Diagnostic protocol for pancreatic neuroendocrine tumors (PNETs)

Modesto Varas1, Joan Gornals2, José Luis Prieto3 and Julio Iglesias-García4. Grupo de trabajo de Ultrasonografía Endoscópica de la SEPD

1Unit of Echoendoscopy. Centro Médico Teknon and Hospital Universitario del Valle Hebrón. Barcelona, Spain. 2Unit of Endoscopy. Hospital Universitario de Bellvitge. Hospital Llobregat, Barcelona, and Centro Médico Teknon. Barcelona, Spain. 3Unit of Digestive Diseases. Hospital Punta Europa. Algeciras, Cádiz, Spain. 4Department of Digestive Diseases. Hospital Clínico Universitario de Santiago de Compostela. A Coruña, Spain

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).


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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N.º</th>
<th>% Insulinoma</th>
<th>Size</th>
<th>CT</th>
<th>EUS</th>
<th>MR</th>
<th>SRS</th>
<th>US</th>
<th>A</th>
<th>PET</th>
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<td>18</td>
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<td></td>
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<tr>
<td>Ueno</td>
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<td>7</td>
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<td>57</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Proye</td>
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<td></td>
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<tr>
<td>Anderson</td>
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<td>54</td>
<td>58%</td>
<td>15 mm</td>
<td>93</td>
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<td></td>
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<td>80</td>
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<tr>
<td>Rickes</td>
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<td></td>
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<td></td>
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<td>54</td>
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<tr>
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<tr>
<td>Rappeport</td>
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<td>18 mm</td>
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<td></td>
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<tr>
<td>Koopmans</td>
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<td></td>
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<td>67</td>
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<td></td>
<td></td>
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<tr>
<td>An</td>
<td>2010 (43)</td>
<td>31</td>
<td>100%</td>
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<td></td>
<td>90 USE-PAAF</td>
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<tr>
<td>Versari</td>
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<td>92</td>
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<tr>
<td>Khashab</td>
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<td>32%</td>
<td>32.7 mm</td>
<td>63</td>
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<td>90 USEPAAF</td>
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<tr>
<td>Gornals</td>
<td>2011 (14)</td>
<td>9 y 16 casos</td>
<td>33%</td>
<td>19 mm</td>
<td>88</td>
<td>100</td>
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<tr>
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<td>19</td>
<td>10%</td>
<td>20 mm</td>
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<td>100</td>
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<tr>
<td>Turuga</td>
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<td>Revisión</td>
<td></td>
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<td>70</td>
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<td>Tan</td>
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<td>80-90</td>
<td>&lt;70 sólo US</td>
<td>90-100</td>
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</table>

Pancreatic tumor with PNET suspicion after US/CT/MRI/EUS: hypoechogenic (5% Q)

(Descartar MEN/VHL)

Homogeneous
Well delimited
Hypervascularized

Nonresectable, with infiltration or metastasis
(malignant) (CT/PET-CT)

EUE-FNA if doubts or NF-NET

MEDICAL THERAPY

SMS analogues
Chemotherapy
New agents
Etc.

No metastases and resectable (benign?)

CT, Octreoscan (85%) or EUS
with symptoms and positive hormones +
FUNCTIONING

SURGERY

Dubious (small, NF, etc.)
US/EUS-Contrasts (= 95%) vs.
Sonoelastography (< 95-100%)
EUS-FNA (> 90%)
PET-TC (75-100%)

No doubt

SURGERY

Fig. 1. General diagnostic algorithm (modified from reference 22).
**INSULINOMA:** CT + EUS (100%) (24) versus CT + MRI (26)
- Isolated insulinoma: enucleation following palpation plus IUS
- Multiple insulinoma: pancreatectomy

**GASTRINOMA:** OCTREOSCAN vs. PET with octreotide + EUS
- Duodenal endoscopic/surgical transillumination
- Sporadic gastrinoma: resection
- MEN-1: resection if > 2.5 cm

**NON-FUNCTIONING:** CT + EUS-FNA (1,45)
- Sporadic NFT: resection or surveillance if small in size (41)
- MEN-1: resection if > 2 cm
- VHL: resection if > 2.3 cm

**REMAINING FUNCTIONING TUMORS:**
CT + Octreoscan + EUS

Fig. 2. Diagnostic algorithm for most common types.

- **Well-differentiated endocrine carcinoma:** low malignancy. Macroscopic local invasion and/or metastasis (malignant). No vascular invasion.
- **Poorly-differentiated endocrine carcinoma:** high malignancy, 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, identified (mean size: 3 cm) and then operated upon, 19% were classified as benign, 52% as with uncertain behavior, and 30% as malignant.

**REFERENCES**


