2011 (35)	19	10%	20 mm	88	100		80	83		100
Turuga	2011 (37)	Revisión			80		70	85			100
Tan	2011 (38)	Revisión			94	80-90		80-90	<70 sólo US 66%		90-100

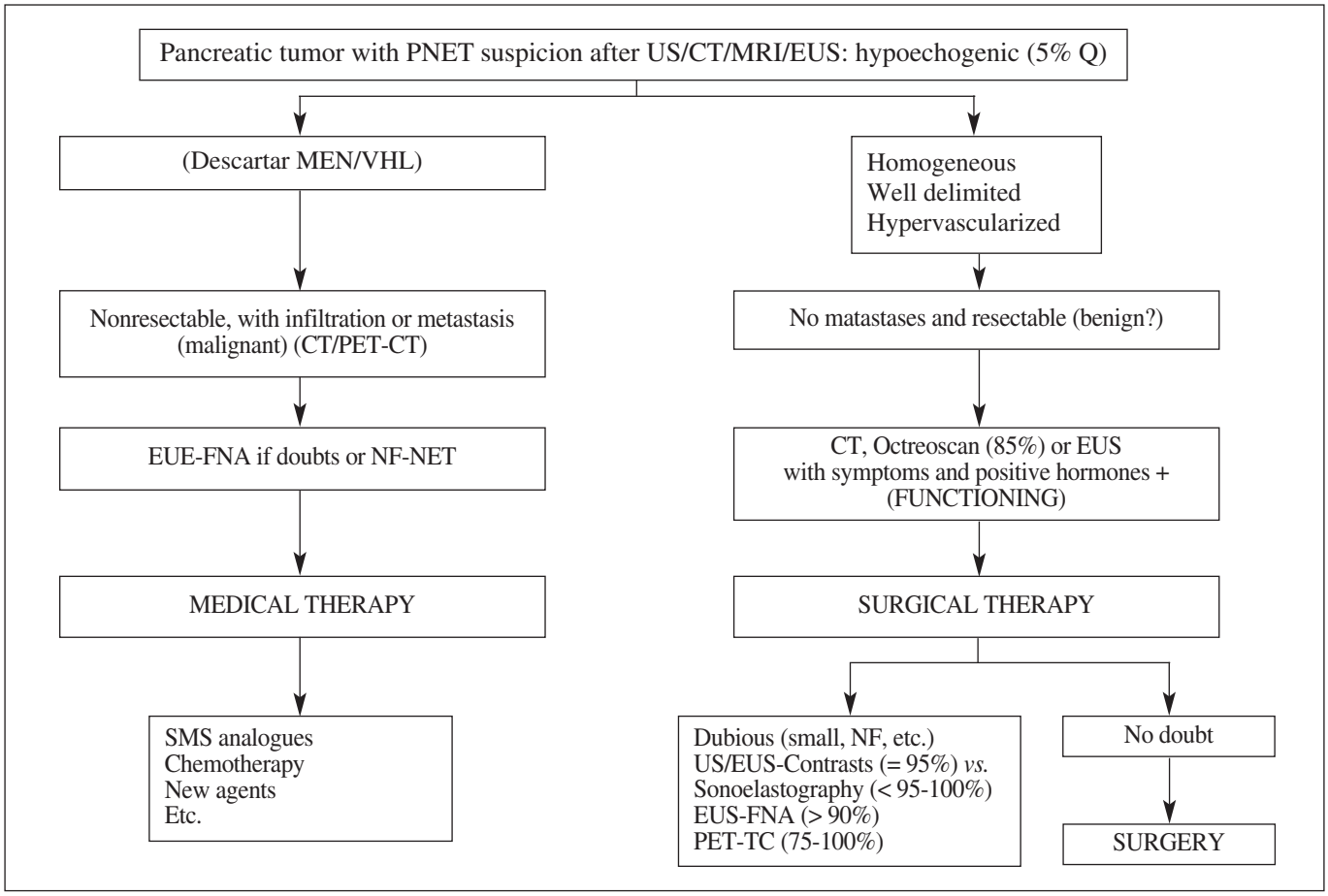

Fig. 1. General diagnostic algorithm (modified from reference 22).

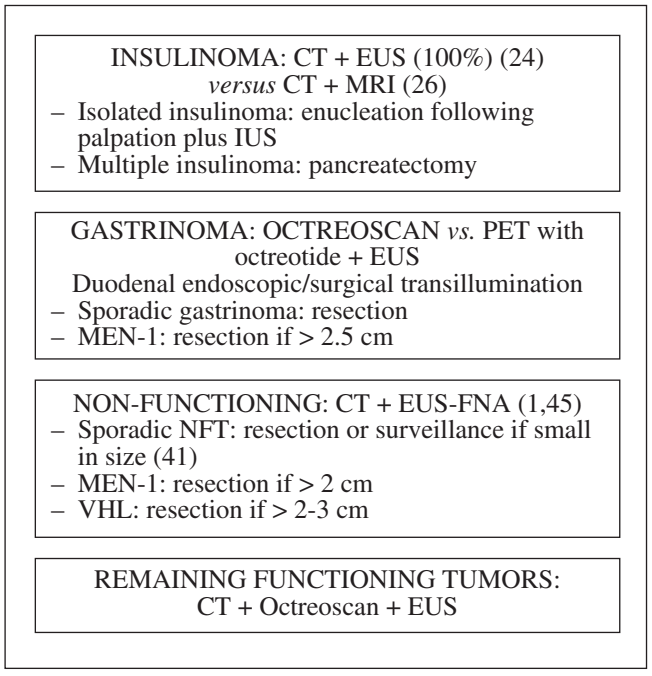

Fig. 2. Diagnostic algorithm for most common types.

– *Well-differentiated endocrine carcinoma:* low malignity. Macroscopic local invasion and/or metastasis (malignant). No vascular invasion.
– *Poorly-differentiated endocrine carcinoma:* high malignity, over 10-20 mitoses per 10 HPFs. Ki-67 above 15-20%. Vascular invasion.

For instance, in a series of 139 NF-PNETs incidentally identified (mean size: 3 cm) and then operated upon, 19% were classified as benign, 52% as with uncertain behavior, and 28% as malignancies. Mean 3-year follow-up of 80% (112 cases) revealed an actuarial survival of 89, 92.5, and 50%, respectively, at 5 years (44).

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