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Pancreatic endocrine neoplasms: Epidemiology and prognosis of pancreatic endocrine tumors

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Abstract

Pancreatic endocrine neoplasms (PETs) are uncommon tumors with an annual incidence less than 1 per 100,000 persons per year in the general population. PETs that produce hormones resulting in symptoms are designated as functional. The majority of PETs are nonfunctional. 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.

Pancreatic neuroendocrine tumors or pancreatic endocrine tumors (PETs) are uncommon neoplasms with incidence lower than 1 per 100,000 persons per year in population studies.(Buchanan, et al. 1986; Carriaga and Henson 1995; Eriksson, et al. 1989; Halfdanarson, et al. 2007; Lam and Lo 1997; Moldow and Connelly 1968; Watson, et al. 1989) 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 less than 3% of all pancreatic neoplasms.(Carriaga and Henson 1995; Cubilla and Hajdu 1975; Fesinmeyer, et al. 2005; Öberg and Eriksson 2005) Pancreatic endocrine tumors are generally more indolent than adenocarcinoma of the pancreas and have a better prognosis.(Carriaga and 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 will 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

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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).(Heitz, et al. 2004;Klöppel, et al. 2004;Solcia, et al. 2000) 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.(de Herder, et al. 2006;Falconi, 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 a well defined entity 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 one case of pancreatic adenoma arising in an islet of Langerhans among 1514 patients.(Nicholls 1902) Segie reported 132 tumors of the pancreas among 11,500 autopsies but none appeared to have arisen from the islet cells.(Frantz 1959;Nicholls 1902) Korpássy found four cases (0.8%) of macroscopic islet cell adenomas in 500 autopsies in 1938.(Korpássy 1939) Twenty-four cases (0.3%) of "benign islet cell neoplasms" were observed in a series of 9158 consecutive autopsies reported by Frantz.(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 six (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 the annual incidence of symptomatic PETs 0.2/100,000.(Lam and Lo 1997)

Several studies on the incidence of PETs in defined populations have been performed (Table 3).(Buchanan et al. 1986;Carriaga and Henson 1995;Eriksson et al. 1989;Halfdanarson et al. 2007;Lam and Lo 1997;Lepage, et al. 2004;Moldow and Connelly 1968;Watson et al. 1989) Moldow and Raymond reported on all patients diagnosed with pancreatic tumors in Connecticut 1957 to 1963.(Moldow and Connelly 1968) Of the 856 pancreatic tumors, islet cell tumors accounted for less than 5 percent. 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 less than 1/100,000. (Moldow and Connelly 1968) A Swedish study reported annual incidence of 0.4/100,000 (Eriksson et al. 1989) and a study from Northern Ireland found an 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 was 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) 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 less than 0.6/100,000 for all age groups.(Carriaga and 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 decade 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).(Cullen and Ong 1987;Eriksson et al. 1989;Eriksson, et al. 1990;Jacobsen, et al. 1986;Service, et al. 1991;Stamm, et al. 1991;Watson et al. 1989) Insulinoma is the most frequently encountered functional PET and is usually a benign tumor and almost always located in the pancreas.(Öberg and Eriksson 2005;Soga and Yakuwa 1994) The incidence of insulinoma in a well defined population in Olmsted County in South-Eastern 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.(Cullen and Ong 1987;Eriksson et al. 1989;Kavlie and White 1972;Watson et al. 1989) The annual incidence of malignant insulinoma in the SEER registry is 0.1/million (Halfdanarson et al. Submitted manuscript). Gastrinoma is the second most commonly encountered functional PET but gastrinomas are also frequently found outside the pancreas. (Norton, et al. 1999;Öberg and Eriksson 2005;Roy, et al. 2000;Soga and Yakuwa 1998a) Pancreatic gastrinomas may be more aggressive and more frequently associated with liver metastases.(Weber, et al. 1995) Up to 30% of gastrinomas are associated with multiple endocrine neoplasia type 1 (MEN-1).(Roy et al. 2000;Soga and Yakuwa 1998a) Gastrinoma is the most common functional PET seen in patients with MEN-1 and the prognosis may be worse than in sporadic gastrinoma.(Gibril, et al. 2001;Norton 2005;Norton et al. 1999)

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 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. Submitted manuscript).

Epidemiologic data on functioning PETs other than insulinoma and gastrinoma is sparse. Pancreatic endocrine tumors secreting vasoactive intestinal peptide (VIPoma) comprise less than 10% of all PETs and appear to be slightly more common in females according to some but not all reports.(Klöppel and Heitz 1988; Peng, et al. 2004; Smith, et al. 1998; Soga and Yakuwa 1998c; Solcia, et al. 1997) VIPomas are found in extrapancreatic locations in up to 25% of cases.(Soga and 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 less than 10% of PETs and are almost exclusively found within the pancreas.(Klöppel and Heitz 1988; Solcia et al. 1997) Glucagonomas are very rare and their annual incidence has been estimated to be around or less than 0.1 per million.(Eriksson et al. 1989; Watson et al. 1989) Glucagonomas may be slightly more common among females and patients are usually in their fifth decade at the time of diagnosis.(Soga and Yakuwa 1998b; Wermers, et al. 1996) PETs secreting somatostatin (somatostatinoma) are rare and account for less than 5% of all PETs and the true incidence of these tumors is unknown. Somatostatinomas typically present in the fifth and sixth decade 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 and Yakuwa 1999) Pancreatic tumors secreting other hormones such as cholecystokinin (CCK), gastric inhibitory peptide, gastrin-releasing peptide (GRP), ACTH, GHRH, PTHrP and ghrelin are extremely rare and their incidence is unknown.

Nonfunctioning tumors comprise a substantial proportion of all PETs and have been reported to comprise 25–100% of all PETs. The annual incidence of symptomatic nonfunctional 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 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.(Francalanci, et al. 2003; Fujisawa, et al. 2002; Tan, et al. 1996; Verhoef, et al. 1999)

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 30–75% and these tumors are frequently multifocal and metastatic at the time of diagnosis.(Burgess, et al. 1998a; Burgess, et al. 1998b; Le Bodic, et al. 1996; Skogseid, et al. 1991; Vasen, et al. 1989) Gastrinomas are the most commonly encountered PETs, followed by non-functioning tumors and insulinomas.(Brandi et al. 2001; Gibril and 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.(Dean, et al. 2000; Doherty, et al. 1998; Wilkinson, et al. 1993) Von Hippel-Lindau disease is an autosomal dominant tumor predisposition syndrome caused by a germline mutation in the VHL gene.(Lonser, et al. 2003) The typical features of von Hippel-Lindau 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 von Hippel-Lindau disease.(Binkovitz, et al. 1990; Blansfield, et al. 2007; Hammel, et al. 2000; Libutti, et al. 1998) PETs associated with von Hippel-Lindau disease are virtually always nonfunctional.(Blansfield et al. 2007)

Prognosis following resection

Functional and nonfunctional tumors

Patients with PETs generally have a much better prognosis than patients with pancreatic adenocarcinoma. Recent studies using the SEER database have reported improved survival after resection or a median overall survival of 58 to 97 months compared to 15 to 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, 7 and 8).(Bartsch, et al. 2000; Broughan, et al. 1986; Cheslyn-Curtis, et al. 1993; Chu, et al. 2002; Closset, et al. 1996; Corleto, et al. 2001; Cubilla and Hajdu 1975; Dralle, et al. 2004; Eckhauser, et al. 1986; Evans, et al. 1993; Furukawa, et al. 1998; Grama, et al. 1992; Gullo, et al. 2003; Guo, et al. 2004; Hellman, et al. 2000; Hochwald, et al. 2002; House, et al. 2006; Jarufe, et al. 2005; Kang, et al. 2005; Kazanjian, et al. 2006; Kent, et al. 1981; Kouvaraki, et al. 2005; La Rosa, et al. 1996; Legaspi and Brennan 1988; Lepage et al. 2004; Liang, et al. 2004; Lo, et al. 1996; Madeira, et al. 1998; Madura, et al. 1997; Matthews, et al. 2000; Norton, et al. 2003; Panzuto, et al. 2005; Pape, et al. 2004; Phan, et al. 1997; Phan, et al. 1998; Sarmiento, et al. 2002; Schurr, et al. 2007; Service et al. 1991; Solorzano, et al. 2001; Thompson, et al. 1988; Tomassetti, et al. 2005; Venkatesh, et al. 1990; White, et al. 1994; Yang, et al. 2000)

Table 6 lists 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.(Chu et al. 2002;Hochwald et al. 2002;House et al. 2006;Legaspi and Brennan 1988;Lepage et al. 2004;Lo et al. 1996;Madeira et al. 1998;Panzuto et al. 2005;Pape et al. 2004;Phan et al. 1997;Thompson et al. 1988;Tomassetti et al. 2005) 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 nonfunctional tumors.(Phan et al. 1998;Sarmiento et al. 2002;Thompson et al. 1988) Other studies have either reported worse prognosis of functional tumors or no effect of functional status on prognosis. (Cubilla and 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 nonfunctional 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 patients with other malignant and functional PETs, especially after surgery with curative intent.(Norton et al. 1999) As expected, patients with more advanced and metastatic disease as well as patients with residual disease following resection had shorter survival.

Nonfunctional tumors

Several studies have been limited to nonfunctional PETs (Table 7).(Bartsch et al. 2000;Cheslyn-Curtis et al. 1993;Closset et al. 1996;Eckhauser et al. 1986;Evans et al. 1993;Furukawa et al. 1998;Gullo et al. 2003;Guo et al. 2004;Kang et al. 2005;Kent et al. 1981;La Rosa et al. 1996;Liang et al. 2004;Madura et al. 1997;Matthews et al. 2000;Solorzano et al. 2001;Yang et al. 2000) Similar to the studies combining functional and nonfunctional 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 in the series combining both functional and nonfunctional tumors. However, the heterogeneity among the studies and the potential for selection bias makes any comparison problematic.(Dralle et al. 2004;Kouvaraki et al. 2005) Nonfunctional PETs seem to have inferior prognosis when compared to functional PETs, even after adjusting known prognostic factors such as age, stage and grade.(Halfdanarson et al. 2007)

La Rosa et al. studied 61 patients with nonfunctional PETs.(La Rosa et al. 1996) The tumors were considered malignant if there was direct invasion into adjacent tissues or organs or if distant metastases were present. Multiple tumor characteristics predicted malignant behavior in a univariate analysis, including tumor diameter, vascular and perineural invasion, presence of mitoses, nuclear atypia, and high proliferative index (>2%) as evaluated by Ki-67 immunohistochemical staining. The tumors were classified according to 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%) and the presence of 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). (Boukhman, et al. 1998;Chen, et al. 2002;Danforth, et al. 1984;Feng, et al. 2002;Grama et al. 1992;Grant 2005;Harrison, et al. 1973;Hirshberg, et al. 2005;Kang, et al. 2006;Lundstam, et al. 1979;Matthews, et al. 2002;Norton et al. 1999;Service et al. 1991;Starke, et al. 2005;Weber et al. 1995;Zeng, et al. 1988) 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 1927–1986. (Service et al. 1991) The study included 244 patients with insulinoma, including 8 patients who were residents of Olmsted County in South-Eastern Minnesota. Thirteen patients (5.8%) had malignant insulinoma and 17 patients (7.6%) also had MEN-1. 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%. 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 225 patients with benign insulinoma who underwent resection from 1982–2004. (Grant 2005) The outcome for this cohort of patients was excellent, with 98% of patients being cured with resection. The generally good outcome of patients with insulinoma may thus skew the outcome results in series where patients with insulinomas are grouped with patients having other functional tumors or nonfunctional tumors.

Norton et al. reported their experience with 151 patients with gastrinoma undergoing surgery. (Norton et al. 1999) Their cohort of patients included 36 (24%) patients with pancreatic gastrinoma, of which 19 had MEN-1. The gastrinoma was localized to the pancreas in seventeen 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.(Ilias, et al. 2005; Maton, et al. 1986)

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) Histologic findings such as grade and the number of mitotic figures have been found to predict survival in a few studies. Hochwald et al. retrospectively evaluated 136 patients with low-grade or intermediate-grade PETs who had undergone tumor resection.(Hochwald et al. 2002) 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 gastro-enteropathic 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.(Böhmig, et al. 2005; Clarke, et al. 1997; Couvelard, et al. 2006; Gentil Perret, et al. 1998; Goto, et al. 2004; Jorda, et al. 2003; La Rosa et al. 1996; Lloyd 1998; Panzuto et al. 2005; Pelosi, et al. 1996; Pelosi, et al. 1997) 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 where 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(Ali, et al. 2006; Goto et al. 2004) 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 gastroenteropancreatic 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 to non-metastatic tumors. These aberrations involve multiple chromosomes, including 1,3,5,6,7,14,22 and the X chromosome.(Barghorn, et al. 2001a; Barghorn, et al. 2001b; Chen, et al. 2004; Chen, et al. 2003; Guo, et al. 2002a; Guo, et al. 2002b; Speel, et al. 1999; Wild, et al. 2002; Zhao, et al. 2001) Chromosomal instability as manifested by the number of aberrations per tumor has been shown to be an indicator for the development of metastases in patients with sporadic insulinoma, and loss of sex chromosomes may predict shorter survival in patients with functional and nonfunctional PETs.(Jonkers, et al. 2005; Missiaglia, et al. 2002)

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^6*-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.(Bloomston, et al. 2004; Capurso, et al. 2006; Couvelard et al. 2006; Durkin, et al. 2004; Hansel, et al. 2004; Maitra, et al. 2003) Numerous genes have been found to be either overexpressed 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 to non-metastatic PETs include met proto-oncogene, insulin-like growth factor binding protein 3 gene (IGFBP3) as well as various genes involved in angiogenesis, signal transduction, cell cycle control and ion transport.(Couvelard et al. 2006; Hansel et al. 2004) 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 VEGF has been associated with more aggressive tumor growth, presence of metastases and shorter progression-free survival in patients with low-grade neuroendocrine tumors when compared to 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.(Couvelard et al. 2006; Couvelard, et al. 2005; La Rosa, et al. 2003; Marion-Audibert, et al. 2003; Takahashi, et al. 2007; Tan, et al. 2004)

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 of adenocarcinoma of the

pancreas. PETs are uncommon tumors with annual incidence less than 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 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.

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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

Table 2

Published autopsy series of islet cell tumors

Author, year	Number of autopsies	Number of islet cell tumors	Percent
Segie, 1885(Nicholls 1902)	11,500	0	0
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 et al. 1966)	4566	42	0.9
Becker, 1972(Becker 1971)	4280	62	1.4
Grimelius, 1975(Grimelius et al. 1975)	1366	11	0.8
Kimura, 1991(Kimura et al. 1991) Overall 5 mm sections*	800 60	20 6	2.5 10
Lam, 1997(Lam and Lo 1997)	11,472	13	0.1

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

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 and Connelly 1968)	NR	< 1/100,000*	All cases in Connecticut, USA over a given period. PETs grouped with other rare tumors of the pancreas
Eriksson, 1989(Eriksson et al. 1989)	84	0.4/100,000	Well defined region in Sweden. Single referral hospital
Watson, 1989(Watson et al. 1989)	94	0.23/100,000	Well defined Northern Irish population. Same series as Buchanan et al.(Buchanan et al. 1986)
Carriaga, 1995(Carriaga and Henson 1995)	402	< 0.6/100,000*	SEER data 1973–1987. Exact incidence of PETs not provided.
Lam, 1997(Lam and Lo 1997)	53	0.2/100,000	Referral to a single hospital in Hong Kong
Lepage, 2004(Lepage et al. 2004)	47	♀: 0.12/100,000 ♂: 0.19/100,000	Well defined geographic region in France
Halfdanarson, 2007 (Halfdanarson et al. 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

*Accurate figure not provided for pancreatic endocrine tumors

Table 4

Annual incidence (cases per million) of functional PETs

Author, year	Country	Annual incidence of all PETs	Insulinoma	Gastrinoma	VIPoma	Glucagonoma
Eriksson, 1989(Eriksson et al. 1989)	Sweden	4	1.1	1.2	0.64	0.04
Watson, 1989(Watson et al. 1989)	Northern- Ireland	2.3	1.2	0.5	0.12	0.12
Service, 1991(Service et al. 1991)	USA	-	4	-	-	-
Cullen, 1987(Cullen and Ong 1987)	New Zealand		0.67	-	-	-
Jacobsen, 1986(Jacobsen et al. 1986)	Denmark	-	-	0.5	-	-
Stamm, 1991(Stamm et al. 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[§]	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[*]	rare	< 1	-	-	-	unknown
Nonfunctioning[‡] (clinically silent)	≤1 0.1–10% in autopsy series	25–100[†]	50–60	> 50	100	0–21

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

[*] Data on these tumors is insufficient for further analysis

[†] The higher percentage comes from autopsy studies

[‡] Includes tumors that produce pancreatic polypeptide (PP)

[§] Malignant behavior based on the presence of invasion and metastases

Table 6

Selected studies of both functional and nonfunctional 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 et al., 1975 (Cubilla and Hajdu 1975)	30	12 (34)	4 (13)	LN: 19 (63) Liver: 21 (70)	5-OS:57% MS: 4.3 (N) and 2.8 (F) years	Functional tumor
Broughan et al., 1986 (Broughan et al. 1986)	84	63 (75)	41 (49)	Liver and/or LN: 39 (46%)	5-OS: 63.1% (N), 68.4% (G), 96.9 (I)	Non-insulinoma or non-functional[§]
Phan et al., 1998(Phan et al. 1998)	125[*] 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[§]
Sarmiento et al., 2002 (Sarmiento et al. 2002)	29	9 (31)	3 (10)	LN: 16 (55), Liver: 1 (3)	5-OS: 81% (all), 100% (F), 70% (N).	Nonfunctional, positive lymph nodes[§]
White et al., 1994 (White et al. 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[§]
Jarufe et al., 2005 (Jarufe et al. 2005)	44	24 (55)	16 (36)	22 (50)	5-OS: 74.4%	Metastases (multivariate analysis)
Thompson et al., 1988 (Thompson et al. 1988)	58	31 (54)	8 (14)	LN: 25 (43), Liver: 19 (33)	5-OS:42%	Liver metastases, non-functional tumor (vs. gastrinoma) [§]
Panzuto et al., 2005 (Panzuto et al. 2005)	156[*] (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 et al., 1988 (Legaspi and Brennan 1988)	33	11 (33)	0	Distant metastases 16 (48)	3 year survival 76%	Incomplete resection or residual tumor[§]
Lepage et al., 2004 (Lepage et al. 2004)	47	NR	NR	NR	5-OS: 42%	Metastatic disease and advanced age (multivariate analysis)
Venkatesh et al., 1990 (Venkatesh et al. 1990)	98	55 (56)	7 (7)	47 (48)	Mean survival 42.7 ± 49 months	Nonfunctional tumors[§] Metastatic disease and advanced age (multivariate analysis)
Tomassetti et al., 2005 (Tomassetti et al. 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. MEN1[§]
Chu et al., 2002(Chu et al. 2002)	50	21 (42)	6 (12)	Liver: 29 (58)	MS 40 months 5-OS: 36%	Incomplete resection and liver metastases.

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
				Synchronous liver metastases		Less aggressive treatment of liver metastases[§]
Lo et al., 1996(Lo et al. 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[§]
Madeira et al., 1998 (Madeira et al. 1998)	82[*] (including 62 PET)	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 et al., 2004(Pape et al. 2004)	254[*] (including 73 PETs)	53 (32)	6 (8)	53 (73)	MS: 47 months, 5-OS: 42.9%	Metastases at diagnosis and incomplete resection[§]
Hochwald et al., 2002 (Hochwald et al. 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 et al., 2006 (House et al. 2006)	31	8 (26)	1 (3)	100	MS: Resection of primary tumor and liver metastases: 78 months (5-OS: 65%) Resection of primary tumor only: 17 months	Incomplete resection
Kazanjian et al., 2006 (Kazanjian et al. 2006)	70	20 (29)	16 (23)	LN: 21 (57)[†] Liver: 9 (24)[†]	5-OS: 89%	Malignant tumors (neuron-endocrine carcinoma)
Norton et al., 2003 (Norton et al. 2003)	20	11 (55)[‡]	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[*] including 41 PETs	18 (44)	5 (12)	NR	NR	NR

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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
Schurr et al., 2007 (Schurr et al. 2007)	62	26	10 (16) (with hypo-glycemia)	19 (31) Liver: 16 (26)	5-OS: 64% (all patients)	Incomplete resection[§]

[*] The study included both pancreatic and extrapancreatic tumors.

[§] Univariate analysis (results of univariate analyses are not reported where results of multivariate analyses are provided)

[†] The number patients with metastatic lesions relates to the 37 patients with neuroendocrine carcinoma.

[≠] Ten of eleven functional tumors were gastrinomas

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: nonfunctional PET, NR: not reported, NS: not significant

Table 7

Selected studies of nonfunctional pancreatic endocrine tumors.

Study (author, year)	Number of patients	Metastasis at diagnosis (%)	Survival	Factors adversely affecting survival
Kent et al., 1981(Kent et al. 1981)	25	18 (72), liver 11 (44)	3 and 5 year OS: 60% and 44%	NR
Eckhauser et al., 1986 (Eckhau ser et al. 1986)	11	9 (82) Liver: 5 (45) LN: 7 (64)	Mean survival 23 months (4–72 months)	No predictors identified
Evans et al., 1993(Evans et al. 1993)	73	37 (51)	5 year OS: 50%	Metastatic disease and incomplete resection[§]
Cheslyn- Curtis et al., 1993(Chesly n-Curtis et al. 1993)	20	Liver: 5 (25) LN: 5 (25)	Median survival. Curative resection: 42 months No curative resection: 32 months	
La Rosa et al., 1996(La Rosa et al. 1996)	61	34 (56)	Mean survival (months): Increased risk: 50.7 Well differentiated: 44.2 Poorly differentiated: 3.7	Capsular penetration, distant metastases, vascular micro- invasion and high Ki-67 proliferative index[§]
Matthews et al., 2000 (Matthews et al. 2000)	28	6 (21)	2 year survival: Node negative 77.8%, node-positive 71.4 and metastatic 36.4	Liver metastases[§]
Bartsch et al., 2000 (Bartsch et al. 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 vs. 14.3% in patients treated with palliative intent.	Incomplete resection[§]
Solorzano et al., 2001 (Solorza no et al. 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 et al., 2003(Gullo et al. 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[§]
Liang et al., 2004(Liang et al. 2004)	43	6 (14)	5 and 10 year OS: 58% and 29%	Incomplete resection (multivariate analysis)
Kang et al., 2005(Kang et al. 2005)	19	7 (37)	5-year OS: 32% (curative resection 90%)	Metastases, unresectable disease, macroscopic invasion[§]
Guo et al., 2004(Guo et al. 2004)	41 (all patients had resection)	4 (10) Only LN metastases	NR	NR. Tumors recurred in 3 patients following enucleation
Furukawa et al., 1998 (Furuka wa et al. 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 et al., 2000(Yang et al. 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

Study (author, year)	Number of patients	Metastasis at diagnosis (%)	Survival	Factors adversely affecting survival
Madura et al., 1997 (Madura et al. 1997)	14	LN: 7 (50)	Median survival 31.2 months	LN metastases

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

§ Univariate analysis

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 (%) Number of patients with metastases	Survival	Factors adversely affecting survival
Service et al., 1991 (Service et al. 1991)	244	47	Insulinoma	5.8	10 year OS: 78% for benign and 29% for malignant insulinoma	Malignant insulinoma, advanced age.
Grant et al., 2005(Grant 2005)	225	NR	Insulinoma	0	98% cure rate	NR
Grama et al., 1992(Grama et al. 1992)	85	NR	Insulinoma56%	47	10 OS: insulinoma 50%, malignant PET28%	Liver metastases, tumor > 4 cm, complete resection
Norton et al., 1999(Norton et al. 1999)	151 (36 with pancreatic gastrino ma)	48 (mean age)	Gastrinoma*	NR	5 year OS:100% for sporadic gastrinoma. 42% free of disease at 5 years	MEN1 (lower disease free survival)
Danforth et al., 1984 (Danforth et al. 1984)	17		Insulinoma	17 (100) LN: 8 (47) Liver: 12 (70)	NR	NR
Hirshberg et al., 2005 (Hirshberg et al. 2005)	10		Insulinoma	100	Survival ranged from 4 months to 30 years	NR
Matthews et al., 2002 (Matthews et al. 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 et al., 1973 (Harrison et al. 1973)	35		Insulinoma	Metastases: 3 (9%)	NR	Metastatic disease (2 of 3 patients died shortly after referral
Starke et al., 2005(Starke et al. 2005)	77		Insulinoma	Metastases 10 (13)	2 year survival (metastatic only): 2.6 years	NR
Chen et al., 2002(Chen et al. 2002)	74		Insulinoma	Malignant insulinoma: 2 (3%)	All patients with benign insulinoma were cured. One patient with malignant insulinoma survived 18 years.	NR
Feng et al., 2002(Feng et al. 2002)	105		Insulinoma	Malignant insulinoma: 4 (4%)	All patients with benign insulinoma were cured. 3 of 4	NR

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
					patients with malignant insulinoma had relief of their symptoms and 1 died	
Boukhman et al., 1998 (Boukhman et al. 1998)	67		Insulinoma	Malignant insulinoma: 10 (15%)	89% underwent a successful operation (no survival data reported)	NR
Kang et al., 2006(Kang et al. 2006)	14		Insulinoma: 12 (86%) Gastrinoma: 2 (14%)	Two malignant tumors (1 insulinoma and 1 gastrinoma)	10 year survival: 81% (one patient died from unrelated causes)	NR
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)	4 cases with recurrent hypoglycemia. No information on the metastatic cases	NR

* Pancreatic and non-pancreatic gastrinoma

LN: Lymph nodes, NR: Not reported, OS: overall survival.