Pancreatic endocrine tumors or apudomas

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ABSTRACT

Introduction and objective: pancreatic endocrine tumors (PET) are difficult to diagnose. Their accurate localization using imaging techniques is intended to provide a definite cure. The goal of this retrospective study was to review a PET series from a private institution.

Patients and methods: the medical records of 19 patients with PETs were reviewed, including 4 cases of MEN-1, for a period of 17 years (1994-2010). A database was set up with ten parameters: age, sex, symptoms, imaging techniques, size and location in the pancreas, metastasis, surgery, complications, adjuvant therapies, definite diagnosis, and survival or death.

Results: a total of 19 cases were analyzed. Mean age at presentation was 51 years (range: 26-67 y) (14 males, 5 females), and tumor size was 5 to 80 mm (X: 20 mm). Metastatic disease was present in 37% (7/19). Most underwent the following imaging techniques: ultrasounds, computed tomography (CT) and magnetic resonance imaging (MRI). Fine needle aspiration puncture (FNA) was performed for the primary tumor in 4 cases. Non-functioning: 7 cases (37%), insulinoma: 2 cases [1 with possible multiple endocrine neoplasia (MEN)], Zollinger-Ellison syndrome (ZES) from gastrinoma: 5 (3 with MEN-1), glucagonoma: 2 cases, 2 somatostatinomas; carcioid: 1 case with carcinoid-like syndrome.

Most patients were operated upon: 14/19 (73%). Four (4/14: 28%) has postoperative complications following pancreatectomy: pancreatitis, pseudocyst, and abdominal collections. Some patients received chemotherapy (4), somatostatin (3) and interferon (2) before or after surgery.

Median follow-up was 48 months.

Actuarial survival during the study was 73.6% (14/19).

Conclusions: age was similar to that described in the literature. Males were predominant. Most cases were non-functioning (37%). Most patients underwent surgery (73%) with little morbidity (28%) and an actuarial survival of 73.6% at the time of the study.


INTRODUCTION

Gastro-entero-pancreatic neuroendocrine tumors (GEPETs) originate in the diffuse endocrine cell system (APUD system); 60-70% are digestive tract carcinoids, and 20-40% are located in the pancreas (PETs).

The incidence of PETs is on the rise as it had been estimated in fewer than 1 case/100,000 (0.2/100,000/year) (1-7) but has been presently reported as 4.4 cases/100,000 population and year, with non-functioning tumors predominating (8). Insulinomas and gastrinomas account for 1 case per million population.

These tumors may be sporadic or associated with multiple endocrine neoplasia (MEN) (5). They may be benign or malignant according to the presence of metastasis.

They are categorized as functioning (with specific hormonal syndromes: Zollinger-Ellison syndrome (ZES) or ZES from gastrinoma, etc.) (5), and non-functioning, which are most common (8).

The frequency of non-functioning tumors (NFPETs) is 15 to 75%, reaching 91% in some series (8). Their mean incidence may be around 55-60%.
When functioning (around 40%), these tumors may result in multiple hormone secretion (MHS) or be associated with MEN-1, Von Hippel-Landau disease, Von Recklinghausen disease (neurofibromatosis 1), and tuberous sclerosis (1,5).

In an early series (84 patients with PET) mean age at presentation was 53 years with no clear gender predominance; most were located in the tail of the pancreas (41%) and were malignant (70%). Non-functioning tumors represented 24%, whereas gastrinomas (30%) and insulinomas (27%) were most common. Vipomas, glucagonomas and somatostatinomas were a minority (9).

Relevant series have been subsequently described (10-13) that detail the individual characteristics of these fascinating, uncommon tumor types (5).

Overall survival varies according to tumor type and functional status, stage, and treatment.

**OBJECTIVE**

The goal of this retrospective research was to review a private institution’s series of PET, and to compare it with an updated review of the literature.

**PATIENTS AND METHODS**

When the matter was theoretically reviewed in 2008 (5) 14 cases were recorded in our site. A data base was set up and the medical records of 19 patients followed up for 17 years at one private institution were retrospectively reviewed (1994-2010). Two patients with MEN-1 had each one child affected.

Demographic parameters were studied by setting up a database with ten parameters (age and sex, symptoms, imaging techniques, size and location in the pancreas, metastasis, surgery, complications, complementary therapies, definite diagnosis, and survival), which were compared to those in the literature.

Mean, median, standard deviation, and percentage values were estimated using specific formulas.

**RESULTS**

Mean age at presentation was 51 years (range: 26-67 years); 73% (14/19) were males.

Mean tumor size: 20 mm (5-80 mm). They were located in the head of the pancreas: 8 (47%), uncinated process: 1, pancreas body: 3, tail: 5 cases (30%). Nearly one half were located in the head and the other half in the body-tail of the pancreas. Most were non-functioning tumors (37%) in addition to gastrinomas (26%), insulinomas (10%), somatostatinomas (10%), glucagonomas (10%) (1 with MHS), and carcinoids (5%).

<table>
<thead>
<tr>
<th>Arteriography: 0/1</th>
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<tbody>
<tr>
<td>US:</td>
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<tr>
<td>CT:</td>
</tr>
<tr>
<td>Octreoscan:</td>
</tr>
<tr>
<td>PET-CT:</td>
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<tr>
<td>EUS:</td>
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<tr>
<td>EUS-FNAP:</td>
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</table>

Imaging techniques used for diagnosis and localization: most cases underwent US/CT/MRI. Octreoscan for five cases and EUS for six, half of which further underwent EUS-FNAP. One underwent PET. One case had an arteriogram performed, which was negative (Table I).

Metastasis: 37% (7/19), most to the liver.

Surgery was performed for 73% of cases without operative mortality.

Morbidity: 28% (two acute pancreatitis cases, one pseudocyst, and two abdominal collections). All complications occurred in pancreatectomized patients. No post-operative complications occurred in two patients (insulinomas) who underwent enucleation.

Median follow-up was 48 m.

Actuarial survival: 73.6%.

Deceased patients presented with obstructive jaundice or had metastasis.

**DISCUSSION**

Of all GEPETs, 60-70% are digestive tract carcinoids, and 20-40% are located in the pancreas.

In a series (14) of 86 GEPETs seen over 10 years, most were located in the stomach, mean age was 52 years, male:female ratio was 0.87, and 35% were malignant. While women predominate in some series, there is no clear preference for either gender.

Regarding 907 cases in the Spanish national registry for endocrine cancer (15) 55% were carcinoids, 32% PET (20% non-functioning, 8% insulinomas, 4% gastrinomas), with 44% malignancies. Overall 5-year survival was 75.4%. Independent predictors of survival only included stage and Ki 67 index.

In our patients mean age was 51 years, most were males, 37% were NF tumors, and 37% also had metastases, with actuarial survival being estimated at 73.6%.

In an early reported series (9) with 84 PETs mean age was 53 years, most were located in the tail (41%) and were malignant (70%).

In our series most were located in the head of the pancreas.

The most extensive American study (16) with 168 PETs in one same center mean age was 56 years; 51%
women, 76% benign, 24% malignant, 57.7% NF, and 33% insulinomas; 63% were located in the body or tail of the pancreas. Survival at 5-10 years was 77 and 62%, respectively.

In a recent Italian multicenter study (17) of 297 PETs mean age was 58 years: 51% women, 57% malignant, 24.6% functioning, and 75.4% non-functioning. Mean tumor size was 20 mm (2-150 mm), similar to ours, 20 mm (5-80 mm).

NFPETs (18-38) are usually most common, oscillating from 15-52% to 70-85-91%, with survival according to tumor size and malignity (metastasis); 70% are greater than 5 cm, and half are malignant (50%). In a series (23) of 43 cases (65% malignant) mainly in younger women, good results were obtained after surgery with curative intent, including cases of liver metastases (24) (Table II).

Insulinomas are usually pancreatic, benign, small, and multiple; nearly 90% (28) may be healed with surgical enucleation or resection (5), and survival is thus very high (almost 100%).

Gastrinomas are malignant in around 50% of cases, and 90% are located in the so-called “gastrinoma triangle” in order of frequency, pancreas (45%), duodenum (20%), and others (2%); 75% are sporadic and 25% have MEN-1.

When operated on with curative intent gastrinomas have a 1-year survival of 98% versus 74% (39) for non-surgical patients; 29% of non-surgical patients developed liver metastases (primary concern when caring for ZES). Vipomas (15%) (10-11), glucagonomas (7%) (12), pancreatic somatostatinomas (4%) (13), and carcinoids (1% of all carcinoids) (40) are much less common.

The most relevant issue to achieve a definite cure is assessing their exact location (41-43). Combined US/CT had a sensitivity of 84% (28). Of all imaging techniques EUS with or without FNAP in association with CT (100%) is the best approach, particularly for insulinomas (5,41,43). Most of our cases were localized using US/CT/EUS.

The best approach for gastrinomas is likely a combination of EUS and Octreoscan (41) or PET-CT (Fig. 1). EUS localizes up to 93% of PETs (44), and 87% of insulinomas (45) with a sensitivity of 89.5% (46). EUS-FNAP reaches a diagnosis in 90-100% of cases (47-49) (Fig. 2).

Once localized and staged, the best option—when possible—is surgery with curative intent: enucleation versus resection or partial pancreatectomy (50) after careful palpation and intraoperative US (IUS), which localizes 93% of insulinomas (52).

In a national surgical series (32) with 48 cases (22 years’ experience: 2 cases per year approximately), 39 of them benign (81%) and with predominant insulinomas (28 cases), with a mean age of 49 years (22 males/27 females: 0.81), 20 tumors were enucleated. Morbidity: 6 fistulas (22%), 3 abdominal collections, 1 pancreatitis, 1 pseudocyst.

In our series of 19 cases with 14 patients operated upon (73%), morbidity was 28% at the expense of pancreatitis and abdominal collections in patients undergoing pancreatectomy. In other series (34) morbidity was intermediate -25% (Table IV).

Complementary or alternative therapies (1,5) include somatostatin analogues, interferon, angiogenesis inhibitors, palliative chemotherapy and radiation therapy,

<table>
<thead>
<tr>
<th>Author and year</th>
<th>No. cases</th>
<th>Metastasis</th>
<th>Survival at 3 , 5 , 10 &amp; 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kent, 1981 (18)</td>
<td>25</td>
<td>(25)</td>
<td>40% 60% 44% 50%</td>
</tr>
<tr>
<td>Evans, 1993</td>
<td>73</td>
<td>(51%)</td>
<td>NR</td>
</tr>
<tr>
<td>La Rosa, 1996</td>
<td>61</td>
<td>(56%)</td>
<td>NR</td>
</tr>
<tr>
<td>Solorzano, 2001</td>
<td>163</td>
<td>(62%)</td>
<td>NR</td>
</tr>
<tr>
<td>Gullo, 2003</td>
<td>184</td>
<td>(38%)</td>
<td>77% vs. 29% 60%</td>
</tr>
<tr>
<td>Guo, 2004</td>
<td>41 Op.</td>
<td>(41%)</td>
<td>NR</td>
</tr>
<tr>
<td>Liang, 2004</td>
<td>43</td>
<td>(65%)</td>
<td>58% 29%</td>
</tr>
<tr>
<td>Hung, 2007</td>
<td>13 Op.</td>
<td>(38%)</td>
<td>85% NR</td>
</tr>
<tr>
<td>Chung, 2007</td>
<td>25</td>
<td>(91%)</td>
<td>NR</td>
</tr>
<tr>
<td>Bettini, 2008</td>
<td>180</td>
<td>(52%) Op.</td>
<td>67% 44%</td>
</tr>
<tr>
<td>Franko, 2010</td>
<td>2,158 Op.</td>
<td>(32%)</td>
<td>33% 17% 10%</td>
</tr>
<tr>
<td>Falconi, 2010</td>
<td>50 Op.</td>
<td>(50%)</td>
<td>49% 30% 10%</td>
</tr>
</tbody>
</table>

NR: Not recorded; Op.: Operated on; X: arithmetic mean.
etc. Most of our patients were treated with chemotherapy and somatostatin analogues.

Survival at 5 years among 70 operated patients (23% insulinomas, 71% non-functioning and 53% malignant) was 77% (27). In shorter series (28,34), with 36 (19% non-functioning) and 20 cases, survival was 92 versus 50% for malignancies, and 70% at 5 years. In larger series (31) survival at 5 years was 59.3%, and at 10 years 37.7%. In the multivariate analysis, age, stage, metastasis, functionality, and type of resection were all independent predictors of survival following resection.

The Swedish Uppsala team (53) studies prognostic factors in 324 patients with PET, with survival at 5 and 10 years of 64 and 44%, respectively. In the univariate analysis, stage, radical surgery, functional status, high Ki 67 index and Cg-A (highly sensitive and specific for PET), tumor size, and sporadic (rather than familial) nature are significant prognostic factors; in the multivariate analysis only stage, radical surgery, and Ki 67 above 2% were relevant. Non-functioning tumors were an independent marker of poorer prognosis.

Bettini et al. (54) study 180 cases of NFPET with survival at 5, 10 and 15 years of 67, 49 and 33%, respective-

### Table III. PET series

<table>
<thead>
<tr>
<th>Author and year</th>
<th>No. cases</th>
<th>X age</th>
<th>M</th>
<th>NFPET</th>
<th>Status</th>
<th>S at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson, 1989 (9)</td>
<td>84 74% Op.</td>
<td>53 y.</td>
<td>70%</td>
<td>24%</td>
<td>Tail: 41%</td>
<td>?</td>
</tr>
<tr>
<td>Phan, 1998 (26)</td>
<td>125</td>
<td>51 y.</td>
<td>52%</td>
<td>48%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Kazanjian, 2006</td>
<td>70</td>
<td>53%</td>
<td>71%</td>
<td>77%M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagefi, 2006</td>
<td>168</td>
<td>56 y.</td>
<td>26%</td>
<td>58%</td>
<td>C-C: 63%</td>
<td>77%</td>
</tr>
<tr>
<td>Liu, 2007</td>
<td>36</td>
<td>47 y.</td>
<td>19%</td>
<td>92 vs. 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schurr, 2007</td>
<td>62 78% Op.</td>
<td>55 y.</td>
<td>31%</td>
<td>NR</td>
<td>80% vs. 64%</td>
<td></td>
</tr>
<tr>
<td>Bilimoria, 2007</td>
<td>9,821 40% Op.</td>
<td>60 y.</td>
<td>56%</td>
<td>85%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Halfdanarson, 2008</td>
<td>1,483</td>
<td>58 y.</td>
<td>60%</td>
<td>91%</td>
<td>48 vs. 31%</td>
<td></td>
</tr>
<tr>
<td>Ekeblad, 2008</td>
<td>324</td>
<td>NR</td>
<td>17%</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz-Tovar, 2008</td>
<td>48 46% Op.</td>
<td>49 y.</td>
<td>21%</td>
<td>70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jagad, 2008</td>
<td>54 39% Op.</td>
<td>57%</td>
<td>64%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonney, 2008</td>
<td>20 M y Op.</td>
<td>54 y.</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strosberg, 2009</td>
<td>90 M</td>
<td></td>
<td></td>
<td>56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nissen, 2009</td>
<td>46</td>
<td>52%</td>
<td>70%</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isailovic, 2009</td>
<td>45 58% Op.</td>
<td>52 y.</td>
<td>42%</td>
<td>56% vs. 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hill, 2009</td>
<td>728 43% Op.</td>
<td>57 y.</td>
<td>&gt; 80%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yildiz, 2009</td>
<td>86 in 10 y.</td>
<td>52 y.</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figueiredo, 2009</td>
<td>86 35% Op.</td>
<td>58 y.</td>
<td>80%</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zerb, 2010</td>
<td>297 85% Op.</td>
<td>58 y.</td>
<td>57%</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botis, 2010 (58)</td>
<td>98 85% Op.</td>
<td>60 y.</td>
<td>81%</td>
<td>B-T: 48%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Pais, 2010 (59)</td>
<td>92 63% Op.</td>
<td>55 y.</td>
<td>66%</td>
<td>Ca: 46%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>X:</td>
<td></td>
<td>53 y.</td>
<td>45%</td>
<td>59%</td>
<td></td>
<td></td>
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</tbody>
</table>

M: Metastasis or malignity; B-T: body-tail of the pancreas. Op.: operated on; X: arithmetic mean.

The Swedish Uppsala team (53) studies prognostic factors in 324 patients with PET, with survival at 5 and 10 years of 64 and 44%, respectively. In the univariate analysis, stage, radical surgery, functional status, high Ki 67 index and Cg-A (highly sensitive and specific for PET), tumor size, and sporadic (rather than familial) nature are significant prognostic factors; in the multivariate analysis only stage, radical surgery, and Ki 67 above 2% were relevant. Non-functioning tumors were an independent marker of poorer prognosis.

Bettini et al. (54) study 180 cases of NFPET with survival at 5, 10 and 15 years of 67, 49 and 33%, respective-

### INSULINOMA:

EUS + CT (61) vs. CT + MR (62)

### GASTRINOMA:

EUS + OCTREOSCAN (63)

When in no doubt: Surgery with INTRAOPERATIVE PALPATION AND US
When in doubt or NFPET: EUS-FNAP (64)
TEP-CT for localisation in the primary (65)

Fig. 1. An algorithm for most common PETs.
ly, which confirms that metastases (to nodes and liver), poor differentiation, Ki 67 index, and weight loss are prognostic factors regarding survival.

In a recent study by the Verona team (55) of 137 NF cases the authors claim that primary tumor size is correlated to malignity and survival, thus defining surgery extent -1 cm excludes a carcinoma, 2 cm is the most widely used limit in clinical practice.

However, NF tumors usually show a mean size of 5 cm (21,56) versus 2 cm for functioning growths (21); 70% are greater than 5 cm at diagnosis, hence surgical treatment is an issue. Nevertheless, early detection and treatment with enucleation or pancreatic resection have been attempted, as for insulinomas, with very good results (57); no death occurred after a mean follow-up of 58 months.

Mean 5-year survival for all PETs is 65%, lower for NF tumors (49%) (Tables II-IV).

Our actuarial survival was 73.6%; the presence of obstructive jaundice and metastasis were associated with a poorer prognosis.

**REFERENCES**


