

# Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors

Thorvardur R Halfdanarson, Joseph Rubin, Michael B Farnell<sup>1</sup>, Clive S Grant<sup>1</sup> and Gloria M Petersen<sup>2</sup>

Division of Oncology, Department of Medical Oncology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

<sup>1</sup>Department of Surgery, Rochester, Minnesota, USA

<sup>2</sup>Department of Health Sciences Research, Rochester, Minnesota, USA

(Correspondence should be addressed to T R Halfdanarson who is now at Division of Hematology, Oncology and Blood and Marrow Transplantation, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, Iowa 52242, USA; Email: thorvardur-halfdanarson@uiowa.edu)

## 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.

*Endocrine-Related Cancer* (2008) 15 409–427

## Introduction

Pancreatic endocrine tumors (PETs) are uncommon neoplasms with an incidence of <1 per 100 000 person-years in population studies (Moldow & Connelly 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

**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.

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

Author, year	Number of autopsies	Number of islet cell tumors	Percent
Nicholls 1902 (Nicholls 1902)	1514	1	0.07
Korpássy 1939 (Korpássy 1939)	500	4	0.8
Frantz 1959 (Frantz 1959)	9158	24	0.3
Warren 1966 (Warren <i>et al.</i> 1966)	4566	42	0.9
Becker 1971 (Becker 1971)	4280	62	1.4
Grimelius 1975 (Grimelius <i>et al.</i> 1975)	1366	11	0.8
Kimura 1991 (Kimura <i>et al.</i> 1991)			
Overall	800	20	2.5
5 mm sections <sup>a</sup>	60	6	10
Lam 1997 (Lam & Lo 1997)	11 472	13	0.1

<sup>a</sup>Sixty patients of the 800 were randomly selected for a thorough pathological examination with 5 mm sections of the pancreas.

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

**Table 3** Population studies of pancreatic endocrine tumors

Author, year	Number of PET cases in the population	Annual incidence (all types)	Comments
Moldow 1968 (Moldow & Connelly 1968)	NR	<1/100 000 <sup>a</sup>	All cases in Connecticut, USA over a given period; PETs grouped with other rare tumors of the pancreas
Eriksson 1989 (Eriksson <i>et al.</i> 1989)	84	0.4/100 000	Well-defined region in Sweden; single referral hospital
Watson 1989 (Watson <i>et al.</i> 1989)	94	0.23/100 000	Well-defined Northern Irish population; same series as Buchanan <i>et al.</i> (1986)
Carriaga 1995 (Carriaga & Henson 1995)	402	<0.6/100 000 <sup>a</sup>	SEER data 1973–1987; exact incidence of PETs not provided
Lam 1997 (Lam & Lo 1997)	53	0.2/100 000	Referral to a single hospital in Hong Kong
Lepage 2004 (Lepage <i>et al.</i> 2004)	47	♀: 0.12/100 000 ♂: 0.19/100 000	Well-defined geographic region in France
Halfdanarson 2007 (Halfdanarson <i>et al.</i> 2007)	1488	♀: 0.2/100 000 ♂: 0.3/100 000	SEER data 1973–2000; all (neuro)endocrine tumors of the pancreas

NR, not reported; SEER, surveillance, epidemiology, and end results.

<sup>a</sup>Accurate figure not provided for pancreatic endocrine tumors.

*et al.* 2004). 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 ( $0.7\text{--}0.8/100\ 000$ ) 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  $0.1/\text{million}$  (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  $0.1/\text{million}$ , 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  $0.1\text{--}0.6$  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 or  $<0.1$  per million (Eriksson *et al.* 1989, Watson *et al.* 1989). Glucagonomas may be slightly more common among females and

**Table 4** Annual incidence (cases per million) of functional pancreatic endocrine neoplasms (PETs)

Author, year	Country	Annual incidence of all PETs	Insulinoma	Gastrinoma	VIPoma	Glucagonoma
Eriksson 1989 (Eriksson <i>et al.</i> 1989)	Sweden	4	1.1	1.2	0.64	0.04
Watson 1989 (Watson <i>et al.</i> 1989)	Northern Ireland	2.3	1.2	0.5	0.12	0.12
Service 1991 (Service <i>et al.</i> 1991)	USA	–	4	–	–	–
Cullen 1987 (Cullen & Ong 1987)	New Zealand	–	0.67	–	–	–
Jacobsen 1986 (Jacobsen <i>et al.</i> 1986)	Denmark	–	–	0.5	–	–
Stamm 1991 (Stamm <i>et al.</i> 1991)	Switzerland	–	–	2–4	–	–

**Table 5** Subtypes of pancreatic endocrine tumors

Tumor type	Annual incidence (cases per million)	Percentage of all PETs	Age (years)	Percent malignant <sup>a</sup>	Percent located in the pancreas	Percent associated with MEN-1
Insulinoma	0.7–4.0	30–45	30–60	5–10	>95	4–8
Gastrinoma	0.5–4.0	16–30	20–70	40–90	25–70	12–22
VIPoma	0.1–0.6	<10	20–80	>50	75–90	6–11
Glucagonoma	≤0.1	<10	40–60	>50	>95	5–13
Somatostatinoma	<0.1	<5	30–80	>60	40–70	2–7
Other hormones <sup>b</sup>	Rare	<1	–	–	–	Unknown
Non-functioning <sup>c</sup> (clinically silent)	≤1	25–100 <sup>d</sup>	50–60	>50	100	0–21
	0.1–10% in autopsy series					

Data compiled from original articles and reviews (Grimelius *et al.* 1975, Creutzfeldt 1980, Weil 1985, Harris *et al.* 1987, Klöppel & Heitz 1988, Eriksson *et al.* 1989, Watson *et al.* 1989, Demeure *et al.* 1991, Kimura *et al.* 1991, Service *et al.* 1991, Soga & Yakuwa 1994, 1998b, 1999, Wermers *et al.* 1996, Lam & Lo 1997, Solcia *et al.* 1997, Smith *et al.* 1998, Jensen 1999, Roy *et al.* 2000, Tomassetti *et al.* 2001, Lepage *et al.* 2004, Mansour & Chen 2004, Öberg & Eriksson 2005, Warner 2005, Halfdanarson *et al.* 2007).

<sup>a</sup>Malignant behavior based on the presence of invasion and metastases.

<sup>b</sup>Data on these tumors are insufficient for further analysis.

<sup>c</sup>Includes tumors that produce pancreatic polypeptide (PP).

<sup>d</sup>The higher percentage comes from autopsy studies.

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

Patients with PETs generally have a much better prognosis than those with pancreatic adenocarcinoma. Recent studies using the SEER database have reported improved survival after resection or a median overall survival of 58–97 months compared with 15–21 months in patients not undergoing surgery, although the number of patients with information regarding the surgery was small (Fesinmeyer *et al.* 2005, Halfdanarson *et al.* 2007). Numerous retrospective reports on PETs have been published, which provide valuable information about the mode of presentation and the prognosis of patients with these tumors, but there is marked heterogeneity among the patient populations studied as well as a large potential for referral bias, decreasing the generalizability of the results (Tables 6–8; Cubilla & Hajdu 1975, Kent *et al.* 1981, Broughan *et al.* 1986, Eckhauser *et al.* 1986, Legaspi & Brennan 1988, Thompson *et al.* 1988, Venkatesh *et al.* 1990, Service *et al.* 1991, Grama *et al.* 1992, Cheslyn-Curtis *et al.* 1993, Evans *et al.* 1993, White *et al.* 1994, Closset *et al.* 1996, Lo *et al.* 1996, La Rosa *et al.* 1996, Madura *et al.* 1997, Phan *et al.* 1997, 1998, Furukawa *et al.* 1998, Madeira *et al.* 1998, Bartsch *et al.* 2000, Hellman *et al.* 2000, Matthews *et al.* 2000, Yang *et al.* 2000, Corleto *et al.* 2001, Solorzano *et al.* 2001, Chu *et al.* 2002, Hochwald *et al.* 2002, Sarmiento *et al.* 2002, Gullo *et al.* 2003, Norton *et al.* 2003, Dralle *et al.* 2004, Guo *et al.* 2004, Lepage *et al.* 2004, Liang *et al.* 2004, Pape *et al.* 2004, Jarufe *et al.* 2005, Kang *et al.* 2005, Kouvaraki *et al.* 2005, Panzuto *et al.* 2005, Tomassetti *et al.* 2005, House *et al.* 2006, Kazanjian *et al.* 2006, Schurr *et al.* 2007).

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

Several studies have been limited to non-functional PETs (Table 7; Kent *et al.* 1981, Eckhauser *et al.* 1986, Cheslyn-Curtis *et al.* 1993, Evans *et al.* 1993, Closset *et al.* 1996, La Rosa *et al.* 1996, Madura *et al.* 1997, Furukawa *et al.* 1998, Bartsch *et al.* 2000, Matthews *et al.* 2000, Yang *et al.* 2000, Solorzano *et al.* 2001, Gullo *et al.* 2003, 2004, Liang *et al.* 2004, Kang *et al.* 2005). Similar to the studies combining functional and non-functional tumors, the presence of distant metastases and incomplete resection predict worse survival. The 5-year overall survival ranges from 26 to 58% and appears lower than those in the series combining both functional and non-functional tumors. However, the heterogeneity among the studies and the potential for selection bias make any comparison problematic (Dralle *et al.* 2004, Kouvaraki *et al.* 2005). Non-functional PETs seem to have inferior prognosis when compared with functional PETs, even after adjusting known prognostic factors such as age, stage, and grade (Halfdanarson *et al.* 2007).

La Rosa *et al.* (1996) studied 61 patients with non-functional PETs. The tumors were considered malignant if there was a direct invasion into adjacent tissues or organs or if distant metastases were present.

**Table 6** Selected studies of both functional and non-functional pancreatic endocrine tumors

Study (author, year)	Number of patients	Number (%) of functioning tumors	Number (%) insulinomas	Number of patients with metastases at diagnosis (%)	Survival	Factors adversely affecting overall survival or disease-free survival
Cubilla <i>et al.</i> 1975 (Cubilla & Hajdu 1975)	30	12 (34)	4 (13)	LN: 19 (63)	5-OS: 57%	Functional tumor
Broughan <i>et al.</i> 1986 (Broughan <i>et al.</i> 1986)	84	63 (75)	41 (49)	Liver: 21 (70) Liver and/or LN: 39 (46%)	MS: 4.3 (N) and 2.8 (F) years 5-OS: 63.1% (N), 68.4% (G), 96.9 (I)	Non-insulinoma or non-functional <sup>a</sup>
Phan <i>et al.</i> 1998 (Phan <i>et al.</i> 1998)	125 <sup>b</sup> (including 86 PETs)	64 of all tumors (52)	35 (28)	NR	5-OS: 65% (all), 77% (F), 52% (N)	Non-functional tumors, positive margins, malignant tumors <sup>a</sup>
Sarmiento <i>et al.</i> 2002 (Sarmiento <i>et al.</i> 2002)	29	9 (31)	3 (10)	LN: 16 (55) Liver: 1 (3)	5-OS: 81% (all), 100% (F), 70% (N)	Non-functional, positive lymph nodes <sup>a</sup>
White <i>et al.</i> 1994 (White <i>et al.</i> 1994)	28	19 (68)	3 (11)	44% (N) 53% (NF)	DFS at 2 years: 67% (N) and 40% (F)	No difference between functioning and non-functioning tumors <sup>a</sup>
Jarufe <i>et al.</i> 2005 (Jarufe <i>et al.</i> 2005)	44	24 (55)	16 (36)	22 (50)	5-OS: 74.4%	Metastases (multivariate analysis)
Thompson <i>et al.</i> 1988 (Thompson <i>et al.</i> 1988)	58	31 (54)	8 (14)	LN: 25 (43) Liver: 19 (33)	5-OS: 42%	Liver metastases, non-functional tumor (versus gastrinoma) <sup>a</sup>
Panzuto <i>et al.</i> 2005 (Panzuto <i>et al.</i> 2005)	156 <sup>b</sup> (including 67 PETs)	26 (39)	1 (1.5)	LN: 6 (9) Liver: 28 (42) Extra-hepatic: 11 (16)	5-OS: 62%	Poorly differentiated tumors, distant metastases (multivariate analysis)
Legaspi <i>et al.</i> 1988 (Legaspi & Brennan 1988)	33	11 (33)	0	Distant metastases: 16 (48)	3-year survival 76%	Incomplete resection or residual tumor <sup>a</sup>
Lepage <i>et al.</i> 2004 (Lepage <i>et al.</i> 2004)	47	NR	NR	NR	5-OS: 42%	Metastatic disease and advanced age (multivariate analysis)
Venkatesh <i>et al.</i> 1990 (Venkatesh <i>et al.</i> 1990)	98	55 (56)	7 (7)	47 (48)	Mean survival 42.7 ± 49 months	Non-functional tumors <sup>a</sup> metastatic disease and advanced age (multivariate analysis)
Tomassetti <i>et al.</i> 2005 (Tomassetti <i>et al.</i> 2005)	83	31 (37)	7 (8)	LN: 47 (60) Liver: 27 (33)	MS: 90 months 5-OS: 55.3%	Liver and lymph node metastases at diagnosis and incomplete resection, MEN-1 <sup>a</sup>
Chu <i>et al.</i> 2002 (Chu <i>et al.</i> 2002)	50	21 (42)	6 (12)	Liver: 29 (58) Synchronous liver metastases	MS 40 months 5-OS: 36%	Incomplete resection and liver metastases, less aggressive treatment of liver metastases <sup>a</sup>
Lo <i>et al.</i> 1996 (Lo <i>et al.</i> 1996)	64	30 (47)	4 (6)	LN: 38 (59) Liver: 39 (61)	3-year survival: curative resection: 80%, non-curative resection 62%	Liver metastases, non-curative resection <sup>a</sup>
Madeira <i>et al.</i> 1998 (Madeira <i>et al.</i> 1998)	82 <sup>b</sup> (including 62 PETs)	38 (46)	3 (4)	LN: 52 (83) Liver: 49 (60) (among all 82 patients)	5-OS: No liver metastases 100% Liver metastases 40%	Liver metastases, poor differentiation and incomplete resection (multivariate analysis)
Pape <i>et al.</i> 2004 (Pape <i>et al.</i> 2004)	254 <sup>b</sup> (including 73 PETs)	53 (32)	6 (8)	53 (73)	MS: 47 months 5-OS: 42.9%	Metastases at diagnosis and incomplete resection <sup>a</sup>
Hochwald <i>et al.</i> 2002 (Hochwald <i>et al.</i> 2002)	136	47 (35)	21 (15)	NR	DFS after curative resection: 110 months (N) and 152 months (F)	High mitotic rate (DSS), presence of tumor necrosis, LN or liver metastases (DFS) (multivariate analysis)
House <i>et al.</i> 2006 (House <i>et al.</i> 2006)	31	8 (26)	1 (3)	100	MS: resection of primary tumor and liver metastases: 78 months (5-OS: 65%)	Incomplete resection

Table 6 continued

Study (author, year)	Number of patients	Number (%) of functioning tumors	Number (%) insulinomas	Number of patients with metastases at diagnosis (%)	Survival	Factors adversely affecting overall survival or disease-free survival
Kazanjan et al. 2006 (Kazanjan et al. 2006)	70	20 (29)	16 (23)	LN: 21 (57) <sup>c</sup> Liver: 9 (24) <sup>c</sup>	Resection of primary tumor only: 17 months 5-OS: 89%	Malignant tumors (neuroendocrine carcinoma)
Norton et al. 2003 (Norton et al. 2003)	20	11 (55) <sup>d</sup>	1 (5)	LN: 14 (70) Liver: 8 (40)	5-OS: 80%	NR
Hellman et al. 2000 (Hellman et al. 2000)	31	7 (23)	NR	LN: 10 (32) Liver: 10 (32)	5-OS: 75%	NR
Corleto et al. 2001 (Corleto et al. 2001)	98 <sup>a</sup> (including 41 PETs)	18 (44)	5 (12)	NR	NR	NR
Schurr et al. 2007 (Schurr et al. 2007)	62			19 (31) Liver: 16 (26)		

DFS, disease-free survival; DSS, disease-specific survival; F, functional PET; G, gastrinoma; I, insulinoma; LN, lymph nodes; MS, median survival; 5-OS, 5-year overall survival; N, non-functional PET; NR, not reported; NS, not significant.

<sup>a</sup>Univariate analysis (results of univariate analyses are not reported where results of multivariate analyses are provided).

<sup>b</sup>The study included both pancreatic and extrapancreatic tumors.

<sup>c</sup>The number patients with metastatic lesions relates to the 37 patients with neuroendocrine carcinoma.

<sup>d</sup>Out of 11 functional tumors, 10 were gastrinomas.

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, Boukhanan 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

Study (author, year)	Number of patients	Metastasis at diagnosis (%)	Survival	Factors adversely affecting survival
Kent <i>et al.</i> 1981 (Kent <i>et al.</i> 1981)	25	18 (72) Liver 11 (44)	3- and 5-year OS: 60 and 44%	NR
Eckhauser <i>et al.</i> 1986 (Eckhauser <i>et al.</i> 1986)	11	9 (82) Liver: 5 (45) LN: 7 (64)	Mean survival: 23 months (4–72 months)	No predictors identified
Evans <i>et al.</i> 1993 (Evans <i>et al.</i> 1993)	73	37 (51)	5-year OS: 50%	Metastatic disease and incomplete resection <sup>a</sup>
Cheslyn-Curtis <i>et al.</i> 1993 (Cheslyn-Curtis <i>et al.</i> 1993)	20	Liver: 5 (25) LN: 5 (25)	Median survival: Curative resection: 42 months No curative resection: 32 months	
La Rosa <i>et al.</i> 1996 (La Rosa <i>et al.</i> 1996)	61	34 (56)	Mean survival (months): Increased risk: 50.7 Well differentiated: 44.2 Poorly differentiated: 3.7	Capsular penetration, distant metastases, vascular microinvasion, and high Ki-67 proliferative index <sup>a</sup>
Matthews <i>et al.</i> 2000 (Matthews <i>et al.</i> 2000)	28	6 (21)	2-year survival: node negative 77.8%, node positive 71.4 and metastatic 36.4	Liver metastases <sup>a</sup>
Bartsch <i>et al.</i> 2000 (Bartsch <i>et al.</i> 2000)	17	LN: 15 (83) Distant: 6 (33)	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	Incomplete resection <sup>a</sup>
Solorzano <i>et al.</i> 2001 (Solorzano <i>et al.</i> 2001)	163	101 (62)	5-year OS: 43% (77% in patients with localized and resected disease, 16% in patients with metastatic disease and no resection)	Incomplete resection, no anti-cancer therapy and age > 65 years (multivariate analysis)
Gullo <i>et al.</i> 2003 (Gullo <i>et al.</i> 2003)	184	69 (38)	5-year OS: resected 76.9%, not resected 28.6%	Metastatic disease, incomplete resection, symptomatic at diagnosis and tumor > 3 cm <sup>a</sup>
Liang <i>et al.</i> 2004 (Liang <i>et al.</i> 2004)	43	6 (14)	5- and 10-year OS: 58 and 29%	Incomplete resection (multivariate analysis)
Kang <i>et al.</i> 2005 (Kang <i>et al.</i> 2005)	19	7 (37)	5-year OS: 32% (curative resection 90%)	Metastases, unresectable disease, macroscopic invasion <sup>a</sup>
Guo <i>et al.</i> 2004 (Guo <i>et al.</i> 2004)	41 (all patients had resection)	4 (10) Only LN metastases	NR	NR Tumors recurred in three patients following enucleation
Furukawa <i>et al.</i> 1998 (Furukawa <i>et al.</i> 1998)	16	4 (25) LN: 2 (13) Liver: 2 (13)	5-year OS: 83%	Both patients with liver metastasis died secondary to their malignancy
Yang <i>et al.</i> 2000 (Yang <i>et al.</i> 2000)	16	LN: 8 (50) Liver: 2 (13)	All patients alive after a mean follow-up time of 5.3 years (one with recurrent disease)	NR
Madura <i>et al.</i> 1997 (Madura <i>et al.</i> 1997)	14	LN: 7 (50)	Median survival 31.2 months	LN metastases

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

<sup>a</sup>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

Study (author, year)	Number of patients	Median age (years)	Type of tumor (hormone produced)	Malignant PET (%)		Factors adversely affecting survival
				number of patients with metastases	Survival	
Service <i>et al.</i> 1991 (Service <i>et al.</i> 1991)	244	47	Insulinoma	5.8	10-year OS: 78% for benign and 29% for malignant insulinoma	Malignant insulinoma, advanced age
Grant 2005 (Grant 2005)	225	NR	Insulinoma	0	98% cure rate	NR
Grama <i>et al.</i> 1992 (Grama <i>et al.</i> 1992)	85	NR	Insulinoma 56%	47	10 OS: insulinoma 50%, malignant PET 28%	Liver metastases, tumor > 4 cm, complete resection
Norton <i>et al.</i> 1999 (Norton <i>et al.</i> 1999)	151 (36 with pancreatic gastrinoma)	48 (mean age)	Gastrinoma <sup>a</sup>	NR	5-year OS: 100% for sporadic gastrinoma, 42% free of disease at 5 years	MEN-1 (lower disease-free survival)
Danforth <i>et al.</i> 1984 (Danforth <i>et al.</i> 1984)	17		Insulinoma	17 (100) LN: 8 (47) Liver: 12 (70)	NR	NR
Hirshberg <i>et al.</i> 2005 (Hirshberg <i>et al.</i> 2005)	10		Insulinoma	100	Survival ranged from 4 months to 30 years	NR
Matthews <i>et al.</i> 2002 (Matthews <i>et al.</i> 2002)	20		Gastrinoma: 8 (40) Insulinoma: 7 (35) Glucagonoma: 4 (20) VIPoma: 1 (5) MEN: 3 (15)	Metastases: 5 (20)	63% survival at a mean follow-up of 47 months	NR
Harrison <i>et al.</i> 1973 (Harrison <i>et al.</i> 1973)	35		Insulinoma	Metastases: 3 (9%)	NR	Metastatic disease (two out of three patients died shortly after referral)
Starke <i>et al.</i> 2005 (Starke <i>et al.</i> 2005)	77		Insulinoma	Metastases 10 (13)	2-year survival (metastatic only): 2.6 years	NR
Chen <i>et al.</i> 2002 (Chen <i>et al.</i> 2002)	74		Insulinoma	Malignant insulinoma: 2 (3%)	All patients with benign insulinoma were cured. One patient with malignant insulinoma survived 18 years	NR
Feng <i>et al.</i> 2002 (Feng <i>et al.</i> 2002)	105		Insulinoma	Malignant insulinoma: 4 (4%)	All patients with benign insulinoma were cured; three out of four patients with malignant insulinoma had relief of their symptoms and one died	NR
Boukhman <i>et al.</i> 1998 (Boukhman <i>et al.</i> 1998)	67		Insulinoma	Malignant insulinoma: 10 (15%)	89% underwent a successful operation (no survival data reported)	NR
Kang <i>et al.</i> 2006 (Kang <i>et al.</i> 2006)	14		Insulinoma: 12 (86%) Gastrinoma: 2 (14%)	Two malignant tumors (one insulinoma and one gastrinoma)	10 year survival: 81% (one patient died of unrelated causes)	NR

Table 8 continued

Study (author, year)	Number of patients	Median age (years)	Type of tumor (hormone produced)	Malignant PET (%) number of patients with metastases	Survival	Factors adversely affecting survival
Lundstam et al. 1979 (Lundstam et al. 1979)	12		Insulinoma	1 (8)	All patients with benign insulinoma survived	NR
Zeng et al. 1988 (Zeng et al. 1988)	110		Insulinoma	3 (3)	Four cases with recurrent hypoglycemia; no information on the metastatic cases	NR

LN, lymph nodes; NR, not reported; OS, overall survival.  
<sup>a</sup>Pancreatic and non-pancreatic gastrinoma.

metastases in patients with sporadic insulinoma, and loss of sex chromosomes may predict shorter survival in patients with functional and non-functional PETs (Missiaglia et al. 2002, Jonkers et al. 2005).

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*, *O<sup>6</sup>-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.

2003, Phan *et al.* 2006). 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 necroses 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.

## Acknowledgements

We thank Ricardo V Lloyd MD, PhD for reviewing the manuscript. Research support: Mayo Clinic SPORC in Pancreatic Cancer (P50 CA 102701). The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

## References

- Ali A, Serra S, Asa SL & Chetty R 2006 The predictive value of CK19 and CD99 in pancreatic endocrine tumors. *American Journal of Surgical Pathology* **30** 1588–1594.
- Barghorn A, Komminoth P, Bachmann D, Rutimann K, Saremaslani P, Muletta-Feurer S, Perren A, Roth J, Heitz PU & Speel EJ 2001a Deletion at 3p25.3–p23 is frequently encountered in endocrine pancreatic tumours and is associated with metastatic progression. *Journal of Pathology* **194** 451–458.
- Barghorn A, Speel EJ, Farspour B, Saremaslani P, Schmid S, Perren A, Roth J, Heitz PU & Komminoth P 2001b Putative tumor suppressor loci at 6q22 and 6q23–q24 are involved in the malignant progression of sporadic endocrine pancreatic tumors. *American Journal of Pathology* **158** 1903–1911.
- Bartsch DK, Schilling T, Ramaswamy A, Gerdes B, Celik I, Wagner HJ, Simon B & Rothmund M 2000 Management of nonfunctioning islet cell carcinomas. *World Journal of Surgery* **24** 1418–1424.
- Becker V 1971 Pathologicoanatomical aspects of tumors with endocrine activity. *Langenbecks Archiv für Chirurgie* **329** 426–437.
- Binkovitz LA, Johnson CD & Stephens DH 1990 Islet cell tumors in von Hippel–Lindau disease: increased prevalence and relationship to the multiple endocrine neoplasias. *American Journal of Roentgenology* **155** 501–505.
- Blansfield JA, Choyke L, Morita S, Choyke PL, Pingpank JF, Alexander HR, Seidel G, Shutack Y, Yuldasheva N, Eugeni M *et al.* 2007 Clinical, genetic and radiographic analysis of 108 patients with von Hippel–Lindau disease (vHL) manifested by pancreatic neuroendocrine tumors. In *Presented at the 28th Annual Meeting of the American Association of Endocrine Surgeons*. Tucson, Arizona.
- Bloomston M, Durkin A, Yang I, Rojiani M, Rosemurgy AS, Enkmann S, Yeatman TJ & Zervos EE 2004 Identification of molecular markers specific for pancreatic neuroendocrine tumors by genetic profiling of core biopsies. *Annals of Surgical Oncology* **11** 413–419.
- Le Bodic MF, Heymann MF, Lecomte M, Berger N, Berger F, Louvel A, De Micco C, Patey M, De Mascarel A, Burtin F *et al.* 1996 Immunohistochemical study of 100 pancreatic tumors in 28 patients with multiple endocrine neoplasia, type I. *American Journal of Surgical Pathology* **20** 1378–1384.
- Böhmig M, Pape UF, Tiling N, Berndt U, Müller-Nordhorn J, Willich SN & Wiedenmann B 2005 Prognostic factors in gastroenteropancreatic neuroendocrine tumors – a retrospective multivariate analysis. *Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings* **23** (Abstract 4086).
- Boukhman MP, Karam JH, Shaver J, Siperstein AE, Duh QY & Clark OH 1998 Insulinoma – experience from 1950 to 1995. *Western Journal of Medicine* **169** 98–104.
- Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A

- et al. 2001 Guidelines for diagnosis and therapy of MEN type 1 and type 2. *Journal of Clinical Endocrinology* **86** 5658–5671.
- Broughan TA, Leslie JD, Soto JM & Hermann RE 1986 Pancreatic islet cell tumors. *Surgery* **99** 671–678.
- Buchanan KD, Johnston CF, O'Hare MM, Ardill JE, Shaw C, Collins JS, Watson RG, Atkinson AB, Hadden DR, Kennedy TL et al. 1986 Neuroendocrine tumors. A European view. *American Journal of Medicine* **81** 14–22.
- Burgess JR, Greenaway TM, Parameswaran V, Challis DR, David R & Shepherd JJ 1998a Enteropancreatic malignancy associated with multiple endocrine neoplasia type 1: risk factors and pathogenesis. *Cancer* **83** 428–434.
- Burgess JR, Greenaway TM & Shepherd JJ 1998b Expression of the MEN-1 gene in a large kindred with multiple endocrine neoplasia type 1. *Journal of Internal Medicine* **243** 465–470.
- Capurso G, Lattimore S, Crnogorac-Jurcevic T, Panzuto F, Milione M, Bhakta V, Campanini N, Swift SM, Bordi C, Delle Fave G et al. 2006 Gene expression profiles of progressive pancreatic endocrine tumours and their liver metastases reveal potential novel markers and therapeutic targets. *Endocrine-Related Cancer* **13** 541–558.
- Carriaga MT & Henson DE 1995 Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* **75** 171–190.
- Chen X, Cai WY, Yang WP & Li HW 2002 Pancreatic insulinomas: diagnosis and surgical treatment of 74 patients. *Hepatobiliary & Pancreatic Diseases International* **1** 458–461.
- Chen YJ, Vortmeyer A, Zhuang Z, Huang S & Jensen RT 2003 Loss of heterozygosity of chromosome 1q in gastrinomas: occurrence and prognostic significance. *Cancer Research* **63** 817–823.
- Chen YJ, Vortmeyer A, Zhuang Z, Gibril F & Jensen RT 2004 X-chromosome loss of heterozygosity frequently occurs in gastrinomas and is correlated with aggressive tumor growth. *Cancer* **100** 1379–1387.
- Cheslyn-Curtis S, Sitaram V & Williamson RC 1993 Management of non-functioning neuroendocrine tumours of the pancreas. *British Journal of Surgery* **80** 625–627.
- Chu QD, Hill HC, Douglass HO Jr, Driscoll D, Smith JL, Nava HR & Gibbs JF 2002 Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. *Annals of Surgical Oncology* **9** 855–862.
- Clarke MR, Baker EE, Weyant RJ, Hill L & Carty SE 1997 Proliferative activity in pancreatic endocrine tumors: association with function, metastases, and survival. *Endocrine Pathology* **8** 181–187.
- Closset J, Delhaye M, Sperduto N, Rickaert F & Gelin M 1996 Nonfunctioning neuroendocrine tumors of the pancreas: clinical presentation of 7 patients. *Hepatogastroenterology* **43** 1640–1644.
- Corleto VD, Panzuto F, Falconi M, Cannizzaro R, Angeletti S, Moretti A, Delle Fave G & Farinati F 2001 Digestive neuroendocrine tumours: diagnosis and treatment in Italy. A survey by the Oncology Study Section of the Italian Society of Gastroenterology (SIGE). *Digestive and Liver Disease* **33** 217–221.
- Couvelard A, O'Toole D, Turley H, Leek R, Sauvanet A, Degott C, Ruszniewski P, Belghiti J, Harris AL, Gatter K et al. 2005 Microvascular density and hypoxia-inducible factor pathway in pancreatic endocrine tumours: negative correlation of microvascular density and VEGF expression with tumour progression. *British Journal of Cancer* **92** 94–101.
- Couvelard A, Hu J, Steers G, O'Toole D, Sauvanet A, Belghiti J, Bedossa P, Gatter K, Ruszniewski P & Pezzella F 2006 Identification of potential therapeutic targets by gene-expression profiling in pancreatic endocrine tumours. *Gastroenterology* **131** 1597–1610.
- Creutzfeldt W 1980 Endocrine tumors of the pancreas: clinical, chemical and morphological findings. *Monographs in Pathology* **21** 208–230.
- Cubilla AL & Hajdu SI 1975 Islet cell carcinoma of the pancreas. *Archives of Pathology* **99** 204–207.
- Cullen RM & Ong CE 1987 Insulinoma in Auckland 1970–1985. *New Zealand Medical Journal* **100** 560–562.
- Danforth DN Jr, Gorden P & Brennan MF 1984 Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. *Surgery* **96** 1027–1037.
- Dean PG, van Heerden JA, Farley DR, Thompson GB, Grant CS, Harnsen WS & Ilstrup DM 2000 Are patients with multiple endocrine neoplasia type I prone to premature death? *World Journal of Surgery* **24** 1437–1441.
- Demeure MJ, Klonoff DC, Karam JH, Duh QY & Clark OH 1991 Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. *Surgery* **110** 998–1005.
- Deschamps L, Handra-Luca A, O'Toole D, Sauvanet A, Ruszniewski P, Belghiti J, Bedossa P & Couvelard A 2006 CD10 expression in pancreatic endocrine tumors: correlation with prognostic factors and survival. *Human Pathology* **37** 802–808.
- Deshpande V, Fernandez-del Castillo C, Muzikansky A, Deshpande A, Zukerberg L, Warshaw AL & Lauwers GY 2004 Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors. *American Journal of Surgical Pathology* **28** 1145–1153.
- Doherty GM 2005 Multiple endocrine neoplasia type 1. *Journal of Surgical Oncology* **89** 143–150.
- Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells SA Jr & Norton JA 1998 Lethality of multiple endocrine neoplasia type I. *World Journal of Surgery* **22** 581–587.
- Dralle H, Krohn SL, Karges W, Boehm BO, Brauckhoff M & Gimm O 2004 Surgery of resectable nonfunctioning neuroendocrine pancreatic tumors. *World Journal of Surgery* **28** 1248–1260.
- Durkin AJ, Bloomston M, Yeatman TJ, Gilbert-Barnes E, Cojita D, Rosemurgy AS & Zervos EE 2004 Differential expression of the Tie-2 receptor and its ligands in human pancreatic tumors. *Journal of the American College of Surgeons* **199** 724–731.

- Eckhauser FE, Cheung PS, Vinik AI, Strodel WE, Lloyd RV & Thompson NW 1986 Nonfunctioning malignant neuroendocrine tumors of the pancreas. *Surgery* **100** 978–988.
- Eriksson B, Öberg K & Skogseid B 1989 Neuroendocrine pancreatic tumors. Clinical findings in a prospective study of 84 patients. *Acta Oncologica* **28** 373–377.
- Eriksson B, Skogseid B, Lundqvist G, Wide L, Wilander E & Öberg K 1990 Medical treatment and long-term survival in a prospective study of 84 patients with endocrine pancreatic tumors. *Cancer* **65** 1883–1890.
- Evans DB, Skibber JM, Lee JE, Cleary KR, Ajani JA, Gagel RF, Sellin RV, Fenoglio CJ, Merrell RC & Hickey RC 1993 Nonfunctioning islet cell carcinoma of the pancreas. *Surgery* **114** 1175–1182.
- Falconi M, Plockinger U, Kwekkeboom DJ, Manfredi R, Korner M, Kvols L, Pape UF, Ricke J, Goretzki PE, Wildi S *et al.* 2006 Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology* **84** 196–211.
- Feng LS, Ma XX, Tang Z, Zhao YF, Ye XX & Xu PQ 2002 Diagnosis and treatment of insulinoma: report of 105 cases. *Hepatobiliary & Pancreatic Diseases International* **1** 137–139.
- Fesinmeyer MD, Austin MA, Li CI, De Roos AJ & Bowen DJ 2005 Differences in survival by histologic type of pancreatic cancer. *Cancer Epidemiology, Biomarkers and Prevention* **14** 1766–1773.
- Formica V, Norman AR, Cunningham D, Wotherspoon A, Sirohi B, Oates J & Chong G 2006 The prognostic role of the WHO classification, urinary 5-hydroxyindoleacetic acid (u5HIAA) and liver function tests (LFTs) in metastatic neuroendocrine carcinomas (NECs) of the gastroenteropancreatic (GEP) tract. *Journal of Clinical Oncology* **24** 4092.
- Francalanci P, Diomedi-Camassei F, Purificato C, Santorelli FM, Giannotti A, Dominici C, Inserra A & Boldrini R 2003 Malignant pancreatic endocrine tumor in a child with tuberous sclerosis. *American Journal of Surgical Pathology* **27** 1386–1389.
- Frantz VK 1959 Tumors of the pancreas. In *Atlas of Tumor Pathology*, pp 79–149. Washington, DC: Armed Forces Institute of Pathology.
- Fujisawa T, Osuga T, Maeda M, Sakamoto N, Maeda T, Sakaguchi K, Onishi Y, Toyoda M, Maeda H, Miyamoto K *et al.* 2002 Malignant endocrine tumor of the pancreas associated with von Recklinghausen's disease. *Journal of Gastroenterology* **37** 59–67.
- Furukawa H, Mukai K, Kosuge T, Kanai Y, Shimada K, Yamamoto J, Mizuguchi Y & Ushio K 1998 Non-functioning islet cell tumors of the pancreas: clinical, imaging and pathological aspects in 16 patients. *Japanese Journal of Clinical Oncology* **28** 255–261.
- Gentil Perret A, Mosnier JF, Buono JP, Berthelot P, Chipponi J, Balique JG, Cuilleret J, Dechelotte P & Boucheron S 1998 The relationship between MIB-1 proliferation index and outcome in pancreatic neuroendocrine tumors. *American Journal of Clinical Pathology* **109** 286–293.
- Gibril F & Jensen RT 2004 Zollinger–Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion. *Current Gastroenterology Reports* **6** 454–463.
- Gibril F, Venzon DJ, Ojeaburu JV, Bashir S & Jensen RT 2001 Prospective study of the natural history of gastrinoma in patients with MEN1: definition of an aggressive and a nonaggressive form. *Journal of Clinical Endocrinology* **86** 5282–5293.
- Goto A, Niki T, Terado Y, Fukushima J & Fukayama M 2004 Prevalence of CD99 protein expression in pancreatic endocrine tumours (PETs). *Histopathology* **45** 384–392.
- Grama D, Eriksson B, Martensson H, Cedermark B, Ahren B, Kristofferson A, Rastad J, Öberg K & Akerstrom G 1992 Clinical characteristics, treatment and survival in patients with pancreatic tumors causing hormonal syndromes. *World Journal of Surgery* **16** 632–639.
- Grant CS 2005 Insulinoma. *Best Practice & Research. Clinical Gastroenterology* **19** 783–798.
- Grimelius L, Hultquist GT & Stenkvist B 1975 Cytological differentiation of asymptomatic pancreatic islet cell tumours in autopsy material. *Virchows Archiv. A, Pathological Anatomy and Histopathology* **365** 275–288.
- Gullo L, Migliori M, Falconi M, Pederzoli P, Bettini R, Casadei R, Delle Fave G, Corleto VD, Ceccarelli C, Santini D *et al.* 2003 Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. *American Journal of Gastroenterology* **98** 2435–2439.
- Guo SS, Arora C, Shimoide AT & Sawicki MP 2002a Frequent deletion of chromosome 3 in malignant sporadic pancreatic endocrine tumors. *Molecular and Cellular Endocrinology* **190** 109–114.
- Guo SS, Wu AY & Sawicki MP 2002b Deletion of chromosome 1, but not mutation of MEN-1, predicts prognosis in sporadic pancreatic endocrine tumors. *World Journal of Surgery* **26** 843–847.
- Guo KJ, Liao HH, Tian YL, Guo RX, He SG & Shen K 2004 Surgical treatment of nonfunctioning islet cell tumor: report of 41 cases. *Hepatobiliary and Pancreatic Diseases International* **3** 469–472.
- Halfdanarson TR, Rabe K, Rubin J & Petersen GM 2007 Pancreatic endocrine tumors (PETs): incidence and recent trend toward improved survival. *Presented at the 2007 Gastrointestinal Cancers Symposium in Orlando, FL.*
- Halfdanarson T, Rabe KG, Rubin J & Petersen GM 2008 Pancreatic Neuroendocrine Tumors (PNETs): Incidence, prognosis and recent trend toward improved survival. *Annals of Oncology* [in press].
- Hammel PR, Vilgrain V, Terris B, Penforis A, Sauvanet A, Correas JM, Chauveau D, Balian A, Beigelman C, O'Toole D *et al.* 2000 Pancreatic involvement in von Hippel–Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel–Lindau. *Gastroenterology* **119** 1087–1095.
- Hansel DE, Rahman A, Hermans J, de Krijger RR, Ashfaq R, Yeo CJ, Cameron JL & Maitra A 2003 Liver metastases

- arising from well-differentiated pancreatic endocrine neoplasms demonstrate increased VEGF-C expression. *Modern Pathology* **16** 652–659.
- Hansel DE, Rahman A, House M, Ashfaq R, Berg K, Yeo CJ & Maitra A 2004 Met proto-oncogene and insulin-like growth factor binding protein 3 over-expression correlates with metastatic ability in well-differentiated pancreatic endocrine neoplasms. *Clinical Cancer Research* **10** 6152–6158.
- Harris GJ, Tio F & Cruz AB Jr 1987 Somatostatinoma: a case report and review of the literature. *Journal of Surgical Oncology* **36** 8–16.
- Harrison TS, Child CG, Fry WJ, Floyd JC Jr & Fajans SS 1973 Current surgical management of functioning islet cell tumors of the pancreas. *Annals of Surgery* **178** 485–495.
- Heitz PU, Komminoth P, Perren A, Klimstra DS, Dayal Y, Bordi C, Lechago J, Centeno BA & Klöppel G 2004 Pancreatic endocrine tumors: introduction. In *Pathology and Genetics of Tumours of Endocrine Organs. WHO Classification of Tumours*, pp 177–182. Eds DA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon, France: IARC Press.
- Hellman P, Andersson M, Rastad J, Juhlin C, Karacagil S, Eriksson B, Skogseid B & Akerstrom G 2000 Surgical strategy for large or malignant endocrine pancreatic tumors. *World Journal of Surgery* **24** 1353–1360.
- de Herder WW, Niederle B, Scoazec JY, Pauwels S, Kloppel G, Falconi M, Kwekkeboom DJ, Oberg K, Eriksson B, Wiedenmann B *et al.* 2006 Well-differentiated pancreatic tumor/carcinoma: insulinoma. *Neuroendocrinology* **84** 183–188.
- Heymann MF, Joubert M, Nemeth J, Franc B, Visset J, Hamy A, le Borgne J, le Neel JC, Murat A, Cordel S *et al.* 2000 Prognostic and immunohistochemical validation of the Capella classification of pancreatic neuroendocrine tumours: an analysis of 82 sporadic cases. *Histopathology* **36** 421–432.
- Hirshberg B, Cochran C, Skarulis MC, Libutti SK, Alexander HR, Wood BJ, Chang R, Kleiner DE & Gorden P 2005 Malignant insulinoma: spectrum of unusual clinical features. *Cancer* **104** 264–272.
- Hochwald SN, Zee S, Conlon KC, Colleoni R, Louie O, Brennan MF & Klimstra DS 2002 Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *Journal of Clinical Oncology* **20** 2633–2642.
- House MG, Herman JG, Guo MZ, Hooker CM, Schulick RD, Cameron JL, Hruban RH, Maitra A & Yeo CJ 2003a Prognostic value of hMLH1 methylation and micro-satellite instability in pancreatic endocrine neoplasms. *Surgery* **134** 902–909.
- House MG, Herman JG, Guo MZ, Hooker CM, Schulick RD, Lillemoie KD, Cameron JL, Hruban RH, Maitra A & Yeo CJ 2003b Aberrant hypermethylation of tumor suppressor genes in pancreatic endocrine neoplasms. *Annals of Surgery* **238** 423–431.
- House MG, Cameron JL, Lillemoie KD, Schulick RD, Choti MA, Hansel DE, Hruban RH, Maitra A & Yeo CJ 2006 Differences in survival for patients with resectable versus unresectable metastases from pancreatic islet cell cancer. *Journal of Gastrointestinal Surgery* **10** 138–145.
- Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA & Nieman LK 2005 Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *Journal of Clinical Endocrinology* **90** 4955–4962.
- Imam H, Eriksson B & Öberg K 2000 Expression of CD44 variant isoforms and association to the benign form of endocrine pancreatic tumours. *Annals of Oncology* **11** 295–300.
- Jacobsen O, Bardram L & Rehfeld JF 1986 The requirement for gastrin measurements. *Scandinavian Journal of Clinical and Laboratory Investigation* **46** 423–426.
- Jarufe NP, Coldham C, Orug T, Mayer AD, Mirza DF, Buckels JA & Bramhall SR 2005 Neuroendocrine tumours of the pancreas: predictors of survival after surgical treatment. *Digestive Surgery* **22** 157–162.
- Jensen RT 1999 Pancreatic endocrine tumors: recent advances. *Annals of Oncology* **10** 170–176.
- Jonkers YMH, Claessen SMH, Perren A, Schmid S, Komminoth P, Verhofstad AA, Hofland LJ, de Krijger RR, Slootweg PJ, Ramaekers FCS *et al.* 2005 Chromosomal instability predicts metastatic disease in patients with insulinomas. *Endocrine-Related Cancer* **12** 435–447.
- Jorda M, Ghorab Z, Fernandez G, Nassiri M, Hanly A & Nadji M 2003 Low nuclear proliferative activity is associated with nonmetastatic islet cell tumors. *Archives of Pathology and Laboratory Medicine* **127** 196–199.
- Kang CM, Kim KS, Choi JS, Lee WJ & Kim BR 2005 Experiences with nonfunctioning neuroendocrine neoplasms of the pancreas. *Digestive Surgery* **22** 453–458.
- Kang CM, Park SH, Kim KS, Choi JS, Lee WJ & Kim BR 2006 Surgical experiences of functioning neuroendocrine neoplasm of the pancreas. *Yonsei Medical Journal* **47** 833–839.
- Kavlie H & White TT 1972 Pancreatic islet beta cell tumors and hyperplasia: experience in 14 Seattle hospitals. *Annals of Surgery* **175** 326–335.
- Kazanjan KK, Reber HA & Hines OJ 2006 Resection of pancreatic neuroendocrine tumors: results of 70 cases. *Archives of Surgery* **141** 765–770.
- Kent RB III, van Heerden JA & Weiland LH 1981 Nonfunctioning islet cell tumors. *Annals of Surgery* **193** 185–190.
- Kimura W, Kuroda A & Morioka Y 1991 Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Digestive Diseases and Sciences* **36** 933–942.
- Klöppel G & Heitz PU 1988 Pancreatic endocrine tumors. *Pathology, Research and Practice* **183** 155–168.
- Klöppel G, Perren A & Heitz PU 2004 The gastroentero-pancreatic neuroendocrine cell system and its tumors: the WHO classification. *Annals of the New York Academy of Sciences* **1014** 13–27.
- Konomi K, Chijiwa K, Katsuta T & Yamaguchi K 1990 Pancreatic somatostatinoma: a case report and review of the literature. *Journal of Surgical Oncology* **43** 259–265.

- Korpássy B 1939 Die Basalzellenmetaplasie des Ausführungsgänge des Pankreas. *Virchows Archiv. A: Pathology. Pathologische Anatomie* **303** 359–373.
- Kouvaraki MA, Solorzano CC, Shapiro SE, Yao JC, Perrier ND, Lee JE & Evans DB 2005 Surgical treatment of non-functioning pancreatic islet cell tumors. *Journal of Surgical Oncology* **89** 170–185.
- Lakhani VT, You YN & Wells SA 2007 The multiple endocrine neoplasia syndromes. *Annual Review of Medicine* **58** 253–265.
- Lam KY & Lo CY 1997 Pancreatic endocrine tumour: a 22-year clinico-pathological experience with morphological, immunohistochemical observation and a review of the literature. *European Journal of Surgical Oncology* **23** 36–42.
- Lam KY, Lo CY, Fan ST & Luk JM 2000 Telomerase activity in pancreatic endocrine tumours: a potential marker for malignancy. *Molecular Pathology* **53** 133–136.
- Legaspi A & Brennan MF 1988 Management of islet cell carcinoma. *Surgery* **104** 1018–1023.
- Lepage C, Bouvier AM, Phelip JM, Hatem C, Vernet C & Faivre J 2004 Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* **53** 549–553.
- Liang H, Wang P, Wang XN, Wang JC & Hao XS 2004 Management of nonfunctioning islet cell tumors. *World Journal of Gastroenterology* **10** 1806–1809.
- Libutti SK, Choyke PL, Bartlett DL, Vargas H, Walther M, Lubensky I, Glenn G, Linehan WM & Alexander HR 1998 Pancreatic neuroendocrine tumors associated with von Hippel–Lindau disease: diagnostic and management recommendations. *Surgery* **124** 1153–1159.
- Liu L, Broaddus RR, Yao JC, Xie S, White JA, Wu TT, Hamilton SR & Rashid A 2005 Epigenetic alterations in neuroendocrine tumors: methylation of RAS-association domain family 1, isoform A and p16 genes are associated with metastasis. *Modern Pathology* **18** 1632–1640.
- Lloyd RV 1998 Utility of Ki-67 as a prognostic marker in pancreatic endocrine neoplasms. *American Journal of Clinical Pathology* **109** 245–247.
- Lo CY, van Heerden JA, Thompson GB, Grant CS, Soreide JA & Harnsen WS 1996 Islet cell carcinoma of the pancreas. *World Journal of Surgery* **20** 878–884.
- Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM & Oldfield EH 2003 von Hippel–Lindau disease. *Lancet* **361** 2059–2067.
- Lundstam S, Lundholm K & Schersten T 1979 A ten-year material of insulinoma: diagnosis and surgical treatment. *Scandinavian Journal of Gastroenterology* **14** 653–656.
- Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, Vilgrain V, Belghiti J, Bernades P & Ruszniewski P 1998 Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut* **43** 422–427.
- Madura JA, Cummings OW, Wiebke EA, Brodie TA, Goulet RL Jr & Howard TJ 1997 Nonfunctioning islet cell tumors of the pancreas: a difficult diagnosis but one worth the effort. *American Surgeon* **63** 573–578.
- Maitra A, Hansel DE, Argani P, Ashfaq R, Rahman A, Naji A, Deng S, Geradts J, Hawthorne L, House MG *et al.* 2003 Global expression analysis of well-differentiated pancreatic endocrine neoplasms using oligonucleotide microarrays. *Clinical Cancer Research* **9** 5988–5995.
- Mansour JC & Chen H 2004 Pancreatic endocrine tumors. *Journal of Surgical Research* **120** 139–161.
- Marion-Audibert AM, Barel C, Gouysse G, Dumortier J, Pilleul F, Pourreyron C, Hervieu V, Poncet G, Lombard-Bohas C, Chayvialle JA *et al.* 2003 Low microvessel density is an unfavorable histoprognostic factor in pancreatic endocrine tumors. *Gastroenterology* **125** 1094–1104.
- Maton PN, Gardner JD & Jensen RT 1986 Cushing's syndrome in patients with the Zollinger–Ellison syndrome. *New England Journal of Medicine* **315** 1–5.
- Matthews BD, Heniford BT, Reardon PR, Brunicardi FC & Greene FL 2000 Surgical experience with nonfunctioning neuroendocrine tumors of the pancreas. *American Surgeon* **66** 1116–1122.
- Matthews BD, Smith TI, Kercher KW, Holder WD Jr & Heniford BT 2002 Surgical experience with functioning pancreatic neuroendocrine tumors. *American Surgeon* **68** 660–666.
- Missiaglia E, Moore PS, Williamson J, Lemoine NR, Falconi M, Zamboni G & Scarpa A 2002 Sex chromosome anomalies in pancreatic endocrine tumors. *International Journal of Cancer* **98** 532–538.
- Moldow RE & Connelly RR 1968 Epidemiology of pancreatic cancer in Connecticut. *Gastroenterology* **55** 677–686.
- Nicholls AG 1902 Simple adenoma of the pancreas arising from an island of Langerhans. *Journal of Medical Research* **8** 385–395.
- Norton JA 2005 Surgical treatment and prognosis of gastrinoma. *Best Practice & Research. Clinical Gastroenterology* **19** 799–805.
- Norton JA, Fraker DL, Alexander HR, Venzon DJ, Doppman JL, Serrano J, Goebel SU, Peghini PL, Roy PK, Gibril F *et al.* 1999 Surgery to cure the Zollinger–Ellison syndrome. *New England Journal of Medicine* **341** 635–644.
- Norton JA, Kivlen M, Li M, Schneider D, Chuter T & Jensen RT 2003 Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. *Archives of Surgery* **138** 859–866.
- Öberg K & Eriksson B 2005 Endocrine tumours of the pancreas. *Best Practice & Research. Clinical Gastroenterology* **19** 753–781.
- O'Toole D, Salazar R, Falconi M, Kaltsas G, Couvelard A, de Herder WW, Hyrdel R, Nikou G, Krenning E & Vullierme MP 2006 Rare functioning pancreatic endocrine tumors. *Neuroendocrinology* **84** 189–195.
- Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, Di Fonzo M, Tornatore V, Milione M, Angeletti S *et al.* 2005 Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocrine-Related Cancer* **12** 1083–1092.

- Pape U-F, Böhmig M, Berndt U, Tiling N, Wiedenmann B & Plöckinger U 2004 Survival and clinical outcome of patients with neuroendocrine tumors of the gastroenteropancreatic tract in a German Referral Center. *Annals of the New York Academy of Sciences* **1014** 222–233.
- Pelosi G, Bresaola E, Bogina G, Pasini F, Rodella S, Castelli P, Iacono C, Serio G & Zamboni G 1996 Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. *Human Pathology* **27** 1124–1134.
- Pelosi G, Pasini F, Bresaola E, Bogina G, Pederzoli P, Biolo S, Menard S & Zamboni G 1997 High-affinity monomeric 67-kD laminin receptors and prognosis in pancreatic endocrine tumours. *Journal of Pathology* **183** 62–69.
- Peng SY, Li JT, Liu YB, Fang HQ, Wu YL, Peng CH, Wang XB & Qian HR 2004 Diagnosis and treatment of VIPoma in China: (case report and 31 cases review) diagnosis and treatment of VIPoma. *Pancreas* **28** 93–97.
- Phan GQ, Yeo CJ, Cameron JL, Maher MM, Hruban RH & Udelsman R 1997 Pancreaticoduodenectomy for selected periampullary neuroendocrine tumors: fifty patients. *Surgery* **122** 989–996.
- Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA & Cameron JL 1998 Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. *Journal of Gastrointestinal Surgery* **2** 472–482.
- Phan AT, Wang L, Xie K, Zhang J, Rashid A, Evans D, Vauthey J, Abdalla E, Abbruzzese JL & Yao JC 2006 Association of VEGF expression with poor prognosis among patients with low-grade neuroendocrine carcinoma. *Journal of Clinical Oncology* **24** 4091.
- La Rosa S, Sessa F, Capella C, Riva C, Leone BE, Klersy C, Rindi G & Solcia E 1996 Prognostic criteria in nonfunctioning pancreatic endocrine tumours. *Virchows Archiv* **429** 323–333.
- La Rosa S, Uccella S, Finzi G, Albarello L, Sessa F & Capella C 2003 Localization of vascular endothelial growth factor and its receptors in digestive endocrine tumors: correlation with microvessel density and clinicopathologic features. *Human Pathology* **34** 18–27.
- La Rosa S, Rigoli E, Uccella S, Novario R & Capella C 2007 Prognostic and biological significance of cytokeratin 19 in pancreatic endocrine tumours. *Histopathology* **50** 597–606.
- Roy PK, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL, Gibril F & Jensen RT 2000 Zollinger-Ellison syndrome. Clinical presentation in 261 patients. *Medicine* **79** 379–411.
- Sarmiento JM, Farnell MB, Que FG & Nagorney DM 2002 Pancreaticoduodenectomy for islet cell tumors of the head of the pancreas: long-term survival analysis. *World Journal of Surgery* **26** 1267–1271.
- Schurr PG, Strate T, Rese K, Kaifi JT, Reichelt U, Petri S, Kleinhans H, Yekebas EF & Izbicki JR 2007 Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. *Annals of Surgery* **245** 273–281.
- Service FJ, McMahon MM, O'Brien PC & Ballard DJ 1991 Functioning insulinoma – incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clinic Proceedings* **66** 711–719.
- Skogseid B, Eriksson B, Lundqvist G, Lorelius LE, Rastad J, Wide L, Akerstrom G & Öberg K 1991 Multiple endocrine neoplasia type 1: a 10-year prospective screening study in four kindreds. *Journal of Clinical Endocrinology* **73** 281–287.
- Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB, Grant CS & van Heerden JA 1998 Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. *Surgery* **124** 1050–1055.
- Soga J & Yakuwa Y 1994 Pancreatic endocrinomas: a statistical analysis of 1857 cases. *Journal of Hepato-Biliary-Pancreatic Surgery* **1** 522–529.
- Soga J & Yakuwa Y 1998a The gastrinoma/Zollinger-Ellison syndrome: statistical evaluation of a Japanese series of 359 cases. *Journal of Hepato-Biliary-Pancreatic Surgery* **5** 77–85.
- Soga J & Yakuwa Y 1998b Glucagonomas/diabetico-dermatogenic syndrome (DDS): a statistical evaluation of 407 reported cases. *Journal of Hepato-Biliary-Pancreatic Surgery* **5** 312–319.
- Soga J & Yakuwa Y 1998c Vipoma/diarrheogenic syndrome: a statistical evaluation of 241 reported cases. *Journal of Experimental and Clinical Cancer Research* **17** 389–400.
- Soga J & Yakuwa Y 1999 Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. *Journal of Experimental and Clinical Cancer Research* **18** 13–22.
- Solcia E, Capella C & Klöppel G 1997 Tumors of the endocrine pancreas. In *Atlas of Tumor Pathology*, pp 145–209. Washington, DC: Armed Forces Institute of Pathology.
- Solcia E, Klöppel G & Sobin LH 2000 Histological typing of endocrine tumours. In *World Health Organization International Histological Classification of Tumours*, edn 2, pp 61–68. Berlin: Springer.
- Solorzano CC, Lee JE, Pisters PW, Vauthey JN, Ayers GD, Jean ME, Gagel RF, Ajani JA, Wolff RA & Evans DB 2001 Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery* **130** 1078–1085.
- Speel EJ, Richter J, Moch H, Egenter C, Saremaslani P, Rutimann K, Zhao J, Barghorn A, Roth J, Heitz PU et al. 1999 Genetic differences in endocrine pancreatic tumor subtypes detected by comparative genomic hybridization. *American Journal of Pathology* **155** 1787–1794.
- Stamm B, Hacki WH, Klöppel G & Heitz PU 1991 Gastrin-producing tumors and the Zollinger-Ellison syndrome. In *Endocrine Pathology of the Gut and Pancreas*, pp 155–194. Ed Y Dayal., 1 Boca Raton, FL: CRC Press.

- Starke A, Saddig C, Mansfeld L, Koester R, Tschahargane C, Czygan P & Goretzki P 2005 Malignant metastatic insulinoma-postoperative treatment and follow-up. *World Journal of Surgery* **29** 789–793.
- Takahashi Y, Akishima-Fukasawa Y, Kobayashi N, Sano T, Kosuge T, Nimura Y, Kanai Y & Hiraoka N 2007 Prognostic value of tumor architecture, tumor-associated vascular characteristics, and expression of angiogenic molecules in pancreatic endocrine tumors. *Clinical Cancer Research* **13** 187–196.
- Tan CC, Hall RI, Semeraro D, Irons RP & Freeman JG 1996 Ampullary somatostatinoma associated with von Recklinghausen's neurofibromatosis presenting as obstructive jaundice. *European Journal of Surgical Oncology* **22** 298–301.
- Tan G, Cioc AM, Perez-Montiel D, Ellison EC & Frankel WL 2004 Microvascular density does not correlate with histopathology and outcome in neuroendocrine tumors of the pancreas. *Applied Immunohistochemistry and Molecular Morphology* **12** 31–35.
- Tang SJ, Dumot JA, Wang L, Memmesheimer C, Conwell DL, Zuccaro G, Goormastic M, Ormsby AH & Cowell J 2002 Telomerase activity in pancreatic endocrine tumors. *American Journal of Gastroenterology* **97** 1022–1030.
- Thompson GB, van Heerden JA, Grant CS, Carney JA & Ilstrup DM 1988 Islet cell carcinomas of the pancreas: a twenty-year experience. *Surgery* **104** 1011–1017.
- Tomassetti P, Migliori M, Lalli S, Campana D, Tomassetti V & Corinaldesi R 2001 Epidemiology, clinical features and diagnosis of gastroenteropancreatic endocrine tumours. *Annals of Oncology* **12** S95–S99.
- Tomassetti P, Campana D, Piscitelli L, Casadei R, Santini D, Nori F, Morselli-Labate AM, Pezzilli R & Corinaldesi R 2005 Endocrine pancreatic tumors: factors correlated with survival. *Annals of Oncology* **16** 1806–1810.
- Triponez F, Dosseh D, Goudet P, Cougard P, Bauters C, Murat A, Cadiot G, Niccoli-Sire P, Chayvialle JA, Calender A *et al.* 2006 Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. *Annals of Surgery* **243** 265–272.
- Vasen HF, Lamers CB & Lips CJ 1989 Screening for the multiple endocrine neoplasia syndrome type I. A study of 11 kindreds in The Netherlands. *Archives of Internal Medicine* **149** 2717–2722.
- Venkatesh S, Ordonez NG, Ajani J, Schultz PN, Hickey RC, Johnston DA & Samaan NA 1990 Islet cell carcinoma of the pancreas. A study of 98 patients. *Cancer* **65** 354–357.
- Verhoef S, van Diemen-Steenvoorde R, Akkersdijk WL, Bax NM, Ariyurek Y, Hermans CJ, van Nieuwenhuizen O, Nikkels PG, Lindhout D, Halley DJ *et al.* 1999 Malignant pancreatic tumour within the spectrum of tuberous sclerosis complex in childhood. *European Journal of Pediatrics* **158** 284–287.
- Vezzosi D, Bouisson M, Escourrou G, Laurell H, Selves J, Seguin P, Pradayrol L, Caron P & Buscail L 2006 Clinical utility of telomerase for the diagnosis of malignant well-differentiated endocrine tumours. *Clinical Endocrinology* **64** 63–67.
- Vortmeyer AO, Huang S, Lubensky I & Zhuang Z 2004 Non-islet origin of pancreatic islet cell tumors. *Journal of Clinical Endocrinology* **89** 1934–1938.
- Warner RR 2005 Enteroendocrine tumors other than carcinoid: a review of clinically significant advances. *Gastroenterology* **128** 1668–1684.
- Warren S, LeCompte PM & Legg MA 1966 *The Pathology of Diabetes Mellitus*. Philadelphia: Lea & Febiger.
- Watson RG, Johnston CF, O'Hare MM, Anderson JR, Wilson BG, Collins JS, Sloan JM & Buchanan KD 1989 The frequency of gastrointestinal endocrine tumours in a well-defined population – Northern Ireland 1970–1985. *Quarterly Journal of Medicine* **72** 647–657.
- Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, Gibril F, Metz DC, Fraker DL, Norton JA *et al.* 1995 Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology* **108** 1637–1649.
- Weil C 1985 Gastroenteropancreatic endocrine tumors. *Klinische Wochenschrift* **63** 433–459.
- Wermers RA, Fatourehchi V, Wynne AG, Kvoles LK & Lloyd RV 1996 The glucagonoma syndrome. Clinical and pathologic features in 21 patients. *Medicine* **75** 53–63.
- White TJ, Edney JA, Thompson JS, Karrer FW & Moor BJ 1994 Is there a prognostic difference between functional and nonfunctional islet cell tumors? *American Journal of Surgery* **168** 627–630.
- Wild A, Langer P, Celik I, Chaloupka B & Bartsch DK 2002 Chromosome 22q in pancreatic endocrine tumors: identification of a homozygous deletion and potential prognostic associations of allelic deletions. *European Journal of Endocrinology* **147** 507–513.
- Wilkinson S, Teh BT, Davey KR, McArdle JP, Young M & Shepherd JJ 1993 Cause of death in multiple endocrine neoplasia type 1. *Archives of Surgery* **128** 683–690.
- Yang CS, Shyr YM, Chiu CT, Su CH, Lin CP & Lin JT 2000 Non-functioning islet cell tumors of the pancreas – a multicentric clinical study in Taiwan. *Hepatogastroenterology* **47** 1747–1749.
- Zeng XJ, Zhong SX, Zhu Y, Fei LM, Wu WJ & Cai LX 1988 Insulinoma: 31 years of tumor localization and excision. *Journal of Surgical Oncology* **39** 274–278.
- Zhao J, Moch H, Scheidweiler AF, Baer A, Schaffer AA, Speel EJ, Roth J, Heitz PU & Komminoth P 2001 Genomic imbalances in the progression of endocrine pancreatic tumors. *Genes, Chromosomes and Cancer* **32** 364–372.
- Zikusoka MN, Kidd M, Eick G, Latich I & Modlin IM 2005 The molecular genetics of gastroenteropancreatic neuroendocrine tumors. *Cancer* **104** 2292–2309.