Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors

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Abstract

Pancreatic endocrine tumors (PETs) are uncommon tumors with an annual incidence <1 per 100 000 person-years in the general population. The PETs that produce hormones resulting in symptoms are designated as functional. The majority of PETs are non-functional. Of the functional tumors, insulinomas are the most common, followed by gastrinomas. The clinical course of patients with PETs is variable and depends on the extent of the disease and the treatment rendered. Patients with completely resected tumors generally have a good prognosis, and aggressive surgical therapy in patients with advanced disease may also prolong survival. The epidemiology, prognosis, and established and novel prognostic markers of PETs are reviewed.

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Introduction

Pancreatic endocrine tumors (PETs) are uncommon neoplasms with an incidence of <1 per 100 000 person-years in population studies (Moldow & Connolly 1968, Buchanan et al. 1986, Eriksson et al. 1989, Watson et al. 1989, Carriaga & Henson 1995, Lam & Lo 1997, Halfdanarson et al. 2007). The incidence is higher in autopsy studies, ranging from 0.8 to 10% suggesting that these tumors frequently go unnoticed (Grimelius et al. 1975, Kimura et al. 1991). PETs comprise <3% of all pancreatic neoplasms (Cubilla & Hajdu 1975, Carriaga & Henson 1995, Fesinmeyer et al. 2005, Öberg & Eriksson 2005). Pancreatic endocrine tumors are generally more indolent than adenocarcinoma of the pancreas and have a better prognosis (Carriaga & Henson 1995, Fesinmeyer et al. 2005). The origin of these tumors is not fully known, but they may arise from pluripotent cells within the exocrine pancreas (Vortmeyer et al. 2004). PETs are frequently divided into two groups based on their functional status, but unfortunately there is no uniformly accepted definition of a functional PET. Patients with ‘functional’ PETs commonly manifest symptoms resulting from hormone production of the tumor, although these tumors may also produce hormones without the patient having any symptoms secondary to the overproduced hormones. For the purpose of this review, we consider patients without symptoms of hormone production to have non-functional tumors even though elevated levels of hormones are detected in the blood, but we acknowledge the limitations of that definition. Multiple studies have addressed the epidemiology and prognosis of PETs but there are few large population studies available. A substantial proportion of the literature regarding these tumors stems from case reports and case series, often involving highly selected groups of patients, limiting the generalizability of the results. The purpose of this article is to review the epidemiology and prognosis of PETs and the commonly used prognostic predictors. We briefly discuss the role of novel prognostic markers.
Pathology and classification of PETs

Pancreatic endocrine tumors are frequently graded and classified according to the WHO classification of endocrine tumors (Table 1; Solcia et al. 2000, Heitz et al. 2004, Klöppel et al. 2004). The diagnosis of PETs rests upon confirming the neuroendocrine nature of the malignant cells. These tumors can have heterogeneous microscopic findings, and immunohistochemical staining with markers, such as chromogranin A, synaptophysin, and neuron-specific enolase, can usually confirm the neuroendocrine origin. It can be difficult to accurately assess the degree of malignancy of pancreatic endocrine tumors but the current WHO classification provides guidance in that respect. Other features of the tumors, including local invasion and metastases to lymph nodes and distant organs, have also been helpful in defining their malignant nature. The European Neuroendocrine Tumor Society has recently published guidelines on the management of PETs (Falconi et al. 2006, de Herder et al. 2006, O’Toole et al. 2006).

Epidemiology of PETs

Our knowledge of the epidemiology and risk factors for PETs is limited. While multiple studies have evaluated prognosis after diagnosis and therapy, few studies have focused on the epidemiology of PETs in defined populations. Not all studies separated PETs from other gastroenteropancreatic (GEP) neuroendocrine tumors, and thus provided limited information on tumors located in the pancreas. Other studies did not separate tumors with more indolent clinical behavior, such as insulinomas, from tumors showing more malignant behavior. Studies from large referral centers are common but may not represent the general population of patients with PETs. Furthermore, definitions of PETs have varied over the years, and until recently there was no consensus among pathologists regarding the diagnostic criteria or the criteria for malignant behavior.

The diverse nature of pancreatic tumors has been known for more than a century. It is of historical interest to review earlier reports on pancreatic tumors other than adenocarcinoma (Table 2). These studies have to be interpreted with caution as PETs were not well-defined entities at the time they were conducted, and there likely are substantial inaccuracies regarding the diagnoses. An autopsy study from the early twentieth century by Nicholls reports a case of pancreatic adenoma arising in the islet of Langerhans among 1514 patients (Nicholls 1902). Korpássy (1939) found four cases (0.8%) of macroscopic islet cell adenomas in 500 autopsies in 1938. Twenty-four cases (0.3%) of ‘benign islet cell neoplasms’ were observed in a series of 9158 consecutive autopsies reported by Frantz (1959). Warren et al. reported 24 islet cell tumors among 2708 autopsies of patients without diabetes and 18 tumors in 1858 diabetic patients, corresponding to a prevalence of 0.9% (Warren et al. 1966). Similar prevalence of 1.4% was reported by Becker where 62 ‘islet cell adenomas’ were found in 4280 autopsies (Becker 1971).

More recent studies have used more accurate diagnostic criteria for PETs providing better information on the prevalence of PETs in patients undergoing autopsy (Table 2). Eleven ‘endocrine adenomas’ were found among 1366 Swedish autopsy cases (0.8%; Grimelius et al. 1975). No patients carried the diagnosis of pancreatic tumor in life or had evidence of hormone overproduction. Twenty PETs were found among 800 consecutive patients (2.5%) undergoing autopsy in a Japanese geriatric hospital (Kimura et al. 1991). None of these patients had symptoms of excessive hormone secretion prior to their death but one patient had a prior history of resected gastrinoma. A randomly selected subset of 60 patients had 5 mm thick sections of the pancreas examined thoroughly and 6 (10%) were found to have an occult PET (Kimura et al. 1991). This study suggests that PETs may be much more common than previously thought the patients are frequently asymptomatic. Another study described 53 Chinese patients with PETs and estimated the annual incidence of symptomatic PETs to be 0.2/100 000. Furthermore, 11 472 autopsies were reviewed yielding 13 PETs (0.11%) where only 4 patients were symptomatic antemortem. The autopsy prevalence of asymptomatic PETs was thus 0.08% and

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Table 1 WHO classification of pancreatic endocrine tumors (Heitz et al. 2004)

1. Well-differentiated endocrine tumor
   1.1. Benign behavior
       Confined to the pancreas, <2 cm in diameter, ≤2 mitoses per 10 HPF, ≤2% Ki-67-positive cells, no angioinvasion, or perineural invasion
   1.2. Uncertain behavior
       Confined to the pancreas and one or more of the following features: ≥2 cm in diameter, >2 mitoses per 10 HPF, >2% Ki-67-positive cells, angioinvasion, perineural invasion

2. Well-differentiated endocrine carcinoma
   Low-grade malignant
   Gross local invasion and/or metastases

3. Poorly differentiated carcinoma
   High-grade malignant
   >10 mitoses per HPF

HPF, high-power field.
the annual incidence of symptomatic PETs 0.2/100 000 (Lam & Lo 1997).

Several studies on the incidence of PETs in defined populations have been performed (Table 3; Moldow & Connelly 1968, Buchanan et al. 1986, Eriksson et al. 1989, Watson et al. 1989, Carriaga & Henson 1995, Lam & Lo 1997, Lepage et al. 2004, Halfdanarson et al. 2007). Moldow & Connelly reported on all patients diagnosed with pancreatic tumors in Connecticut during 1957–1963 (Moldow & Connelly 1968). Out of the 856 pancreatic tumors, islet cell tumors accounted for <5%. In this study, no effort was made to distinguish between islet cell tumors and other rare pancreatic tumors. These tumor types in addition to PETs comprised 5% of all pancreatic tumors and the incidence was <1/100 000 (Moldow & Connelly 1968). A Swedish study reported an annual incidence of 0.4/100 000 (Eriksson et al. 1989) and a study from Northern Ireland found an annual incidence of 0.18/100 000 (Buchanan et al. 1986). The latter study was later updated reporting the incidence to be 0.23/100 000 (Watson et al. 1989).

A recent French study using a population-based cancer registry found the overall annual crude incidence of malignant digestive endocrine tumors to be 1.15/100 000 for men and 0.91/100 000 for women. Pancreatic tumors accounted for 20.5% of all tumors in this cohort. The age-standardized incidence rates of PETs were 0.19/100 000 and 0.12/100 000 for men and women respectively, with a male-to-female ratio of 1.6 (Lepage et al. 2004).

### Table 2 Published autopsy series of islet cell tumors

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of autopsies</th>
<th>Number of islet cell tumors</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholls 1902 (Nicholls 1902)</td>
<td>1514</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Korpássy 1939 (Korpássy 1939)</td>
<td>500</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Frantz 1959 (Frantz 1959)</td>
<td>9158</td>
<td>24</td>
<td>0.3</td>
</tr>
<tr>
<td>Warren 1966 (Warren et al. 1966)</td>
<td>4566</td>
<td>42</td>
<td>0.9</td>
</tr>
<tr>
<td>Becker 1971 (Becker 1971)</td>
<td>4280</td>
<td>62</td>
<td>1.4</td>
</tr>
<tr>
<td>Grimelius 1975 (Grimelius et al. 1975)</td>
<td>1366</td>
<td>11</td>
<td>0.8</td>
</tr>
<tr>
<td>Kimura 1991 (Kimura et al. 1991)</td>
<td>Overall</td>
<td>800</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>5 mm sections*</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Lam 1997 (Lam &amp; Lo 1997)</td>
<td>11 472</td>
<td>13</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Sixty patients of the 800 were randomly selected for a thorough pathological examination with 5 mm sections of the pancreas.

### Table 3 Population studies of pancreatic endocrine tumors

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of PET cases in the population</th>
<th>Annual incidence (all types)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moldow 1968  (Moldow &amp; Connelly 1968)</td>
<td>NR</td>
<td>&lt;1/100 000a</td>
<td>All cases in Connecticut, USA over a given period; PETs grouped with other rare tumors of the pancreas</td>
</tr>
<tr>
<td>Eriksson 1989  (Eriksson et al. 1989)</td>
<td>84</td>
<td>0.4/100 000</td>
<td>Well-defined region in Sweden; single referral hospital</td>
</tr>
<tr>
<td>Watson 1989  (Watson et al. 1989)</td>
<td>94</td>
<td>0.23/100 000</td>
<td>Well-defined Northern Irish population; same series as Buchanan et al. (1986)</td>
</tr>
<tr>
<td>Carriaga 1995  (Carriaga &amp; Henson 1995)</td>
<td>402</td>
<td>&lt;0.6/100 000a</td>
<td>SEER data 1973–1987; exact incidence of PETs not provided</td>
</tr>
<tr>
<td>Lam 1997 (Lam &amp; Lo 1997)</td>
<td>53</td>
<td>0.2/100 000</td>
<td>Referral to a single hospital in Hong Kong</td>
</tr>
<tr>
<td>Lepage 2004  (Lepage et al. 2004)</td>
<td>47</td>
<td>&lt;.0.12/100 000</td>
<td>Well-defined geographic region in France</td>
</tr>
<tr>
<td>Halfdanarson 2007  (Halfdanarson et al. 2007)</td>
<td>1488</td>
<td>☞: 0.19/100 000</td>
<td>SEER data 1973–2000; all (neuro)endocrine tumors of the pancreas</td>
</tr>
</tbody>
</table>

NR, not reported; SEER, surveillance, epidemiology, and end results.
aAccurate figure not provided for pancreatic endocrine tumors.
The incidence rates were low in persons under 40 years of age but increased steadily with age, reaching a peak at the age of 75 for men and 65 for women. A study using the Surveillance, Epidemiology, and End Results (SEER) registry data from 1973 to 1987 found the annual incidence of <0.6/100 000 for all age groups (Carriaga & Henson 1995). We have recently presented our data on all PETs in the SEER registry from 1973 to 2000. The overall annual incidence of PETs was 0.2/100 000 with the highest incidence (0.7–0.8/100 000) in the sixth and seventh decades with a slight male predominance (Halfdanarson et al. 2007). The incidence has increased over time, possibly related to increased awareness of these tumors among clinicians.

The frequency of the various subtypes of functional PETs has been described in several studies (Tables 4 and 5; Jacobsen et al. 1986, Cullen & Ong 1987, Eriksson et al. 1989, 1990, Watson et al. 1989, Service et al. 1991, Stamm et al. 1991). Insulinoma is the most frequently encountered functional PET and is usually a benign tumor and almost always located in the pancreas (Soga & Yakuwa 1994, Öberg & Eriksson 2005). The incidence of insulinoma in a well-defined population in Olmsted County in southeastern Minnesota was found to be 0.4 per 100 000 person-years (Service et al. 1991). Other investigators have reported annual incidence rates ranging from 0.07 to 0.12/100 000 in populations less well defined than in Olmsted County (Kavlie & White 1972, Cullen & Ong 1987, Eriksson et al. 1989, Watson et al. 1989). The annual incidence of malignant insulinoma in the SEER registry is 0.1/million (Halfdanarson et al. 2008). Gastrinoma is the second most commonly encountered functional PET but gastrinomas are also frequently found outside the pancreas (Soga & Yakuwa 1998a, Norton et al. 1999, Roy et al. 2000, Öberg & Eriksson 2005). Pancreatic gastrinomas may be more aggressive and frequently associated with liver metastases (Weber et al. 1995). Up to 30% of gastrinomas are associated with multiple endocrine neoplasia type 1 (MEN-1; Soga & Yakuwa 1998a, Roy et al. 2000). Gastrinoma is the most common functional PET seen in patients with MEN-1 and the prognosis may be worse than that in sporadic gastrinoma (Norton et al. 1999, Gibril et al. 2001, Norton 2005). Investigators in Denmark estimated the incidence of gastrinoma to be 0.5 per million per year (Jacobsen et al. 1986). A higher incidence of 2–4 per million has been found in Switzerland (Stamm et al. 1991). Other studies have reported an annual incidence of 0.5–1.2 cases per million (Eriksson et al. 1989, Watson et al. 1989). Our recent study using the SEER registry suggested an annual incidence of 0.1/million, but this may be a substantial underestimate given the way that SEER registers these tumors (Halfdanarson et al. 2008).

Epidemiological data on functioning PETs other than insulinoma and gastrinoma is sparse. Pancreatic endocrine tumors secreting vasoactive intestinal peptide (VIPoma) comprise <10% of all PETs and appear to be slightly more common in females according to some but not all reports (Klöppel & Heitz 1988, Solcia et al. 1997, Smith et al. 1998, Soga & Yakuwa 1998c, Peng et al. 2004). VIPomas are found in extrapancreatic locations in up to 25% of cases (Soga & Yakuwa 1998c). Two studies have reported the annual incidence of VIPoma to be 0.1–0.6 per million but the incidence of pancreatic VIPoma is not well known (Eriksson et al. 1989, Watson et al. 1989). Glucagon-secreting tumors (glucagonomas) represent <10% of PETs and are almost exclusively found within the pancreas (Klöppel & Heitz 1988, Solcia et al. 1997). Glucagonomas are very rare and their annual incidence has been estimated to be around <0.1 per million (Eriksson et al. 1989, Watson et al. 1989). Glucagonomas may be slightly more common among females and

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Annual incidence of all PETs</th>
<th>Insulinoma</th>
<th>Gastrinoma</th>
<th>VIPoma</th>
<th>Glucagonoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson 1989 (Eriksson et al. 1989)</td>
<td>Sweden</td>
<td>4</td>
<td>1.1</td>
<td>1.2</td>
<td>0.64</td>
<td>0.04</td>
</tr>
<tr>
<td>Watson 1989 (Watson et al. 1989)</td>
<td>Northern Ireland</td>
<td>2.3</td>
<td>1.2</td>
<td>0.5</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Service 1991 (Service et al. 1991)</td>
<td>USA</td>
<td>–</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cullen 1987 (Cullen &amp; Ong 1987)</td>
<td>New Zealand</td>
<td>–</td>
<td>–</td>
<td>0.67</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jacobsen 1986 (Jacobsen et al. 1986)</td>
<td>Denmark</td>
<td>–</td>
<td>–</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stamm 1991 (Stamm et al. 1991)</td>
<td>Switzerland</td>
<td>–</td>
<td>2–4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
patients are usually in their fifth decade at the time of diagnosis (Wermers et al. 1996, Soga & Yakuwa 1998b). PETs secreting somatostatin (somatostatinoma) are rare and account for < 5% of all PETs and the true incidence of these tumors is unknown. Somatostatinomas typically present in the fifth and sixth decades of life with a slight female preponderance. Up to 50% of somatostatinomas arise outside the pancreas (Harris et al. 1987, Konomi et al. 1990, Soga & Yakuwa 1999). Pancreatic tumors secreting other hormones such as cholecystokinin, gastric inhibitory peptide, gastrin-releasing peptide (GRP), adrenocorticotrophin (ACTH), growth hormone-releasing hormone, PTHrP, and ghrelin are extremely rare and their incidence is unknown.

Non-functioning tumors comprise a substantial proportion of all PETs and have been reported to comprise 25–100% of all PETs. The annual incidence of symptomatic non-functional PETs has been estimated to be 0.07–0.1/100 000 (Eriksson et al. 1989, Watson et al. 1989). Autopsy studies have shown much higher incidence than that reported in clinical series (Kimura et al. 1991).

### PETs associated with hereditary syndromes

Pancreatic endocrine tumors are commonly observed in MEN-1 and less frequently in von Hippel–Lindau disease (VHL). Cases of PET in association with the tuberous sclerosis complex and type 1 neurofibromatosis have also been reported but are rare (Tan et al. 1996, Verhoef et al. 1999, Fujisawa et al. 2002, Francalanci et al. 2003).

The MEN-1 syndrome is an autosomal dominant inherited disorder characterized by multiple endocrine and non-endocrine tumors (Brandi et al. 2001, Doherty 2005, Lakhani et al. 2007). The endocrine tumors most frequently described in patients with MEN-1 include parathyroid adenomas, pituitary adenomas, and PETs. Multiple other tumors of varying penetrance have been reported in association with MEN and include tumors of the adrenal glands, carcinoid tumors, angiofibroma, collagenoma, and lipoma. The penetrance of PETs in MEN-1 patients ranges from 30 to 75% and these tumors are frequently multifocal and metastatic at the time of diagnosis (Vasen et al. 1989, Skogseid et al. 1991, Le Bodic et al. 1996, Burgess et al. 1998a,b). Gastrinomas are the most commonly encountered PETs, followed by non-functioning tumors and insulinomas (Brandi et al. 2001, Gibril & Jensen 2004, Triponez et al. 2006). A recent study suggested that non-functioning tumors were more common than gastrinomas in MEN-1 patients (Triponez et al. 2006). PETs are a major cause of morbidity and mortality in patients with MEN-1, but discussion of screening and treatment of these patients is outside the scope of this review (Wilkinson et al. 1993, Doherty et al. 1998, Dean et al. 2000). VHL disease is an autosomal dominant tumor predisposition syndrome caused by a germ line mutation in the VHL gene (Lonser et al. 2003). The typical features of VHL disease include retinal and brain hemangioblastoma, renal cell carcinoma, renal cysts, pheochromocytoma, and pancreatic tumors and cysts (Lonser et al. 2003). Pancreatic
endocrine tumors are found in 9.5–17% of patients with VHL disease (Binkovitz et al. 1990, Libutti et al. 1998, Hammel et al. 2000, Blansfield et al. 2007). The PETs associated with VHL disease are virtually always non-functional (Blansfield et al. 2007).

Prognosis following resection

Functional and non-functional tumors


Table 6 lists the studies of patients with both functional and non-functional tumors, who have undergone resection. The extent of the disease and the completeness of resection were major predictors of survival in most of these series (Legaspi & Brennan 1988, Thompson et al. 1988, Lo et al. 1996, Phan et al. 1997, Madeira et al. 1998, Chu et al. 2002, Hochwald et al. 2002, Lepage et al. 2004, Pape et al. 2004, Panzuto et al. 2005, Tomassetti et al. 2005, House et al. 2006). Several studies have suggested that the functional status of the tumors may affect prognosis. Functional tumors have been reported to have a better prognosis than non-functional tumors (Thompson et al. 1988, Phan et al. 1998, Sarmiento et al. 2002). Other studies have either reported worse prognosis of functional tumors or no effect of functional status on prognosis (Cubilla & Hajdu 1975, White et al. 1994). We have recently reported our analysis of the SEER data on PETs where functional tumors had a better prognosis after adjusting for other predictors such as age and stage. We also found that prognosis has improved with time and the improvement does not seem to be explained by stage migration. It is possible that more aggressive surgical therapy or improved medical care has resulted in better prognosis (Halfdanarson et al. 2007).

Taken together, these studies of heterogeneous cohorts of patients with both functional and non-functional tumors have not consistently shown functional status to be a prognostic factor in terms of survival when the benign insulinomas have been excluded. The heterogeneity of the studies makes all comparisons difficult. Ninety percent of insulinomas are benign and have excellent prognosis after resection (Service et al. 1991). Patients with gastrinoma seem to have a better survival than those with other malignant and functional PETs, especially after surgery with curative intent (Norton et al. 1999). As expected, patients with more advanced and metastatic diseases as well as those with residual disease following resection had shorter survival.

Non-functional tumors


The tumors were considered malignant if there was a direct invasion into adjacent tissues or organs or if distant metastases were present.
<table>
<thead>
<tr>
<th>Study (author, year)</th>
<th>Number of patients</th>
<th>Number (%) of functioning tumors</th>
<th>Number (%) of insulinomas</th>
<th>Number of patients with metastases at diagnosis (%)</th>
<th>Survival</th>
<th>Factors adversely affecting overall survival or disease-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubilla et al. 1975 (Cubilla &amp; Hajdu 1975)</td>
<td>30</td>
<td>12 (34)</td>
<td>4 (13)</td>
<td>LN: 19 (63)</td>
<td>5-OS: 57%</td>
<td>Functional tumor</td>
</tr>
<tr>
<td>Broughan et al. 1986 (Broughan et al. 1986)</td>
<td>84</td>
<td>63 (75)</td>
<td>41 (49)</td>
<td>Liver: 21 (70)</td>
<td>MS: 4.3 (N) and 2.8 (F) years</td>
<td>Non-insulinoma or non-functional&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phan et al. 1998 (Phan et al. 1998)</td>
<td>125&lt;sup&gt;b&lt;/sup&gt; (including 86 PETs)</td>
<td>64 of all tumors (52)</td>
<td>35 (28)</td>
<td>NR</td>
<td>5-OS: 65% (all), 77% (F), 52% (N)</td>
<td>Non-functional tumors, positive margins, malignant tumors&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sarmiento et al. 2002 (Sarmiento et al. 2002)</td>
<td>29</td>
<td>9 (31)</td>
<td>3 (10)</td>
<td>LN: 16 (55) Liver: 1 (3)</td>
<td>5-OS: 81% (all), 100% (F), 70% (N)</td>
<td>Non-functional, positive lymph nodes&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>White et al. 1994 (White et al. 1994)</td>
<td>28</td>
<td>19 (68)</td>
<td>3 (11)</td>
<td>44% (N) 53% (NF)</td>
<td>DFS at 2 years: 67% (N) and 40% (F)</td>
<td>No difference between functioning and non-functioning tumors&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Jarufe et al. 2005 (Jarufe et al. 2005)</td>
<td>44</td>
<td>24 (55)</td>
<td>16 (36)</td>
<td>22 (50)</td>
<td>5-OS: 74.4%</td>
<td>Metastases (multivariate analysis)</td>
</tr>
<tr>
<td>Thompson et al. 1988 (Thompson et al. 1988)</td>
<td>58</td>
<td>31 (54)</td>
<td>8 (14)</td>
<td>LN: 25 (43) Liver: 19 (33)</td>
<td>5-OS: 42%</td>
<td>Liver metastases, non-functional tumor (versus gastrinoma)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Panzuto et al. 2005 (Panzuto et al. 2005)</td>
<td>156&lt;sup&gt;b&lt;/sup&gt; (including 67 PETs)</td>
<td>26 (39)</td>
<td>1 (1.5)</td>
<td>LN: 6 (9) Liver: 28 (42) Extra-hepatic: 11 (16)</td>
<td>5-OS: 62%</td>
<td>Poorly differentiated tumors, distant metastases (multivariate analysis)</td>
</tr>
<tr>
<td>Legaspi et al. 1988 (Legaspi &amp; Brennan 1988)</td>
<td>33</td>
<td>11 (33)</td>
<td>0</td>
<td>Distant metastases: 16 (48)</td>
<td>3-year survival 76%</td>
<td>Incomplete resection or residual tumor&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lepage et al. 2004 (Lepage et al. 2004)</td>
<td>47</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5-OS: 42%</td>
<td>Metastatic disease and advanced age (multivariate analysis)</td>
</tr>
<tr>
<td>Venkatesh et al. 1990 (Venkatesh et al. 1990)</td>
<td>98</td>
<td>55 (56)</td>
<td>7 (7)</td>
<td>47 (48)</td>
<td>Mean survival 42.7±49 months</td>
<td>Non-functional tumors&lt;sup&gt;a&lt;/sup&gt; metastatic disease and advanced age (multivariate analysis)</td>
</tr>
<tr>
<td>Tomassetti et al. 2005 (Tomassetti et al. 2005)</td>
<td>83</td>
<td>31 (37)</td>
<td>7 (8)</td>
<td>LN: 47 (60) Liver: 27 (33)</td>
<td>MS: 90 months 5-OS: 55.3%</td>
<td>Liver and lymph node metastases at diagnosis and incomplete resection, MEN-1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chu et al. 2002 (Chu et al. 2002)</td>
<td>50</td>
<td>21 (42)</td>
<td>6 (12)</td>
<td>Liver: 29 (58) Synchronous liver metastases</td>
<td>MS 40 months 5-OS: 36%</td>
<td>Incomplete resection and liver metastases, less aggressive treatment of liver metastases&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lo et al. 1996 (Lo et al. 1996)</td>
<td>64</td>
<td>30 (47)</td>
<td>4 (6)</td>
<td>LN: 38 (59) Liver: 39 (61)</td>
<td>3-year survival: curative resection: 80%, non-curative resection 62%</td>
<td>Liver metastases, non-curative resection&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Madeira et al. 1998 (Madeira et al. 1998)</td>
<td>82&lt;sup&gt;b&lt;/sup&gt; (including 62 PETs)</td>
<td>38 (46)</td>
<td>3 (4)</td>
<td>LN: 52 (83) Liver: 49 (60) (among all 82 patients)</td>
<td>5-OS: No liver metastases 100% Liver metastases 40%</td>
<td>Liver metastases, poor differentiation and incomplete resection (multivariate analysis)</td>
</tr>
<tr>
<td>Pape et al. 2004 (Pape et al. 2004)</td>
<td>254&lt;sup&gt;b&lt;/sup&gt; (including 73 PETs)</td>
<td>53 (32)</td>
<td>6 (8)</td>
<td>53 (73)</td>
<td>MS: 47 months 5-OS: 42.9%</td>
<td>Metastases at diagnosis and incomplete resection&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hochwald et al. 2002 (Hochwald et al. 2002)</td>
<td>136</td>
<td>47 (35)</td>
<td>21 (15)</td>
<td>NR</td>
<td>DFS after curative resection: 110 months (N) and 152 months (F)</td>
<td>High mitotic rate (DSS), presence of tumor necrosis, LN or liver metastases (DFS) (multivariate analysis)</td>
</tr>
<tr>
<td>House et al. 2006 (House et al. 2006)</td>
<td>31</td>
<td>8 (26)</td>
<td>1 (3)</td>
<td>100</td>
<td>MS: resection of primary tumor and liver metastases: 78 months (5-OS: 65%)</td>
<td>Incomplete resection</td>
</tr>
</tbody>
</table>
Multiple tumor characteristics predicted malignant behavior in a univariate analysis, including tumor diameter, vascular and perineural invasion, the presence of mitoses, nuclear atypia, and high proliferative index (>2%) as evaluated by Ki-67 immunohistochemical staining. The tumors were classified according to the histological features and Ki-67 proliferative index (Ki-67 PI) into four groups. Malignant tumors were also classified as poorly differentiated based on the appearance of the tumor cells and the presence of mitoses and areas of necrosis. All other PETs were classified into limited risk tumors (LRT) and increased risk tumors (IRT) based on the presence of either high Ki-67 PI (>2%) or vascular and/or perineural invasion. These subtypes were found to predict survival in a univariate analysis. LRT had better prognosis than IRT, which in turn had better prognosis than well-differentiated carcinomas. The poorly differentiated carcinomas had the worst prognosis. Even though capsular penetration, the presence of distant metastases, vascular microinvasion, and high Ki-67 PI all were found to adversely affect prognosis in a univariate analysis, the predictive value disappeared on a multivariate analysis (La Rosa et al. 1996).

**Functional tumors**

Several studies have focused solely on therapy and outcome of functional PETs (Table 8; Harrison et al. 1973, Lundstam et al. 1979, Danforth et al. 1984, Zeng et al. 1988, Service et al. 1991, Grama et al. 1992, Weber et al. 1995, Boukhman et al. 1998, Norton et al. 1999, Chen et al. 2002, Feng et al. 2002, Matthews et al. 2002, Grant 2005, Hirshberg et al. 2005, Starke et al. 2005, Kang et al. 2006). The largest study of insulinomas is a retrospective review by Service et al. from the Mayo Clinic in Rochester, spanning a 60-year period from 1927 to 1986 (Service et al. 1991). The study included 244 patients with insulinoma, including eight patients who were residents of Olmsted County in southeastern Minnesota. Thirteen patients (5.8%) had malignant insulinoma and 17 patients (7.6%) had MEN-1 in addition. As expected, the survival of patients with benign insulinoma was long following therapy and did not differ from expected survival of this population. The 10-year survival of patients with benign insulinoma was 78%. The factors adversely affecting the prognosis were malignant phenotype, advanced age, and patients diagnosed early in the study period. Patients with MEN-1 had shorter survival but the difference was not statistically significant. A more recent report from the same institution reported...
Table 7 Selected studies of non-functional pancreatic endocrine tumors

<table>
<thead>
<tr>
<th>Study (author, year)</th>
<th>Number of patients</th>
<th>Metastasis at diagnosis (%)</th>
<th>Survival</th>
<th>Factors adversely affecting survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kent et al. 1981 (Kent et al. 1981)</td>
<td>25</td>
<td>18 (72) Liver 11 (44)</td>
<td>3- and 5-year OS: 60 and 44%</td>
<td>NR</td>
</tr>
<tr>
<td>Eckhauser et al. 1986 (Eckhauser et al. 1986)</td>
<td>11</td>
<td>9 (82) Liver: 5 (45) LN: 7 (64)</td>
<td>Mean survival: 23 months (4–72 months)</td>
<td>No predictors identified</td>
</tr>
<tr>
<td>Evans et al. 1993 (Evans et al. 1993)</td>
<td>73</td>
<td>37 (51)</td>
<td>5-year OS: 50%</td>
<td>Metastatic disease and incomplete resection*</td>
</tr>
<tr>
<td>La Rosa et al. 1996 (La Rosa et al. 1996)</td>
<td>61</td>
<td>34 (56) LN: 5 (25)</td>
<td>Mean survival (months): Increased risk: 50.7 Well differentiated: 44.2 Poorly differentiated: 3.7</td>
<td>Capsular penetration, distant metastases, vascular microinvasion, and high Ki-67 proliferative index*</td>
</tr>
<tr>
<td>Matthews et al. 2000 (Matthews et al. 2000)</td>
<td>28</td>
<td>6 (21)</td>
<td>2-year survival: node negative 77.8%, node positive 71.4 and metastatic 36.4</td>
<td>Liver metastases*</td>
</tr>
<tr>
<td>Bartsch et al. 2000 (Bartsch et al. 2000)</td>
<td>17</td>
<td>LN: 15 (83) Distant: 6 (33)</td>
<td>5- and 10-year OS: 65.4% and 49.1%. 5-year OS 100% in the completely resected patients versus 14.3% in patients treated with palliative intent</td>
<td>Incomplete resection*</td>
</tr>
<tr>
<td>Solorzano et al. 2001 (Solorzano et al. 2001)</td>
<td>163</td>
<td>101 (62)</td>
<td>5-year OS: 43% (77% in patients with localized and resected disease, 16% in patients with metastatic disease and no resection)</td>
<td>Incomplete resection, no anti-cancer therapy and age &gt; 65 years (multivariate analysis)</td>
</tr>
<tr>
<td>Gullo et al. 2003 (Gullo et al. 2003)</td>
<td>184</td>
<td>69 (38)</td>
<td>5-year OS: resected 76.9%, not resected 28.6%</td>
<td>Metastatic disease, incomplete resection, symptomatic at diagnosis and tumor &gt; 3 cm*</td>
</tr>
<tr>
<td>Liang et al. 2004 (Liang et al. 2004)</td>
<td>43</td>
<td>6 (14)</td>
<td>5- and 10-year OS: 58 and 29%</td>
<td>Incomplete resection (multivariate analysis)</td>
</tr>
<tr>
<td>Kang et al. 2005 (Kang et al. 2005)</td>
<td>19</td>
<td>7 (37)</td>
<td>5-year OS: 32% (curative resection 90%)</td>
<td>Metastases, unresectable disease, macroscopic invasion*</td>
</tr>
<tr>
<td>Guo et al. 2004 (Guo et al. 2004)</td>
<td>41 (all patients had resection)</td>
<td>4 (10)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Furukawa et al. 1998 (Furukawa et al. 1998)</td>
<td>16</td>
<td>4 (25) LN: 2 (13) Liver: 2 (13)</td>
<td>5-year OS: 83%</td>
<td>Tumors recurred in three patients following enucleation</td>
</tr>
<tr>
<td>Yang et al. 2000 (Yang et al. 2000)</td>
<td>16</td>
<td>LN: 8 (50) Liver: 2 (13)</td>
<td>All patients alive after a mean follow-up time of 5.3 years (one with recurrent disease)</td>
<td>Both patients with liver metastasis died secondary to their malignancy</td>
</tr>
<tr>
<td>Madura et al. 1997 (Madura et al. 1997)</td>
<td>14</td>
<td>LN: 7 (50)</td>
<td>Median survival 31.2 months</td>
<td>LN metastases</td>
</tr>
</tbody>
</table>

LN, lymph nodes; NR, not reported; OS, overall survival.

*Univariate analysis.
225 patients with benign insulinoma, who underwent resection from 1982 to 2004 (Grant 2005). The outcome for this cohort of patients was excellent, with 98% of patients being cured with resection. The general good outcome of patients with insulinoma may thus skew the outcome results in a series where patients with insulinomas are grouped with patients having other functional or non-functional tumors.

Norton et al. 1999 reported their experience with 151 patients with gastrinoma undergoing surgery. Their cohort of patients included 36 (24%) patients with pancreatic gastrinoma, of which 19 had MEN-1. Gastrinoma was localized to the pancreas in 17 out of 123 (14%) patients with sporadic tumors. The 5- and 10-year disease-specific survival of all patients with sporadic gastrinoma was 100 and 95% respectively and 40% of the patients were free of disease at 5 years postoperatively. A previous study by the same investigators showed that survival was primarily determined by the presence of liver metastases (Weber et al. 1995). Gastrinomas associated with the Cushing syndrome seem to have a particularly poor prognosis (Maton et al. 1986, Ilias et al. 2005).

Other prognostic factors

Several investigators have attempted to evaluate previously established and novel prognostic factors in PETs. The WHO classification of PETs has been shown to be useful in predicting the clinical behavior of these tumors Heymann et al. (2000). Histological findings such as grade and the number of mitotic figures have been found to predict survival in a few studies. Hochwald et al. (2002) retrospectively evaluated 136 patients with low-grade or intermediate-grade PETs who had undergone tumor resection. After adjusting for other prognostic factors including the presence of distal metastases, tumor necrosis was found to be associated with shorter disease-free survival (DFS). Higher tumor mitotic rate (>2 per 50 high-power fields (HPFs)) was associated with shorter disease-specific survival (DSS). There was no difference in DFS or DSS between functional and non-functional tumors. The authors proposed a simple system for grading these tumors based on the presence of necrosis and the number of mitoses where patients with a low-grade tumor (<2 mitoses per 50 HPFs and no necrosis) had a significantly longer DFS and DSS (Hochwald et al. 2002). Other authors have suggested a prognostic model for well-differentiated gastroenteropathic neuroendocrine tumors (GEP-NET) using abnormal liver chemistries and urinary excretion of 5-HIAA, but the model has not been validated in patients with tumors limited to the pancreas (Formica et al. 2006). Proliferation markers such as Ki-67 immunohistochemistry have been found to predict prognosis in patients with PETs (Lloyd 1998). However, the results have not uniformly supported the prognostic value of increased Ki-67 expression, especially after adjusting for other known prognostic variables such as stage (La Rosa et al. 1996, Pelosi et al. 1996, 1997, Clarke et al. 1997, Gentil Perret et al. 1998, Lloyd 1998, Jorda et al. 2003, Goto et al. 2004, Böhmig et al. 2005, Panzuto et al. 2005, Couvelard et al. 2006). Recent studies have identified additional markers that may be of prognostic value. Positive staining for CK19 was shown to be a powerful prognostic factor predicting shorter survival, even after controlling for variables such as the number of mitoses, tumor necrosis, and Ki-67 expression (Deshpande et al. 2004). CK19 may not be predictive of survival in patients with non-functional PETs (La Rosa et al. 2007). Expression of CD10 has also been shown to predict worse survival, and a correlation was found between CD10 expression and the WHO classification where the more malignant tumors were more likely to express CD10 (Deschamps et al. 2006). There was also a correlation between positive CD10 staining and higher proliferative index, larger tumor size, and the presence of hepatic metastases. Loss of expression of CD99 has been suggested to predict worse outcome by some authors but not others (Goto et al. 2004, Ali et al. 2006) and expression of CD44 isoforms v6 and v9 may be indicative of more benign behavior and better prognosis in patients with PET (Imam et al. 2000).

With advances in genetic and molecular biology, multiple potential prognostic markers have been identified. These markers have not yet been validated in large cohorts of patients and have not found their way into routine clinical use. The molecular genetics of GEP tumors have been reviewed in detail elsewhere (Zikusoka et al. 2005). Certain chromosomal aberrations have been found more frequently in patients with metastatic PETs when compared with non-metastatic tumors. These aberrations involve multiple chromosomes, including 1,3,5,6,7,14,22 and the X chromosome (Speel et al. 1999, Barghorn et al. 2001a,b, Zhao et al. 2001, Guo et al. 2002a,b, Wild et al. 2002, Chen et al. 2003, 2004). Chromosomal instability as manifested by the number of aberrations per tumor has been shown to be an indicator for the development of
Table 8: Selected studies of functional pancreatic endocrine tumors

<table>
<thead>
<tr>
<th>Study (author, year)</th>
<th>Number of patients</th>
<th>Median age (years)</th>
<th>Type of tumor (hormone produced)</th>
<th>Malignant PET (%) number of patients with metastases</th>
<th>Survival</th>
<th>Factors adversely affecting survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service et al. 1991 (Service et al. 1991)</td>
<td>244</td>
<td>47</td>
<td>Insulinoma</td>
<td>5.8</td>
<td>10-year OS: 78% for benign and 29% for malignant insulinoma</td>
<td>Malignant insulinoma, advanced age</td>
</tr>
<tr>
<td>Grant 2005 (Grant 2005)</td>
<td>225</td>
<td>NR</td>
<td>Insulinoma</td>
<td>0</td>
<td>98% cure rate</td>
<td>NR</td>
</tr>
<tr>
<td>Grama et al. 1992 (Grama et al. 1992)</td>
<td>85</td>
<td>NR</td>
<td>Insulinoma 56%</td>
<td>47</td>
<td>10 OS: insulinoma 50%, malignant PET 28%</td>
<td>Liver metastases, tumor &gt; 4 cm, complete resection</td>
</tr>
<tr>
<td>Norton et al. 1999 (Norton et al. 1999)</td>
<td>151 (36 with pancreatic gastrinoma)</td>
<td>48 (mean age)</td>
<td>Gastrinoma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>5-year OS: 100% for sporadic gastrinoma, 42% free of disease at 5 years</td>
<td>MEN-1 (lower disease-free survival)</td>
</tr>
<tr>
<td>Danforth et al. 1984 (Danforth et al. 1984)</td>
<td>17</td>
<td>Insulinoma</td>
<td>17 (100) LN: 8 (47) Liver: 12 (70)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Hirshberg et al. 2005 (Hirshberg et al. 2005)</td>
<td>10</td>
<td>Insulinoma</td>
<td>100</td>
<td>Survival ranged from 4 months to 30 years</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Harrison et al. 1973 (Harrison et al. 1973)</td>
<td>35</td>
<td>Insulinoma</td>
<td>Metastases: 3 (9%)</td>
<td>NR</td>
<td>Metastatic disease (two out of three patients died shortly after referral)</td>
<td></td>
</tr>
<tr>
<td>Starke et al. 2005 (Starke et al. 2005)</td>
<td>77</td>
<td>Insulinoma</td>
<td>Metastases 10 (13)</td>
<td>2-year survival (metastatic only): 2.6 years</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Chen et al. 2002 (Chen et al. 2002)</td>
<td>74</td>
<td>Insulinoma</td>
<td>Malignant insulinoma: 2 (3%)</td>
<td>All patients with benign insulinoma were cured. One patient with malignant insulinoma survived 18 years</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Feng et al. 2002 (Feng et al. 2002)</td>
<td>105</td>
<td>Insulinoma</td>
<td>Malignant insulinoma: 4 (4%)</td>
<td>All patients with benign insulinoma were cured; three out of four patients with malignant insulinoma had relief of their symptoms and one died</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Boukhman et al. 1998 (Boukhman et al. 1998)</td>
<td>67</td>
<td>Insulinoma</td>
<td>Malignant insulinoma: 10 (15%)</td>
<td>89% underwent a successful operation (no survival data reported)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Kang et al. 2006 (Kang et al. 2006)</td>
<td>14</td>
<td>Insulinoma: 12 (86%) Gastrinoma: 2 (14%)</td>
<td>Two malignant tumors (one insulinoma and one gastrinoma)</td>
<td>10 year survival: 81% (one patient died of unrelated causes)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Methylation of tumor suppressor genes has been implicated as an important factor in the etiology of various tumors. House et al. have shown that silencing of multiple tumor suppressor genes by promoter hypermethylation is frequent in PETs and may be associated with more advanced tumor stage and shorter survival (House et al. 2003b). The most frequently silenced genes were RASSF1A, p16/INK4A, O6-MGMT, RAR-β, and hMLH1 (House et al. 2003b). The association between RASSF1A and p16/INK4A methylation and more advanced stage was confirmed by other authors (Liu et al. 2005). Methylation of hMLH1 has also been shown to result in microsatellite instability in patients with PETs and may be associated with a favorable prognosis (House et al. 2003a). Telomerase activity has also been suggested as being useful in the diagnosis of PETs, and it has been suggested that the presence of telomerase activity may predict an unfavorable outcome (Lam et al. 2000, Tang et al. 2002, Vezzosi et al. 2006).

Studies using gene expression analysis can be powerful tools for prognostication of various tumors. Several investigators have used gene expression analysis in tumor tissue from patients with PET using microarray methods (Maitra et al. 2003, Bloomston et al. 2004, Durkin et al. 2004, Hansel et al. 2004, Capurso et al. 2006, Couvelard et al. 2006). Numerous genes have been found to be either over- or underexpressed, and these findings have been validated with immunohistochemical studies and PCR studies for several of the overexpressed genes. Genes found to be overexpressed in metastatic PETs when compared with non-metastatic PETs include Met proto-oncogene, IGF-binding protein 3 gene (IGFBP-3) as well as various genes involved in angiogenesis, signal transduction, cell cycle control, and ion transport (Hansel et al. 2004, Couvelard et al. 2006). Other investigators using a different set of overexpressed genes did not show a significant difference in gene expression between primary and metastatic lesions (Capurso et al. 2006).

Angiogenesis is important for tumor growth and formation of metastases, and several studies have evaluated the prognostic role of angiogenesis markers and mediators. Expression of Vascular endothelial growth factor (VEGF) has been associated with more aggressive tumor growth, the presence of metastases, and shorter progression-free survival in patients with low-grade neuroendocrine tumors when compared with tumors not expressing VEGF (Hansel et al. 2004).
Microvessel density (MVD) in PETs has also received attention recently and decreased MVD may be an adverse prognostic factor according to some studies but not others (Marion-Audibert et al. 2003, La Rosa et al. 2003, Tan et al. 2004, Couvelard et al. 2005, 2006, Takahashi et al. 2007).

Conclusions

Pancreatic endocrine tumors (PETs) are uncommon tumors thought to originate from pluripotent cells in the exocrine pancreas. PETs account for only 1–3% of all neoplasms of the pancreas and their clinical behavior is much more indolent than that of adenocarcinoma of the pancreas. PETs are uncommon tumors with an annual incidence of <0.4 cases per 100 000. Asymptomatic PETs appear to be much more common according to large autopsy studies and frequently are undiagnosed in life. Functioning PETs are rare except for insulinomas and gastrinomas. The prognosis of PET is much better than that of pancreatic adenocarcinoma, even though patients are frequently diagnosed with metastatic disease. Multiple studies have shown that metastatic tumor and incomplete resection portend worse prognosis. Aggressive resection of the primary tumor as well as metastatic lesions may improve survival. Functional tumors may have a better prognosis in some studies, which may partly be explained by the much more benign nature and the favorable prognosis of the hormonally active insulinomas. Patients with functional tumors may also be diagnosed at an earlier stage, especially if they present with classical symptoms of hormone overproduction. Other prognostic factors include higher proliferative rate as manifested by increased number of mitoses as well as tumor necrosis but those histological features are not universally reported by pathologists. Novel prognostic factors include increased expression of Ki-67, overexpression of angiogenesis markers, chromosomal aberrations, and overexpression of various genes as identified on microarray studies. Given the heterogeneous nature of PETs, it is unlikely that there will be a prognostic model applicable to all subtypes of these uncommon tumors.

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arising from well-differentiated pancreatic endocrine neoplasms demonstrate increased VEGF-C expression. Modern Pathology 16 652–659.


