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# Pancreatic Disease

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With 82 Figures

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# Neuroendocrine Tumours

# 1 Epidemiology of Pancreatic Neuroendocrine Tumours

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Pancreatic neuroendocrine tumours are rare neoplastic growths of endocrine pancreatic tissue with both neural and endocrine features, frequently causing clinical syndromes from uncontrolled hormone secretion.[1,2] Those tumours that cause such syndromes have been classified as 'functional' whilst those without obvious hypersecretion have been classified as 'non-functional'.[1–3] However, 'non-functional' tumours secrete various peptides and proteins, including chromogranins, plasma levels of which can be used as tumour markers.[1,3,4] There are a number of well recognised syndromic tumours, the commonest being insulinoma and gastrinoma, although many gastrinomas arise in the duodenum (see Table 1.1). A minority of patients presenting with pancreatic neuroendocrine tumours have one of four inherited disorders producing tumours at many sites: multiple endocrine neoplasia type 1 (MEN-1)[5], von Hippel-Lindau disease[6] (see Ch. 12), neurofibromatosis[7] and tuberous sclerosis.[8]

## Incidence and Prevalence

### Autopsy Series

Pancreatic neuroendocrine tumours have been found in 0.1–1.6% of autopsies in unselected series.[10] This wide variation is likely to be attributable to varying methods of identification; systematic sectioning of the pancreas in transverse blocks 0.3–0.5 cm thick, with subsequent thorough examination of all slides made from each block, will give higher figures. In one autopsy series using meticulous identification the percentage with pancreatic neuroendocrine tumours was 10%.[16] However, as in other endocrine glands, many tumours are small adenomas that are slow growing and without significant hormonal effects, and so do not present during life. In a 25 year study of 11 472 autopsies conducted in Hong Kong, pancreatic neuroendocrine tumours were identified in only 10 cases, only one of which had presented during life.[10] Another study suggests that tumours not presenting in life are more likely to occur in the body and tail of the gland, and contain more pancreatic polypeptide than any other hormone.[18] Such studies have helped to develop our understanding of natural history, but provide limited insight into clinical features.

**Table 1.1.** Principal clinical features of less rare types of pancreatic neuroendocrine tumours

| Tumour | Symptoms | Diagnosis | Malignancy | Survival |
|---|---|---|---|---|
| Insulinoma | Confusion, sweating, dizziness, weakness, unconsciousness, relief with eating | Inappropriate insulin secretion during hypoglycaemia from up to 72 h fasting | 10% of patients develop metastases | Complete resection cures most patients |
| Gastrinoma | Zollinger–Ellison syndrome of severe peptic ulceration and diarrhoea | Elevated serum gastrin when patient off all acid suppression treatment | Metastases develop in 60% of patients; likelihood correlated with size of primary | Complete resection results in 10 year survival of 90%; less likely if large primary |
| Glucagonoma | Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea | Elevated serum glucagon. Other hormones can be elevated | Metastases develop in 60% or more patients | More favourable with complete resection; prolonged even with liver metastases |
| Vipoma | Verner–Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia | Hypochlorhydria, + hypercalcaemia; elevated serum VIP | Metastases develop in up to 70% of patients; majority found at presentation. | Complete resection: five year survival of 95%; with metastases: 60% |
| Somatostatinoma | Symptomatic cholelithiasis; weight loss; diarrhoea and steatorrhoea | Elevated serum somatostatin | Metastases likely in about 50% of patients | Complete resection associated with five year survival of 95%; with metastases, 60% |
| Non-syndromic pancreatic neuroendocrine tumour | Symptoms from pancreatic mass and/or liver metastases | A variety of hormones may be elevated, including chromogranins | Metastases develop in up to 50% of patients | Complete resection associated with five year survival of at least 50% |

## Clinical and Surgical Series

Clinical series have been compiled from collections of cases that include tumours identified incidentally on radiological imaging or pathological examination of a pancreatic specimen performed for another reason. In surgical series functioning tumours have more often been reported.[17,19] Without assessment of the population base from which each series was drawn, no proper epidemiological picture can be drawn.

## Prevalence

For indolent neoplastic lesions such as pancreatic neuroendocrine tumours, prevalence is an important measure of population disease burden. Prevalence estimates are reported at 1.0 per 100 000,[20,21] but these estimates were made over three decades ago using older histological techniques. More recent data from the SEER project identified 401 islet cell tumours amongst 22 747 pancreatic cancers (< 2%).[21] However, these data are also limited, because only malignant tumours were included, and more importantly, most pancreatic cancers are associated with a survival of less than six months, quite different from most pancreatic neuroendocrine tumours.

## Incidence

### *All Pancreatic Neuroendocrine Tumours*

There are two population-based studies that have assessed the overall incidence of pancreatic neuroendocrine tumours identified during life,[6,7] but in neither was the autopsy rate reported. Watson and co-workers used cases identified in Northern Ireland that had been entered into a neuroendocrine tumour database compiled in conjunction with a specialist reference laboratory conducting hormone assays.[22] From these data they estimated the incidence to be 2.0 per million per year. Eriksson and co-workers took all cases treated in Uppsala over a 20 year period and assumed a local population base, despite an international referral practice; they calculated 4.0 cases per million per year.[23]

### *Insulinoma*

Estimates for this tumour have ranged from 0.67–4.0 cases per million per year, varying widely despite the use of reference populations.[6,8,9,23,24]

### *Gastrinoma*

The reported incidence of this tumour has ranged from 0.1–4.0 cases per million per year,[23,25] with that for the defined Northern Ireland population the incidence reported by Watson and colleagues was 0.5 per million per year.[22] Historically,

insulinoma was considered the most common pancreatic neuroendocrine tumour but more recent reports suggest that gastrinoma is more common.[22,26] However, the terms Zollinger–Ellison syndrome and gastrinoma have been used interchangeably, without specification as to tumour location, and most studies have given combined pancreatic and extra-pancreatic gastrinoma rates. Earlier studies cited the pancreas as the organ most frequently harbouring a gastrinoma (40–53%).[27,28] However these reports contained a significant number of cases where tumour was not detected (27–34%). Small, occult duodenal gastrinomas account for a significant number of such cases.[1,3]

### *Glucagonoma*

The Northern Ireland study of Watson and colleagues estimated the annual incidence of glucagonoma at 0.05 per million (1 per 20 000 000) per year,[22] accounting for 2.5% of all their pancreatic neuroendocrine tumours. Other estimates suggest that glucagonoma accounts for 8% of all syndromic pancreatic neuroendocrine tumours and for 5% of all pancreatic endocrine tumours presenting during life.[29,30] A more recent report suggests that glucagonoma is an underdiagnosed condition, because it is asymptomatic for long periods, and produces non-specific symptoms; this report suggests that the true incidence may approach that of insulinoma and gastrinoma,[31] although this has not been confirmed.

### *Vipoma*

VIPomas, which are usually located in the pancreas, produce the Verner–Morrison or WDHA (watery diarrhoea, hypokalaemia and achlorhydria) syndrome from an excess of vasoactive intestinal polypeptide.[1,3,22] Their incidence has been estimated at 0.12–2.0 per million per year,[6,23] comprising 3–5% of all pancreatic neuroendocrine tumours.[32]

### *Ppoma*

Marked differences in the reported incidence of pancreatic polypeptide producing tumours (PPoma) have arisen because historically, many non-syndromic tumours were not tested for pancreatic polypeptide. The principal documented physiological action of pancreatic polypeptide is inhibition of biliary and pancreatic exocrine secretion.[37] The incidence of pancreatic polypeptide hypersecretion is variable depending on the type of endocrine cell tumour; all pure PPomas present with elevated pancreatic polypeptide levels.[37,38] Thus, although 50–75% of patients with non-syndromic tumours have increased basal levels of pancreatic polypeptide,[18] and cells producing pancreatic polypeptide are found in 28–74% of other syndromic tumours, pure or dominant PPoma have been estimated to comprise only 1–2% of all pancreatic neuroendocrine tumours.[38]

### *Rarer Syndromic Tumours*

The more infrequent pancreatic neuroendocrine tumours are reported primarily as case series; incidence is difficult to estimate. Somatostatinomas, like gastrino-

mas, occur in both pancreatic and extra-pancreatic sites, although the distinction between sites has rarely been made.[40,41] Somatostatinomas have been estimated to account for about 1% of all active neuroendocrine tumours of the gut and pancreas.[42] Other very occasional tumours include those producing growth factor releasing hormone or growth hormone, parathyroid hormone or parathyroid related hormone, or adrenocorticotrophic hormone.[1-3] Some of these tumours may be misclassified as non-syndromic if a full screen of potential ectopic hormones is not performed.

### *Carcinoid*

Carcinoid tumours of the pancreas are rare, and reports must include at least immunohistochemical analysis or appropriate hormone assays to avoid confusion from vague terminology. A detailed report is that of thirty cases collected up to 1995,[43] which found the most frequent symptom to be pain, followed by diarrhoea and weight loss. An atypical carcinoid syndrome characterised by skin flushing was found in 10 cases (33%). Elevated urinary 5-hydroxyindole acetic acid levels were found in 25 (83%).

### *Small Cell Carcinoma*

Small cell carcinoma is a poorly differentiated pancreatic tumour composed of small to intermediate sized cells with neuroendocrine features. It is extremely rare and estimated to account for less than 1% of all (exocrine and endocrine) pancreatic malignancy.[44]

### *Non-syndromic Pancreatic Neuroendocrine Tumours*

The reported incidence of non-syndromic tumours has varied from 15–40%,[18,33,34] depending on assay and classification procedures.[36] Earlier reports included glucagonoma and somatostatinoma as non-syndromic tumours, as these do not produce obvious hormone-specific symptoms when serum hormone levels are low.[30] However, more recent reports suggest higher numbers of non-syndromic tumours, because of increased accuracy in their detection[1,3,16,22] (see Table 1.2).

### *Incidence Trends Over Time*

In the past 20 years more accurate identification of pancreatic neuroendocrine tumours has resulted from heightened awareness, supported by improved diagnostic technology as well as development of specialist tertiary referral units. Specific reports detailing changes in the incidence of these tumours over time suggest that the percentage of non-syndromic tumours has increased during the last two to three decades.[26,32] A study from the Mayo Clinic examining insulinomas diagnosed in Olmstead County between 1927–1986 demonstrated a significant increase in incidence over time, with no detectable change in age or gender distribution,[26] However, clinical practice has changed so dramatically it is not possible to conclude whether such an increase is real or artefactual.

**Table 1.2.** Location, association with MEN-1 and incidence of less rare types of pancreatic neuroendocrine tumours

| Tumour | Location | Metastases | % MEN-1 | Incidence |
|---|---|---|---|---|
| Insulinoma | Pancreas | 10% | 5% | 1–2 per million |
| Gastrinoma | 50% pancreas | 60% | 25–40% | 1–2 per million |
| Glucagonoma | Pancreas | 50–80% | 10% | 0.1 per million |
| Vipoma | Pancreas | 40–70% | 5% | 0.1 per million |
| Somatostatinoma | 50% pancreas | 70% | 45% | < 0.1 per million |
| Non-syndromic tumour | Pancreas | 60% | 20% | 1–2 per million |

### Sex Distribution

The overall sex distribution for all pancreatic neuroendocrine tumours appears to be approximately equal, with variations between syndromic types. For insulinoma most series have reported a higher incidence in women;[8,18,31,45,46] for gastrinoma the male to female ratio has been reported at 3:2;[47,48] whilst for glucagonoma it is 1:2.[31] Somatostatinoma has been reported to be commoner in women[42,49] as has VIPoma,[18,50] whereas small cell carcinoma has been found predominantly in men.[44,51]

### Age Distribution

The crude median age for all pancreatic neuroendocrine tumours has been reported to be 52 years, with children below 15 years of age rarely affected.[23,44] Insulinoma has a very wide age range but the crude peak incidence occurs between 40–50 years.[8,29,45,46] Gastrinomas can occur at any age and in one series children formed almost one in 10 of those affected.[47] The peak incidence of sporadic gastrinoma occurs between 40–60 years, whereas in association with multiple endocrine neoplasia, the peak age is between 20–40 years.[25] The reported median age for glucagonoma is between 40–70 years,[1,52] for somatostatinoma between 30–60 years[42,49] and small cell carcinoma between 40–75;[44,51] as the numbers are few, the ranges are wide.

### Geographical and Ethnic Variation

There are no studies examining geographical variation in a meaningful way, although there are reported series from both east and west.[6,10]

## Risk Factors for Pancreatic Neuroendocrine Tumours

### Inherited Diseases

#### *Multiple Endocrine Neoplasia Type 1(MEN-1)*

This syndrome is characterised by pituitary, parathyroid and pancreatic islet cell tumours, produced by mutation of the MEN-1 gene encoding menin,[5,55] a nuclear protein that suppresses cell proliferation.[56] Numerous microscopic neuroen-

docrine tumours (0.3–5 mm in diameter) occur throughout the pancreas, occassionally associated with one or more larger tumours. In individuals with an established diagnosis of MEN-1, between 30–85% have clinical evidence of pancreatic neuroendocrine tumours.[30,58] Autopsies of patients with MEN-1 have shown pancreatic neuroendocrine tumours to be invariably present,[58] but most are non-syndromic and clinically silent. Thus in one surgical series of 132 patients with pancreatic neuroendocrine tumours, non-syndromic tumours were identified in only eight of 36 (22%) patients with MEN-1, the other 28 having syndromic tumours.[59] Of these, gastrinoma is the commonest; up to 50% of MEN-1 patients display typical symptoms.[60] Of all patients with gastrinomas, MEN-1 is present in one of every four.[31]

### *Von Hippel–Lindau Disease (VHL)*

This disease is inherited as an autosomal dominant disorder with high penetrance, this produces brain and spinal cord haemangioblastomas, retinal angiomas, renal cell carcinomas, pancreatic neuroendocrine tumours, phaeochromocytomas, endolymphatic sac tumours and also papillary cystadenomas of the epididymis and broad ligament.[6] It results from mutation of the tumour suppressor VHL gene, and may rise de novo through somatic mutation.[3,6]. (See Ch. 12.)

### *Neurofibromatosis*

Type 1 neurofibromatosis (NF1) affects about 1 in 4000 individuals, and is inherited as an autosomal dominant condition with variable penetrance of mutations in the tumour suppressor NF1 gene encoding the protein neurofibromin; 50% of affected individuals have new mutations.[7] It is characterised by multiple pigmented and thickened patches of skin, neurofibromata of nerves and occasionally, phaeochromocytomas. Pancreatic neuroendocrine tumours occur in a small minority of affected individuals.[1,3]

### *Tuberous Sclerosis*

This rare disorder arises from mutation in the tumour suppressor TSC1 or TSC2 genes, producing focal hyperplasia of neuroglia and neuronal tissue of the brain, astrocytoma, rhabdomyoma of the heart, adenoma sebaceum, and uncommonly, pancreatic neuroendocrine tumours.[8]

## Sporadic Pancreatic Neuroendocrine Tumours:

Allelic loss of chromosome 11Q, which includes the MEN-1 gene, is the most frequent chromosomal alteration in these tumours.[61] Somatic mutations of the MEN-1 gene have been found in 25–50% of sporadic pancreatic neuroendocrine tumours, excepting insulinoma, in which somatic MEN-1 mutations are uncommon.[62,63] Somatic mutations of VHL have been found occasionally. It appears that

many of the commoner oncogenes and tumour suppressor genes (p53, DPC4/SMAD4, PTEN, K-ras, c-myc, c-erb2, c-fos) are of little importance in pancreatic neuroendocrine tumour development, although p16/MTS1 may have a role in gastrinoma.[61,64]

## Risk of Malignancy

Traditional histopathological criteria of malignancy have limited application in the assessment of primary pancreatic neuroendocrine tumours. Thus uniformity of tumour cell appearance can be deceptively reassuring, whilst vascular and/or perineural invasion are unusual. Only the presence of local invasion and/or metastases are definitive in determining malignancy.[34,63,64] Metastases are most commonly found in the liver (up to 80% of cases), less frequently in regional lymph nodes, whilst dissemination to other distant sites is unusual.[65] Generally, tumours composed of cells producing eutopic hormones (that are normally produced by pancreatic islets) have a much lower malignancy risk that tumours producing ectopic hormones (gastrin, VIP, neurotensin, ACTH), which is useful in prognostic evaluation.[64] Overt malignancy has been found in 4–16% of patients with insulinoma,[33,46,46,64–67] with a large series of 951 patients reporting overt metastatases in 5%.[46] In contrast, malignant features have been reported in 23–90% of patients with gastrinomas, with a consensus of around 60%.[33,47,64,68–70] Over 60% of patients with glucagonoma have invasive or metastatic disease,[33] as do 50–75% of those with somatostatinomas[33,49] and 50–90% of those with VIPomas.[33,50] Between 45–90% of patients with non-syndromic tumours have been reported to have invasive or metastatic disease, a wide range that is probably a reflection of selection factors such as referral patterns, as well as methods of classification and management.[7,33,35] The vast majority of tumours secreting hormones such as ACTH, PTH and vasopressin are malignant.[64]

## Management and Prognosis

### Staging

Until recently (see Table 1.3[74]), there has been no relevant staging system, and only now are randomised controlled trials underway to test alternative strategies in therapy. Furthermore, gastrointestinal carcinoids and pancreatic neuroendocrine tumours have often been considered together as gastroenteropancreatic endocrine tumours, so that figures for survival are imprecise.

### Survival

#### *Overall Survival*

The Uppsala group reported a median survival from diagnosis of 8.7 years for all pancreatic neuroendocrine tumours, reduced to 6.7 years for those with malignant tumours; 80% of those with benign tumours were alive at 10 years.[2,23] Most malig-

**Table 1.3.** Consensus classification of pancreatic neuroendocrine tumours developed under the auspices of the World Health Organisation [74]

| |
|---|
| Well differentiated: |
| Confined to pancreas: |
| Benign behaviour: |
| Nonangioinvasive |
| < 2 cm in size |
| Ki-67 proliferation index < 2% |
| < 2 mitoses per10 high power fields |
| Uncertain behaviour: |
| Angioinvasion |
| > 2 cm in size |
| Ki-67 proliferation index >2% |
| Gross local invasion or metastasis: |
| Low grade malignant: |
| Often have angioinvasion and/or perineural invasion |
| Metastases |
| Poorly differentiated: |
| High grade malignant: |
| Highly atypical cells |
| Metastases |

nant pancreatic neuroendocrine tumours grow slowly and are generally associated with far longer survivals than other solid tumours. For patients with regional and/or distant metastases, overall 5-year survivals of between 30 and 40% have been reported.[29,66,73,74] In patients with untreated or unresponsive metastatic disease, a median survival of 3–4 years has been observed from the time of diagnosis,[73] approximately 8 years from the onset of symptoms.[75] Whilst curative resections are rarely possible for metastatic disease, combinations of therapies including surgical debulking and hormonal inhibition can achieve effective palliation for prolonged periods.[76] Now that the effects of life-threatening hypersecretion can usually be controlled, the commonest cause of death is liver failure from slow tumour progression.[36,64,76] However, pharmacological suppression of hormonal hypersecretion is not always effective, and the debilitating effects of liver metastases may still warrant hepatic resection or other ablative therapies.[77]

## *Comparison of Syndromic and Non-syndromic Tumours*

The overall survival for syndromic tumours, especially those producing eutopic hormones, has been consistently longer than for non-syndromic tumours. These latter tend to present at a later stage; the rate of liver metastasis amongst patients with non-syndromic tumours has been estimated at 60–90% of cases.[64] Eriksson and coworkers reported a 5 year survival rate of 42% for non-syndromic tumours compared to 80% for syndromic tumours.[7,17] Most series confirm non-syndromic tumours to have a poorer survival[7,19] but some authors contradict this.[35,64,80]

## *Insulinoma*

All series report insulinoma to have an excellent prognosis because of the high incidence of benign disease, and surgical excision is curative for most patients.[78] In

earlier reports, peri-operative mortality was attributed to pancreatic fistulas, pseudocysts and pancreatitis; more often after enucleation than after distal pancreatectomy,[19,46] but with increasing specialisation the complications of pancreatic surgery have fallen. Even limited metastatic disease can be cured by surgery: 5-year survival rates for metastatic insulinoma have been reported at 30–46%.[8,34]

### *Gastrinoma*

Zollinger reported an overall survival of 50% at 10 years for malignant gastrinoma.[68] Even with liver metastasis the overall 5-year survival has been reported at 20–38%.[66,68] Gastrinoma is associated with lymph node involvement in 60–80% of cases.[23] Interestingly, lymph node involvement without hepatic or distant metastasis does not appear to exert a major influence on survival from gastrinoma.[48] This finding suggests that the presence of lymph node metastases should not necessarily discourage an aggressive surgical approach.

### *Other Syndromic Tumours*

The majority of patients with glucagonoma have metastatic disease at the time of presentation. However, this tumour tends to progress slowly and patients may survive for years without treatment.[66] VIPomas, often metastatic at the time of diagnosis, may be associated with extended survivals, with a median of 3.6 years.[27] Patients with pancreatic carcinoids have fared less well, the median survival being 7 months in a series of 30 patients, 21 of whom had metastases.[79]

## Summary

Pancreatic neuroendocrine tumours are a rare group of neoplasms with complex patterns of behaviour requiring detailed specialist management. Interpretation of the current literature is limited by difficulties in classification, diagnosis and staging, with no randomised controlled trials that compare alternative treatments. Descriptive epidemiological studies are based on clinical or autopsy series with poorly defined reference populations. Only two population-based studies provide estimates of the incidence in life, one at 2.0 per million per year, the other at 4.0 per million per year, whilst autopsy series suggest a more frequent occurrence. The course of these tumours is often indolent, and although ectopic hormone production can be life threatening, crude survival rates of 50% or more at 5 years have been recorded, even for more malignant forms. There is a need for further population-based studies with accurate ascertainment to evaluate the epidemiology of these tumours.

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