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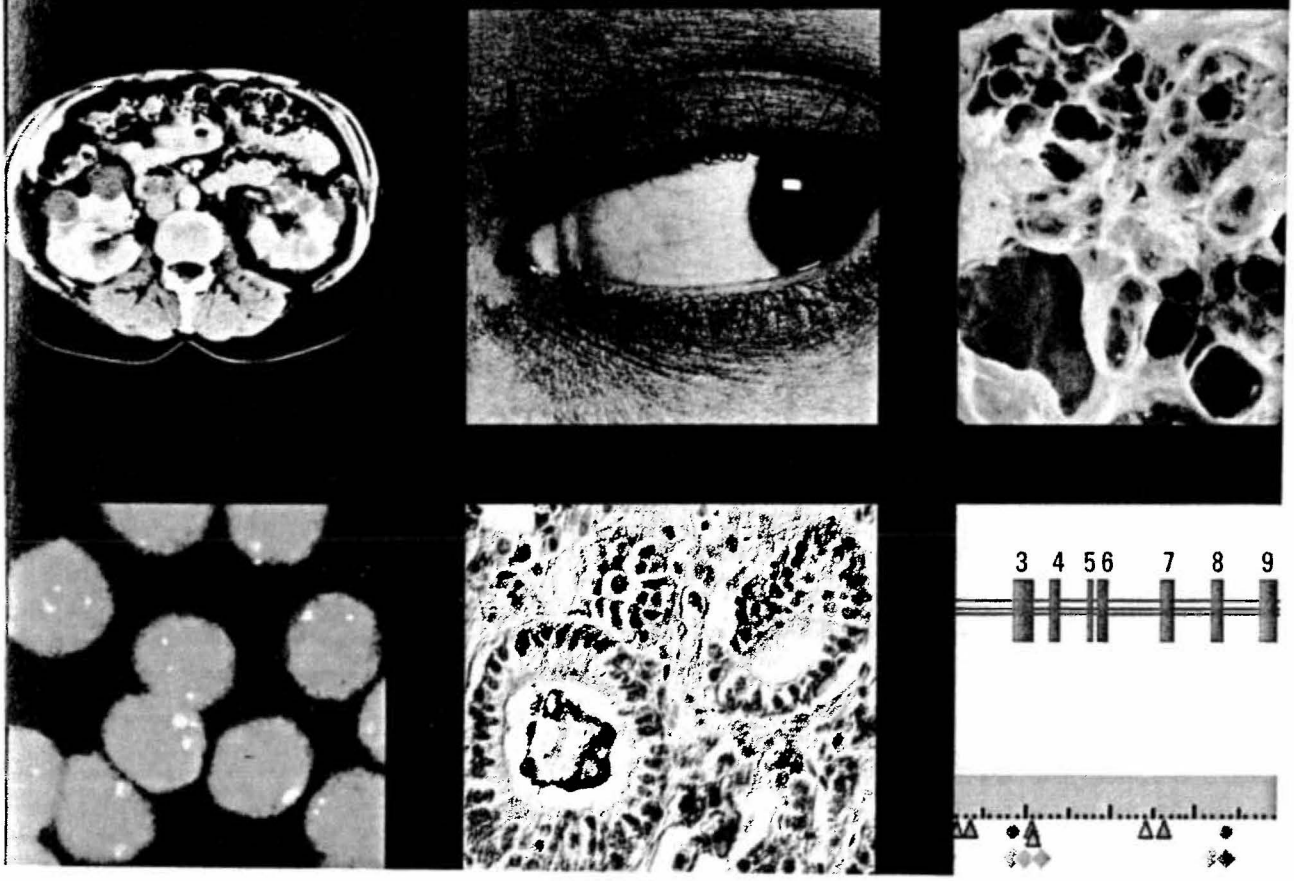
# Pathology & Genetics

# Tumours of Endocrine Organs

Edited by Ronald A. DeLellis, Ricardo V. Lloyd, Philipp U. Heitz, Charis Eng



World Health Organization Classification of Tumours

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International Agency for Research on Cancer (IARC)

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Edited by

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IARC*Press*

Lyon, 2004

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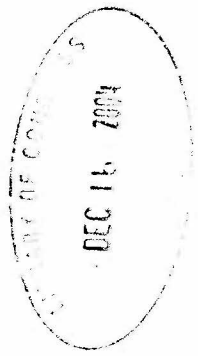


# Pathology and Genetics of Tumours of Endocrine Organs

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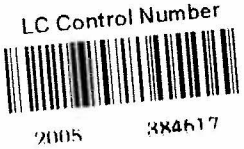


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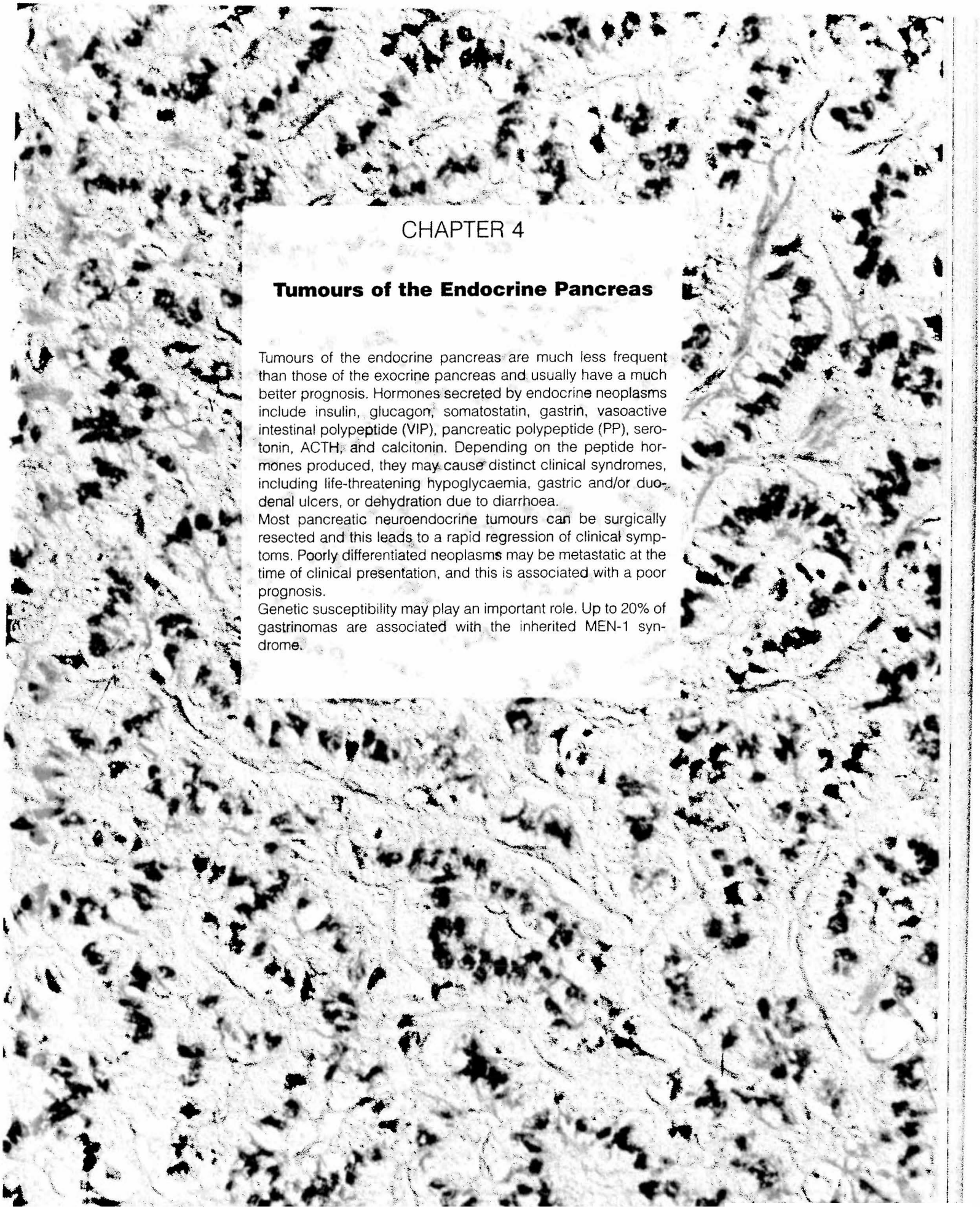

# CHAPTER 4

## Tumours of the Endocrine Pancreas

Tumours of the endocrine pancreas are much less frequent than those of the exocrine pancreas and usually have a much better prognosis. Hormones secreted by endocrine neoplasms include insulin, glucagon, somatostatin, gastrin, vasoactive intestinal polypeptide (VIP), pancreatic polypeptide (PP), serotonin, ACTH, and calcitonin. Depending on the peptide hormones produced, they may cause distinct clinical syndromes, including life-threatening hypoglycaemia, gastric and/or duodenal ulcers, or dehydration due to diarrhoea.

Most pancreatic neuroendocrine tumours can be surgically resected and this leads to a rapid regression of clinical symptoms. Poorly differentiated neoplasms may be metastatic at the time of clinical presentation, and this is associated with a poor prognosis.

Genetic susceptibility may play an important role. Up to 20% of gastrinomas are associated with the inherited MEN-1 syndrome.

# WHO histological classification of tumours of the endocrine pancreas

| | |
|---|---|
| **Well-differentiated endocrine tumour** | 8150/1[1] |
| Functioning | |
| Insulin-producing (insulinoma) | 8151/1 |
| Glucagon-producing (glucagonoma) | 8152/1 |
| Somatostatin-producing (somatostatinoma) | 8156/1 |
| Gastrin-producing (gastrinoma) | 8153/1 |
| VIP-producing (VIPoma) | 8155/1 |
| Others | |
| Non-functioning | |
| Microadenoma (<0.5 cm) | 8150/0 |
| Others | |

| | |
|---|---|
| **Well-differentiated endocrine carcinoma** | 8150/3 |
| Functioning | |
| Insulin-producing (insulinoma) | 8151/3 |
| Glucagon-producing (glucagonoma) | 8152/3 |
| Somatostatin-producing (somatostatinoma) | 8156/3 |
| Gastrin-producing (gastrinoma) | 8153/3 |
| VIP-producing (VIPoma) | 8155/3 |
| Serotonin producing with carcinoid syndrome | 8241/3 |
| ACTH producing with Cushing syndrome | 8150/3 |
| Non-functioning | 8150/3 |
| **Poorly-differentiated endocrine carcinoma - small cell carcinoma** | 8041/3 |
| **Mixed exocrine – endocrine carcinoma** | 8154/3 |

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {664} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

# Pancreatic endocrine tumours: Introduction

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## Terminology

In this chapter the term "pancreatic endocrine tumour" replaces earlier terms, e.g. pancreatic neuroendocrine tumour, islet cell tumour, and APUDoma.

## Epidemiology

Pancreatic endocrine tumours are uncommon and represent 1-2% of all pancreatic neoplasms. The tumours show no significant gender predilection and occur at all ages, with a peak incidence between 30-60 years. Clinically unrecognised or asymptomatic, and usually small tumours (diameter less than 1 cm) have been found in 0.4-1.5% of unselected autopsies {779,1086,1154,1356, 1874, 2097}.

The reported overall incidence of tumours of the endocrine pancreas has increased during recent years. This is probably due to the application of more sensitive diagnostic approaches such as imaging techniques, reliable laboratory tests and careful "morphofunctional" analysis by immunohistochemical and molecular biological techniques {2097}.

## Endocrine function

Pancreatic endocrine tumours are separated based on their clinical manifestation, into functioning and non-functioning.

*Functioning tumours* are associated with clinical syndromes caused by inappropriate secretion of hormones. Within this group are insulinomas, glucagonomas, somatostatinomas, gastrinomas, VIPomas, and other less common tumours. The clinical syndromes are described under the headings of the various functioning tumours.

*Non-functioning tumours* (or inactive, clinically silent, nonsyndromic) are not associated with a distinct hormonal syndrome but may still show elevated hormone levels in the blood or immunoreactivity in tissue sections. For this reason, the term "nonsyndromic" pancreatic endocrine tumour may more accurately describe this group, but is not widely used {2094}. Therefore, tumours with the majority of cells expressing (and often secreting) pancreatic polypeptide (PP), or neurotensin are included in the group of non-functioning tumours (as are many "D-cell tumours" or "somatostatin producing tumours"), because they do not cause a distinct hormonal syndrome. Non-functioning tumours only become clinically apparent due to their large size, to invasion of adjacent organs, or the occurrence of metastases. Rarely they may present as acute pancreatitis. Increasingly, they are incidentally detected on imaging tests.

Tumours with a diameter of less than 0.5 cm, the minimum size required for gross detection, are defined as microadenomas and are, as a rule, non-functioning.

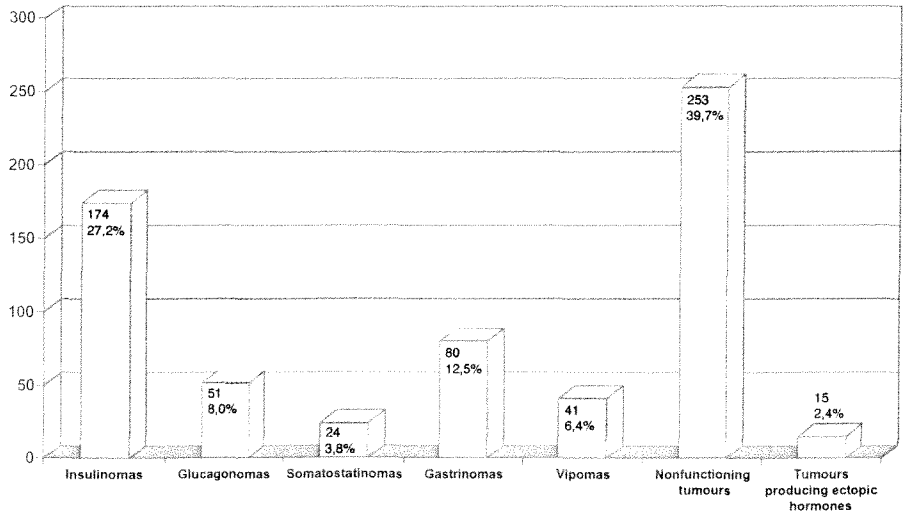


**Fig. 4.01** Frequency of various types of pancreatic endocrine tumours, based on a series of 638 cases.

## Macroscopy

The majority of the tumours are well demarcated and solitary, showing a white-yellow or pink-brown colour. The consistency is variable. Rarely, they are cystic {1301}.

Their diameter ranges usually around 1-5 cm. Among the functioning tumours, insulinomas are usually smaller (less than 2 cm in diameter) than glucagonomas, somatostatinomas, gastrinomas or VIPomas, but the size of the tumours is not related to the severity of the hormonally induced symptoms.

Non-functioning tumours are generally larger than 2 cm in diameter (often 5 cm or more). They are probably detected relatively late because they do not induce a clinical syndrome due to inappropriate hormone secretion.

Tumours with a diameter of more than 2 cm have an increased risk of malignant behaviour and those over 3 cm are usually malignant.

## Cytopathology

Fine needle aspiration biopsy (FNAB) is a useful method for investigating pancreatic endocrine tumours and their metastases. Guidance techniques include computed tomography (CT), transabdominal ultrasonography (TUS) and, more recently, endoscopic ultrasonography (EUS). The cytomorphological features of pancreatic endocrine tumours are the same for functioning and non-functioning tumours {25, 161,401,2072}. Smears are usually uniformly cellular and composed of a relatively monotonous population of cells predominantly arranged singly, but also in loose clusters or pseudorosettes. The round to ovoid, smoothly contoured nuclei demonstrate a salt-and-pepper chromatin pattern. The cytoplasm is

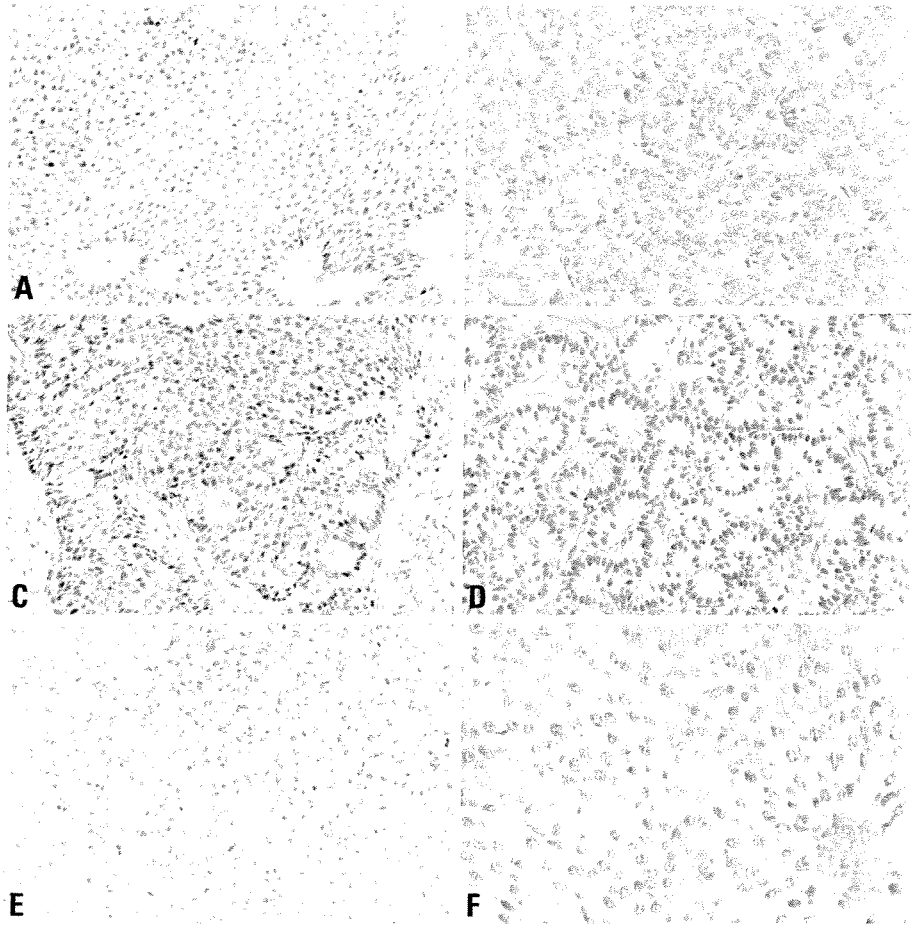


**Fig. 4.02** Growth patterns of pancreatic endocrine tumours. **A** Solid growth pattern. **B** Trabecular growth pattern. **C** Gland formation. The cells lining the lumina are cytologically identical to those of the remainder of the tumour. **D** Gyriform growth pattern: Nested architecture and peripheral palisading of nuclei. **E** Clear lipid-rich cells.H&E. **F** Solid growth pattern and focal oncocytic metaplasia.

amphophilic and varies in quantity and density. Some cells may be stripped of their cytoplasm whereas others may have abundant cytoplasm and a plasmacytoid appearance.

### Histopathology

Most pancreatic endocrine tumours are well differentiated showing various histological patterns, characterised by a solid, trabecular, glandular, gyriform, tubuloacinar or pseudorosette arrangement of their cells. The cells are relatively uniform, show finely granular eosinophilic cytoplasm and a centrally located round to oval nucleus that may display a distinct nucleolus. Occasionally, clear cells, vacuolated lipid-rich cells, oncocytes or"rhabdoid" features {1717} may be observed. The amount of stroma and degree of fibrosis vary. These patterns differ considerably from one tumour to another and may vary within the same tumour. However, in most instances these features are sufficiently distinctive to permit recognition of the endocrine nature of a given tumour.

In general, the histological pattern of a tumour does not allow a conclusion as to its functional state or type of the hormone produced. There are two exceptions to this rule: amyloid deposits are indicative of insulinomas, and glandular structures containing psammoma bodies are commonly observed in somatostatin producing tumours of the periampullary duodenum.

Poorly differentiated endocrine carcinomas are uncommon. These highly aggressive neoplasms are hardly recognizable as endocrine tumours at first sight and require immunohistochemical examination to reveal their neuroendocrine phenotype. They show rather pleomorphic cells, usually in a solid arrangement, with hyperchromatic nuclei and an elevated mitotic index (>10 pe 10 HPF).

#### *Markers of neuroendocrine differentiation*

Pancreatic endocrine tumours can clear ly be identified by using antibodies to markers common to all or most neuroendocrine cells, i.e. synaptophysin, an integral membrane glycoprotein of synaptic vesicles, or protein gene product (PGP) 9.5, a cytoplasmic protein. Neuron specific enolase (NSE) is widely reported to stain these tumours, but the results should be interpreted with caution in light of the low specificity of this marker. The presence of immunoreactive chromogranins, which are glycoprotein components of the matrix of neuroendocrine secretory granules, indicates the presence of secretory granules, i.e. some degree of differentiation of the tumour cells {1874,2097}. In less well granulated examples, chromogranin staining is generally less intense and extensive, despite diffuse strong staining for synaptophysin. Pancreatic endocrine tumours also contain cytokeratins 8, 18 and 19 and may often contain neurofilaments as well.

#### *Hormonal markers*

The use of these markers is helpful in characterizing tumour cell types and their specific hormonal products. However, functioning tumours are defined on the basis of clinical symptoms due to inappropriate hormone secretion rather than immunohistochemical findings.

In the majority of functioning tumours, the hormone causing the syndrome can be detected by immunohistochemistry. However, staining intensity or the number of positive cells is not related to the severity of symptoms. This is in part due to the impairment of the genetic and posttranslational regulation of hormone synthesis and secretion. There is a high degree of heterogeneity among the individual tumour cells in the content of immunoreactive peptide hormones and corresponding mRNA. In addition, immunoreactive hormones with reduced biological activity or with a greatly shortened or prolonged half-life in the serum may be produced. Highly functioning tumours may paradoxically lack immunohistochemically detectable hormones, presumably due to their rapid secretion. In such cases, mRNA detection tech-

niques may be useful. On the other hand, an immunoreactive hormone may not be secreted due to an impaired secretory pathway. Thus, immunoreactive hormones very often can be localized to cells of non-functioning tumours.
Upon careful investigation it has become obvious that many tumours are composed of more than one phaenotype (multihormonal tumours). As a rule however, only one cell type correlates with an associated syndrome of endocrine hyperfunction. The classification of the tumours must therefore be "morphofunctional", i.e. not only based on cell typing. It must primarily take into consideration the clinical signs and symptoms, and determination of circulating hormone concentrations. Metastases may produce hormones other than those found in the primary {2097}.

**Table 4.01**
Immunophaenotyping of pancreatic endocrine tumours.

| |
|---|
| **General neuroendocrine markers** |
| Synaptophysin |
| Protein Gene Product (PGP) 9.5 |
| CD56 |
| MAP18 |
| **Markers of the matrix of secretory granules** |
| Chromogranins |
| **Hormone (cell type) – specific markers** |
| Insulin |
| Glucagon |
| Somatostatin |
| Gastrin |
| Vasoactive Intestinal Polypeptide (VIP) |
| Pancreatic Polypeptide (PP) |
| Serotonin |
| ACTH |
| Neurotensin |
| Calcitonin |

**Table 4.02**
Criteria for the clinicopathological classification of pancreatic endocrine tumours.

| |
|---|
| **1 Well-differentiated endocrine tumour** |
| 1.1 'Benign' behaviour<br>Confined to the pancreas, non-angioinvasive, no perineural invasion, <2 cm in diameter, <2 mitoses/10 HPF and <2% Ki-67 positive cells |
| 1.2 Uncertain behaviour<br>Confined to the pancreas and one or more of the following features: ≥2 cm in diameter, 2-10 mitoses/10 HPF, >2% Ki-67 positive cells, angioinvasion, perineural invasion |
| **2 Well-differentiated endocrine carcinoma**<br>Low grade malignant<br>Gross local invasion and/or metastases |
| **3 Poorly-differentiated endocrine carcinoma**<br>High grade malignant<br>>10 mitoses / 10 HPF |

## Staging and prognosis

No staging system, such as the UICC TNM system, has been applied to pancreatic endocrine tumours.
The most reliable evidence of malignant behaviour in pancreatic endocrine tumours is metastasis to the regional lymph nodes or the liver or gross infiltration of adjacent organs. Many of the smaller examples, including most insulinomas, probably have malignant potential, but interruption of their natural history by surgical resection prevents the expression of such potential. A proposal has been made to separate pancreatic endocrine tumours into prognostic groups based on mitotic rate and necrosis {899}.
Among the functioning tumours, most insulinomas show benign behaviour. In contrast, the other types of functioning tumours fall either into the categories of well-differentiated tumours with uncertain behaviour (approx. 10-15%) or, more frequently, of well-differentiated carcinomas (approx. 85-90%).
A small number of non-functioning tumours are well-differentiated tumours showing benign or uncertain behaviour; however, the vast majority (approx. 90-95%) are well-differentiated carcinomas. Poorly differentiated endocrine carcinomas are uncommon {2097}.

## Clinicopathological correlations

There is an obvious need to establish a close correlation between morphological classification and tumour-associated syndromes. This is emphasized by the difficulty in predicting the biological behaviour of well-differentiated endocrine tumours based on histological criteria alone. In addition, available follow-up studies most often refer to tumours diagnosed according to the associated clinical syndrome due to inappropriate hormone secretion.
To definitely establish the benign nature of a tumour, a long clinical follow-up period is needed, because metastases may develop years after removal of the primary lesion.
With the exception of the poorly differentiated endocrine carcinomas, the progression of the disease is often remarkably slow. Survival for five to ten years after appearance of liver metastases is not uncommon. However, inappropriate secretion of hormones may cause life-threatening hypoglycaemia, gastric and/or duodenal ulcers, or important loss of fluid by watery diarrhoea.
The final 'morpho-functional' classification of an endocrine tumour of the pan-

**Fig. 4.03** Fine needle aspiration (FNA) of a pancreatic endocrine tumour. Amphophilic cytoplasm, uniform nuclei and finely granular chromatin, imparting a salt-and-pepper appearance.

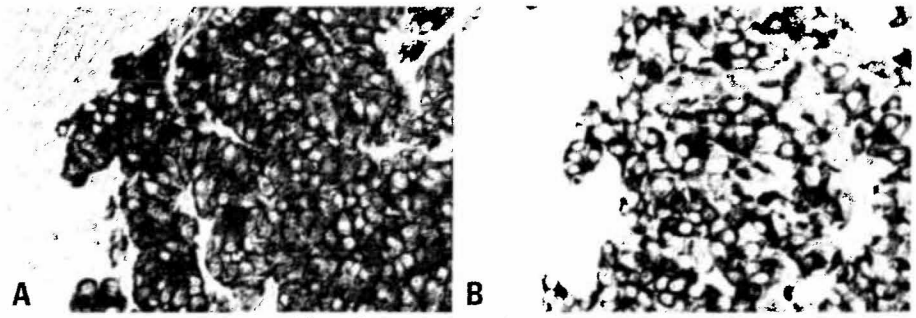


**Fig. 4.04** Gastrinoma. Endocrine differentiation is more universal than cell-specific hormone production. **A** Virtually all tumour cells contain synaptophysin. **B** The majority, but clearly fewer cells contain chromogranin A.

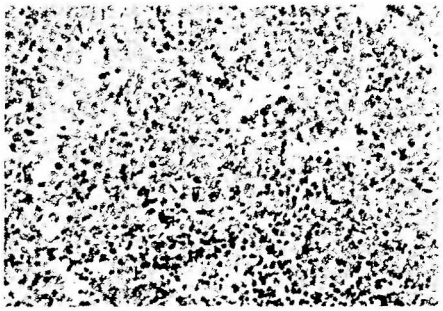

**Fig. 4.05** Poorly differentiated endocrine carcinoma. Diffuse sheets of cells with nuclear pleomorphism, necrosis and a high mitotic rate.

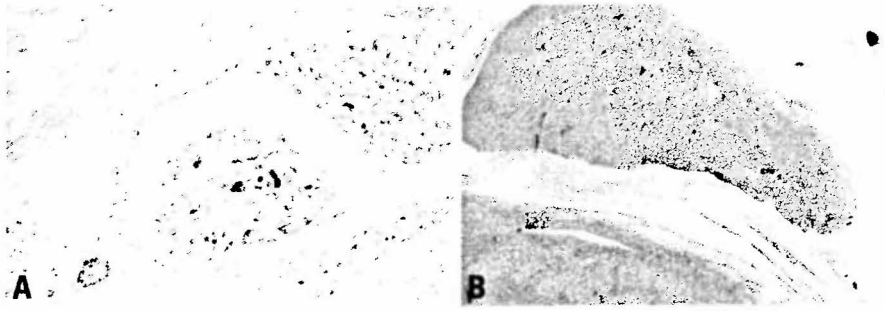


**Fig. 4.06** **A** Pancreatic endocrine tumour. Vascular invasion. **B** Well differentiated endocrine carcinoma with massive vascular invasion.

creas should take into consideration (1) the clinical syndrome induced by or associated with, a tumour, (2) determination of the blood concentration of hormone(s) to identify the hormone(s) secreted by the tumour, (3) the size (mass) of the tumour, (4) the histological differentiation and probable biological behaviour of the tumour, (5) the phaenotype(s) of the various tumour cells and, if necessary and feasible, (6) molecular genetic analysis of the tumour.

### Differential diagnosis

*Histopathology*

Most pancreatic endocrine tumours are recognizable without much difficulty. The use of immunohistochemical markers of the neuroendocrine phenotype and of hormonal content most often can establish the diagnosis unequivocally.

An important differential diagnostic problem is to distinguish solid-pseudopapillary neoplasms from endocrine tumours of the pancreas. Solid-pseudopapillary neoplasms morphologically resemble endocrine tumours, and furthermore, produce CD56, NSE and sometimes synaptophysin, as has been demonstrated by immunohistochemistry. Arguments in favour of the diagnosis of a solid-pseudopapillary neoplasm of the pancreas are the following: 1) it does not produce a hormonal syndrome but only local symptoms, 2) it is usually large, with a diameter often over 5 cm, 3) it contains clusters of cells with a clear foamy cytoplasm, 4) it often shows aggregates of PAS-positive hyaline globules in and between the tumour cells, 5) it contains broad, hyalinized septa including small blood vessels, 6) it displays haemorrhages, necrotic foci and occasionally cholesterol crystals, 7) it lacks expression of chromogranin and usually also cytokeratin, but expresses vimentin, alpha-1-antitrypsin and CD10, 8) it lacks immunohistochemical expression of peptide hormones, 9) it occurs predominantly in young women, and 10) most tumours show a benign biological behaviour {1874}.

Further tumours which may be confused with pancreatic endocrine tumours are acinar cell carcinoma, pancreatoblastomas {1537}, poorly differentiated ductal adenocarcinoma, clear cell carcinoma, epithelioid gastrointestinal stromal tumours, primitive neuroectodermal tumours (PNET) and pancreatic metastases (e.g., renal cell carcinoma, small cell lung carcinoma, melanoma)

Acinar cell carcinomas, which histologically may be very difficult to distinguish from endocrine tumours of the pancreas, usually produce trypsin (-ogen) and other pancreatic (pro-) enzymes. The same is true for pancreatoblastomas. Both neoplasms may contain scattered endocrine cells. Truly mixed acinar-endocrine or ductal-endocrine carcinomas are very rare. In these tumours the endocrine cell component should account for at least one third of the entire cell population. Poorly differentiated ductal adenocarcinomas as well as clear cell carcinomas reveal focal expression of mucin (MUC1) and carcinoembryonic antigen (CEA). Most epithelioid gastrointestinal stromal tumours (GIST) are characterized by the expression of C-KIT (CD117) and absence of staining for neuroendocrine markers. PNETs express a set of markers, including CD99. Metastases of clear cell carcinomas of the kidney lack neuroendocrine markers, but in addition to cytokeratins frequently express vimentin and CD10.

*Cytopathology*

The key entity in the differential diagnosis is acinar cell carcinoma. It can be distinguished from pancreatic endocrine tumours by its arrangement in loose grapelike clusters, granular cytoplasm and prominent cherry red nucleoli {1191}. The neoplastic cells from a solid-pseudopapillary tumour, when detached from the fibrovascular cores may be mistaken for those of a pancreatic endocrine tumour. A search in the remainder of the smear for structures with the characteristic three-layered papillary architecture (a central capillary, a middle layer of myxoid stroma and an outer layer of neoplastic cells) will yield the correct interpretation {760}.

Pancreatic endocrine tumours may be mistaken for lymphomas because they

**Table 4.03**
Adverse prognostic factors of well-differentiated pancreatic endocrine tumours.

| | |
|---|---|
| Metastasis | Regional lymph nodes, liver |
| Gross invasion | Adjacent organs |
| Tumour diameter | 2 cm or more |
| Angioinvasion | Veins, lymphatic vessels |
| Perineural invasion | Intrapancreatic nerves |
| Mitoses | >2 per 10 HPF |
| Proliferative index Ki-67 / MIB-1 | >2% |
| Necrosis | |
| Functioning tumours except insulinoma | |

**Table 4.04**
Genetic alterations detected by loss of heterozygosity analysis (LOH), comparative genomic hybridization (CGH) and mutation analysis.

| Locus | LOH | Gene | Mutation | CGH {2105,2107,2154,2490} | Reference |
|---|---|---|---|---|---|
| 1p36- | 10/29 (34%) | | | 21/102 (21%) | {541} |
| 1q32- | 8/29 (28%) | | | 16/102 (16%) | {1830} |
| 3p23- | 23/31 (74%) | | | 19/102 (19%) | {120} |
| 3p25-26- | 31/73 (42%) | *VHL* | 1/75 (1%) | 19/102 (19%) | {382,879,1530,1830} |
| 6q22- | 43/69 (62%) | | | 29/102 (28%) | {121,1830} |
| 9p- | 12/37 (32%) | *CDKN2A/p16* | 1/44 (2%) | 0/102 (0%) | {1531,2008} |
| 9q+ | | | | 29/102 (28%) | |
| 10q23- | 8/16 (50%) | *PTEN* | 1/31 (3%) | 14/102 (14%) | {1723} |
| 11p14- | | | | 28/102 (27%) | |
| 11q13 | 75/111 (67%) | *MEN1* | 33/155 (21%) | 31/102 (30%) | {441,750,879,880,1530,2018,2350,2495} |
| 11q22-23 | 20/37 (54%) | *SDHD* | 0/20 (0%) | 31/102 (30%) | {1721,1830} |
| 12p12+ | | *K-Ras* | 1/39 (3%) | 23/102 (23%) | {1531} |
| 15q- | | *SMAD3* | 0/18 (0%) | 6/102 (6%) | {2025} |
| 17p13- | 15/40 (38%) | *TP53* | 1/40 (3%) | 2/102 (2%) | {1531,1830} |
| 17p+ | | | | 32/102 (31%) | |
| 18q21- | 23/68 (34%) | *DPC4* | 0/41 (0%) | 6/102 (6%) | {879,1531,1722} |
| 22q12.1 | 9/12 (75%) | | | 4/102 (4%) | {2385} |
| Xq- | 11/23 (48%) | | | 14/46 (30%) | {1512} |
| Y- | 5/14 (36%) | | | 14/56 (25%) | {1512} |

are dyscohesive and may lack much cytoplasm {161}. However, an absence of lymphoglandular bodies in the background and the formation of loosely cohesive epithelial structures will exclude the diagnosis of lymphoma. Possibly more likely to occur is the misdiagnosis of a pancreatic endocrine tumour as a plasmacytoma, since pancreatic endocrine tumours may have a very plasmacytoid appearance {505}. Features that will help to avoid this error are the presence of a salt-and-pepper chromatin pattern in the nuclei rather than the clock-face chromatin pattern seen in a plasmacytoma, greater variability in nuclear size and shape, and an absence of a paranuclear halo in the pancreatic endocrine tumour.

## Molecular genetic analysis

Whereas the molecular basis of familial pancreatic endocrine tumours associated with multiple endocrine neoplasia type 1 (MEN 1) and von Hippel-Lindau (VHL) syndrome has recently been established {351,1241}, little is known about the oncogenesis and the molecular basis of progression of sporadic tumours.

A small number of published studies indicate that, in contrast to other human tumours, the activation of oncogenes is not a common event in pancreatic endocrine tumours {903,980,1346}. In particular, the common genetic mutations identified in pancreatic ductal adenocarcinomas (e.g., *TP53*, *K-RAS*, *CDKN2A/p16*, *DPC4*) are not found in pancreatic endocrine tumours {931}.

Molecular and cytogenetic analyses have identified a number of chromosomal alterations in pancreatic endocrine tumours.

### *Chromosomal imbalances*

Comparative genomic hybridization (CGH) studies of 102 pancreatic endocrine tumours revealed that chromosomal losses occur slightly more frequently than gains, while amplifications are uncommon {2105,2107,2154,2490}. Furthermore, the total number of genomic changes per tumour appears to be associated with both tumour volume and disease stage, indicating that genetic alterations accumulate during tumour progression {2105}. Thus, large tumours or those with increased malignant potential, and especially metastases, harbour more genetic alterations than small and clinically benign neoplasms {2105,2490}. These findings point toward a tumour suppressor pathway and genomic instability as important mechanisms associated with tumour progression.

In the majority of tumour types chromosomal alterations are not randomly distributed but are particularly common in certain chromosomal regions, including 4pq (17%), 5q (25%), 7pq (41%), 9q (28%), 12q (23%), 14q (32%), 17pq (31%) and 20q (27%) (gains) and 1p (21%), 3p (19%), 6q (28%), 10pq (14%), 11q (30%), Y (31%) and X (31%) (losses). Additional losses of 3p, 6pq, 10pq and gains of 5q, 12q, 18q and 20q are associated with malignant behaviour {2490}.

Losses of chromosome 1 and 11q as well as gains of 9q appear to be early events in the development of pancreatic endocrine tumours, since they are already present in a substantial number of small (<2 cm) tumours {2490}. The other aforementioned alterations appear to occur later, accumulating during progression and are frequently associated with malignant biological behaviour. Prevalent chromosomal aberrations common in metastases include gains of both chromosomes 4 and 7, and losses of 21q {2490}, implying that these chromosomal

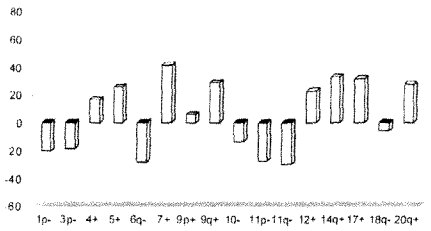


**Fig. 4.07** Pancreatic endocrine tumours. Summary of the results obtained by CGH. Gains of chromosomal material are prominent on chromosomes 4, 5, 7, 9, 14, 17 and 20, while losses are concentrated on chromosomes 1, 3, 6 and 11.

imbalances may contribute to tumour dissemination.

*Loss of heterozygosity (LOH)*

When comparing the results of LOH studies using PCR microsatellite markers with those of CGH, similar chromosomal regions exhibit genetic losses. However, in general the rate of LOH is roughly twice that of allelic losses detected by CGH. At regions 3p23, 6q22, 9p, 11q13, 18q21 and 22q12.1 the differences are even more pronounced, indicating that small deletions, not detectable by CGH, are involved {2385}. Only a small number of candidate genes located at some of the above mentioned chromosomal loci have been thoroughly investigated and many genes remain to be identified.

Pooled data indicate that somatic *MEN1* mutations are present in 21% (33/155) of spontaneous neoplasms and that 68% (75/111) harbour losses of 11q13 and/or of more distal parts of the long arm of chromosome 11. These findings indicate that another yet unknown tumour suppressor gene might be involved {441, 443,750,879,880,1530,1721,1830,2018, 2350,2495}. However, the *SDHD* gene has recently been excluded as a candidate gene {1721}.

*Point mutations*

Point mutations in tumour-associated genes, including *VHL*, *CDKN2A/p16*, *PTEN*, *K-RAS*, *TP53* appear to be extremely rare (1-3%) {382,750,1531, 1723, 2008}. Mutations have not been identified in *DPC4/SMAD4*, *RET*, *ZAC*, *BRAF* and *SMAD3* {1131,1531,1722,1725,2025}.

*Synopsis*

When comparing molecular data of the different types of sporadic tumours it appears that (1) the highest average number of chromosomal aberrations and allelic losses are present in non-functioning tumours, followed by glucagonomas and VIPomas, (2) many of these aberrations are associated with malignant clinical behaviour, (3) insulinomas and especially gastrinomas exhibit fewer genetic alterations than the other tumour types, (4) the frequency of *MEN1* mutations in insulinomas is remarkably low, (5) functioning tumours other than insulinomas exhibit a higher frequency of *MEN1* mutations and associated LOH at 11q13 than non-functioning tumours.

These observations indicate that different types of pancreatic endocrine tumours evolve along different genetic pathway and that somatic inactivation of *MEN1* i involved in a significant proportion c functioning tumours, but only exceptio ally in insulinomas.

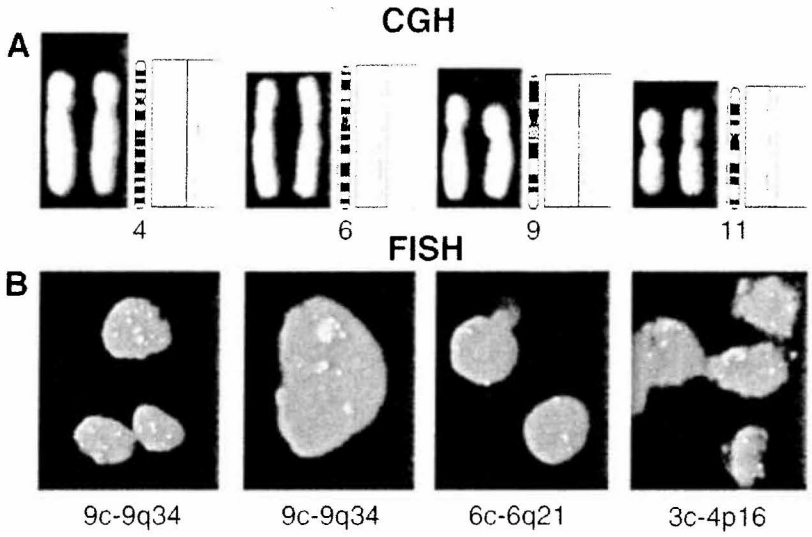


**Fig. 4.08** Pancreatic endocrine tumour. Analysis by comparative genomic hybridization(CGH) and fluorescence in-situ hybridization (FISH). Small functioning and non-functioning tumours of the pancreas: Gain o 9q34 is an early event in insulinomas (green fluorescence in FISH; red: centromere of chromosome 9). There is a deletion of one copy of 6q21 (green fluorescence) in the presence of both centromeres of chromosom 6 (red). A duplication of 4p16 as shown by FISH (green) is present as compared with the centromere 3 (red From: E.J. Speel et al. {2107}.

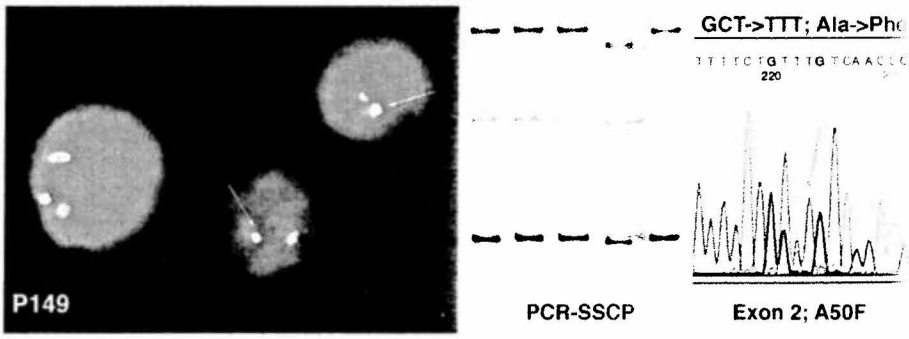


**Fig. 4.09** Sporadic pancreatic neuroendocrine tumour. Loss of one chromosome 11 (red), including th MEN-1 locus (green) in the majority of tumour cells. PCR-SSCP shows a band shift in exon 2 (red arrow heads) which is caused by a A50F missense mutation as shown by sequence analysis. From: B. Gortz et a {750}.

# Insulinoma

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## Definition

An insulinoma is a functionally active and commonly benign endocrine tumour of the pancreas with evidence of B-cell differentiation and clinical symptoms of hypoglycaemia due to inappropriate secretion of insulin.

## ICD-O code

Insulin producing tumour 8151/1
Insulin producing carcinoma 8151/3

## Synonyms

Related, but not universally applicable terms for these tumours include "functioning beta-cell tumour", "insulin producing pancreatic endocrine tumour" or "insulin producing islet cell tumour".
Symptoms of hypoglycaemia due to inappropriate secretion of insulin were first described by Harris in 1924 {836} and three years later the association between insulin secreting pancreatic endocrine tumours and hypoglycaemia was reported by Wilder et al {2386}.

## Epidemiology

Insulinomas are the most frequent of all functioning pancreatic endocrine tumours (see Pancreatic endocrine tumours) {1154,1874}. The incidence of insulinoma was reported to be 2-4 patients per million population per year {1207,2012}. Insulinomas have been diagnosed in all age groups but rarely occur below the age of 15. The highest incidence is found between 40-60 years. Approximately 10% of the patients are younger than 20 years and 10% older than 60 {603,714,2011,2120}. Females seem to be slightly more frequently affected (1.5:1 ratio) in most reported series {682,714,729,1255,2011,2012, 2295}.

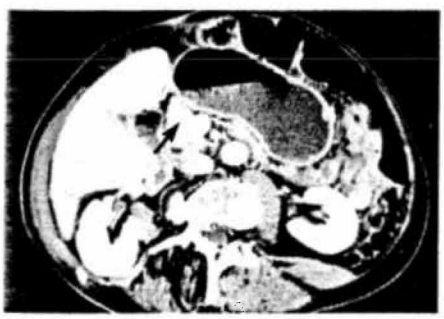

**Fig. 4.10** Abdominal CT of a patient with a small insulinoma (arrow).

## Etiology

The etiology and pathogenesis of insulinomas are unknown. No risk factors have been associated with these tumours. Embryologically, pancreatic tumours arise from similar precursor cells as pancreatic islet cells which are derived from the endoderm {1253}. The results of a recent clonality study on pancreatic endocrine tumours are consistent with the hypothesis that these tumours primarily might be polyclonal or oligoclonal neoplasms which are eventually outgrown by a more aggressive cell clone that may give rise to invasive growth and/or metastasis {1724}.

## Localization

The majority of insulinomas are located in the pancreas or are directly attached to it. Ectopic (extrapancreatic) insulinomas with symptoms of hypoglycaemia are extremely rare (1.8%) and are most commonly found in the duodenal wall {627,2120}. Other reported locations include the ileum, jejunum, gastric wall, hilus of the spleen, gastrosplenic ligament, lung, cervix and ovary {11,1075, 1124,1714,2017,2036,2458}.
Compiled data indicate that insulinomas are equally distributed between the head, body and tail of the pancreas with a slight predominance in the head and tail region {516,627,925,1542,2120}. Approximately 85% of insulinomas occur singly, 6-13% are multiple and 4-6% are associated with MEN1 {516,682,714, 729,1255,2011,2120,2295}.

## Clinical features

### *Signs and symptoms*

Patients with insulinoma manifest symptoms that can be grouped into two major categories: neurological symptoms and the autonomic nervous system response. The most common and convincing symptoms result from neuroglucopenia, followed by the catecholamine response. Most prominent are symptoms of central nervous system dysfunction including diplopia, blurred vision, confusion, abnormal behaviour and amnesia. Some patients may develop loss of consciousness and coma or even permanent brain damage. Sometimes the patients also present with focal seizures. When triggered by hypoglycaemia the release of catecholamines produce symptoms such as sweating, weakness, hunger, tremor, nausea, anxiety and palpitation. These symptoms, although highly suggestive, are not pathognomonic for hypoglycaemia and a low blood glucose level must be demonstrated during their occurrence. The Whipple triad includes: (1) symptoms of hypoglycaemia, (2)

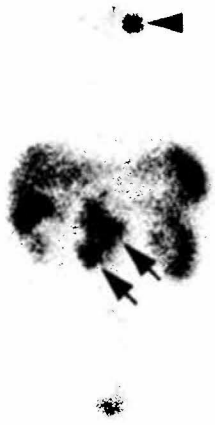

**Fig. 4.11** Octreoscan of a patient with an endocrine tumour of the ileum. Note paraaortal metastases (arrows) and infraclavicular lymph node metastases (arrowhead). The latter were confirmed by cytology.

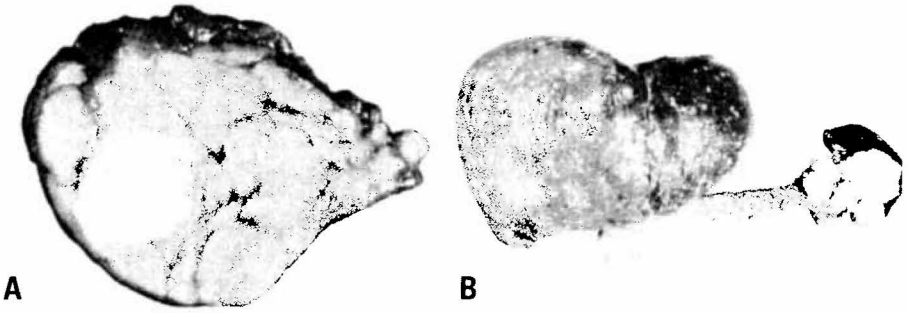

**Fig. 4.12** **A** Insulinoma. The tumour is small, sharply demarcated. **B** Malignant insulinoma invading the spleen. Numerous small liver metastases are present.

plasma glucose levels <3.0 mmol per litre; and (3) relief of symptoms with administration of glucose {1620,2010, 2120, 2497}.

*Imaging*

Transabdominal ultrasonography yields a sensitivity of 20-65% in various series, CT scan 25-60%, angiography 35-75%, and intraoperative ultrasonography 90-100%. More specific methods include octreoscan and PET-scan.

*Diagnostic procedures*

Determination of plasma insulin and proinsulin concentrations by radioimmunoassay has greatly facilitated and simplified the diagnosis of insulinoma. Usually insulin, proinsulin, C-peptide and blood glucose are measured together to demonstrate an inappropriately high secretion of insulin in relation to blood glucose and to distinguish endogenous from factitious hyperinsulinaemia. In general, 80-85% of all insulinomas are diagnosed by these measurements. Inappropriately high plasma insulin levels, during 48-72 hour fasting, is also regarded as a sensitive diagnostic test. Alternatively, C-peptide suppression is also a valuable screening or confirmatory test for insulinoma.

## Macroscopy

Grossly, insulinomas are well-circumscribed tumours, softer than the surrounding pancreatic parenchyma and have a red-brown cut surface. Tumours with abundant stroma or amyloid are firmer. Insulinomas are frequently discovered while still small with 75% of the tumours measuring 0.5-2 cm in diameter and less than 2 g in weight. The reported diameter ranges from 0.5-11 cm {1154}. Tumour size is unrelated to severity of symptoms. Degenerative, necrotic and cystic changes are uncommon and most often restricted to large tumours.

Insulinomas producing a hypoglycaemic syndrome in MEN1 patients are usually larger than 1 cm. Microadenomas, i.e. tumours below 0.5 cm in diameter, with insulin expression, no matter how numerous they are, seem to remain functionally silent {1114}. This implies that the insulinomas in MEN1 patients are among the grossly apparent and palpable pancreatic tumours. If there are several large tumours usually only one of them is an insulinoma.

## Tumour spread and staging

Malignant insulinomas may show gross local invasion of peripancreatic fatty tissue and/or adjacent organs such as the duodenum or the spleen. The first metastases are usually found in regional lymph nodes (peripancreatic, coeliac, periaortic) and the liver. Spread to other distant sites is unusual. So far there is no staging system that specifically applies to insulinomas (see Pancreatic endocrine tumours).

## Histopathology

Insulinomas exhibit four main histological patterns including a solid, trabecular, gland-like (tubular or acinar) tumour growth and mixed forms {858,1154}. Larger tumours are encapsulated but the capsule is usually incomplete. Smaller tumours and microadenomas (see Nonfunctioning tumours, microadenomas, others) are rarely encapsulated. Tumour cells frequently exhibit a bland cytology and cells with large, pleomorphic nuclei are rare. If present, these features are not predictive of malignant behaviour. A relatively uncommon, but characteristic finding in insulinomas is the deposition of amyloid. Its major component is islet amyloid polypeptide (IAPP) or amylin, that can be visualized by immunohistochemistry {2388}. Calcifications and intracytoplasmatic pigments may rarely be seen in insulinomas {957,2405}.

*Immunohistochemistry*

Almost all insulinomas exhibit immunoreactivity for insulin and proinsulin. The intensity and extent of this immunoreactivity, however, does not correlate with circulating insulin levels. Strong positivity for insulin at the secretory pole of the cells and proinsulin in the perinuclear

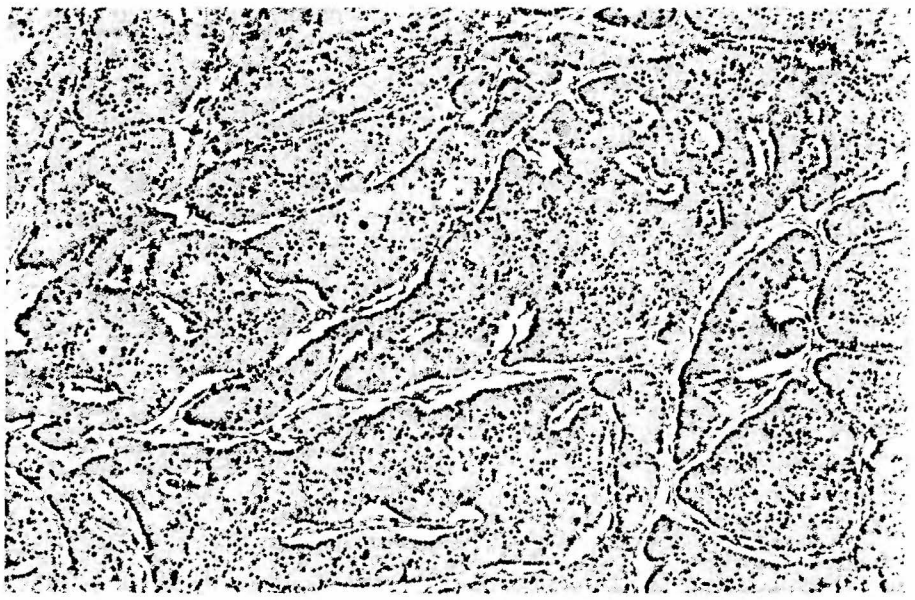

**Fig. 4.13** Insulinoma with trabecular architecture.

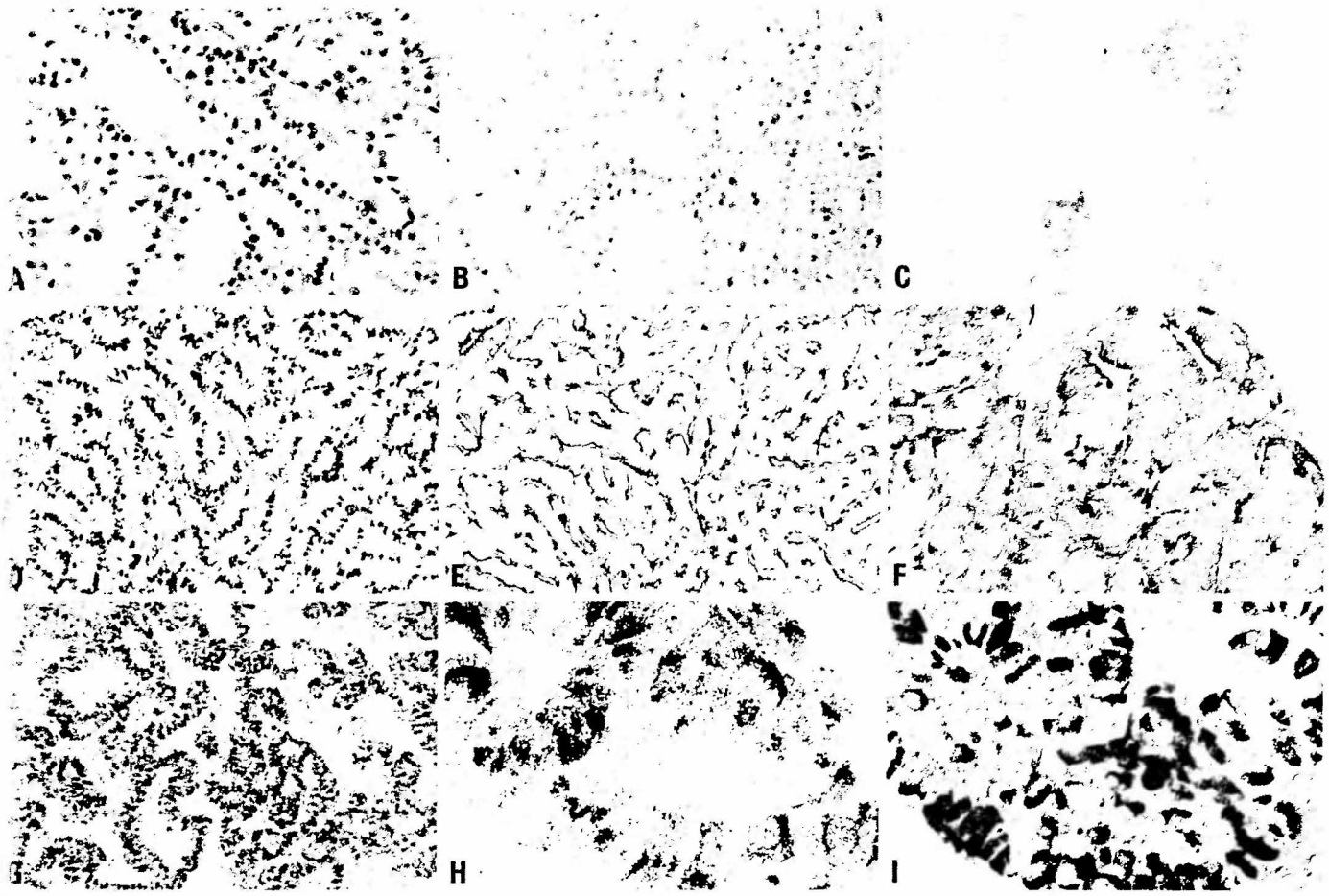


**Fig. 4.14** **A** Insulinoma with trabecular architecture. **B** Insulinoma. Stroma-containing amyloid. **C** Amyloid visualized by Congo red staining. **D** Insulinoma, highly differentiated, trabecular architecture. Proinsulin localized to the paranuclear Golgi area. Antibody specific for proinsulin. **E** Insulin predominantly localized at a secretory pole of the tumour cells. **F** Insulinoma with a trabecular growth pattern. Localization of insulin at the secretory pole of the tumour cells and partly within the cytoplasm. Antibody to insulin. **G** mRNA for insulin visualized by in-situ hybridization. **H** Proinsulin is partly located in the paranuclear Golgi area but also in the cytoplasm and at the secretory pole of the tumour cells. Proinsulin is secreted together with insulin in these tumours. Antibody specific for proinsulin. **I** Insulin is localized within the entire cytoplasm and at the secretory pole of the cells.

region, i.e. the Golgi region can be seen in some highly differentiated insulinomas. More often, however, an abnormal staining pattern for insulin and proinsulin is found {1871,1872}. About 50% of insulinomas are multihormonal. In such tumours insulin positive cells are admixed with cells expressing glucagon, somatostatin, pancreatic polypeptide or other hormones {1154}.

Useful additional immunohistochemical markers for the classification of insulinomas are MIB-1 (to assess proliferation index), CD31 (to visualize angioinvasion) and somatostatin receptor subtypes {1681}. In cases with non-detectable insulin by immunohistochemistry in-situ hybridization may be helpful to identify insulin mRNA in tissue sections {2106}.

*Electron microscopy*

There are several classifications of insulinomas based on the ultrastructrural shape of their secretory granules {174, 429,430,2164}. However, as it has become more and more obvious that insulinomas are extremely heterogeneous, containing poorly and well-granulated cells in the same tumour, the use of these classifications is limited. In a more recent study it was demonstrated that the pathophysiology of insulinomas is less likely caused by decreased storage capacity for insulin, as proposed earlier, than by impaired conversion of proinsulin to insulin {1873}.

## Precursor lesions

No definite precursor lesion has been identified for insulinoma. Proliferation of β cells (β cell hyperplasia, nesidioblastosis), in patients with persistent hyperinsulinaemic hypoglycaemia cannot be considered a precursor lesion of insulinoma because it is genetically different {2006}.

## Histogenesis

The histogenesis of insulinoma is uncertain {1835}. Ductal proliferation may sometimes be associated with insulinoma, suggesting a potential duct cell origin. Alternatively, an islet origin of β cell tumours is suggested by histology in MEN1 patients {2094} and is supported by observations that transgenic mice consistently developed islet B-cell hyperplasia, dysplasia and insulinomas, in the absence of ductuloinsular proliferation {815,1834,1835,1837}.

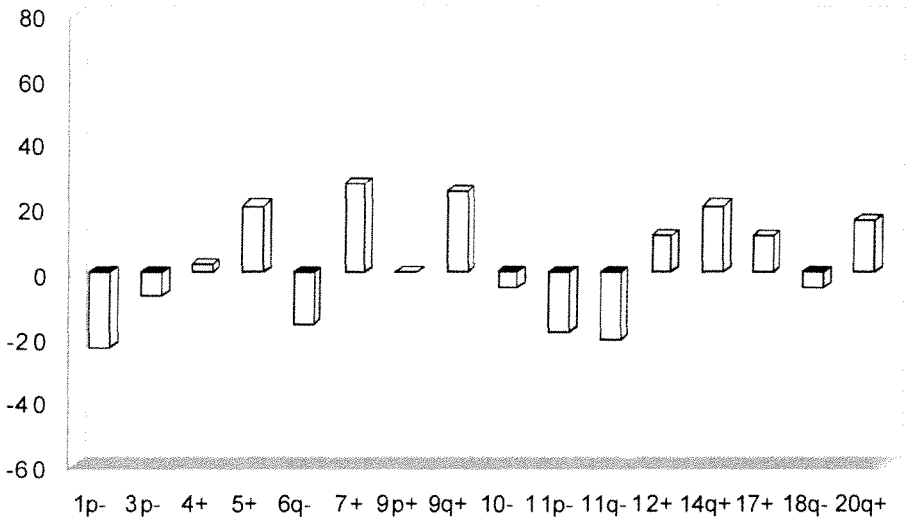


**Fig. 4.15** Summary of the results obtained by CGH analysis of insulinomas. Gains of chromosomal material mainly occur on chromosomes 5, 7, 9q, 14q and 20q while losses are shown on 1p, 6q, 11p and 11q.

**Fig. 4.16** Insulinoma. The proliferative index is less than 2 %. Antibody Ki-67.

### Somatic genetics

Compiled data from 43 analysed tumours indicate that as compared to other pancreatic endocrine tumours, insulinomas exhibit fewer genomic alterations by CGH (see Pancreatic endocrine tumours) {2105,2107,2154, 2490}. In particular, losses of 3p and other malignancy-associated alterations are rare. Losses of 3q and gains of 15q appear to be more frequently encountered in insulinomas than in the other pancreatic endocrine tumour types. Gains of 9q34 and losses of 1p36 and 11q appear to be early alterations already detectable in tumours smaller than 2 cm.

Despite allelic losses of up to 40% at 11q13 (the locus of *MEN1*), somatic mutations of the *MEN1* gene appear to be rare when compared to the other endocrine tumour types. They were identified in only 7.7% (5/65) of sporadic insulinomas {750,879,1530,2018,2105, 2350,2495}. Somatic mutations in other genes such as *VHL* and *CDKN2A/p16* are only occasionally encountered (1/22 and 1/9) {1530,1531}.

### Genetic susceptibility

Insulinoma is the second most frequent functioning enteropancreatic tumour in MEN1 patients after gastrinoma, the latter often arising in the duodenum {1250}. Rare examples of insulinomas have also been described in patients suffering from NF1 {672}. Approximately 4-7% of unselected patients with insulinomas suffer from MEN 1 {2012} .Between 10 and 30% of the pancreatic endocrine tumours in MEN1 patients are associated with symptoms of hypoglycaemia due to inappropriate insulin secretion {757, 1154,1939}. Between 12 and 17% of VHL patients develop pancreatic endocrine tumours which may show focal insulin immunoreactivity {1357}. However, most of these tumours are clinically non-functioning.

### Prognosis and predictive factors

In contrast to the other types of pancreatic endocrine tumours, the vast majority of insulinomas are benign at the time of diagnosis {2094}. This may be due in part to their early detection as they already become symptomatic when still small {1113,2092}. The percentage of malignant insulinoma ranges from 2.4-17.9 % with an average of 8.4 % {682, 714,729,1255,2011,2092,2120,2295}. Malignant insulinomas occur in an older age group and are rare in children {426,2152}. It appears that males are more frequently affected than females {449}.

Insulinomas of less than 2 cm in diameter without signs of angioinvasion, gross invasion or metastases and showing a mitotic rate of <2 mitoses per 10 HPF or <2% Ki-67 (or MIB-1) staining index are considered benign (macroadenomas) {2097}. There are no immunohistochemical markers available which reliably predict the biological behaviour of insulinomas {1133,1190,1291}. Risk factors in insulinomas that are not overtly malignant include: diameter larger than 2 cm, high mitotic/MIB1 index and necrosis {899}. Malignant insulinomas contain a higher number of genetic alterations than benign tumours {2106,2107}. Furthermore, it has been shown that losses of chromosomes 3pq and 6q as well as gains of 17pq and 20q are associated with malignant behaviour {2107}. The involved genes, however, remain to be identified.

# Glucagonoma

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## Definition

A glucagonoma is a functionally active and usually malignant endocrine tumour of the pancreas with evidence of A-cell differentiation and clinical symptoms of the glucagonoma syndrome, due to inappropriate secretion of glucagon, and including a skin rash (necrolytic migratory erythema), stomatitis, mild diabetes mellitus and weight loss.

Pancreatic endocrine tumours with A-cell differentiation but without a glucagonoma syndrome should not be considered glucagonomas, but non-functioning pancreatic endocrine tumours.

## ICD-O code

Glucagon producing tumour 8152/1
Glucagon producing carcinoma 8152/3

## Epidemiology

Glucagonomas represent about 5% of all clinically relevant pancreatic endocrine tumours and 8-13% of functioning tumours (see Pancreatic endocrine tumours) {2094}. The estimated incidence of the glucagonoma syndrome is 1 per 20 million per year {1771}. Patients most often present between the ages of 40-70 years (range 19-72 years) and women are slightly more often affected {1885}.

## Etiology

Glucagonomas are occasionally part of MEN1 {2112,2355}.

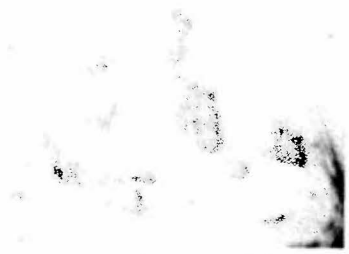

**Fig. 4.17** Glucagonoma syndrome: necrolytic migratory erythema. From E. Ruttman et al. {1885}.

## Localization

Glucagonomas commonly occur in the tail of the pancreas or attached to the pancreas {1885}. Extrapancreatic glucagonomas are extremely rare {1852}.

## Clinical features

### *Signs and symptoms*

The *glucagonoma syndrome* was described in detail in 1974 {1397} but had already been observed in 1960 {752}. The glucagonoma syndrome is thought to reflect the catabolic action of excessively elevated glucagon levels {883,1397,1771}.

The most common presenting feature of the glucagonoma syndrome is *necrolytic migratory erythema* found in about 70% of all patients. The rash usually starts in the groins and the perineum and migrates to the distal extremities. The syndrome also includes mild glucose intolerance, normochromic normocytic anaemia, weight loss, depression, diarrhoea and a tendency to develop deep vein thrombosis. The skin rash may be associated with angular stomatitis, cheilitis, atrophic glossitis, alopecia, onycholysis, vulvovaginitis and urethritis. The cause of the rash is still unknown. A direct effect of glucagon on the skin, prostaglandin release, deficiency of amino acids, free fatty acids or zinc have been proposed as the underlying mechanisms. Marked weight loss occurs in around 65% of all patients and diabetes mellitus is seen in about 50% of all cases. Normochromic and normocytic anaemia occurs in about 1/3 of patients and is probably due to direct bone marrow suppression by glucagon or to the deficiency of amino acids. Diarrhoea occurs in 1/5 of the cases as do psychiatric disturbances. A tendency to venous thrombosis is increased, occurring in around 10-15% of all patients and may be life-threatening {53, 201,1185,2111}.

### *Imaging*

Imaging procedures include helical CT, ultrasonography, MRI and somatostatin receptor scintigraphy and PET-scan. These tumours are usually large at diagnosis unless they occur in patients with MEN 1. Somatostatin receptor scintigraphy (octreoscan) is the most sensitive localization procedure and also an important method for staging of the disease. Small tumours may be detected by endoscopic ultrasonography.

### *Diagnostic procedures*

The diagnosis of glucagonoma is made on the basis of raised fasting plasma glucagon concentration together with demonstrable tumour and characteristic clinical features. Fasting plasma glucagon concentration is usually elevated 10 to 20 fold; however, in some patients it may be only marginally so. Tolbutamide or arginine stimulation tests may be used to confirm the diagnosis. Approximately 1/5 of glucagonoma patients also have raised fasting plasma gastrin concentration.

## Macroscopy

Most glucagonomas are rather large, solitary pancreatic tumours reaching up to 35 cm in greatest diameter. The mean diameter is approximately 7 cm {1885,2094}. The colour of the cut surface is brown-red to pink, and the consistency is usually soft. Because of their large size, degenerative changes, such as haemorrhage, necrosis and cystic change are frequently seen in these tumours.

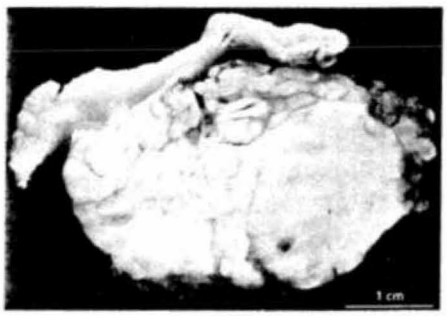


**Fig. 4.18** Glucagonoma within the head of the pancreas. The tumour is sharply demarcated.

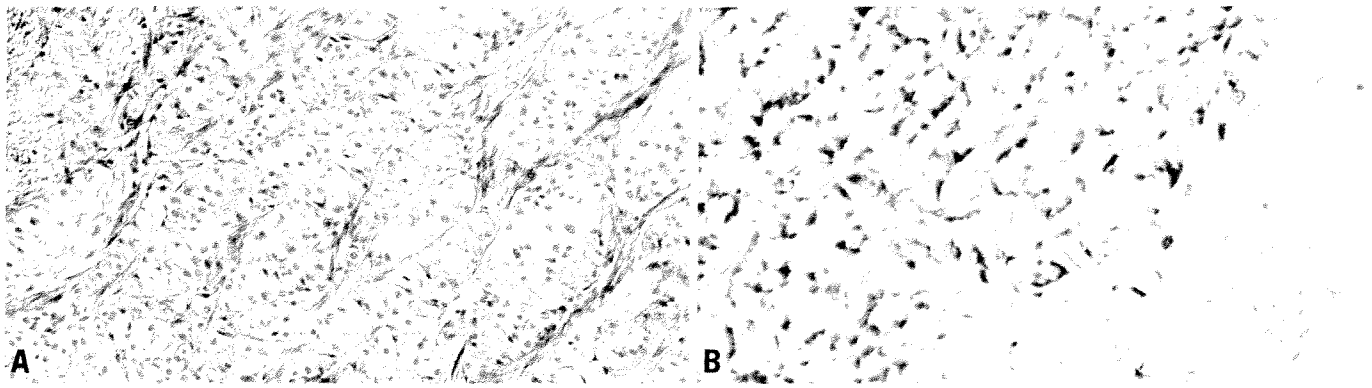


**Fig. 4.19** **A** Glucagonoma with a trabecular architecture. **B** Glucagonoma. Intense glucagon production by tumour cells.

### Tumour spread and staging

As in other endocrine tumours of the pancreas, glucagonomas spread by local invasion into surrounding tissues and metastasize to the regional lymph nodes and the liver. So far there is no staging system that specifically applies to glucagonomas (see Pancreatic endocrine tumours).

### Histopathology

The histological features of glucagonomas do not differ fundamentally from those of other pancreatic endocrine tumours {230,1885,2094}. They do, however, show a predominance of a mixed trabecular-solid patterns. The tumour cells show faintly granular, often abundant cytoplasm.

*Immunohistochemistry*

Glucagonomas often stain weakly for glucagon, but also show reactivity for peptides derived from proglucagon (glycentin, glucagon-like peptides 1 and 2) {230,806,1885}. In addition, numerous PP immunoreactive cells can often be identified. Mitoses are noted infrequently.

*Electron microscopy*

Electron microscopically, glucagonomas show atypical secretory granules {230, 2355}.

### Somatic genetics

CGH reveals frequent chromosomal gains and losses involving different chromosomes. Only a small number of tumours (12) have been investigated, however, and the results may not be representative. The chromosomal loci involved are similar to those involved in non-functioning tumours, and gains of chromosome 7 are present in up to 80% of cases {2105,2107,2154,2490}. Using LOH analysis corresponding allelic imbalances have been described, though with higher frequencies of losses at 1p36, 3p25-26, 6q22, 10q23 and 11q13 {120,750,879}.

Somatic *MEN1* mutations were reported in 2 of 3 investigated tumours. No mutations could be identified in the genes *VHL, PTEN, SDHD* and *DPC4* {382,1721, 1722}.

### Genetic susceptibility

Glucagon-immunoreactive tumours may occur in the setting of MEN1 {1114,1250, 1941}. In a series of 100 pancreatic tumours in 28 patients with MEN1, 37 displayed glucagon immunoreactivity, and one patient presented with the glucagonoma syndrome {1250}. In MEN1, these tumours tend to be multiple (59%) and benign (75%) {2089}. A glucagon-immunoreactive tumour was associated with familial adenomatous polyposis {2131}. In contrast, glucagon production seems to be uncommon in pancreatic tumours occurring in patients with von Hippel-Lindau disease {1357}.

### Prognosis and predictive factors

Approximately 60-70% of glucagonomas are already metastatic at the time of diagnosis {883,1771,1885}. Even small glucagonomas are considered tumours of uncertain behaviour or well-differentiated endocrine carcinomas (see Pancreatic endocrine tumours). These tumours tend to grow slowly and patients may survive for many years.

Occasionally, in multihormonal tumours, the glucagonoma syndrome may be associated with, or followed by, another syndrome, such as a hypoglycaemic syndrome or VIPoma syndrome {33 1640,2447}.

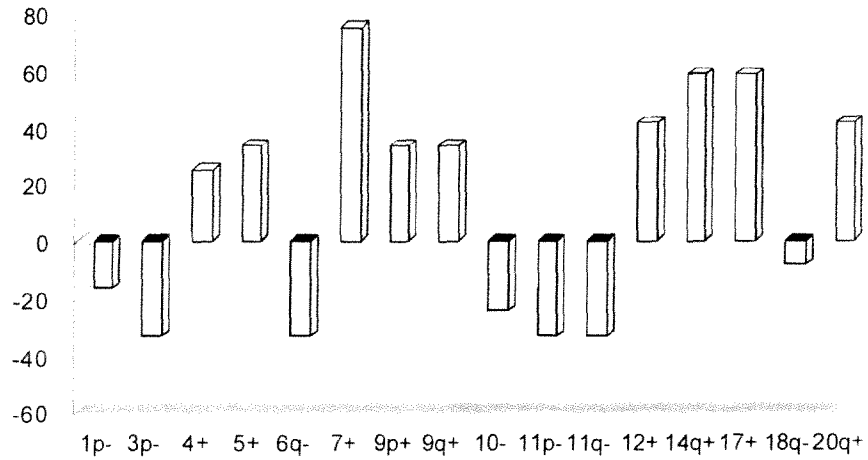


**Fig. 4.20** Analysis of genetic alterations of glucagonomas by CGH. Chromosomal gains are frequent on chromosomes 4, 5, 7, 9, 12, 14, 17 and 20 while losses occur at 1p, 3p, 6q, 10, 11p & q.

# Somatostatinoma

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## Definition

A somatostatinoma is a functionally active and usually malignant endocrine tumour with evidence of D-cell differentiation and clinical symptoms reflecting the diverse pathophysiologic effects of chronic inappropriate secretion of somatostatin (hypersomatostatinemia; somatostatinoma syndrome). Extrapancreatic endocrine tumours such as those of the duodenum, lung, thyroid and paraganglia composed either exclusively or predominantly of somatostatin immunoreactive cells, but unassociated with the somatostatinoma syndrome should therefore be more appropriately designated as somatostatin producing endocrine tumours (or D-cell tumours).

## ICD-O code

Somatostatinoma producing tumour 8156/1
Somatostatinoma producing carcinoma 8156/3

## Historical annotation

Somatostatinomas were independently described by Ganda et al. {687} and Larsson et al. {1236}.

## Epidemiology

Somatostatinomas account for between 1 to 2% of endocrine tumours of the gastroenteropancreaticohepatic (GEPH) axis. Duodenal somatostatin producing tumours appear to be as common as their pancreatic counterparts. Unlike other gastrointestinal and pancreatic endocrine tumours that may occur at any age, somatostatinomas generally arise in adults 25-85 years of age. The vast majority occur between the fourth and sixth decades and are twice as common in females as in males {464,2323}.

## Etiology

While some somatostatinomas are associated with NF1, MEN1 and Von Hippel-Lindau syndromes, the etiology of their sporadic counterparts is unclear, similar to that of endocrine tumours of the GEPH axis.

## Localization

Although somatostatinomas may arise anywhere within the pancreas, they are most commonly located in the head.

## Clinical features

### *Signs and symptoms*

The subtle and nonspecific somatostatinoma syndrome consists of markedly elevated somatostatin concentrations in plasma and/or tumour, diabetes mellitus of recent onset, hypochlorhydria, gallbladder disease (cholelithiasis, suppression of gallbladder motility), diarrhoea, steatorrhoea, anaemia and weight loss {1164}. Although each of these syndromic components can be due to the inhibitory effects of somatostatin on the secretory activity of various endocrine and exocrine cell types and the suppression of gallbladder motility, the very existence of the somatostatinoma syndrome has been questioned on the ground that these features are non-specific and very common in the older age group in which these tumours most often arise.

### *Imaging*

Ultrasonography is the most sensitive method to demonstrate somatostatinomas of the pancreas and duodenum. Extrapancreatic and metastatic lesions can be detected by ultrasonography, CT scan, and MRI. Somatostatin receptor scintigraphy and PET-scan have proven to be the most sensitive methods to demonstrate extrapancreatic and extraduodenal somatostatinomas.

## Diagnostic procedure

The diagnosis is confirmed by documentation of elevated plasma concentrations of somatostatin and the presence of the somatostatinoma syndrome.

## Macroscopy

Irrespective of whether they are pure or mixed, somatostatinomas usually occur as solitary, well-circumscribed, but not encapsulated, soft, grey-white to yellow-tan tumours {2091}, that are generally large (average diameter 5-6 cm) by the time they are discovered {1064,2091}.

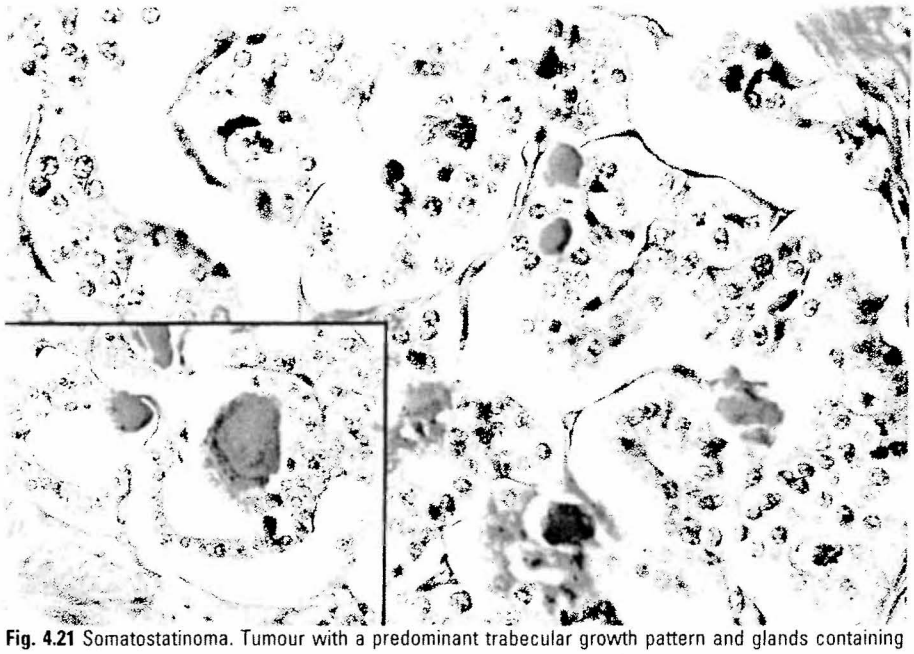

**Fig. 4.21** Somatostatinoma. Tumour with a predominant trabecular growth pattern and glands containing several psammoma bodies. High power micrograph of tumour stroma including psammoma bodies.