CHAPTER 10

Tumours of the Exocrine Pancreas

Pancreatic carcinoma is a highly malignant neoplasm that still carries a very poor prognosis. Ductal adenocarcinoma is the most frequent type. Although cigarette smoking has been established as a causative factor, the risk attributable to tobacco abuse amounting to approximately 30%. An increased risk is also associated with hereditary pancreatitis, but additional aetiological factors remain to be identified.

Significant progress has been made in the understanding of the molecular basis of ductal carcinomas. *KRAS* point mutations and inactivation of the tumour suppressor genes *p16, TP53* and *DPC4* have been identified as most frequent genetic alterations.

Non-ductal pancreatic neoplasms span a wide range of histological features that need to be recognized by pathologists as several entities are associated with distinct opportunities for therapy.

WHO histological classification of tumours of the exocrine pancreas

Epithelial tumours

Benign

Serous cystadenoma	8441/0[1]	Serous cystadenocarcinoma	8441/3
Mucinous cystadenoma	8470/0	Mucinous cystadenocarcinoma	8470/3
Intraductal papillary-mucinous adenoma	8453/0	– non-invasive	8470/2
Mature teratoma	9080/0	– invasive	8470/3

Serous cystadenoma 8441/0[1]
Mucinous cystadenoma 8470/0
Intraductal papillary-mucinous adenoma 8453/0
Mature teratoma 9080/0

Borderline (uncertain malignant potential)
Mucinous cystic neoplasm with moderate dysplasia 8470/1
Intraductal papillary-mucinous neoplasm with moderate dysplasia 8453/1
Solid-pseudopapillary neoplasm 8452/1

Malignant
Ductal adenocarcinoma 8500/3
    Mucinous noncystic carcinoma 8480/3
    Signet ring cell carcinoma 8490/3
    Adenosquamous carcinoma 8560/3
    Undifferentiated (anaplastic) carcinoma 8020/3
    Undifferentiated carcinoma with osteoclast-like giant cells 8035/3
    Mixed ductal-endocrine carcinoma 8154/3

Serous cystadenocarcinoma 8441/3
Mucinous cystadenocarcinoma 8470/3
    – non-invasive 8470/2
    – invasive 8470/3
Intraductal papillary-mucinous carcinoma 8453/3
    – non-invasive 8453/2
    – invasive (papillary-mucinous carcinoma) 8453/3
Acinar cell carcinoma 8550/3
    Acinar cell cystadenocarcinoma 8551/3
    Mixed acinar-endocrine carcinoma 8154/3
Pancreatoblastoma 8971/3
Solid-pseudopapillary carcinoma 8452/3
Others

Non-epithelial tumours

Secondary tumours

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[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, (/2 for in situ carcinomas) and /3 for malignant tumours.

TNM classification of tumours of the exocrine pancreas

TNM classification[1, 2]

Primary Tumour (T)
TX   Primary tumour cannot be assessed
T0   No evidence of primary tumour
Tis   Carcinoma in situ
T1   Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2   Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3   Tumour extends directly into any of the following: duodenum, bile duct, peripancreatic tissues[3]
T4   Tumour extends directly into any of the following: stomach, spleen, colon, adjacent large vessels[4]

Regional Lymph Nodes (N)
NX   Regional lymph nodes cannot be assessed
N0   No regional lymph node metastasis
N1   Regional lymph node metastasis
        N1a Metastasis in a single regional lymph node
        N1b Metastasis in multiple regional lymph nodes

Distant Metastasis (M)
MX   Distant metastasis cannot be assessed
M0   No distant metastasis
MI   Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

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[1] {1, 66}. This classification applies only to carcinomas of the exocrine pancreas.
[2] A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
[3] Peripancreatic tissues include the surrounding retroperitoneal fat (retroperitoneal soft tissue or retroperitoneal space), including mesentery (mesenteric fat), mesocolon, greater and lesser omentum, and peritoneum. Direct invasion to bile ducts and duodenum includes involvement of ampulla of Vater.
[4] Adjacent large vessels are the portal vein, coeliac artery, and superior mesenteric and common hepatic arteries and veins (not splenic vessels).

Ductal adenocarcinoma of the pancreas

G. Klöppel
R.H. Hruban
D.S. Longnecker

G. Adler
S.E. Kern
T.J. Partanen

Definition
A carcinoma occurring almost exclusively in adults that probably arises from and is phenotypically similar to, pancreatic duct epithelia, with mucin production and expression of a characteristic cytokeratin pattern.

ICD-O codes
Ductal adenocarcinoma	8500/3
Mucinous noncystic carcinoma	8480/3
Signet ring cell carcinoma	8490/3
Adenosquamous carcinoma	8560/3
Undifferentiated (anaplastic) carcinoma	8020/3
Undifferentiated carcinoma with osteoclast-like giant cells	8035/3
Mixed ductal-endocrine carcinoma	8154/3

Epidemiology
Incidence and geographical distribution
Ductal adenocarcinoma and its variants are the most common neoplasms in the pancreas, representing 85-90% of all pancreatic neoplasms {359, 941, 1781}. In developed countries, the annual age-adjusted incidence rates (world standard population) range from 3.1 (Herault, France) to 20.8 (central Louisiana, USA, blacks) per 100,000 males and from 2.0 (Herault, France) to 11.0 (San Francisco, CA, USA, blacks) per 100,000 females {1471}. Rates from most developing countries range from 1.0 to close to 10 per 100,000. Incidence and mortality rates are almost identical, since survival rates for pancreatic carcinoma are very low.

Time trends
After a steady increase between 1930 and 1980, the incidence rates have levelled off {593}. It is currently the fifth leading cause of cancer death in Western countries, second only to colon cancer among malignancies of the digestive tract.

Age and sex distribution
Approximately 80% of cases manifest clinically in patients 60-80 years; cases below the age of 40 years are rare {1781}. The incidence of pancreatic carcinoma is slightly higher among men than women, with a male/female ratio of 1.6 in developed nations and 1.1 in developing countries. Blacks have distinctly higher rates than whites {593}.

Aetiology
The development of pancreatic carcinoma is strongly related to cigarette smoking, which carries a 2-3 fold relative risk (RR) that increases with the number of pack-years of smoking {21}. Although the association between cigarette smoking and pancreatic carcinoma is not as strong as that between cigarette smoking and lung cancer (RR > 20), it has been estimated that a substantial reduction of the number of smokers in the European Union could save as many as 68,000 lives that would otherwise be lost to pancreatic cancer during the next 20 years {1293}.
Chronic pancreatitis, past gastric surgery, occupational exposure to chemicals such as chlorinated hydrocarbon solvents, radiation exposure, and diabetes mellitus have also been associated with the development of pancreatic carcinoma {593, 1100, 2080}. A markedly increased risk has been observed in hereditary pancreatitis {1101}.
A number of dietary factors have been putatively connected with pancreatic cancer, including a diet low in fibre and high in meat and fat {593}. Coffee consumption was once thought to be a risk factor for pancreatic carcinoma, but recent studies showed no significant associations {593}.

Localization
60-70% of pancreatic ductal adenocarcinomas are found in the head of the gland, the remainder occur in the body and/or tail. Pancreatic head tumours are mainly localized in the upper half, rarely in the uncinate process {1781}. Rarely, heterotopic pancreatic tissue gives rise to a carcinoma {596, 1898}.

Clinical features
Symptoms and signs
Clinical features include abdominal pain, unexplained weight loss, jaundice and pruritus. Diabetes mellitus is present in
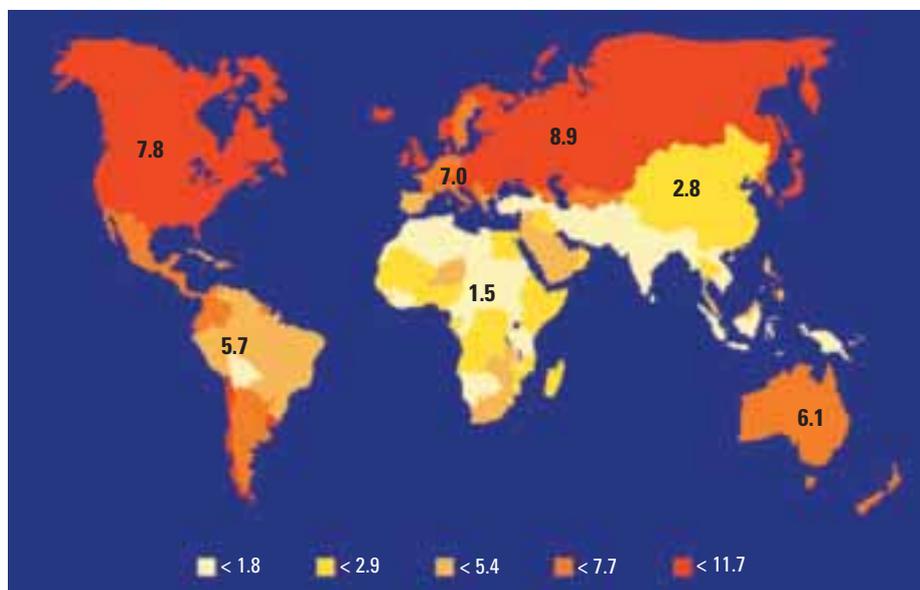

Fig. 10.01 Global distribution of pancreatic cancer (2000). Note the high incidence areas in North America, Europe, and the Russian Federation.

70% of patients, usually with a diabetes history of less than 2 years. Later symptoms are related to liver metastasis and/or invasion of adjacent organs (stomach, colon) or of the peritoneal cavity (ascites). Occasionally, patients present with acute pancreatitis {621}, migratory thrombophlebitis, hypoglycaemia, or hypercalcaemia {1261}.

Imaging and laboratory tests
Currently, the most important tests for establishing the diagnosis of pancreatic carcinoma are ultrasonography (US) and computerised tomography (CT) or magnetic resonance imaging (MRI), with or without guided percutaneous fine-needle biopsy, endoscopic retrograde cholangiography (ERCP), endoscopic ultrasonography (EUS) and tumour marker determination (CA 19-9, Du-Pan 2, CEA, Span-1). The sensitivity and specificity of any of these tests alone ranges between 55 and 95%. By applying combinations of these tests, accuracy rates of more than 95% have been achieved {2061}. On transabdominal US and on EUS, pancreatic ductal adenocarcinomas are characterised as echo-poor and inhomogeneous mass lesions in about 80% of cases. About 10% of the tumours appear echo-rich. With increasing size, tumours tend to become inhomogeneous, with cystic and echo-rich areas. Indirect signs of a pancreatic tumour (dilatation of pancreatic and/or common bile duct) are usually found proximal to tumours larger than 3 cm. On EUS lymph node metastases appear as enlarged echo-poor nodes. ERPC may demonstrate displacement, narrowing, or obstruction of the pancreatic duct. Angiography is helpful in preoperative management. CT shows pancreatic adenocarcinomas as hypodense masses in up to 92% of cases {528}. Diffuse tumour involvement of the pancreas is found in about 4%. In up to 4% the pancreatic and common bile duct are dilated without an identifiable mass.

KRAS mutations. Mutations in codon 12 of the *KRAS* gene have been detected in the stool, in pancreatic juice and/or blood samples from patients with proven ductal adenocarcinoma of the pancreas {224, 960, 1876}, but their diagnostic value in is still controversial.

Fine needle aspiration (FNA)
FNA can be performed percutaneously with guidance by imaging techniques or under direct visualisation at surgery. Aspirates from a typical, well to moderately differentiated ductal adenocarcinoma show a cellular aspirate {32, 940}. Pancreatic juice cytology obtained from ERCP is less sensitive than percutaneous or intraoperative FNA (76 versus 90 to 100%) {32, 1242, 1311}.

Macroscopy
Ductal adenocarcinomas are firm and poorly defined masses. The cut surfaces are yellow to white. Haemorrhage and necrosis are uncommon, but microcystic areas may occur. In surgical series, the size of most carcinomas of the head of the pancreas ranges from 1.5 to 5 cm, with a mean diameter between 2.5 and 3.5 cm. Carcinomas of the body/tail are
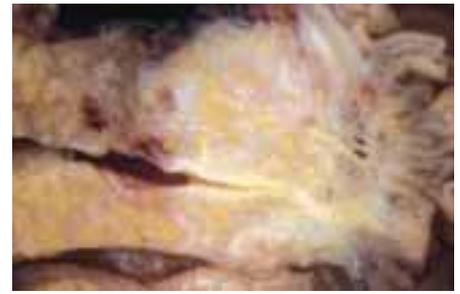

Fig. 10.02 Ductal adenocarcinoma. An ill-defined pale carcinoma in the head of the pancreas.

usually somewhat larger at diagnosis. Tumours with a diameter less than 2 cm are infrequent {697} and may be difficult to recognise by gross inspection. Carcinomas of the head of the pancreas usually invade the common bile duct and/or the main pancreatic duct and produce stenosis that results in proximal dilatation of both duct systems. Complete obstruction of the main pancreatic duct leads to extreme prestenotic duct dilatation with duct haustration and fibrous atrophy of the parenchyma (i.e. obstructive chronic pancreatitis). More advanced pancreatic head carcinomas involve the ampulla of Vater and/or the duodenal wall, causing ulcerations. Carcinomas in the pancreatic body or tail obstruct the main pancreatic duct, but typically do not involve the common bile duct.

Tumour spread and staging
It is an exception to find a resected carcinoma that is still limited to the pancreas {1414}. In head carcinomas, peripancre-
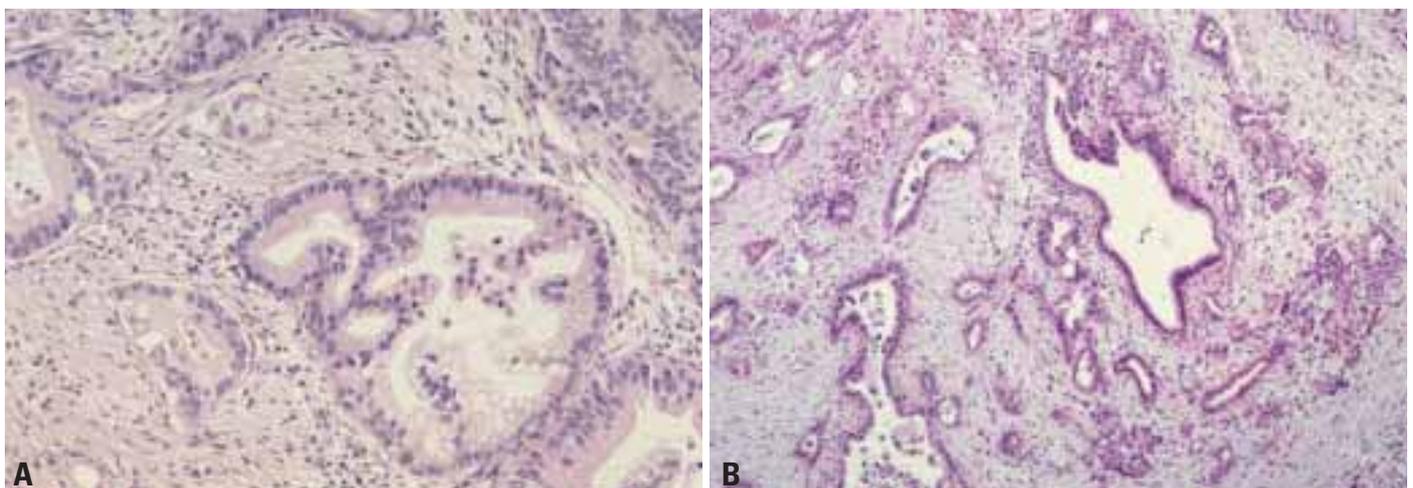

Fig. 10.03 Ductal adenocarcinoma. **A** Well differentiated tumour with desmoplasia and irregular gland formation. **B** Well differentiated neoplasm involving a normal duct (right part).

atic tumour invasion, often via perineural sheaths, primarily involves the retroperitoneal fatty tissue. Subsequently, retroperitoneal veins and nerves are invaded. Direct extension into neighbouring organs and/or the peritoneum is seen in advanced cases. In carcinomas of the body and tail, local extension is usually greater, because of delayed tumour detection, and includes invasion of the spleen, stomach, left adrenal gland, colon, and peritoneum {359, 941}.

Lymphatic spread of pancreatic head carcinomas involves, in descending order of frequency, the retroduodenal (posterior pancreaticoduodenal) and the superior pancreatic head groups, the inferior head and the superior body groups, and the anterior pancreaticoduodenal and the inferior body groups {359}. This lymph node compartment is usually resected together with the head of the pancreas, using a standard Whipple procedure {1955}. More distal nodal metastases may occur in the ligamentum hepatoduodenale, at the coeliac trunk, the root of the superior mesenteric artery, and in para-aortic nodes at the level of the renal arteries. These lymph node compartments are only removed if an extended Whipple procedure is performed. Carcinomas of the body and tail metastasise especially to the superior and inferior body and tail lymph node groups and the splenic hilus lymph nodes. They may also spread via lymphatic channels to pleura and lung.

Haematogenous metastasis occurs, in approximate order of frequency, to the liver, lungs, adrenals, kidneys, bones, brain, and skin {359, 941, 1231}.

Staging
The 1997 TNM classification {66} is presented on page 220. Another staging system has been published by the Japan Pancreas Society {832}.

Histopathology
Most ductal adenocarcinomas are well to moderately differentiated. They are characterized by well-developed glandular structures, which more or less imitate normal pancreatic ducts, embedded in desmoplastic stroma. The large amount of fibrous stroma accounts for their firm consistency. Variations in the degree of differentiation within the same neoplasm are frequent, but well differentiated carcinomas with foci of poor differentiation are uncommon.
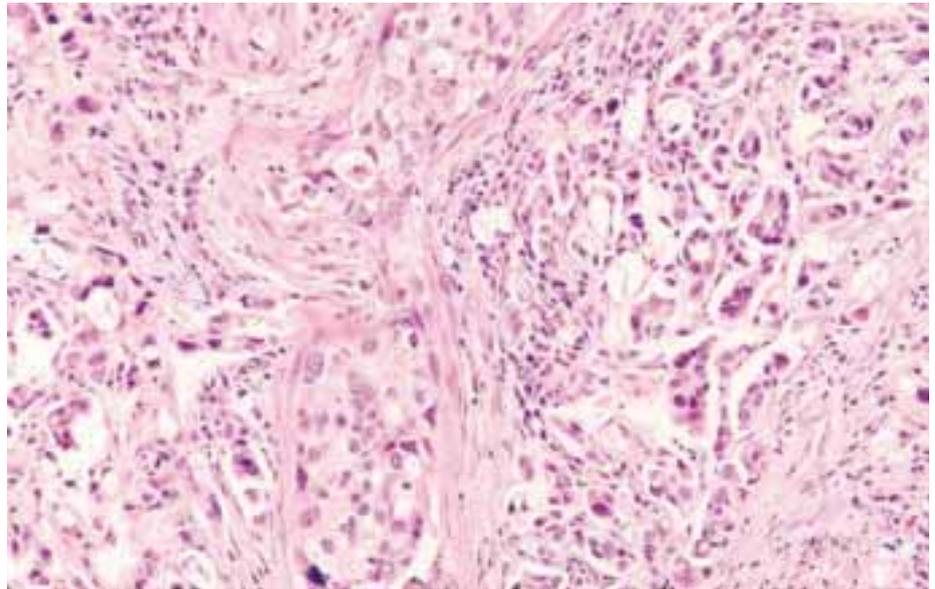

Fig. 10.04 Poorly differentiated ductal adenocarcinoma.

Well differentiated carcinomas consist of large duct-like structures, combined with medium-sized neoplastic glands. Tubular or cribriform patterns are typical; there may also be small irregular papillary projections without a distinct fibrovascular stalk, particularly in large duct-like structures. Mitotic activity is low. In between the neoplastic glands there may be a few non-neoplastic ducts as well as remnants of acini and individual islets.

Sometimes, the neoplastic duct-like glands are so well differentiated that they are difficult to distinguish from non-neoplastic ducts. However, the mucin-containing neoplastic glands may be ruptured or incompletely formed, a feature that is not seen in normal ducts. The mucin-producing neoplastic cells tend to be columnar, have eosinophilic and occasionally pale or even clear cytoplasm, and are usually larger than those of non-neoplastic ducts. They contain large round to ovoid nuclei which may vary in size, with sharp nuclear membranes and distinct nucleoli that are not found in normal duct cells. Moreover, although the neoplastic cell nuclei tend to be situated at the base of the cell, they always show some loss of polarity.

Moderately differentiated carcinomas predominantly show a mixture of medium-sized duct-like and tubular structures of variable shape, embedded in desmoplastic stroma. Incompletely formed glands are common. Compared with the well differentiated carcinoma, there is a greater variation in nuclear size, chromatin structure and prominence of nucleoli. Mitotic figures are rather frequent. The cytoplasm is usually slightly eosinophilic, but clear cells are occasionally abundant. Mucin production appears to be decreased and intraductal in situ components are somewhat less frequent than in well differentiated carcinomas. Foci of poor and irregular glandular differentiation are often found at the leading edge of the neoplasm, particularly where it invades the peripancreatic tissue.

Poorly differentiated ductal carcinomas are infrequent. They are composed of a mixture of densely packed, small irregular glands as well as solid tumour cell sheets and nests, which entirely replace the acinar tissue. While typical large, duct-like structures and intraductal tumour components are absent, there may be small squamoid, spindle cell, or anaplastic foci (comprising by definition less than 20% of the tumour tissue). There may be some scattered inflammatory cells. Foci of necrosis and haemorrhage occur. The neoplastic cells show marked pleomorphism, little or no mucin production, and brisk mitotic activity. At the advancing edge of the carcinoma, the gland and the peripancreatic tissue are infiltrated by small clusters of neoplastic cells.

Changes in non-neoplastic pancreas
All ductal adenocarcinomas are associated with more or less developed fibrosclerotic and inflammatory changes
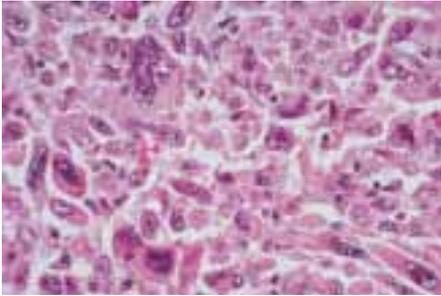
Fig. 10.05 Undifferentiated carcinoma exhibiting extreme pleomorphism with giant cells.

in the adjoining non-neoplastic pancreas, due to carcinomatous duct obstructions (obstructive chronic pancreatitis). In cases of complete occlusion of the main duct, there is marked upstream dilatation of the duct and almost complete fibrotic atrophy of the parenchyma. In contrast to chronic pancreatitis due to alcoholism, intraductal calcifications are generally absent.

Poorly differentiated carcinomas usually destroy the islets. In the well and moderately differentiated neoplasms, however, islets may be found entrapped in neoplastic tissue. In addition, scattered endocrine cells occur attached to or intermingled between neoplastic columnar cells. Only in exceptional cases do the endocrine cells constitute a second cell component of the ductal carcinoma (see mixed ductal-endocrine carcinoma).

Histochemistry and immunohistochemistry

Although no histochemical or immunohistochemical marker is able to unequivocally distinguish pancreatic from extra-pancreatic adenocarcinoma, some markers are useful in separating ductal adenocarcinoma of the pancreas from non duct-type tumours or other gastrointestinal carcinomas.

Mucin. Ductal adenocarcinomas mainly stain for sulphated acid mucins but focally also for neutral mucins {1714}. Immunohistochemically, most ductal adenocarcinomas express MUC1, MUC3 and MUC5/6 (but not MUC2) {1918, 2179}, CA 19-9, Du-Pan 2, Span-1, CA 125 and TAG72 {1714, 1884}. The expression patterns of CA 19-9, Du-Pan 2, Span-1, CA 125 and TAG 72 are largely comparable in their immunoreactivity and specificity. These markers also label the epithelium of normal pancreatic ducts to some extent, particularly in chronic pancreatitis, and the tumour cells of some serous cystadenomas and acinar cell carcinomas {1282}.

Carcinoembryonic antigen (CEA).
Monospecific antibodies against CEA that do not recognise other members of the CEA family are capable of discriminating between non-neoplastic duct changes, such as ductal papillary hyperplasia, and a variety of neoplasms {119}. CEA is negative in serous cystadenoma.

Cytokeratins, vimentin, endocrine markers and enzymes. Normal pancreatic and biliary ductal cells and pancreatic centroacinar cells express the cytokeratins (CK) 7, 8, 18, 19 and occasionally also 4 {1696}. Acinar cells contain only CK 8 and 18, and islet cells 8, 18 and occasionally also 19. Ductal adenocarcinomas express the same set of cytokeratins as the normal duct epithelium, i.e. CK 7, 8, 18 and 19. More than 50% of the carcinomas also express CK 4 {1696}, but are usually negative for CK 20 {1259}. As the usual keratin patterns of non-duct-type pancreatic neoplasms (i.e. acinar carcinomas and endocrine tumours, CK 8, 18 and 19) and gut carcinomas (i.e. CK 8, 18, 19 and 20) differ from that of ductal carcinoma, it is possible to distinguish these tumours on the basis of their CK profile.

Ductal adenocarcinomas are usually negative for vimentin {1696}. With rare exceptions (see mixed ductal-endocrine carcinoma), they also fail to label with endocrine markers such as synaptophysin and the chromogranins, but may contain, particularly if well differentiated, some scattered (possibly non-neoplastic) endocrine cells in close association with the neoplastic cells {167}. They are generally negative for pancreatic enzymes such as trypsin, chymotrypsin and lipase {739, 1282}.

Growth factors and adhesion molecules.
Pancreatic carcinomas overexpress epidermal growth factor and its receptor, c-erbB-2, transforming growth factor alpha {380, 1676, 2163}, metallothionein {1409}, CD44v6 {259, 1880} and membranous E-cadherin {1519}.

Ultrastructure

Ductal adenocarcinoma cells are characterized by mucin granules in the apical cytoplasm, irregular microvilli on the luminal surface, and a more or less polarised arrangement of the differently sized nuclei {359, 901, 1714}. The content of the mucin granules (0.4-2.0 μm) varies from solid-electron dense to filamentous and punctate; often there is a dense
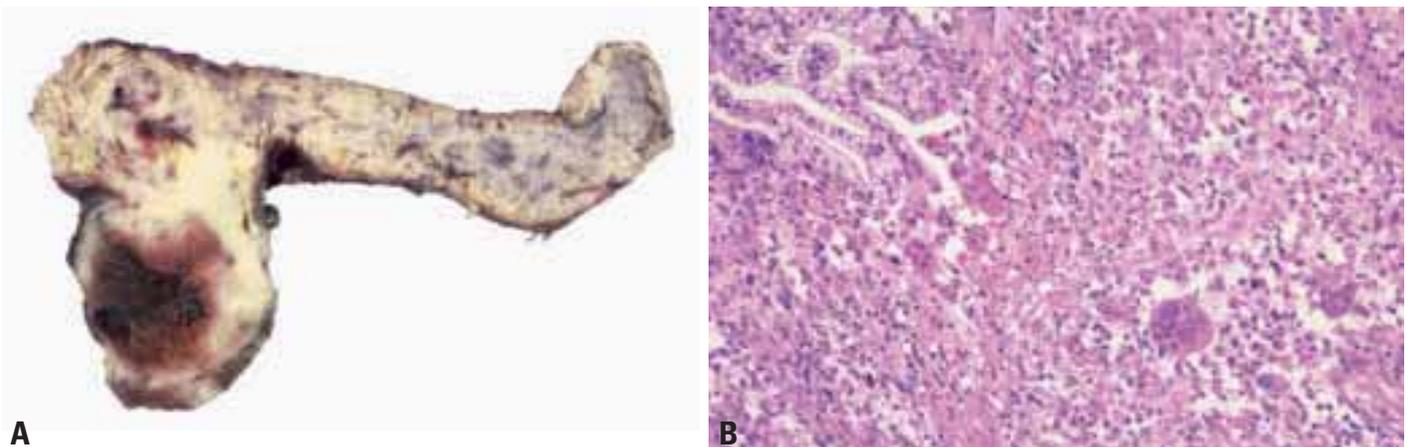

Fig. 10.06 Undifferentiated carcinoma with osteoclast-like giant cells. **A** The carcinoma is in the uncinate process and shows haemorrhagic necrosis. **B** There is marked cellular pleomorphism with scattered osteoclast-like giant cells and a well-differentiated ductal carcinoma component (left upper corner).

eccentric core. Some cells have features of gastric foveolar cells, showing granules with a punctate-cerebroid structure {1714}. Loss of tumour differentiation is characterized by loss of cell polarity, disappearance of a basal lamina, appearance of irregular luminal spaces, and loss of mucin granules {901}.

Histological variants

Adenosquamous carcinoma and undifferentiated (anaplastic) carcinoma (including osteoclast-like giant cell tumours), mucinous noncystic adenocarcinoma and signet-ring cell carcinoma are considered variants of ductal adenocarcinoma because most of these carcinomas, even if poorly differentiated, contain some foci showing neoplastic glands with ductal differentiation {288, 359, 941, 947, 1781}.

Adenosquamous carcinoma

This rare neoplasm, relative frequency 3-4% {941, 359, 813, 1415}, is characterized by the presence of variable proportions of mucin-producing glandular elements and squamous components. The squamous component should account for at least 30% of the tumour tissue. In addition, there may be anaplastic and spindle cell foci. Pure squamous carcinomas are very rare.

Undifferentiated (anaplastic) carcinoma

Also called giant cell carcinoma, pleomorphic large cell carcinoma, and sarcomatoid carcinoma, these tumours have a relative frequency of 2-7%. They are composed of large eosinophilic pleomorphic cells and/or ovoid to spindle-shaped cells that grow in poorly cohesive formations supported by scanty fibrous stroma. Commonly the carcinomas contain small foci of atypical glandular elements {359, 941, 1786, 1962}. Carcinomas consisting predominantly of spindle cells may also contain areas of squamoid differentiation. High mitotic activity as well as perineural, lymphatic, and blood vessel invasion is found in almost all cases. Immunohistochemically, some or most tumour cells express cytokeratins and usually also vimentin {740}. Electron microscopy reveals microvilli and mucin granules in some cases {359}. Undifferentiated carcinomas with a neoplastic mesenchymal component (carcinosarcoma) have so far not been described.
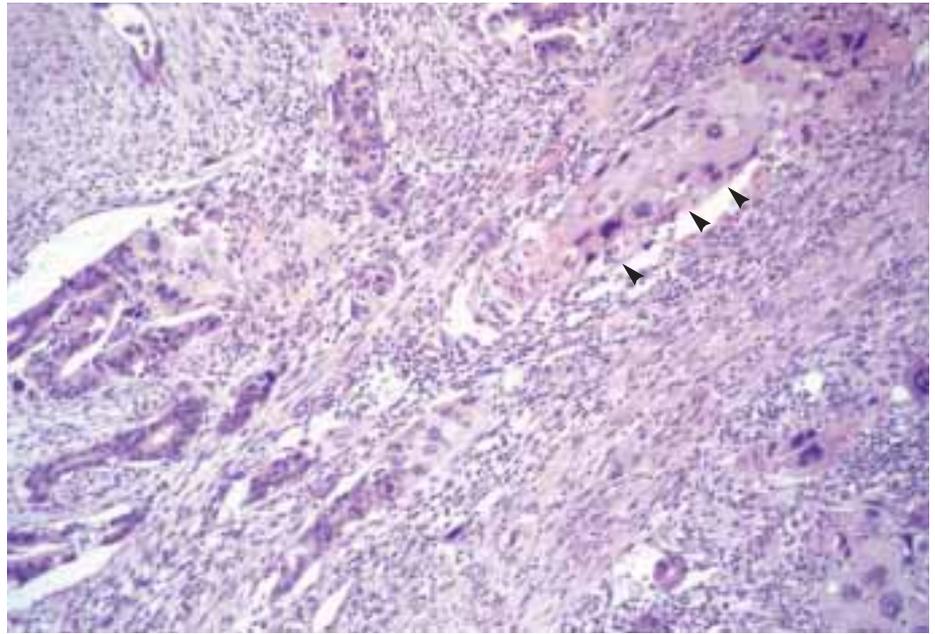

Fig. 10.07 Adenosquamous carcinoma. Note the glandular component on the left and the squamous differentiation on the right (arrowheads).

Undifferentiated carcinoma with osteoclast-like giant cells

This rare neoplasm is composed of pleomorphic to spindle-shaped cells and scattered non-neoplastic osteoclast-like giant cells with usually more than 20 uniformly small nuclei. In many cases there is an associated in situ or invasive adenocarcinoma {359}. The osteoclast-like giant cells are often concentrated near areas of haemorrhage and may contain haemosiderin and, occasionally, phagocytosed mononuclear cells. Osteoid formation may also be found.

Immunohistochemically, at least some of the neoplastic cells express cytokeratin, vimentin and p53 {740, 2095}. The osteoclast-like giant cells, in contrast, are negative for cytokeratin and p53, but positive for vimentin, leukocyte common antigen (CD56) and macrophage markers such as KP1 {740, 1258, 2095}.

The mean age of patients with osteoclast-like giant cell tumours is 60 years but there is a wide age range from 32 to 82 years {1370}. Some tumours are found in association with mucinous cystic neoplasms {1258, 2095, 2198}. In the early reports on this tumour it was suggested that they may have a more favourable prognosis than the usual ductal adenocarcinoma {359}. More recently a mean survival of 12 months has been reported.

Mucinous noncystic carcinoma

This uncommon carcinoma (relative frequency: 1-3%) {941} has also been called 'colloid' or gelatinous carcinoma. Mucin accounts for > 50% of the tumour. The large pools of mucin are partially lined by well-differentiated cuboidal cells and contain clumps or strands of tumour cells. Some floating cells may be of the signet-ring cell type.

Sex and age distribution are similar to those of ductal adenocarcinoma. The tumours may be very large and are usually well demarcated. The development of pseudomyxoma peritonei has been described {285}. It is of interest that the invasive component of some of the intraductal papillary-mucinous tumours resembles mucinous noncystic carcinoma. Mucinous noncystic carcinoma should not be confused with mucinous cystic tumour because of the much better prognosis of the latter (see chapter on mucinous cystic neoplasms).

Signet-ring cell carcinoma

The extremely rare signet-ring cell carcinoma is an adenocarcinoma composed almost exclusively of cells filled with mucin {1781, 1951}. The prognosis is extremely poor; a gastric primary should always be excluded before making this diagnosis.
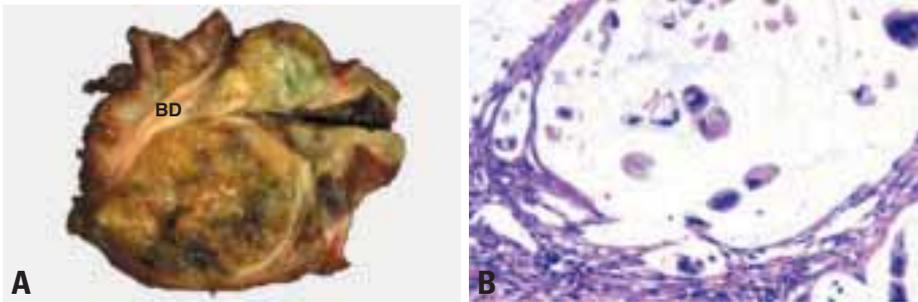
Fig. 10.08 Mucinous non-cystic adenocarcinoma. **A** A mucinous carcinoma in the head of the pancreas obstructs the main pancreatic duct and impinges on the bile duct (BD). **B** The neoplastic cells float in pools of mucin.

Mixed ductal-endocrine carcinoma

Mixed ductal-endocrine carcinoma {947} has also been referred to as mixed carcinoid-adenocarcinoma, mucinous carcinoid tumour {359}, or simply mixed exocrine-endocrine tumour. This neoplasm is characterized by an intimate admixture of ductal and endocrine cells in the primary tumour as well as in its metastases. By definition, the endocrine cells should comprise at least one third to one half of the tumour tissue. The ductal differentiation is defined by mucin production and the presence of a duct type marker such as CEA. The endocrine cells are characterized by the presence of neuroendocrine markers and/or hormonal products; immunoexpression of all four islet hormones, amylin (IAPP), serotonin, pancreatic polypeptide (PP), and occasionally gastrin have been described {167}.

Mixed ductal-endocrine carcinomas, as defined above, seem to be exceptionally rare in the pancreas {1714, 1781}. Biologically, the mixed carcinoma behaves like the usual ductal adenocarcinoma.

Acinar cell carcinomas {739, 1694, 1985} and pancreatoblastomas {741} with some endocrine and ductal elements, and endocrine tumours with ductal components {1372, 1941} are not discussed here, because their behaviour is dictated by their acinar and endocrine elements. Mixed ductal-endocrine carcinomas should also be distinguished from ductal adenocarcinomas with scattered endocrine cells, since scattered endocrine cells are found in 40-80% of ductal adenocarcinomas {167, 289} and seem to be particularly frequent in the well differentiated tumours, where they are ei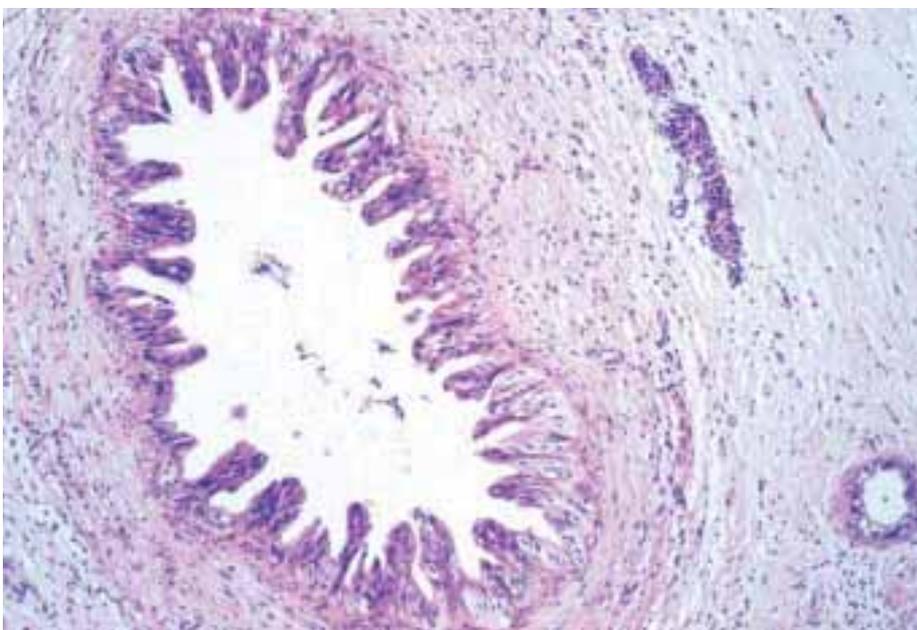ther lined up along the base of the neoplastic ductal structures or lie between the neoplastic columnar cells. 'Collision tumours' composed of two topographically separate components are not included in the mixed ductal-endocrine category.

Other rare carcinomas

Other very rare carcinomas of probable ductal phenotype include *clear cell carcinoma* {359, 882, 1908, 1121} and *ciliated cell carcinoma* (see chapter on miscellaneous carcinomas) {1276, 1786}. Carcinomas with 'medullary' histology have recently been described {590}; these lesions are associated with wild-type *KRAS* status and microsatellite instability.

The so-called *microglandular carcinomas* {359} or microadenocarcinomas are distinguished by a microglandular to solid-cribriform pattern. They most likely do not form an entity of their own but belong to either the ductal, endocrine, or acinar carcinomas.

Grading

A few formal grading systems have been described. Miller et al. graded pancreatic tumours using the system of Broder, which distinguishes four grades of cellular atypia. High-grade carcinomas (Broder grades 3 and 4) were larger and the frequency of venous thrombosis and metastasis higher than in low-grade tumours.

A more recent grading system is based on combined assessment of histological and cytological features and mitotic activity {944, 1119}. If there is intratumour heterogeneity, i.e. a variation in the degree of differentiation and mitotic activity, the higher grade and mitotic activity is assigned. This rule also applies if only a minor component (less than half of the tumour) was of lower grade. Using this system, there is a correlation between grade and survival and grade is an independent prognostic variable {944, 1119}.

Precursor lesions
Pancreatic neoplasms

Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms may progress to invasive cancer. In the case of mucinous cystic neoplasms, the invasive component usually resembles ductal adenocarcinoma {1781}. In the case of intraductal papillary-mucinous

Fig. 10.09 Pancreatic duct showing high-grade intraepithelial neoplasia (PanIN III).

Table 10.01
List of recommended terms with synonyms for focal hyperplastic and metaplastic duct lesions in the human exocrine pancreas.

Recommended WHO term	Previous WHO classification {947}	Other synonyms
Squamous metaplasia Incomplete squamous metaplasia	Squamous metaplasia Incomplete squamous metaplasia	Epidermoid metaplasia, multilayered metaplasia focal epithelial hyperplasia, focal atypical epithelial hyperplasia, multilayered metaplasia
PanIN-IA	Mucinous cell hypertrophy	Mucinous cell hyperplasia, mucinous ductal hyperplasia, mucoid transformation, simple hyperplasia, flat ductal hyperplasia, mucous hypertrophy, hyperplasia with pyloric gland metaplasia, ductal hyperplasia grade 1, non-papillary epithelial hypertrophy, nonpapillary ductal hyperplasia
PanIN-IB	Ductal papillary hyperplasia Adenomatoid ductal hyperplasia	Papillary ductal hyperplasia, ductal hyperplasia grade 2 Adenomatous hyperplasia, ductular cell hyperplasia
PanIN-II	Any PanIN-I lesion with moderate dysplasia as defined in the text	
PanIN-III	Severe ductal dysplasia	Ductal hyperplasia grade 3, atypical hyperplasia Carcinoma in situ

carcinoma, the invasive component either corresponds to a usual ductal adenocarcinoma or to mucinous noncystic carcinoma {1781}.

Severe ductal dysplasia – carcinoma in situ

This change of the ductal epithelium is characterized by irregular epithelial budding and bridging, small papillae lacking fibrovascular stalks, and severe nuclear abnormalities such as loss of polarity, pleomorphism, coarse chromatin, dense nucleoli and mitotic figures. The lesion is often surrounded by one or two layers of fibrosclerotic tissue. Here, no attempt is made to distinguish between severe dysplasia and carcinoma in situ, since it is very difficult, if not impossible, to draw a clear distinction between these two changes, which both represent high-grade intraepithelial neoplasia. The lesion corresponds to PanIN III in the proposed terminology of pancreatic intraepithelial neoplasia (Table 10.01). High-grade intraepithelial neoplasia is commonly found in association with an invasive ductal adenocarcinoma {358, 555, 943}, and may represent either a precursor to invasive carcinoma or continuous intraductal extensions of the invasive tumour. Similar duct changes have also been described remote from the macroscopic tumour {1781} or years before the development of an invasive ductal carcinoma {185, 191}.

Duct changes

With the exception of high-grade intraepithelial neoplasia, the precursors to infiltrating ductal adenocarcinomas are still ill-defined. Putative precursor lesions (Table 10.01) include mucinous cell hypertrophy, ductal papillary hyperplasia with mucinous cell hypertrophy (papillary duct lesion without atypia), adenomatoid (adenomatous) ductal hyperplasia, and squamous metaplasia {1781, 947}. All these lesions may show mild nuclear atypia.

The evidence that some of these duct lesions (i.e. mucinous cell hypertrophy and papillary hyperplasia) may be precursors to invasive carcinoma comes from three areas: morphological studies, clinical reports, and genetic analyses. At the light microscopic level, ductal papillary hyperplasia was found adjacent to invasive carcinomas more frequently than it was in pancreases without cancer {290, 358, 943, 965}. It was also noted

Table 10.02
Histopathological grading of pancreatic ductal adenocarcinoma {1119}.

Tumour grade	Glandular differentiation	Mucin production	Mitoses (per 10 HPF)	Nuclear features
Grade 1	Well differentiated	Intensive	≤ 5	Little polymorphism, polar arrangement
Grade 2	Moderately differentiated duct like structures and tubular glands	Irregular	6-10	Moderate polymorphism
Grade 3	Poorly differentiated glands, mucoepidermoid and pleomorphic structures	Abortive	> 10	Marked polymorphism and increased size

Table 10.03
Genetic alterations in pancreatic ductal carcinoma.

Gene	Chromosome	Mechanism of alteration	% of cancers
Oncogenes			
KRAS	12p	Point mutation	> 90
MYB, AKT2, AIB1	6q, 19q, 20q	Amplification[1]	10-20
HER/2-neu	17q	Overexpression	70
Tumor suppressor genes			
p16	9p	Homozygous deletion	40
		Loss of heterozygosity and intragenic mutation	40
		Promotor hypermethylation	15
TP53	17p	Loss of heterozygosity and intragenic mutation	50-70
DPC4	18q	Homozygous deletion	35
		Loss of heterozygosity and intragenic mutation	20
BRCA2	13q	Inherited intragenic mutation and loss of heterozygosity	7
MKK4	17p	Homozygous deletion, loss of heterozygosity and intragenic mutation	4
LKB1/STK11	19p	Loss of heterozygosity and intragenic mutation, homozygous deletion	5
ALK5 and TGF βR2	9q, 3p	Homozygous deletion	4
DNA Mismatch Repair			
MSH2, MLH1, others	2p, 3p, others	Unknown	< 5

[1] In cases of amplification, it is generally not possible to unambiguously identify the key oncogene due to the participation of multiple genes in an amplicon.

that ductal papillary hyperplasia is similar to severe dysplasia-carcinoma in situ lesions seen in the vicinity of invasive ductal carcinomas {358}. Clinically, Brat et al. {185} and Brockie et al. {191} have reported a total of five patients who developed infiltrating ductal adenocarcinomas years after the identification of atypical duct lesions in their pancreas. Finally, molecular genetic analyses of duct lesions have demonstrated that they contain some of the same genetic alterations seen in infiltrating ductal carcinomas. For example, activating point muta-

tions in codon 12 of the KRAS genealterations of the p16 and TP53 tumour suppressor genes and loss of BRCA2 and DPC4 have all been reported in duct lesions {1286, 1875, 2166, 2105, 589}. Duct lesions and infiltrating cancers from the same pancreas may harbour identical mutations {1120, 1286}.

Only a minority of duct lesions may progress to invasive cancer, as demonstrated by recent data from a study on normal pancreases, which showed that all types of duct lesions and even normal epithelium may harbour KRAS mutations,

and that the lesions are evenly distributed in the pancreas and do not concentrate in the head region where the carcinoma is most frequent {647}. It has recently been suggested that the term 'Pancreatic Intraepithelial Neoplasia (PanIN)' be adopted for these duct lesions (see http://pathology.jhu.edu/ pancreas.panin) {937}. Table 10.01 indicates the general relationship between the previous WHO terminology and this new proposed PanIN terminology.

Genetic susceptibility
Between 3% and 10% of cases of pancreatic cancer are familial {754, 1125, 1126, 499}. Some arise in patients with recognized genetic syndromes, as discussed below, but in most instances the genetic basis for the familial aggregation of pancreatic carcinomas has not been identified. A confounding factor is the possibility of shared environmental factors, such as tobacco use. Nevertheless, some studies show familial aggregations suggestive of a genetic aetiology {485, 577, 499, 1207} Studies of extended families have shown a pattern suggestive of an autosomal dominant mode of inheritance.

Hereditary pancreatitis
This disease is caused by germline mutations in the cationic trypsinogen gene on 7q35 {2098}. This syndrome is characterized by the early onset of severe recurrent bouts of acute pancreatitis, and affected individuals have as high as a 40% lifetime risk of developing pancreatic carcinoma {1101}.

FAMMM syndrome
Familial atypical multiple mole melanoma (FAMMM) is associated with germline mutations in the p16 tumour suppressor gene on 9p. Affected individuals have an increased risk of developing both melanoma and pancreatic carcinoma {601, 1127, 1285, 2097}. The lifetime risk for developing pancreatic carcinoma is about 10%.

BRCA2
The discovery of the second breast cancer gene (BRCA2) on 13q was made possible in large part by the discovery of a homozygous deletion in a pancreatic carcinoma {1697}. Pancreatic carcinomas have been reported in some kindred with BRCA2 mutations and familial breast

cancer {1514, 1934, 591, 479} identified germline mutations in *BRCA2* in about 7% of patients with pancreatic carcinoma. Remarkably, most pancreatic ductal carcinoma patients with such mutations do not have a strong family history of breast or pancreatic carcinoma. A number of them are, however, of Ashkenazi Jewish ancestry {591, 1442}.

Peutz-Jeghers syndrome
Patients with the Peutz-Jeghers syndrome have an increased risk of developing pancreatic carcinoma, and recently the bi-allelic inactivation of the *LKB1/STK11* gene has been demonstrated in a pancreatic carcinoma which arose in a patient with the Peutz-Jeghers syndrome {579, 1851}.

Hereditary nonpolyposis colon cancer (HNPCC)
This syndrome is associated with an increased risk of developing carcinoma of the colon, endometrium, stomach, and ovary {2071}. It can be caused by germline mutations in any one of a number of DNA mismatch repair genes, including *MSH2* on 2p and *MLH1* on 3p {1029, 1078, 2071}. Lynch et al. have reported pancreatic carcinomas in some kindred with HNPCC, and Goggins et al. have recently reported microsatellite instability, a genetic change associated with defects in DNA mismatch repair genes, in about 4% of pancreatic carcinomas {590, 1130, 1487}.

Genetics
Genetic alterations are listed in Table 10.03. At the chromosome level, they include losses and gains of genetic material as well as generalised chromosome instability {608, 625, 626}. The most frequent gains identified cytogenetically include those of chromosomes 12 and 7; the most common recurrent structural abnormalities involve chromosome arms 1p, 6q, 7q, 17p, 1q, 3p, 11p, and 19q, and the most frequent losses involve chromosomes 18, 13, 12, 17, and 6 {626, 625}. Similar patterns of loss have been identified at the molecular level {184, 1716}, using highly polymorphic microsatellite markers. These include very high rates of loss at chromosomes 18q (90%), 17p (90%), 1p (60%), and 9p (85%) and moderately frequent losses at 3p, 6p, 8p, 10q, 12q, 13q, 18p, 21q, and 22q (25-50% of cases).

Recurrent losses of genetic material at specific loci in a carcinoma suggest that these loci harbour tumour suppressor genes which are inactivated in the carcinoma, and, indeed, the *p16* gene on 9p, the T*p53* gene on 17p, and the *DPC4* gene on 18q are all frequently inactivated in pancreatic carcinoma {1716}. The *p16* tumour suppressor gene is inactivated in 40% of pancreatic carcinomas by homozygous deletion, in 40% by loss of one allele coupled with an intragenic mutation in the second, and by hypermethylation of the *p16* promoter in an additional 15% {223, 1698, 2104}. The *Tp53* is inactivated in 75% of pancreatic carcinomas by loss of one allele coupled with an intragenic mutation in the second allele {1570, 1624}. The *DPC4* tumour suppressor gene is inactivated in 55% of pancreatic carcinomas {651}, in 35% of the carcinomas by homozygous deletion and in 20% by loss of one allele coupled with an intragenic mutation in the second allele. The *BRCA2* tumour suppressor gene on 13q is inactivated in about 7% of pancreatic carcinomas {591, 1442, 1697}. Remarkably, in almost all of these cases one allele of *BRCA2* is inactivated by a germline (inherited) mutation in the gene {591}. Other tumour suppressor genes which have been shown to be occasionally inactivated in pancreatic carcinoma include the genes *MKK4*, *RB1*, *LKB1/STK11*, and the transforming growth factor β receptors I and II {592, 761, 1850, 1851}.
Several oncogenes have been shown to be activated in ductal adenocarcinomas of the pancreas. These include the *KRAS* gene on chromosome 12p, which is activated by point mutations in over 90% of the carcinomas, overexpression of the *HER2-neu* gene on 17q in 70% of the carcinomas, and amplification of the *AKT2* gene on chromosome 19q in 10–20% of the carcinomas, the nuclear receptor coactivator gene *AIB1* on chromosome 20q, and the *MYB* gene on chromosome 6q {47, 292, 380, 576, 761, 1242, 2039}. Compared to normal pancreas, *Smad2* mRNA levels are increased in pancreatic carcinoma, which might lead to the over-expression of components of the TGF-beta signalling pathway that is observed in these lesions {931}.
DNA mismatch repair genes, such as *MLH1* and *MSH2*, can also play a role. Microsatellite instability resulting from the inactivation of both alleles of a DNA mis-

match repair gene has been identified in 4% of pancreatic carcinomas {590}. They had wild-type *KRAS* genes and a characteristic 'medullary' histological appearance, forming a distinct subset of pancreatic adenocarcinomas (see section on other rare carcinomas).

Prognosis and predictive factors
Ductal adenocarcinoma is fatal in most cases {639}. The mean survival time of the untreated patient is 3 months, while the mean survival after radical resection varies from 10-20 months {560, 692, 814, 1955}. The overall 5-year survival rate of patients treated by resection is 3-4% {639}, although in selected and stage-stratified series survival figures approaching 25 or even 46% have been reported {560, 1955, 1966, 1976}. Unresectable carcinomas are treated with palliative bypass operations. Response to chemotherapy with 5-fluorouracil or gemcitabine may be seen in up to approximately 10% of patients. Radiotherapy alone is largely ineffective {2061}.

Site, size, and stage
The survival time is longer in patients with carcinomas confined to the pancreas and less than 3 cm in diameter (17-29 months) than in patients with tumours of greater size or retroperitoneal invasion (6-15 months) {2172}. Carcinomas of the body or the tail of the pancreas tend to present at a more advanced stage than those of the head {560, 1955, 1966, 1976}. Some have found that lymph node metastases significantly worsen prognosis, while others have not {710, 1955, 2172}.

Residual tumour tissue
Patients with no residual tumour following resection (R0) have the most favourable prognosis of all patients undergoing surgical resection {2108}. This implies that local spread to peripancreatic tissues, i.e. the retroperitoneal resection margin, is of utmost importance in terms of prognosis {1122}.

Recurrence
Local recurrence seems to be the major factor determining survival after resection of pancreatic ductal carcinoma. The most common sites of recurrences are the tissues surrounding the large mesenteric vessels {646}. Clear retroperitoneal resection margin or margins are therefore

Table 10.04
Genetic syndromes with an increased risk of pancreatic cancer.

Syndrome (MIM No)[1]	Mode of inheritance	Gene (chromosomal location)	Lifetime risk of pancreatic cancer
Early onset familial pancreatic adenocarcinoma associated with diabetes (Seattle family) {479}	Autosomal dominant	Unknown	About 30%; 100-fold increased risk of pancreatic cancer; high risk of diabetes and pancreatitis
Hereditary pancreatitis (167800)	Autosomal dominant	Cationic trypsinogen (7q35)	30%; 50-fold increased risk of pancreatic cancer {1101, 499}
FAMMM: familial atypical multiple mole melanoma (155600)	Autosomal dominant	p16/CMM2 (9p21)	10% {601, 1127, 2097}
Familial breast cancer (600185)	Autosomal dominant	BRCA2 (13q12-q13)	5-10%; 6174delT in Ashkenazi Jews {1442}, 999del5 in Iceland {1934}
Ataxia-telangiectasia (208900) (heterozygote state)	Autosomal recessive	ATM, ATB, others (11q22-q23)	Unknown; somewhat increased
Peutz-Jeghers (175200)	Autosomal dominant	STK11/LKB1 (19p)	Unknown; somewhat increased {579}
HNPCC: hereditary non-polyposis colorectal cancer (120435)	Autosomal dominant	MSH2 (2p), MLH1 (3p), others	Unknown; somewhat increased {1130, 2071}
Familial pancreatic cancer	Possibly autosomal dominant	Unknown	Unknown; 5-10fold increased risk if a first-degree relative has pancreatic cancer {499, 1128, 755}

_____
[1] Mendelian Inheritance in Man: www.ncbi.nlm.nih.gov/omim

required, if a 'curative' resection (R0) is to be achieved {1122}. Second in frequency are recurrences arising from lymph node or liver metastases that were too small to be detected during surgery. The peritoneum and the bone marrow are rare sites of recurrence, although malignant cells are detected cytologically in one quarter of the patients during laparoscopy and one half of the patients when bone marrow trepanation is performed during a Whipple procedure {870}.

Grading
Based on the criteria of the grading system summarised in Table 10.02, it was found that median postoperative survival correlated significantly with tumour grade {944}, mitotic index, and severity of cellular atypia. As grading systems are, however, to a great extent subjective, reproducibility may be low {1119}. Other studies found no relationship between grade and survival {2079}. Nuclear parameters such as median nuclear size, nuclear area, and nuclear perimeter have been shown to be of prognostic value for ductal adenocarcinoma {477, 944}.

DNA content and proliferation
Nondiploid and/or aneuploid DNA content is associated with advanced tumour stage and shorter survival {46, 105, 476, 2079}. Tumours with low argyrophylic nucleolar organizer region (AgNOR) counts per cell (< 3.25) have been reported to have a better prognosis than tumours with a high AgNOR count {1413}. High Ki-67 labeling index is an indicator of poor prognosis, but does not seem to be an independent prognostic parameter {1111, 1119}
The immunohistochemical expression of a number of growth factors has shown weak association with survival {21, 535}.

Serous cystic neoplasms of the pancreas

C. Capella
E. Solcia
G. Klöppel
R.H. Hruban

Serous cystic pancreatic tumours are cystic epithelial neoplasms composed of glycogen-rich, ductular-type epithelial cells that produce a watery fluid similar to serum. Most are benign (serous cystadenomas), either serous microcystic adenoma or serous oligocystic adenoma. Only very rare cases exhibit signs of malignancy (serous cystadenocarcinoma).

A solid variant of serous cystadenoma (solid serous cystadenoma) has been described {1499} but remains to be established as a separate disease entity.

ICD-O codes

Serous cystadenoma	8441/0
Serous cystdenocarcinoma	8441/3
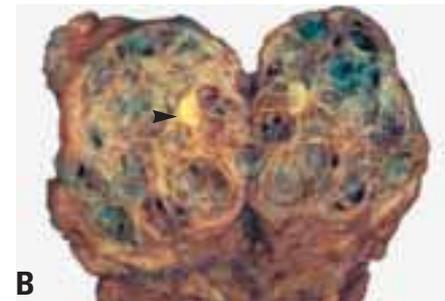
Fig. 10.10 Microcystic serous cystadenoma. **A** CT scan showing a well demarcated, spongy lesion in the head of the pancreas. **B** Cut surface showing a typical honeycomb appearance and a (para-)central stellate scar (arrowhead).

Serous microcystic adenoma

Definition
A benign neoplasm composed of numerous small cysts lined by uniform glycogen-rich cuboidal epithelial cells, disposed around a central stellate scar.

Epidemiology
This is a rare neoplasm, accounting for 1 to 2% of all exocrine pancreatic tumours {1280}. The mean age at presentation is 66 years (range, 34-91 years), with a predominance in women (70%) {1781}. It has been reported in patients with different ethnicity {327, 2151}.

Aetiology
The aetiology and pathogenesis of the neoplasm are unknown. The striking predilection for women suggests that sex hormones or genetic factors may play a role. An association with Von Hippel-Lindau disease has been reported {327, 2026} and confirmed by recent genetic molecular investigations {2026}.

Localization
The neoplasms occur most frequently (50-75%) in the body or tail; the remaining tumours involve the head of the pancreas {49, 327}.

Clinical features
About one third of the neoplasms present as an incidental finding at routine physical examination or at autopsy {445}. Approximately two thirds of patients exhibit symptoms related to local mass effects, including abdominal pain, palpable mass, nausea and vomiting, and weight loss {1544}. Jaundice due to obstruction of the common bile duct is unusual, even in neoplasms originating from the head of the pancreas.

Pancreatic serum tumour markers are generally normal. Calcifications are found in a few patients on plain abdominal roentgenograms. Ultrasonography (US) and computed tomography (CT) reveal a well circumscribed, multilocular cyst, occasionally with an evident central stellate scar and a sunburst type calcification {532, 817, 1544}. On angiography, the tumours are usually hypervascular.

Macroscopy
Serous microcystic adenomas are single, well-circumscribed, slightly bosselated, round lesions, with diameters ranging from 1-25 cm in greatest dimension (average, 6-10 cm). On section, the neoplasms are sponge-like and are made up of numerous tiny cysts filled with serous (clear watery) fluid. The cysts range from 0.01-0.5 cm, with a few larger cysts of up to 2 cm in diameter. Often, the cysts are arranged around a more or less centrally located, dense fibronodular core from which thin fibrous septa radiate to the periphery (central stellate scar).

Histopathology
At low magnification, the pattern of the cysts is similar to a sponge. The cysts contain proteinaceous fluid and are lined by a single layer of cuboidal or flattened epithelial cells. Their cytoplasm is clear and only rarely eosinophilic and granular. The nuclei are centrally located, round to oval in shape, uniform, and have an inconspicuous nucleolus. Due to the presence of abundant intracytoplasmic glycogen, the periodic acid-Schiff (PAS) stain without diastase digestion is positive, whereas PAS-diastase and Alcian blue stains are negative {160}. Mitoses are practically absent and there is no cytological atypia. Occasionally, the neoplastic cells form intracystic papillary projections, usually without a fibrovascular stalk. The central fibrous stellate core is formed of hyalinized tissue with a few clusters of tiny cysts.

Immunohistochemistry
The epithelial nature of these neoplasms is reflected in their immunoreactivity for epithelial membrane antigen and cytokeratins 7, 8, 18, and 19. In addition, the neoplastic cells may focally express CA19-9 and B72.3 {815, 1752}. They are uniformly negative for carcinoembryonic

Fig. 10.11 Serous oligocystic adenoma. This CT scan shows a macrocystic neoplasm in the head of the pancreas.

antigen (CEA), trypsin, chromogranin A, synaptophysin, S-100 protein, desmin, vimentin, factor VIII-related antigen and actin {49, 119, 445, 689, 815, 1752, 1781, 2151}.

Ultrastructure
Electron microscopy shows a single row of uniform epithelial cells lining the cysts and resting on a basal lamina {49, 160, 915}. The apical surfaces have poorly developed or no microvilli. The cytoplasm contains numerous glycogen granules but only a few mitochondria, short profiles of endoplasmic reticulum, lipid droplets, and multivesicular bodies. Golgi complexes are rarely identified. Zymogen granules and neurosecretory granules are absent.
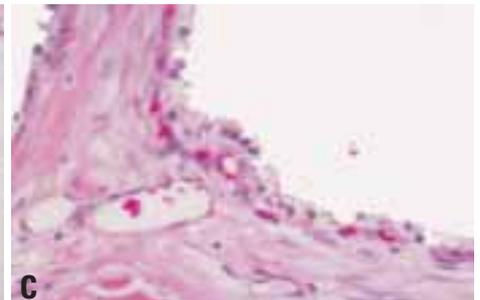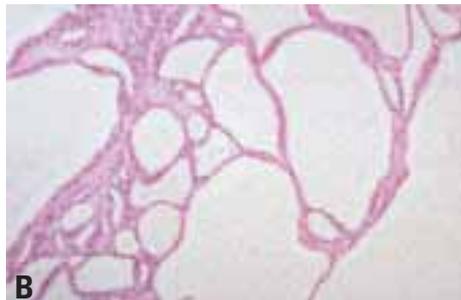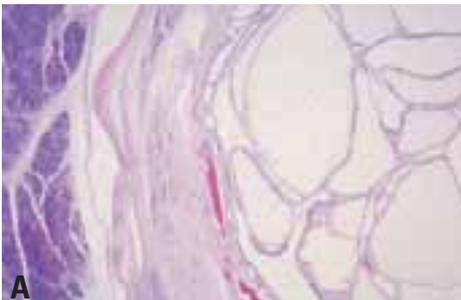
Genetics
Loss of heterozygosity at the von Hippel-Lindau (VHL) gene locus, mapped to chromosome 3p25, was found in 2/2 serous microcystic adenomas associated with VHL disease and in 7/10 sporadic cases {2026}. In contrast to ductal adenocarcinomas, serous microcystic adenomas have wild-type *KRAS* and lack immunoreactivity for *TP53* {815}.

Prognosis
The prognosis of patients with this neoplasm is excellent, since there is only a minimal risk of malignant transformation {1159}.

Serous oligocystic adenoma

Definition
A benign neoplasm composed of few, relatively large cysts, lined by uniform glycogen-rich cuboidal epithelial cells.

Synonyms
This tumour category includes macrocystic serous cystadenoma {257, 1062}, serous oligocystic and ill-demarcated adenoma {445}, and some cystadenomas observed in children {2057}. Whether these neoplasms form a homogeneous group remains to be established.

Epidemiology
Serous oligocystic adenomas are much less common than serous microcystic adenomas {445, 1062}. There is no sex predilection. Adults are usually 60 years and over (age range, 30-69 years; mean, 65 years); the tumour has been described in two male and two female infants, aged between 2 and 16 months {1781}.

Fig. 10.13 Serous cystadenoma. A cystic neoplasm replaces the head of the pancreas; a portion of duodenum is on the right.

Aetiology
The aetiology of this neoplasm is not known. In children, it has been suggested that the lesions may be of malformative origin and not true neoplasms since in two cases there was a cytomegalovirus infection in the adjacent pancreas {52, 273}.

Localization
Most serous oligocystic adenomas are located in the head and body of the pancreas {1781}. In the head, they may obstruct the periampullary portion of the common bile duct.

Clinical features
In most cases reported in adult patients, the neoplasms caused symptoms that led to their discovery and removal. The most common symptom was upper abdominal discomfort or pain {1781}. Other symptoms included jaundice and steatorrhoea. In infants, the tumours presented as a palpable abdominal mass {52, 273}.

Macroscopy
These neoplasms typically appear as a cystic mass with a diameter of 4-10 cm (mean, 6 cm) {1781}. On cut surface,

Fig. 10.12 Serous microcystic cystadenoma. **A** The lesion is well demarcated from the adjacent pancreas. **B** Cysts of varying size. **C** The epithelium is cuboidal and focally PAS-positive.

there are few (occasionally only one) macroscopically visible cysts filled with watery clear or brown fluid. The cysts usually vary between 1 and 2 cm in diameter, but cysts as large as 8 cm have been reported {1062}. The irregularly arranged cysts, sometimes separated by broad septa, lie within a fibrous stroma that lacks a central stellate scar. The cysts and the supporting fibrous tissue may extend into the adjoining pancreatic tissue so that the tumours are poorly demarcated.

Histopathology

Serous oligocystic adenoma has generally the same histological features as serous microcystic adenoma. Occasionally, however, the lining epithelium may be more cuboidal and less flattened, and the nuclei are generally larger. The cytoplasm is either clear, due to the presence of glycogen, or eosinophilic. The stromal framework is well developed and often hyalinized. The tumour border is not well defined and small cysts often extend into the adjoining pancreatic tissue. The immunohistochemical and ultrastructural features are the same as for serous microcystic adenoma {445, 2057}.

Prognosis

There is no evidence of malignant potential {445}.

Serous cystadenocarcinoma

Definition

A malignant cystic epithelial neoplasm composed of glycogen-rich cells.

Epidemiology

So far, only eight cases have been reported {573, 815, 1781}. These patients were
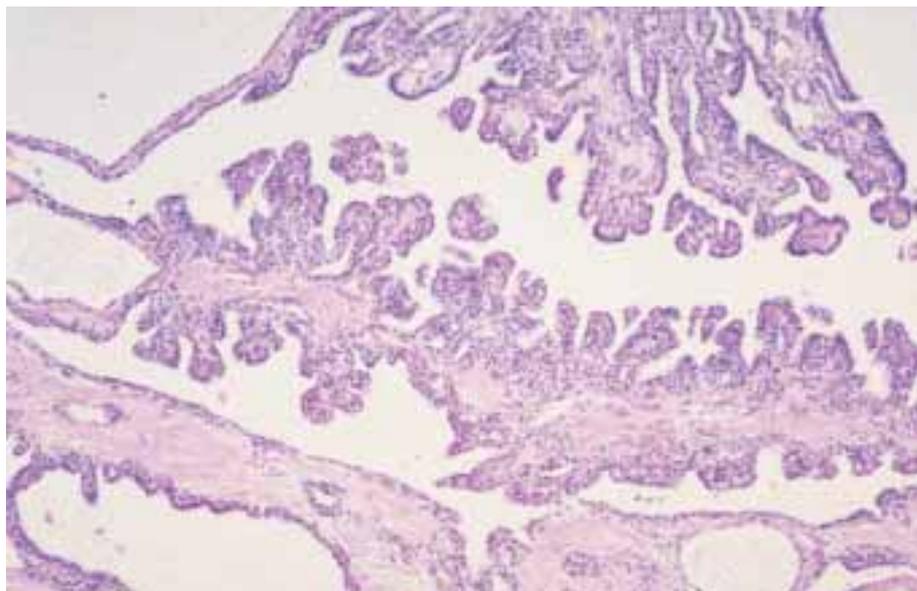

Fig. 10.14 Serous cystadenoma. Characteristic cuboidal epithelium forms intracystic papillary structures in this field.

between 63 and 72 years of age; there were four women and four men. Three patients were Caucasian and four were from Japan {8, 815, 1781}.

Clinical features

Clinical symptoms reported in the cases so far observed include bleeding from gastric varices due to tumour invasion of the wall of the stomach and the splenic vein, a palpable upper abdominal mass, and jaundice. Ultrasonography and CT revealed a hyperechoic mass. CEA and CA19-9 were normal or slightly increased.

Macroscopy

These neoplasms have a spongy appearance {573, 879, 2182}. Their reported size has varied between 2.5 and 12 cm. Liver and lymph node metastases have been reported {573, 815, 1781, 2182}.

Invasion of the spleen and metastasis to the gastric wall were found in one case.

Histopathology

The histological features in the primary tumour as well as in the metastases are remarkably similar to those of serous microcystic adenoma, although focal mild nuclear pleomorphism can be found {573, 2182}. One carcinoma reported showed neural invasion and aneuploid nuclear DNA content {879}, while other cases showed vascular and perivascular invasion {1412} or involvement of a lymph node and adipose tissue {8}.

Prognosis

Serous cystadenocarcinomas are slowly growing neoplasms and palliative resection may be helpful even in advanced stages {2182}.

Mucinous cystic neoplasms of the pancreas

G. Zamboni
G. Klöppel
R.H. Hruban

D.S. Longnecker
G. Adler

Definition

Cystic epithelial neoplasms occurring almost exclusively in women, showing no communication with the pancreatic ductal system and composed of columnar, mucin-producing epithelium, supported by ovarian-type stroma. According to the grade of intraepithelial neoplasia (dysplasia), tumours may be classified as adenoma, borderline (low-grade malignant) and non-invasive or invasive carcinoma.

ICD-O codes

Mucinous cystadenoma   8470/0
Mucinous cystic neoplasm
with moderate dysplasia   8470/1
Mucinous cystadenocarcinoma
      non-invasive   8470/2
      invasive   8470/3

Epidemiology

Although more than 500 cases have been reported in the literature {328, 2198}, mucinous cystic neoplasm (MCN) is still considered a rare lesion, representing approximately 2-5% of all exocrine pancreatic tumours {1781, 1932}. Changes in diagnostic criteria over the years and the high resectability rate compared to that of ductal adenocarcinoma may have led to an overrepresentation of MCNs in histopathology series. The increasing number of these lesions seen in recent years is most likely due to advances in diagnostic techniques, allowing early and correct recognition of MCN.

In a recent study, in which MCNs were defined by the lack of a communication with the pancreatic duct system and the presence of an ovarian type stroma, all occurred in women {2198}. It is likely that many of the cases reported in men in the early literature were intraductal papillary mucinous neoplasms (IPMNs) {328, 1932, 2198}.

The mean age at diagnosis is 49 years (range, 20-82 years) {1781}. Patients with mucinous cystadenocarcinomas are about 10 years older than patients with adenomatous or borderline tumours

(54 versus 44 years), suggesting an adenoma - carcinoma sequence {2198}. MCTNs seem to occur in patients with different ethnic background {1781}.

Aetiology

Pancreatic MCNs share many features with their counterparts in the liver and retroperitoneum, including their morphology and their almost exclusive occurrence in women {328, 2139, 404, 2198}. The possible derivation of the stromal component of MCNs from the ovarian primordium is supported by morphology, tendency to undergo luteinization, presence of hilar-like cells, and immunophenotypic sex cord-stromal differentiation. It has been hypothesized that ectopic ovarian stroma incorporated during embryogenesis in the pancreas, along the biliary tree or in the retroperitoneum may release hormones and growth factors causing nearby epithelium to proliferate and form cystic tumours {2198}. Since the left primordial gonad and the dorsal pancreatic anlage lie side by side during the fourth and fifth weeks of development, this hypothesis could explain

Fig. 10.16 Mucinous cystic neoplasm in the tail of the pancreas. The thick wall shows focal calcification.

the predilection of MCN for the body-tail region of the pancreas {1977}.

Localization

The overwhelming majority of cases occur in the body-tail of the pancreas {328, 1932, 2148, 2198}. The head is only rarely involved, with a predilection for mucinous cystadenocarcinomas {1932, 2198}.

Fig. 10.15 Mucinous cystic neoplasm. The pancreatic duct, which does not communicate with the cyst lumen, has been opened over the surface of the tumour (left, arrowheads). The thick wall and irregular lining of the bisected neoplasm are shown on the right.
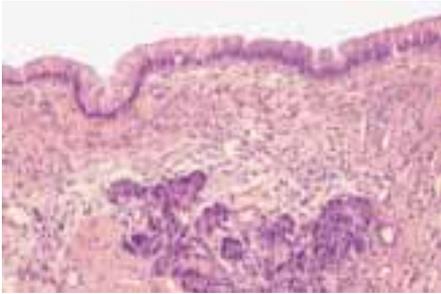
Fig. 10.17 Well differentiated columnar epithelium supported by ovarian-like stroma.

Clinical features

Symptoms and signs

The clinical presentation depends on the size of the tumour. Small tumours (< 3 cm) are usually found incidentally. Larger tumours may produce symptoms that are usually due to compression of adjacent structures, and are often accompanied by a palpable abdominal mass. An association with diabetes mellitus is relatively frequent, whereas jaundice is uncommon {1781}.

Serum tumour markers

An increase in the peripheral blood serum tumour markers CEA, CA 19-9, or high cyst fluid levels of CEA, CA 19-9, TAG-72, CA-15-3 or MCA (mucin-like carcinoma-associated antigen) together with a low amylase level is suggestive of MCN. The highest levels of these markers are seen in cystadenocarcinoma {1063, 1804}.

Imaging

Abdominal X-ray may demonstrate nodular calcifications in the tumour capsule and compression or displacement of the stomach, duodenum or colon. US and CT reveal a sharply demarcated hypoechoic or low density mass with one or more large loculations {1461}. Features suggestive of malignant transformation include an irregular thickening of the cyst wall and/or papillary excrescences projecting into the cystic cavity {201, 2060}. Magnetic resonance imaging may have a complementary role. Endoscopic retrograde cholangiography (RCP) shows a displacement of the main pancreatic duct and the absence of communication with the cystic cavity, a very important finding for the differential diagnosis with IPMN.

Fine needle aspiration cytology (FNAC) can be performed percutaneously with CT or US guidance, or intraoperatively {1019}.

Preoperative diagnosis of MCN is important, since other types of cystic neoplasm may be treated differently. Furthermore, MCNs must be distinguished from an inflammatory pseudocyst, because drainage may be appropriate for patients with a pseudocyst, but is disastrous for patients with MCN, since apparently histologically benign mucinous cystic tumours can recur after drainage as invasive cystadenocarcinomas {328, 2194}. The best approach to obtain an exact preoperative diagnosis is the combined evaluation of all available clinical, serological, radiological, and biopsy findings.

Macroscopy

MCNs typically present as a round mass with a smooth surface and a fibrous pseudocapsule with variable thickness and frequent calcifications. The size of the tumour ranges from 2-35 cm in greatest dimension, with an average size between 6 and 10 cm. The cut surfaces demonstrate a unilocular or multilocular tumour with cystic spaces ranging from a few millimetres to several centimeters in diameter, containing either thick mucin or a mixture of mucin and haemorrhagic-necrotic material. The internal surface of unilocular tumours is usually smooth and glistening, whereas the multilocular tumours often show papillary projections and mural nodules. Malignant tumours are likely to show papillary projections and/or mural nodules and multilocularity {2198}. As a rule, there is no communication of the tumour with the pancreatic duct system, but exceptions have been reported {2148}.

Tumour spread and staging

Invasive mucinous cystadenocarcinoma follows the same pathways of local spread as ductal adenocarcinoma. The first metastases are typically found in the regional peripancreatic lymph nodes and the liver {1781}. Staging follows the protocol for ductal adenocarcinomas.

Histopathology

MCNs show two distinct components: an inner epithelial layer and an outer densely cellular ovarian-type stromal layer. Large locules can be extensively denuded and many sections are often needed to demonstrate the epithelial lining. The epithelium may be flat or it may form papillary or polypoid projections, pseu-
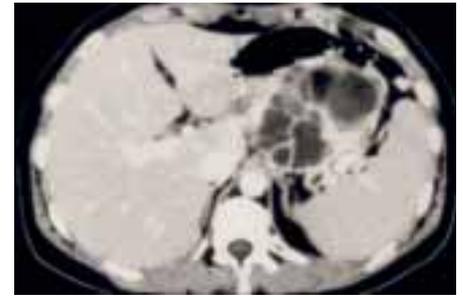

Fig. 10.18 Mucinous cystic neoplasm presenting as multiloculated cystic mass in the tail of the pancreas.

dostratifications and crypt-like invaginations. The columnar cells are characterized by basally located nuclei and abundant intracellular mucin which is diastase-PAS and Alcian blue positive. Pseudopyloric, gastric foveolar, small and large intestinal, and squamous differentiation can also be found. About half of the tumours contain scattered argyrophil and argentaffin endocrine cells at the bases of the columnar cells {33, 36, 328, 2151}.

Spectrum of differentiation

This ranges from histologically benign appearing columnar epithelium to severely atypical epithelium. According to the grade of intraepithelial neoplasia (dysplasia), tumours may be classified as adenoma, borderline (low-grade malignant) and non-invasive or invasive carcinoma {947}.

Mucinous cystadenomas show only a slight increase in the size of the basally located nuclei and the absence of mitosis. Mucinous cystic neoplasms of borderline malignant potential exhibit papillary projections or crypt-like invaginations, cellular pseudostratification with crowding of slightly enlarged nuclei, and mitoses.

Mucinous cystadenocarcinomas may be invasive or non-invasive. They show changes of high-grade intraepithelial neoplasia which are usually focal and may be detected only after careful search of multiple sections from different regions. The epithelial cells, which often form papillae with irregular branching and budding, show nuclear stratification, severe nuclear atypia and frequent mitoses.

Invasive mucinous cystadenocarcinoma is characterized by invasion of the malignant epithelium into the stroma. The invasive component usually resembles the common ductal adenocarcinoma. How-

ever, mucinous cystadenocarcinomas with invasive adenosquamous carcinoma, osteoclast-like giant cell or choriocarcinoma have been reported {328, 1530, 1571, 2194}. Invasive foci may be focal and require careful search.

Stroma
The ovarian-type stroma consists of densely packed spindle-shaped cells with round or elongated nuclei and sparse cytoplasm. It frequently displays a variable degree of luteinization, characterized by the presence of single or clusters of epithelioid cells with round to oval nuclei and abundant clear or eosinophilic cytoplasm. Occasionally, these cells, resembling ovarian hilar cells, can be found associated with (or present in) nerve trunks. Stromal luteinization is found in decreasing order of frequency from adenomatous to carcinomatous cases {2194}. The stroma of large MCNs may become fibrotic and hypocellular. Rare MCNs show mural nodules with a sarcomatous stroma or an associated sarcoma {1932, 2088, 2198}.

Immunohistochemistry
The epithelial component is immunoreactive with epithelial markers including EMA, CEA, cytokeratins 7, 8, 18 and 19 {2151}, and it may show gastroenteropancreatic differentiation, as is also observed in ovarian and retroperitoneal MCN {1714, 1910}. With increasing degrees of epithelial atypia the character of mucin production changes from sulphated to sialated or neutral mucin {1932}. The neoplastic cells express gas-
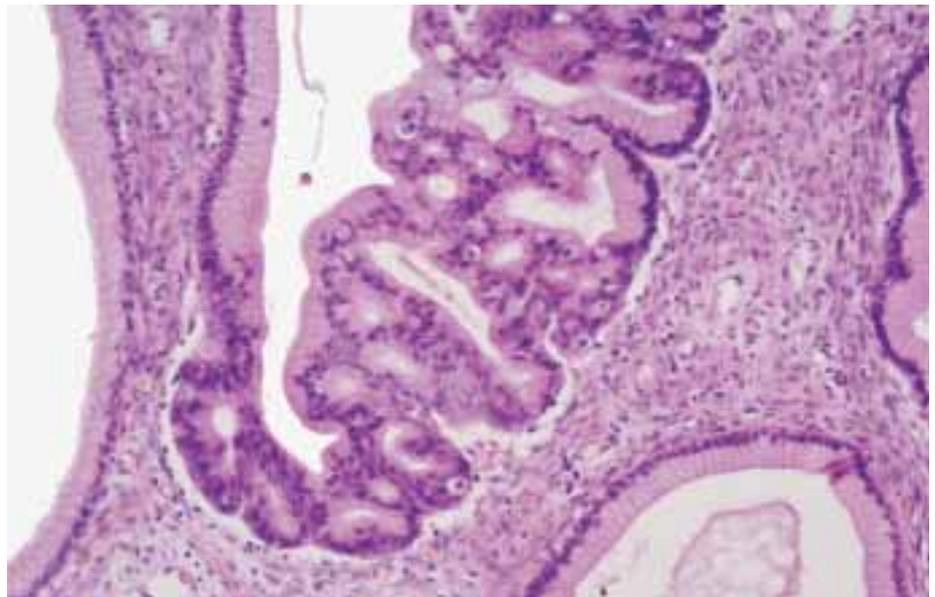

Fig. 10.19 Mucinous cystadenocarcinoma. The neoplasm exhibits well differentiated and poorly differentiated mucinoius epithelium.

tric type mucin marker M1 and PGII, the intestinal mucin markers CAR-5 and M3SI, and the pancreatic type mucin marker DUPAN-2 and CA19-9 {119, 1714, 2151, 2190}. Furthermore, pancreatic, hepatobiliary, and retroperitoneal MCNs share the same types of intraepithelial endocrine cells {613, 1911, 1910}. p-53 nuclear positivity in more than 10% of neoplastic cells, found in 20% of MCN, strongly correlates with mucinous cystadenocarcinoma {2198}.

The stromal component expresses vimentin, alpha smooth muscle actin, desmin and, in a high proportion, progesterone and estrogen receptors {2198}. The luteinized cells are labeled with antibodies against tyrosine hydroxylase, calretinin, which have been shown to recognize testicular Leydig cells and hilar ovarian cells, and the sex cord-stromal differentiation marker inhibin {2198, 2206}.

Ultrastructure
Electron microscopy of tumours with only mild to moderate dysplasia demonstrates columnar epithelial cells resting on a thin basement membrane. The cells may have well-developed microvilli and mucin granules {33}.

Genetics
Activating point mutations in codon 12 of *KRAS* were found in invasive mucinous cystic neoplasms (MCNs) {117} and mucinous cystic neoplasms associated with osteoclast-like giant cells {1485}. Mutations of *KRAS* and allelic losses of 6q, 9p, 8p have been reported in MCNs with sarcomatous stroma {1998}.

Prognosis and predictive factors
The prognosis of MCN, regardless of the degree of cellular atypia, is excellent if the tumour is completely removed {328, 410, 2060, 2198}. The prognosis of invasive mucinous cystadenocarcinoma depends on the extent of tumour invasion. Tumour recurrence and poor outcome correlate with invasion of the tumour wall and peritumoural tissues {2198}. Patients older than 50 years appear to have a lower survival rate {2198}. Other variables such as site, tumour size, macroscopic appearance, grade of differentiation, luteinization of the stroma and p53 positivity have no prognostic significance.

Aneuploidy is a rare event in MCNs, is largely restricted to mucinous cystadenocarcinomas and carries a worse prognosis {1792, 1932, 512}.

Fig. 10.20 Mucinous cystadenocarcinoma. The thick wall of this cystic neoplasm is invaded by mucinous carcinoma at upper left.

Intraductal papillary-mucinous neoplasms of the pancreas

D.S. Longnecker   R.H. Hruban
G. Adler   G. Klöppel

Definition

An intraductal papillary mucin-producing neoplasm, arises in the main pancreatic duct or its major branches. The papillary epithelium component, and the degree of mucin secretion, cystic duct dilatation, and invasiveness are variable. Intraductal papillary-mucin neoplasms are divided into benign, borderline, and malignant non-invasive or invasive lesions.

ICD-O codes

Intraductal papillary-mucinous adenoma
                                     8453/0
Intraductal papillary-mucinous neoplasm with moderate dysplasia   8453/1
Intraductal papillary-mucinous carcinoma
       non-invasive   8453/2
       invasive   8453/3

Synonyms and historical annotation

Papillary pancreatic neoplasms have been recognized for many years {247, 1532}, but the distinction between mucinous cystic neoplasms and intraductal papillary neoplasms was not made until the last two decades {947, 1781, 65, 1404}. Interest in IPMNs was first stimulated when they were recognized clinically {1281}, and pathological descriptions quickly followed {2164, 1093}. The incidence appears to have risen since the first reports, but this may reflect the combined effects of new diagnostic techniques, and progress in recognition and classification of IPMNs {1138, 918}. It is likely that many IPMNs were classified among the mucinous cystic neoplasms as recently as a decade ago.

Epidemiology

The incidence is low and not precisely known because IPMNs are not accurately identified in large population-based registries. Nomenclature and classification have been highly variable until recently, and are not yet standardized worldwide. IPMNs have been estimated to amount to 1-3% of exocrine pancreatic neoplasms, with an incidence rate well below 1 per 100,000 per year {1280, 1095}.

IPMNs are found in a broad age range (30-94) with a median age of diagnosis in the 6-7th decade {1443, 2148, 556}. They occur more frequently in males than in females {1138, 2148}. IPMNs were first reported from France and Japan, but subsequent reports have come from all parts of the world. Two studies provide some evidence that the incidence may be higher among Asians than among whites, but issues of consistency of classification require that this be further evaluated {1095, 941}.

Aetiology

The low incidence and imprecise identification of IPMN in large databases has hindered recognition of aetiological factors. In one series, most patients with IPMNs were cigarette smokers {550}. There is no consistent association with other types of pancreatic neoplasm {2198}.

Localization

The majority of these neoplasms occur in the main pancreatic duct and its branches in the head of the pancreas {1781, 330, 97}. A single cystic mass or segmental involvement of the duct is usual, but diffuse involvement is also described {1093, 1751, 1953}. Multicentric origin is suspected because of recurrence in pancreatic remnants following surgical removal of IPMNs {1088}. IPMNs may extend to the ampulla of Vater, commonly in association with involvement of the duct of Wirsung or the common bile duct {1781}.

Clinical features

Clinical presentation includes epigastric pain, pancreatitis, weight loss, diabetes, and jaundice {2169, 1953, 942}; some patients have no symptoms. Some cases are detected because of dilatation of the pancreatic duct seen incidentally in imaging studies. Serum amylase and lipase are commonly elevated.
Endoscopic ultrasound, ERCP, and endoscopic examination of the pancreatic duct {1596} may all contribute to pre-
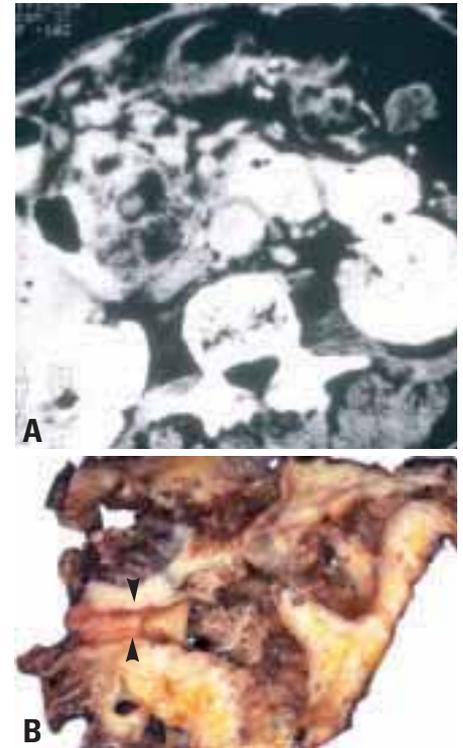
Fig. 10.21 Intraductal papillary-mucinous neoplasm. **A** Large neoplasm in the head of the pancreas containing multiple cystic spaces. **B** The lesion illustrated in A sectioned to demonstrate the dilated, mucin-filled main pancreatic duct (arrowheads).

operative diagnosis. Endoscopic biopsy or cytology may provide histological confirmation, but definitive diagnosis requires surgical removal and extensive histological sampling. Serum markers such as CEA and CA19-9 are too insensitive to be of value {2148, 1953}.

Macroscopy

Depending on the degree of ductal dilatation, IPMNs vary in size from 1 to 8 cm in maximum dimension {17}. They are cystic and may appear multiloculated if branch ducts are involved. The mucin found in IPMN is viscous or sticky and can dilate parts of the duct that are lined by normal appearing epithelium. The lining of cystic spaces may be smooth and glistening, granular, or velvet-like, the latter reflecting papillary growth. When
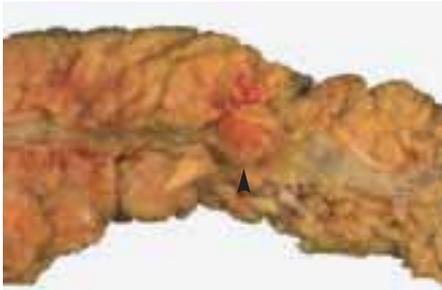
Fig. 10.22 Intraductal papillary mucinous neoplasm in the main pancreatic duct (arrowhead).

papillary growths are large, the dilated ducts may show localized excrescences or be filled with soft papillary masses of tissue.

The pancreatic parenchyma surrounding and retrograde to the tumour is often pale and firm, reflecting changes of chronic obstructive pancreatitis. When there is invasion, gelatinous areas may be identified in fibrotic tissue.

Tumour spread and staging

Adenomas, borderline tumours and non-invasive carcinomas may extend intra-ductally into adjacent portions of the duct system, and evidence of such extension is often encountered adjacent to IPMNs. Recurrence following surgical resection has been reported in patients that had IPMNs extending into the margin of resection {1953}. Invasive neoplasms are staged as ductal adenocarcinomas.

Histopathology

IPMN tumour cells are usually tall columnar mucin-containing epithelial cells that line dilated ducts or cystic spaces arising from dilated branch ducts. The epithelium typically forms papillary or pseudopapillary structures, but portions of the neoplasm may be lined by non-papillary epithelium or be denuded of epithelium. The amount of mucin production varies widely, as does the degree of duct dilatation {97, 872}. Goblet or Paneth cells may be present as a manifestation of intestinal metaplasia in the neoplastic epithelium, and neuroendocrine cells have also been demonstrated.

The recently described intraductal oncocytic papillary neoplasm probably represents a rare related phenotype that is similar macroscopically {1244, 1860}. Oncocytic IPMNs are composed of stratified oncocytic cells with pale pink cytoplasmic granules that are much finer than those seen in Paneth cells. Goblet cells may be interspersed among the oncocytic cells. A characteristic feature of the oncocytic papillary neoplasms is the formation of 'intraepithelial lumina', which are spaces in the epithelium about one quarter the size of the cells.
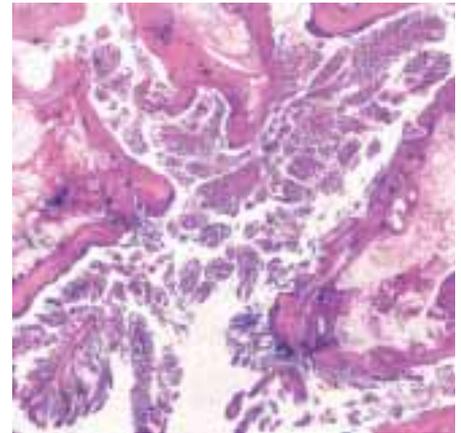

Fig. 10.24 Intraductal papillary-mucinous neoplasm within the dilated main pancreatic duct and branch ducts.

Histochemistry and immunohistochemistry

A variety of abnormalities have been demonstrated in IPMNs using mucin and immunohistochemical stains.

Most IPMNs express epithelial membrane antigen (EMA) as well as several cytokeratins {1917}. A variety of endocrine cell types occur in most tumours but account for fewer than 5 per cent of the tumour cells {1676}.

A change in type of mucin has been suggested as a marker of progression since normal duct cells characteristically secrete sulfated mucin, intraductal papillary-mucinous adenomas characteristically secrete neutral mucin, and dysplastic epithelium secretes predominantly sialomucin {1138, 1916, 1186}. Nearly all IPMNs express MUC2 {2179}.

Overexpression of c-erbB-2 protein occurs in a high fraction of IPMNs {1939, 1675, 1877, 380}.

A study of cell proliferation, as shown by PCNA and Ki67 labelling indices, demonstrated a progressive increase in cell proliferation from normal duct epithelium, to adenomas, to borderline tumours, to carcinomas {1917}. The labeling index in IPM carcinomas was lower than in ductal adenocarcinomas.

Although immunostaining of p53 protein was detected in a lower fraction of IPMN (31%) than is usually seen in solid ductal adenocarcinomas, it was found only in borderline and malignant IPMN and therefore may be a marker of progression {1939}.

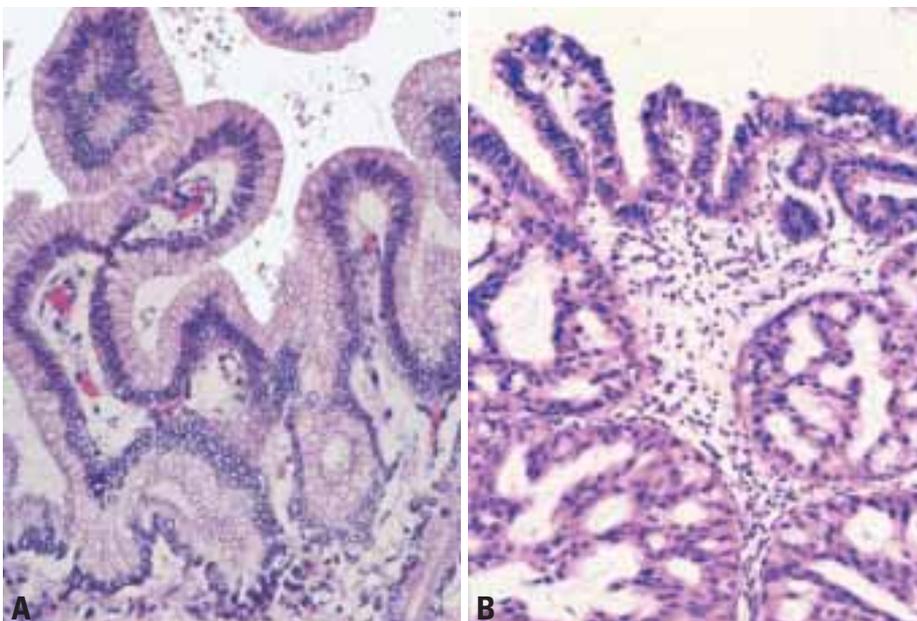Failure of IPMN to elicit the production of a collagenase that mediates invasion was reported {2193}.

Fig. 10.23 Intraductal papillary mucinous neoplasms with **(A)** columnar epithelium and **(B)** oncocytic epithelium.

Classification and grading of IPMNs

IPMNs have been the source of great confusion that is reflected in a diverse nomenclature found in case and series reports and in standard references {1781}. Because of the variability within a tumour, it is important to sample IPMNs well, giving special emphasis to papillary areas because this is where the highest degree of intraepithelial neoplasia (dysplasia) is likely to occur, and to sclerotic areas that may reflect invasion.

IPMNs are classified as benign, borderline, or malignant on the basis of the greatest degree of dysplasia present. In accordance with the previous WHO classification, lesions are specifically designated as intraductal papillary-mucinous adenoma, borderline intraductal papillary-mucinous neoplasm, and intraductal papillary-mucinous carcinoma, with or without invasion {947, 1781}.

A slightly different histopathological classification has been proposed by the Japan Pancreas Society (JPS) {65}, intraductal tumours are designated as intraductal papillary adenoma or adenocarcinoma. The degree of cellular atypia in adenomas is designated as slight, moderate, or severe. The JPS category of adenoma with severe atypia corresponds to the WHO borderline lesion, although some authors also utilize a borderline category {2148}

Intraductal papillary-mucinous adenoma

The epithelium is comprised of tall columnar mucin-containing cells that show slight or no dysplasia, i.e. the epithelium maintains a high degree of differentiation in adenomas.

Borderline intraductal papillary-mucinous neoplasm

IPMNs with moderate dysplasia are placed in the borderline category. The epithelium shows no more than moderate loss of polarity, nuclear crowding, nuclear enlargement, pseudostratification, and nuclear hyperchromatism. Papillary areas maintain identifiable stromal cores, but pseudopapillary structures may be present.

Intraductal papillary-mucinous carcinoma

IPMNs with severe dysplastic epithelial change are designated as carcinoma even in the absence of invasion. Carcinomas are papillary or micropapillary. Cribriform growth and budding of
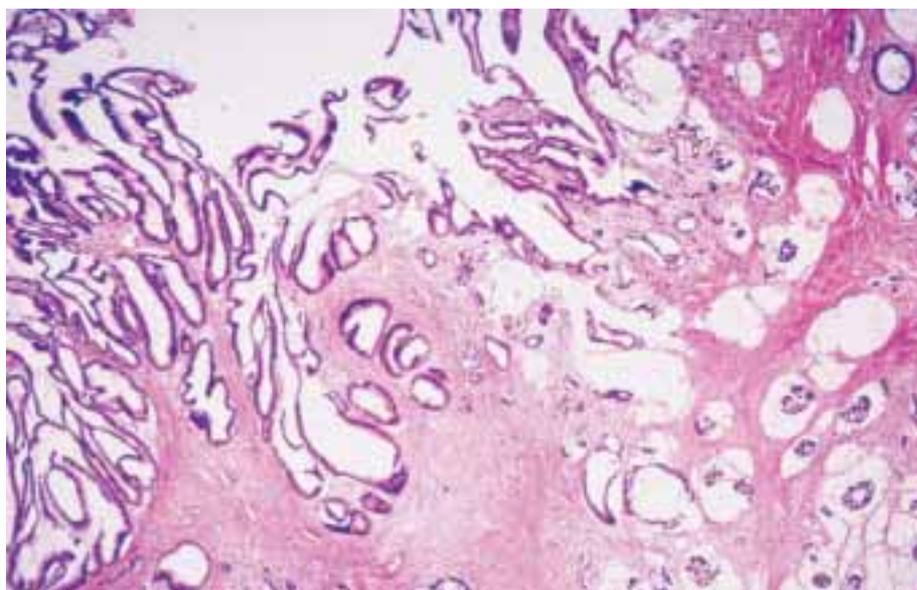

Fig. 10.25 Intraductal papillary-mucinous carcinoma. Intraductal papillary neoplasm (left), invasive mucin secreting carcinoma (right).

small clusters of epithelial cells into the lumen support the diagnosis of carcinoma. Severe dysplasia is manifest cytologically as loss of polarity, loss of differentiated cytoplasmic features including diminished mucin content, cellular and nuclear pleomorphism, nuclear enlargement, and the presence of mitoses (especially if suprabasal or luminal in location). Severely dysplastic cells may lack mucin. Non-invasive lesions are termed non-invasive intraductal papillary-mucinous carcinoma. When invasive, an IPMN may be called a papillary-mucinous carcinoma since it is no longer only intraductal. When IPMNs become invasive, the invasive component may assume the appearance of a tubular ductal adenocarcinoma or a mucinous noncystic carcinoma {17}. If the invasive component is dominant, and is a ductal

Fig. 10.26 Intraductal papillary-mucinous carcinoma. This tumour shows moderately differentiated (left) and well differentiated (right) areas.

or mucinous noncystic carcinoma, then that diagnosis may be used, descriptively noting the association with an IPMN component.

Differential diagnosis

Historically, IPMNs and mucinous cystic neoplasms (MCNs) have been confused because they are both cystic and have a similar epithelial component. However, IPMNs and MCNs are distinct entities and can be separated easily, because MCNs typically occur in women with a median age in the fifth decade, almost always are located in the tail or body of the pancreas, typically exhibit a thick wall with a cellular 'ovarian' stroma, and typically fail to communicate with the pancreatic duct system.

Precursor lesions

The criteria for classifying pancreatic intraepithelial neoplasia (PanIN) lesions (including papillary hyperplasia, see chapter on ductal adenocarcinoma of the pancreas) in IPMNs are not well established {1144, 1744}, and need to be defined. PanIN lesions characteristically occur in intralobular ducts, are not detected macroscopically, and are clinically silent {17}. It seems likely that the earliest stage of development of the IPMN would involve the progression from a flat area of mucous metaplasia to a papillary lesion in a main or branch pancreatic duct as suggested by Nagai et al.
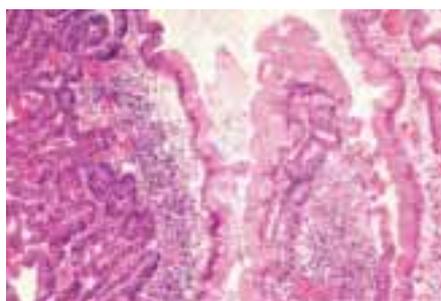
Table 10.05
Summary of mucin histochemistry and immunostaining of IPMN.

Antibody or epitope	Comments on staining in IPMN	Reference
Differentiation markers		
Alcian blue stain	Adenomas contain neutral mucin, carcinomas contain sialomucin	{1138, 1916}
MUC1	Negative>>positive	{2179}
MUC2	Positive>>negative	{2179}
Endocrine markers	< 5% of cells positive in most IPMN	{1676}
Epithelial membrane antigen	Positive	{1917}
Cytokeratins 7, 8, 18, 19	Positive	{1917}
CEA	Positive	{1939}
CA-19-9	Positive	{1939}
B72.3	Positive	{1939}
DUPAN-2	Seen in a minority	{1939}
Oncogene products		
c-erbB-2	13/17 IPMN positive, including all with moderate or severe dysplasia	{1675} {1939}
p27	p27 staining exceeds cyclin E	{556}
Tumour suppressor gene products		
TP53	Often positive in borderline tumours and carcinomas	{1939}
Proliferation markers		
PCNA and Ki67	Labeling index increases with progression from adenoma to carcinoma	{1917}

{1306}. Thus, it will be difficult to recognize the initial stage of an intraductal papillary-mucinous adenoma unless a distinctive molecular marker is identified.

Genetic susceptibility
Excessive rates of colonic and gastric epithelial neoplasms were reported in a group of 42 patients with IPMNs {106}. This suggests the possibility of a predisposing genetic susceptibility, but no specific hereditary syndrome was identified.

Genetics
Activating point mutations in codon 12 of the KRAS gene have been reported in 40-60% of intraductal papillary mucinous neoplasms {1939, 544}. Fujii et al. examined a series of IPMNs using polymorphic microsatellite markers and found allelic loss at 9p in 62% of the cases and at 17p and at 18q in ~40% {544}. These allelic losses include the loci of the p16, TP53, and DPC4 tumour-suppressor genes. In addition to immunohistochemical evidence of p53 abnormality in IPMN {544}, mutations have been demonstrated in two adenomas {876}. Overexpression of anti-apoptotic genes in IPMN is reported {1247}.

Mutations of KRAS and TP53 genes have been detected in DNA from pancreatic juice of patients with IPMN {875}.

Prognosis and predictive factors
The overall 5-year survival rate for a composite series was 83% {2148}. The prognosis is excellent for adenomas and borderline tumours with 3 and 5-year survivals approaching 100%. The survival rates are high for non-invasive carcinomas, and survival rates for patients with invasive IPMNs may also be higher than for patients with typical ductal adenocarcinomas {2148, 97, 2169}. The histological classification, with major emphasis on the presence or absence of invasion, and stage remain the best predictors for survival.

As the distinction between IPMNs and MCNs has been refined, some authors report that MCNs are more often malignant than IPMNs and that the latter have a better prognosis following treatment {97}, but this was not confirmed in other series {1953, 551}. Expression of MUC2 and MUC5AC mucins are associated with a good prognosis relative to ductal adenocarcinomas that do not express these mucins {2179, 2178}.

Acinar cell carcinoma

D.S. Klimstra
D. Longnecker

Definition

A carcinoma occurring mainly in adults, composed of relatively uniform neoplastic cells that are arranged in solid and acinar patterns and produce pancreatic enzymes.

ICD-O codes

Acinar cell carcinoma   8550/3
Acinar cell cystadenocarcinoma   8551/3
Mixed acinar-endocrine carcinoma   8154/3

Epidemiology

Acinar cell carcinomas represent 1-2% of all exocrine pancreatic neoplasms in adults {739, 936}. Most occur in late adulthood, with a mean age of 62 years {825, 979, 2073}. The tumour is rare in adults under the age of 40. Pediatric cases do occur, usually manifesting in patients 8 to 15 years of age {979, 1282}. Males are affected more frequently than females, with an M:F ratio of 2:1 {739, 936}.

Aetiology

The aetiology is unknown.

Localization

Acinar cell carcinomas may arise in any portion of the pancreas but are somewhat more common in the head.

Clinical features

Symptoms and signs
Most acinar cell carcinomas present clinically with relatively non-specific symptoms including abdominal pain, weight loss, nausea, or diarrhoea {739, 936, 979, 2073}. Because they generally push rather than infiltrate into adjacent structures, biliary obstruction and jaundice are infrequent presenting complaints.
A well-described syndrome occurring in 10-15% of patients is the lipase hypersecretion syndrome {1781, 213, 936, 975}. It is most commonly encountered in patients with hepatic metastases, and is characterized by excessive secretion of lipase into the serum, with clinical symptoms including subcutaneous fat necrosis and polyarthralgia. Peripheral blood

eosinophilia may also be noted. In some patients, the lipase hypersecretion syndrome is the first presenting sign of the tumour, while in others it develops following tumour recurrence. Successful surgical removal of the neoplasm may result in the normalization of the serum lipase levels and resolution of the symptoms.

Laboratory analyses
Other than an elevation of serum lipase levels associated with the lipase hypersecretion syndrome, there are no specific laboratory abnormalities in patients with acinar cell carcinoma. A few cases show increased serum alpha-fetoprotein {819, 1426, 1369, 1747}.

Imaging
Acinar cell carcinomas are generally bulky with a mean size of 11 cm {979}. On abdominal CT scans, they are circumscribed and have a similar density to the surrounding pancreas. Because of their larger size and relatively sharp circumscription, acinar cell carcinomas can generally be distinguished from ductal adenocarcinomas radiographically.

Fine needle aspiration cytology
There is usually a high cellular yield from fine needle aspiration {1446, 1978, 2015}. The cytological appearances of acinar cell carcinomas closely mimic of pancreatic endocrine neoplasms, although the latter are more likely to exhibit a plasmacytoid appearance to the cells and a speckled chromatin pattern. Immunohistochemistry may be used on cytological specimens to confirm the diagnosis of acinar cell carcinoma {1446, 1978}.

Macroscopy

Acinar cell carcinomas are generally circumscribed and may be multinodular {739, 936}. Individual nodules are soft and vary from yellow to brown. Areas of necrosis and cystic degeneration may be present. Occasionally, the neoplasm is found attached to the pancreatic surface. Extension into adjacent structures, such as duodenum, spleen, or major

vessels may occur. Multicystic examples of acinar cell carcinoma have been reported as acinar cell cystadenocarcinoma {229, 739, 1815}.

Tumour spread and staging

Metastases most commonly affect regional lymph nodes and the liver, although distant spread to other organs occurs occasionally. Acinar cell carcinomas are staged using the same protocol as ductal adenocarcinomas.

Histopathology

Large nodules of cells are separated by hypocellular fibrous bands. The desmoplastic stroma characteristic of ductal adenocarcinomas is generally absent. Tumour necrosis may occur and is generally infarct-like in appearance. Within the tumour cell islands, there is an abundant fine microvasculature.
Several architectural patterns have been described. The most characteristic is the acinar pattern, with neoplastic cells arranged in small glandular units; there are numerous small lumina within each island of cells giving a cribriform appearance. In some instances, the lumina are more dilated, resulting in a glandular pattern, although separate glandular structures surrounded by stroma are usually not encountered. A number of the micro-
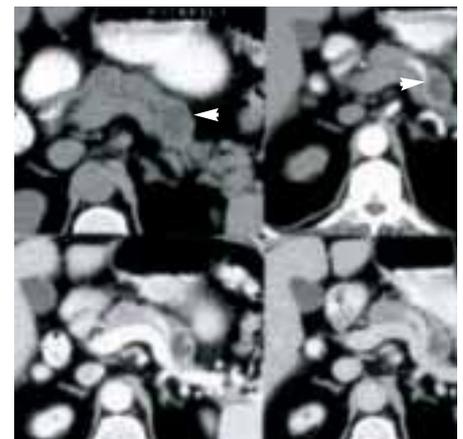

Fig. 10.27 Acinar cell carcinoma. The hypodense lobulated tumour occupies the tail of the pancreas.

glandular tumours previously reported as 'microadenocarcinoma' were more recently shown to have been acinar cell carcinomas (see chapter on miscellaneous carcinomas). The second most common pattern in acinar cell carcinomas is the solid pattern: solid nests of cells lacking luminal formations are separated by small vessels. Within these nests, cellular polarization is generally not evident, but there may be an accentuation of polarization at the interface with the vessels, resulting in basal nuclear localization in these regions and a palisading of nuclei along the microvasculature. In rare instances, a trabecular arrangement of tumour cells may be present, with exceptional cases also showing a gyriform appearance {936}.

The neoplastic cells contain minimal to moderate amounts of cytoplasm that may be more abundant in cells lining lumina. The cytoplasm varies from amphophilic to eosinophilic and is characteristically granular, reflecting the presence of zymogen granules. In many instances, however, only minimal cytoplasmic granularity may be detectable. The nuclei are generally round to oval and relatively uniform, with marked nuclear pleomorphism being exceptional. A single, prominent, central nucleolus is a characteristic finding but not invariably present. The mitotic rate is variable (mean 14 per 10 high power fields, range 0 to > 50 per 10 high power fields).

Zymogen granules are weakly positive with PAS staining, and resistant to diastase. Mucin production is generally not detectable with mucicarmine or Alcian blue stains and, if present, is limited to the luminal membrane in acinar or glandular formations. The histochemical stain for butyrate esterase can be used to identify active lipase within the tumour cells {936, 938}. Due to the scarcity of zymogen granules in many examples of acinar cell carcinoma, histochemical stains are relatively insensitive for documenting acinar differentiation, and very focal staining may be difficult to interpret with confidence.

Immunohistochemistry

Immunohistochemical identification of pancreatic enzyme production is helpful in confirming the diagnosis of acinar cell carcinoma. Antibodies against trypsin, chymotrypsin, lipase, and elastase have all been used {739, 810, 936, 1282}. Both
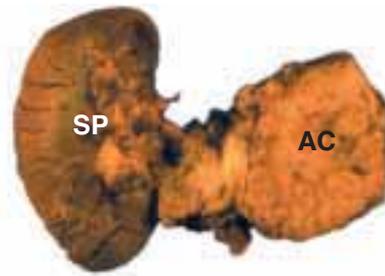

Fig. 10.28 An acinar cell carcinoma (AC) lies near the spleen (SP). The tumour's cut surface is lobulated.

trypsin and chymotrypsin are detectable in over 95% of cases; lipase is less commonly identified (approximately 70% of cases) {936}. Pancreatic stone protein is also commonly expressed {739}. In solid areas, immunohistochemical staining for enzymes may show diffuse cytoplasmic positivity, whereas the reaction product is restricted to the apical cytoplasm in acinar areas.

Immunohistochemical markers of endocrine and ductal differentiation may also be detected in acinar cell carcinomas, generally in a minor cell population {739, 936}. Scattered individual cells stain for chromogranin or synaptophysin are found in over one third of lesions. Over half exhibit focal CEA and B72.3 expression {739, 936}. Uncommonly, there is immunohistochemical positivity for alpha-fetoprotein, generally in cases associated with elevations in serum alpha-fetoprotein {819}.

Ultrastructure

Electron microscopy provides further evidence of enzyme production {675, 408, 936, 1978}. Exocrine secretory features are consistently found, with abundant rough endoplasmic reticulum arranged in parallel arrays and relatively abundant
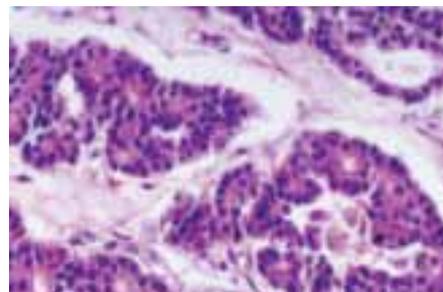

Fig. 10.29 Acinar cell carcinoma showing well differentiated acinar structures.

mitochondria. Cellular polarization is generally evident, with basal basement membranes and apical lumina. Adjacent cells are joined by tight junctions. Although the distribution varies from cell to cell, most acinar cell carcinomas exhibit electron dense zymogen granules. In polarized cells, they are located in the apical cytoplasm, and the secretory contents may be seen within the luminal spaces where granules have fused with the apical membrane. The size range of zymogen granules in acinar cell carcinomas (125-1000 nm) is somewhat greater than that found in non-neoplastic acinar cells (250-1000 nm). In addition to typical zymogen granules, a second granule type, the irregular fibrillary granule, is detected ultrastructurally in many cases {302, 936, 938, 1477}. It has been suggested that irregular fibrillary granules may represent a recapitulation of the fetal zymogen granules, although attempts to document the presence of pancreatic enzymes within them by immunohistochemistry have been unconvincing {936, 938, 1032}.

Acinar cell carcinoma variants
Acinar cell cystadenocarcinoma
Acinar cell cystadenocarcinomas are rare, grossly cystic neoplasms with cytoarchitectural features of acinar cell carcinomas {229, 825, 739, 1815}.

Mixed acinar-endocrine carcinoma
Rare neoplasms have shown a substantial (greater than 25%) proportion of more than one cell type. These neoplasms have been designated 'mixed carcinomas', and, depending upon the cell types identified, as 'mixed acinar-endocrine carcinoma', 'mixed acinar-ductal carcinoma', or 'mixed acinar-endocrine-ductal carcinoma' {997, 1369, 2015}. Of these, the best characterized is the mixed acinar-endocrine carcinoma {997}. In many mixed acinar-endocrine carcinomas, the evidence for divergent differentiation is only provided by immunohistochemical staining. Although different regions of the tumours may suggest acinar or endocrine differentiation morphologically, many areas have intermediate features, and immunohistochemistry generally shows a mixture of cells expressing acinar or endocrine markers (or both). In exceptional cases, however, there is also morphological evidence of multiple lines of differentiation,
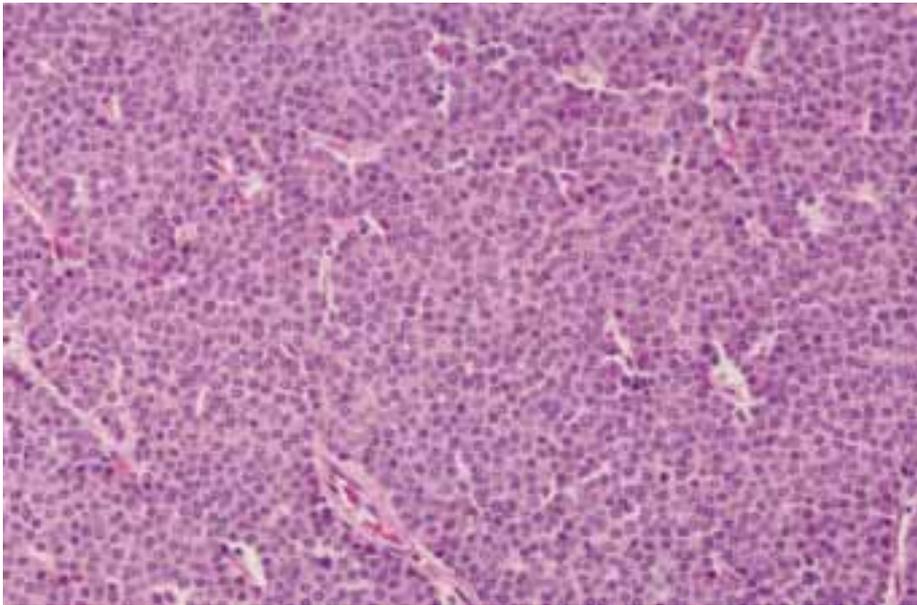
Fig. 10.30 Acinar cell carcinoma. Solid pattern with uniform round nuclei.

with some regions exhibiting obvious acinar features and other areas endocrine features. Most reported acinar-endocrine carcinomas have been composed predominantly of acinar elements based on the proportion of cells staining immunohistochemically {997}. There are insufficient cases recorded to suggest that the biological behaviour of mixed acinar-endocrine carcinomas differs from that of pure acinar cell carcinomas.

Precursor lesions

No documented precursor lesions for acinar cell carcinomas have been defined. Initial suggestions that so-called atypical acinar cell nodules may represent preneoplastic lesions of acinar cells have not been substantiated by later studies {1094}. Atypical acinar cell nodules occur either because of dilatation of the rough endoplasmic reticulum (resulting in reduced basophilia of the basal cytoplasm) or depletion of zymogen granules (resulting in reduced eosinophilia of the apical cytoplasm and an increase in nuclear:cytoplasmic ratio); these lesions are relatively common incidental findings in resected pancreases.

Genetics

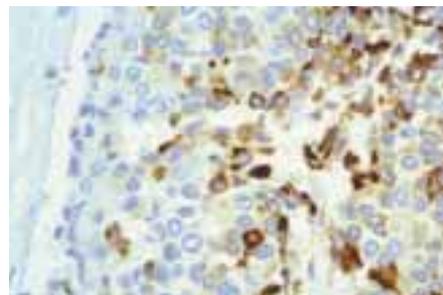In contrast to ductal adenocarcinomas, acinar cell carcinomas very rarely show

Fig. 10.31 Acinar cell carcinoma showing immunoreactivity for chromogranin.

KRAS mutations and TP53 immunoreactivity {739, 1485, 1920, 1921}.

Prognosis and predictive factors

These neoplasms are aggressive, with a median survival of 18 months and a 5-year survival rate of less than 10% {739, 936}. Approximately 50% of patients have metastases at the time of diagnosis, and an additional 25% develop metastatic disease following surgical resection of the primary tumour {936}.

The most important prognostic factor is tumour stage, with patients lacking lymph node or distant metastases surviving longer {936}. Patients with the lipase hypersecretion syndrome were shown to have a particularly short survival, because most of these patients had widespread metastatic disease. Despite poor overall survival rates, there are anecdotal reports of survival for several years in the presence of metastatic disease, and responses to chemotherapy have been noted {936}. Thus, the prognosis of acinar cell carcinoma may be somewhat less poor than that of ductal adenocarcinoma.

No specific grading system for acinar cell carcinomas has been proposed. No association between the extent of acinus formation and prognosis has been observed.

There is an insufficient number of pediatric acinar cell carcinomas to allow an accurate assessment of the biological behaviour in children. Available data suggest that acinar cell carcinomas occurring under the age of 20 may be less aggressive than their adult counterparts 936, 1446}.

Pancreatoblastoma

D.S. Klimstra
D. Longnecker

Definition
A malignant epithelial tumour, generally affecting young children, composed of well-defined solid nests of cells with acinar formations and squamoid corpuscles, separated by stromal bands. Acinar differentiation prevails, often associated with lesser degrees of endocrine or ductal differentiation.

ICD-O code   8971/3

Epidemiology
Incidence
Pancreatoblastoma is an exceedingly rare tumour, less than 75 cases having been reported {782, 939, 2117}. However, it is among the most frequent pancreatic tumours in childhood, probably accounting for 30-50% of pancreatic neoplasms occurring in young children {631}.

Age and sex distribution
The majority of pancreatoblastomas occur in children, most being under the age of 10. The median age of pediatric patients is approximately 4 years {742, 939}, and only a few cases have been described in the second decade of life {782}. A number of congenital examples have also been documented {939}. Rarely, tumours histologically indistinguishable from pancreatoblastomas occur in adult patients ranging between 19 and 56 years of age {939, 1053, 1452}. There is a slight male predominance, with an M:F ratio of 1.3:1 {939}.

Aetiology
The aetiology is unknown.

Localization
The head of the gland is affected in about 50% of cases, the remainder being equally divided between the body and the tail.

Clinical features
The presenting features of pancreatoblastoma are generally non-specific. Especially in the pediatric age group, many patients present with an incidentally detected abdominal mass {782, 939}. Related symptoms include pain, weight loss, and diarrhoea. The paraneoplastic syndromes associated with acinar cell carcinoma (lipase hypersecretion syndrome) and pancreatic endocrine neoplasms have not been described, but one patient developed Cushing syndrome {1478}.

Radiologically, pancreatoblastomas are large, well-defined, lobulated tumours which may show calcifications on CT scan {1833, 2027, 2117}.

There is no consistent elevation of serum tumour markers, but some cases have exhibited increased alpha-fetoprotein levels {802, 939}.

Macroscopy
The size of pancreatoblastomas varies from 1.5-20 cm. Most tumours are solitary, solid neoplasms composed of well-defined lobules of soft, fleshy tissue separated by fibrous bands. Areas of necrosis may be prominent. Uncommonly the
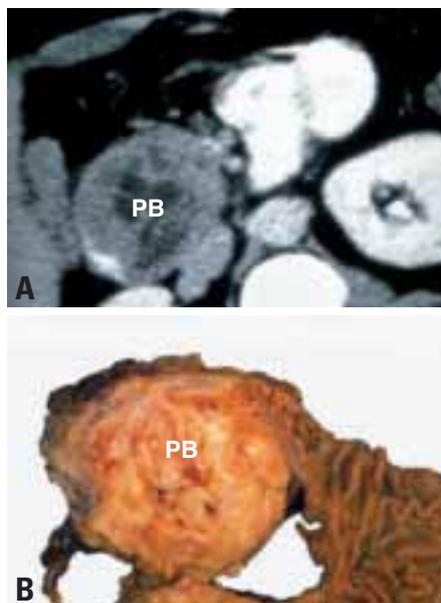

Fig. 10.32 Pancreatoblastoma. **A** CT image showing a large tumour (PB) in the head of the pancreas, with hypodense areas. **B** The cut surface of the neoplasm demonstrates a lobulated structure.

tumours are grossly cystic, a phenomenon reported in all cases associated with the Beckwith-Wiedeman syndrome {432}.

Histopathology
The epithelial elements of pancreatoblastomas are highly cellular and arranged in well-defined islands separated by stromal bands, producing a 'geographic' low power appearance. Solid, hypercellular areas composed of nests of polygonal cells alternate with regions showing more obvious acinar differentiation, with polarized cells surrounding small luminal spaces. In rare tumours, larger glandular spaces lined by mucin-containing cells may be seen {939}. Nuclear atypia is generally minimal.

Squamoid corpuscles. One of the most characteristic features of pancreatoblastoma is the 'squamoid corpuscle'. These enigmatic structures vary from large islands of plump, epithelioid cells to whorled nests of spindled cells to frankly keratinizing squamous islands. The nuclei of the squamoid corpuscles are larger and more oval than those of the surrounding cells; nuclear clearing due to the accumulation of biotin may be seen {1895}. The frequency and composition of the squamoid corpuscles varies in different regions of the tumour and between different cases.

Stroma. Especially in pediatric cases, the stroma of pancreatoblastomas is often hypercellular, in some instances achieving a neoplastic appearance. Rarely, the presence of heterologous stromal elements, including neoplastic bone and cartilage, has been reported {127, 939}.

Histochemistry and immunohistochemistry
Over 90% of pancreatoblastomas exhibit evidence of acinar differentiation in the form of PAS-positive, diastase resistant cytoplasmic granules as well as immunohistochemical staining for pancreatic enzymes, including trypsin, chymotrypsin, and lipase {939, 1282, 1400}. The staining may be focal, often limited to the apical cytoplasm in areas of the tumour with acinar formations. At least focal
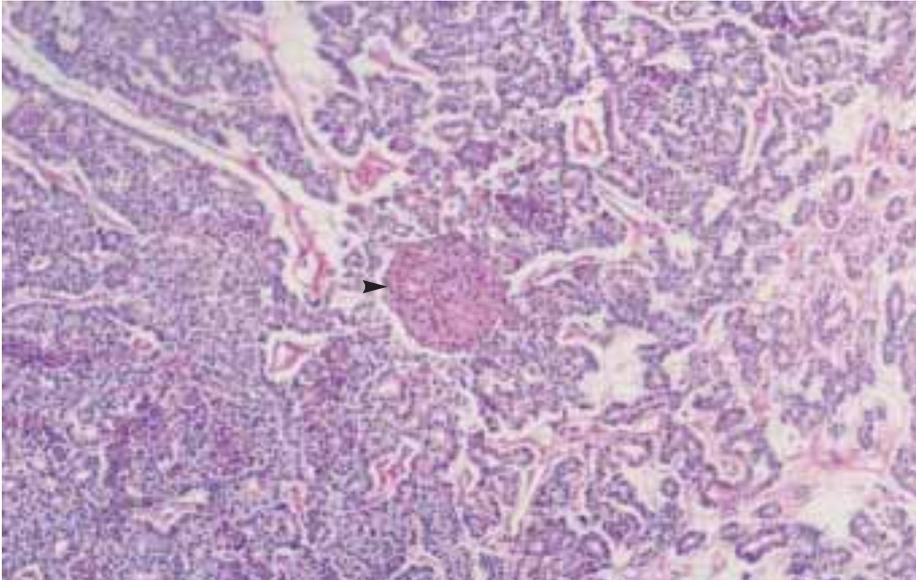
Fig. 10.33 Pancreatoblastoma with squamoid corpuscule (arrowhead), surrounded by solid (left) and tubular (right) structures.

immunoreactivity for markers of endocrine differentiation (chromogranin or synaptophysin) is found in over two-thirds of cases, and expression of markers of ductal differentiation such as CEA, DUPAN-2, or B72.3 is found in more than half of cases {939}. In most instances, the proportion of cells expressing acinar markers outnumbers the proportion expressing endocrine or ductal markers. In cases associated with elevations in the serum levels of alpha-fetoprotein, immunohistochemical positivity for AFP has been detectable {802, 939}.

Immunohistochemical evaluation of the squamoid corpuscles has failed to define a reproducible line of differentiation for this component {939}.

Relationship to acinar cell carcinoma
Both pancreatoblastomas and acinar cell carcinomas consistently exhibit acinar differentiation and may exhibit lesser degrees of endocrine and ductal differentiation. {936, 939}. Histologically, acinar formations are characteristic of pancreatoblastoma, and the solid areas resemble the solid pattern of acinar cell carcinoma. Biologically, the two tumours are also similar, with a relatively favorable prognosis in childhood, but a very poor prognosis in adulthood. For these reasons, some observers have suggested that pancreatoblastoma represents the paediatric counterpart of acinar cell carcinoma. Although this proposal is attractive in many ways, pancreatoblastoma

remains a separately definable neoplasm with characteristic histologic, immunohistochemical, and clinical features.

Ultrastructure
By electron microscopy, pancreatoblastomas generally exhibit evidence of acinar differentiation {939, 1758}, with relatively abundant rough endoplasmic reticulum and mitochondria, and apically located dense zymogen granules. The zymogen granules may be round and uniform, resembling those of non-neoplastic cells. In addition, irregular fibrillary granules similar to those described in acinar cell carcinomas may be found {936, 939}. In rare cases, dense-core neurosecretory-type granules and mucigen granules have also been observed {939}. Examination of the squamoid corpuscles has revealed tonofilaments but no evidence of a specific line of differentiation.

Genetic susceptibility
In several reported cases (all congenital examples), pancreatoblastomas have been a component of the Beckwith-Wiedeman syndrome {432}.

Prognosis
Pancreatoblastomas are malignant tumours. Nodal or hepatic metastases are present in 35% of patients {782, 939}. More widespread dissemination may also occur. In pediatric patients lacking evidence of metastatic disease at first presentation, the prognosis is very good, most patients being cured by a combination of surgery and chemotherapy {894, 1299}. In the presence of metastatic disease or in adult patients with pancreatoblastomas, the outcome is usually fatal {312, 939}, the mean survival being 1.5 years {939}. However, a favourable response to chemotherapy has been noted in some children {235, 2027}.

Solid-pseudopapillary neoplasm

G. Klöppel
J. Lüttges
D. Klimstra

R. Hruban
S. Kern
G. Adler

Definition
A usually benign neoplasm with predominant manifestation in young women, composed of monomorphic cells forming solid and pseudopapillary structures, frequently showing haemorrhagic-cystic changes and variably expressing epithelial, mesenchymal and endocrine markers.

ICD-O codes
Solid pseudopapillary neoplasm   8452/1
Solid pseudopapillary carcinoma   8452/3

Synonyms
Solid-cystic tumour {946}, papillary-cystic tumour {170}, solid and papillary epithelial neoplasm.

Epidemiology
Solid-pseudopapillary neoplasm is uncommon but has been recognized with increasing frequency in recent years {946, 1192, 1358}. It accounts for approximately 1-2% of all exocrine pancreatic tumours {359, 941, 1280}.

Fig. 10.34 Solid-pseudopapillary neoplasm. **A** The round hypodense tumour (T) replaces the tail of the pancreas. **B** The pseudocystic neoplasm is attached to the spleen, and shows haemorrhagic necrosis.

It occurs predominantly in adolescent girls and young women (mean 35 years; range 8-67 years) {1781, 1072}. It is rare in men (mean, 35 years; range 25-72 years) {945, 1193, 1975}. There is no apparent ethnic preference {978, 1395}.

Aetiology
The aetiology is unknown. The striking sex and age distribution point to genetic and hormonal factors, but there are no reports indicating an association with endocrine disturbances including overproduction of oestrogen or progesterone. Moreover, only very few women developed a solid pseudopapillary neoplasm after long-term use of hormonal contraceptives {359, 436, 1655}.

Localization
There is no preferential localization within the pancreas {1282, 1358}.

Clinical features
Usually, the neoplasms are found incidentally on routine physical examination or they cause abdominal discomfort and pain {1358}, occasionally after abdominal trauma {945}. Jaundice is rare {1427}, even in tumours that originate from the head of the pancreas, and there is no associated functional endocrine syndrome. All known tumour markers are normal.

Ultrasonography (US) and computed tomography (CT) reveal a sharply demarcated, variably solid and cystic mass without any internal septation {300}. The tumour margin may contain calcifications. Administration of contrast medium results in enhancement of the solid tumour parts. On angiography, the neoplasms are usually hypovascular or mildly hypervascular lesions with displacement of surrounding vessels {2153}. Fine needle aspiration cytology performed under radiological control shows monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm {234, 2119, 2140}.

Macroscopy
The neoplasms present as large, round, solitary masses (average size 8-10 cm; range, 3-18 cm), and are often fluctuant. They are usually encapsulated and well demarcated from the surrounding pancreas. Multiple tumours are exceptional {1427}. The cut surfaces reveal lobulated, light brown solid areas, zones of haemorrhage and necrosis, and cystic spaces filled with necrotic debris. Occasionally, the haemorrhagic-cystic changes involve almost the entire lesion so that the neoplasm may be mistaken for a pseudocyst. The tumour wall may contain calcifications {1358}. A few tumours have been found to be attached to the pancreas or even in extrapancreatic locations {812, 914, 945}. Invasion of adjacent organs or the portal vein is rare {1655, 1684, 1701}.
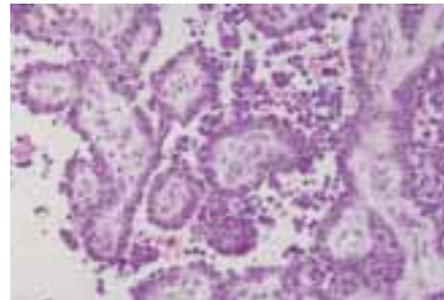

Fig. 10.35 Solid-pseudopapillary neoplasm. The pseudopapillary structures are lined by small monomorphic cells.

Tumour spread
Only few metastasizing solid-pseudopapillary neoplasms have been reported {359, 1358}. Common metastatic sites include regional lymph nodes, the liver, peritoneum, and greater omentum {300, 2209, 1358}.

Histopathology
In large neoplasms, extensive necrosis is typical and the preserved tissue is usually found in the tumour periphery under the fibrous capsule. This tissue exhibits a solid monomorphic pattern with variable sclerosis. More centrally there is a pseudopapillary pattern, and these components often gradually merge into each

other. In both patterns, the uniform poly-hedral cells are arranged around deli-cate, often hyalinized fibrovascular stalks with small vessels {1395}. Neoplastic cells that are arranged radially around the minute fibrovascular stalks may resemble 'ependymal' rosettes. Luminal spaces are consistently absent. In the solid parts, disseminated aggregates of neoplastic cells with foamy cytoplasm or cholesterol crystals surrounded by foreign body cells may be found. The spaces between the pseudopapillary structures are filled with red blood cells. The hyalinized connec-tive tissue strands may contain foci of cal-cification and even ossification {1193}.

The neoplastic cells have either eosino-philic or clear vacuolar cytoplasm. Occasionally they contain eosinophilic, diastase-resistant PAS-positive globules of varying size, which may also occur outside the cells. Glycogen or mucin cannot be detected. Grimelius positive cells may occur. The round to oval nuclei have finely dispersed chromatin and are often grooved or indented. Mitoses are usually rare, but in a few instances prominent mitotic activity is observed {1358}. In rare cases, there is also vessel invasion {2140}. The neoplastic tissue is usually well demarcated from the normal pancreas, although a fibrous capsule may be absent and invasion of tumour cell nests into the surrounding pancreat-ic tissue may occur {1193, 1358}.

Criteria of malignancy
Although criteria of malignancy have not yet been clearly established, it appears that unequivocal perineural invasion, angioinvasion, or deep invasion into the surrounding tissue indicate malignant behaviour, and such lesions should be classified as solid-pseudopapillary carci-noma. Nishihara et al. {1358} compared the histological features of three metasta-sizing and 19 nonmetastasizing solid-pseudopapillary neoplasms, and found that venous invasion, degree of nuclear atypia, mitotic count and prominence of necrobiotic cell nests (cells with pyknotic nuclei and eosinophilic cytoplasm) were associated with malignancy. However, neoplasms in which the above-mentioned histological criteria of malignancy are not detected may also give rise to metas-tases. Consequently, benign appearing solid-pseudopapillary neoplasms must be classified as lesions of uncertain malig-nant potential.
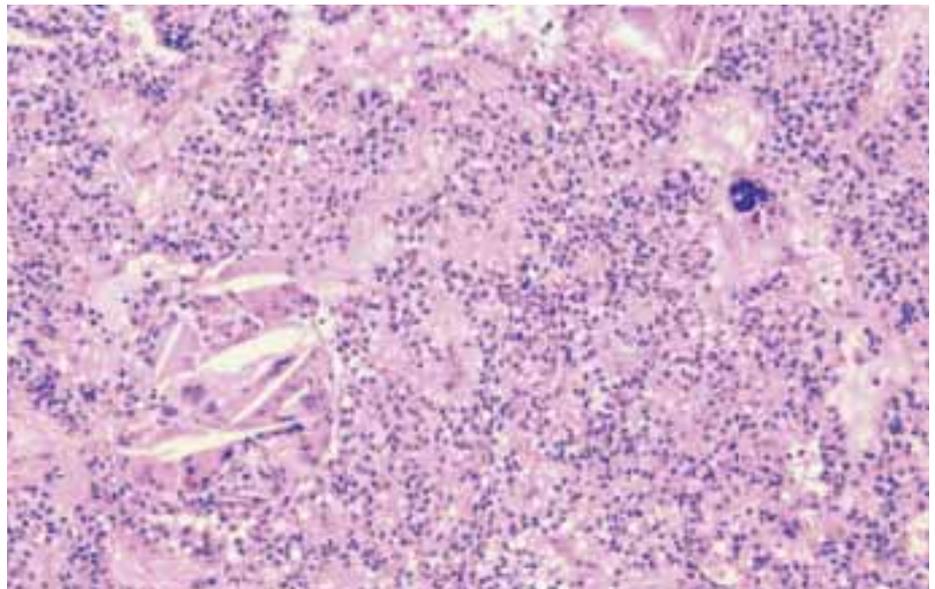

Fig. 10.36 Solid pseudopapillary tumour. Solid area containing cholesterol crystals and foreign body giant cells.
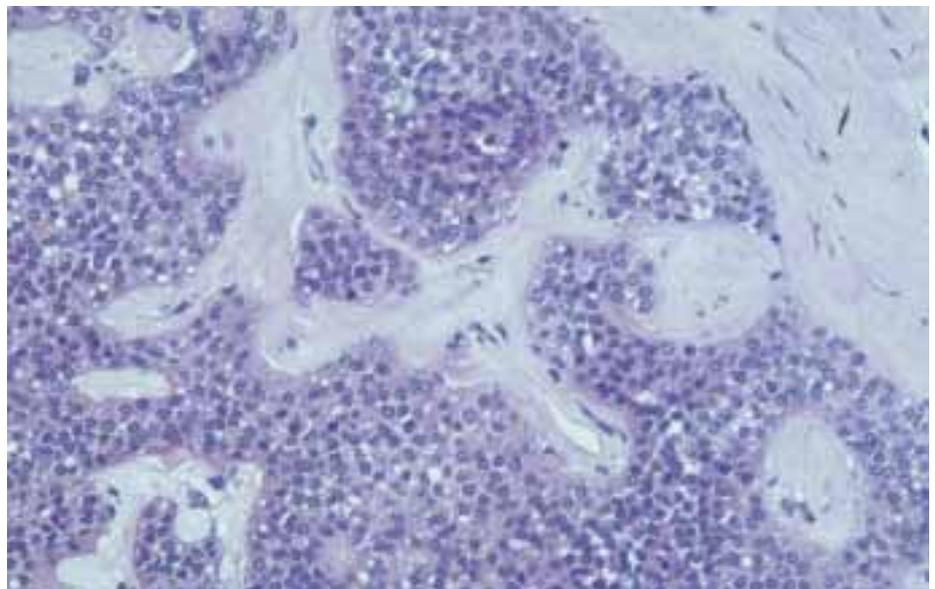

Fig. 10.37 Solid pseudopapillary tumour. In this solid area, the uniform tumour cells are separated by vas-cular hyalinized stroma.

Histochemistry and immunohistochemistry
The most consistently positive markers for solid-pseudopapillary neoplasms are alpha-1-antitrypsin, alpha-1-antichymo-trypsin, neuron specific enolase (NSE), vimentin and progesterone receptors {306, 945, 963, 1226}. The cellular reac-tion for alpha-1-antitrypsin and alpha-1-antichymotrypsin is always intense, but only involves small cell clusters or single cells, a finding that is characteristic of this neoplasm. Alpha-1-antitrypsin also stains the PAS-positive globules. Staining for NSE and vimentin, in contrast, is usu-ally diffuse.

Inconsistent results have been reported for epithelial markers, synaptophysin, pancreatic enzymes, islet cell hormones and other antigens such as CEA or CA 19.9. Most authors report negative results for chromogranin A, CEA, CA 19.9 and AFP. A few neoplasms have been found to express S-100 {945, 1226, 1358}. Cytokeratin is detected in 30% {946} to 70% {963, 2195}, depending on the method of antigen retrieval applied.

Usually, the staining for keratin is focal and faint. The keratin profile (CK 7, 8, 18 and 19) is that of the ductal cell {740, 1844}. Positive immunoreactivity for trypsin, chymotrypsin, amylase and/or phospholipase A2 has been reported {166, 1072, 1192, 1226, 1844}, but has not been confirmed by most other authors {812, 945, 1282}. Similarly, focal positivity for glucagon, somatostatin and/or insulin has been described in some tumours {1226, 2021, 2147}, but was not detected in most other cases {1072, 1282, 1844}.

Ultrastructure
The neoplastic cells have round or markedly indented nuclei containing a small single nucleolus and a narrow rim of marginated heterochromatin. The cells show abundant cytoplasm, which is rich in mitochondria. Zymogen-like granules of variable sizes (500-3000 nm) are conspicuous, probably representing deposits of alpha-1-antitrypsin. The contents of these granules commonly dis-integrate, forming multilamellated vesicles and lipid droplets {946, 1031, 1226, 2154}. Neurosecretory-like granules have been described in a few tumours {867, 880, 1684, 2119, 2147}. Intermediate cell junctions are rarely observed and microvilli are lacking, but small intercellular spaces are frequent.

Genetics
In contrast to infiltrating ductal carcinomas, solid-pseudopapillary neoplasms appear to have wild-type *KRAS* genes and do not immunoexpress p53 {512, 1007, 1039}. An unbalanced translocation between chromosomes 13 and 17 resulting in a loss of 13q14→qter and 17p11→pter has been described in one solid-pseudopapillary neoplasm {616}.

Prognosis and predictive factors
In general, the prognosis is good. After complete removal more than 95% of the patients are cured. Local spread or dissemination to the peritoneal cavity has been reported in the context of abdominal trauma and rupture of the tumour {1060}. Even in patients who had local spread, recurrences {359, 999}, or metastases {234, 1192, 1642}, long disease-free periods have been recorded after initial diagnosis and resection. Only a few patients have died of a metastasizing solid-pseudopapillary neoplasm {1192, 1395}.

Histological criteria. Perineural invasion, angioinvasion, or deep invasion into the surrounding tissue indicate malignant behaviour, and such lesions are classified as solid-pseudopapillary carcinoma. Venous invasion, a high degree of nuclear atypia, mitotic activity and prominence of necrobiotic cell nests (cells with pyknotic nuclei and eosinophilic cytoplasm) were reported to be associated with malignancy {1358}.

DNA content. There is evidence that an aneuploid DNA content assessed by flow cytometry is associated with malignant behaviour, although the number of cases studied is small {867, 1358, 234}.

Miscellaneous carcinomas of the pancreas

G. Zamboni
G. Klöppel

Oncocytic carcinoma

These lesions are characterized by large cells with granular eosinophilic cytoplasm and large nuclei with well-defined nucleoli. Ultrastructurally, the cells show abundant mitochondria and lack zymogen and neuroendocrine granules. Local invasiveness, lymph node and pulmonary metastasis can occur {1781}. Differential diagnosis includes endocrine tumour {1454} and solid pseudopapillary tumour.

Nonmucinous, glycogen-poor cystadenocarcinoma

A large, encapsulated mass with cystic spaces lined by serous adenoma like component and malignant-appearing columnar epithelium. The tumour cells are negative for mucins and show oncocytic features by electron microscopy {533}.

Choriocarcinoma

An aggressive tumour, associated with elevated levels of serum human chorionic gonadotrophin (hCG), composed of cytotrophoblastic cells intermingled with syncytiotrophoblastic cells immunoreactive for hCG. Choriocarcinoma can be 'pure' or associated with mucinous cystadenocarcinoma {1781, 2194}.

Clear cell carcinoma

A carcinoma composed of clear cells, rich in glycogen and poor in mucin, morphologically resembling renal cell carcinoma {941}. Adenocarcinomatous, anaplastic, or intraductal papillary components can be found {1781}. A ductal phenotype has been suggested by the pattern of immunoreactivity for cytokeratins, the lack of vimentin expression, and the presence of *KRAS* mutation {1121}.

Ciliated cell carcinoma

This lesion shows the pattern of ductal adenocarcinoma, but contains many ciliated cells, as demonstrated at the ultrastructural level {1781}.

Microglandular carcinoma

Also known as microadenocarcinoma, this lesion is characterized by cribriform or microglandular pattern of growth {941}. The same cases were reclassified with immunohistochemistry as adenocarcinoma, acinar cell carcinomas and endocrine carcinoma {1090}. Microglandular carcinoma is best regarded as a pattern of growth rather than a distinctive entity.

Medullary carcinoma

This recently described carcinoma shows a syncytial growth pattern and lymphoepithelioma-like features (see chapter on ductal adenocarcinoma, other rare carcinomas) {590}.

Mesenchymal tumours of the pancreas

M. Miettinen
J.Y. Blay
L.H. Sobin

Primary mesenchymal tumours of the pancreas are exceedingly rare. Leiomyosarcomas and malignant gastrointestinal stromal tumours appear to be the least uncommon.

Recently, solitary fibrous tumours, similar to those more commonly seen on the serosal surfaces of the pleura and peritoneum, have been described (1118). Histologically they show bland spindle cells in a collagenous background. The lesional cells are positive for CD34 but negative for KIT and desmin; focal actin positivity may occur.

Lymphoma of the pancreas

H.K. Müller-Hermelink
A. Chott
R.D. Gascoyne
A. Wotherspoon

Definition
Primary lymphoma of the pancreas is defined as an extranodal lymphoma arising in the pancreas with the bulk of the disease localized to this site. Contiguous lymph node involvement and distant spread may be seen but the primary clinical presentation is in the pancreas with therapy directed to this site.

Epidemiology
Primary lymphoma of the pancreas is very rare accounting for less than 0.5% of pancreatic tumours. As with primary lymphomas occurring elsewhere in the digestive tract, patients are more frequently elderly {796}.

Aetiology
Immunodeficiency predisposes to pancreatic lymphoma, both in the setting of HIV infection {866} and as post-transplant lymphoproliferative disorders following solid organ transplantation {240}. Familial pancreatic lymphoma has been reported in a sibling pair (brother and sister) who each presented with a high-grade B-cell lymphoma in their seventh decade {830}. Pancreatic lymphoma has also been described in a patient with short bowel syndrome {903}.

Clinical features
The presentation of primary pancreatic lymphoma may mimic that of carcinoma or pancreatitis {240}. Pain free jaundice can occur {1330}. Ultrasonography may show an echo-poor lesion {1330}.

Histopathology
Primary pancreatic lymphomas are usually of B phenotype. Lymphomas of various types have been described, including low-grade lymphomas of diffuse small cell type {903, 1480}, follicle centre cell lymphoma {1330, 1238}, low-grade MALT lymphoma {1925}, and large B-cell lymphoma {1529, 830}. Only extremely rare cases of pancreatic T-cell lymphoma have been reported, including a single case of anaplastic large cell lymphoma (CD30 positive) of T-cell type {1179} and a case of pancreatic involvement by adult T-cell leukaemia/lymphoma {1408}. The histology of these cases varies little from that seen where these lymphoma types are encountered more frequently.

Prognosis
The distinction between lymphoma and carcinoma is important, as pancreatic lymphomas are associated with better prognosis and may be curable even in advanced stages. Occasional cases of relapse following prolonged remission have been reported in cases treated by chemotherapy {1529}.

Secondary tumours of the pancreas

E. Paál
A. Kádár

Epidemiology
Secondary tumours of the pancreas are in most cases part of an advanced metastatic disease. They account for 3-16% of all pancreatic malignancies, affecting males and females equally {1190, 1012, 1597, 1781}. In our experience based on combined autopsy and histology material, out of 610 neoplasms involving the pancreas 26 (4.25%) were secondary. Any age may be affected, but the highest incidence is in the 6th decade.

Localization
Any anatomic region of the pancreas may be involved and there is no site predilection {934}. Lesions can be solitary, multiple, or diffuse {502}.

Clinical features
There are no specific symptoms for secondary tumours of the pancreas. Abdominal pain, jaundice, and diabetes might be the first sign, or in some cases an attack of acute pancreatitis {1290, 1608, 1772}.

The lesions are most commonly detected by imaging studies {934}. Fine needle aspiration can provide a rapid diagnosis {905, 645, 1250}.

Origin
Both epithelial and non-epithelial secondary tumours occur in the pancreas. The pancreas may be involved by direct spread (e.g. from stomach, liver, adrenal gland, retroperitoneum) or by lymphatic or haematogenous spread from distant sites {905}. Renal cell carcinoma is
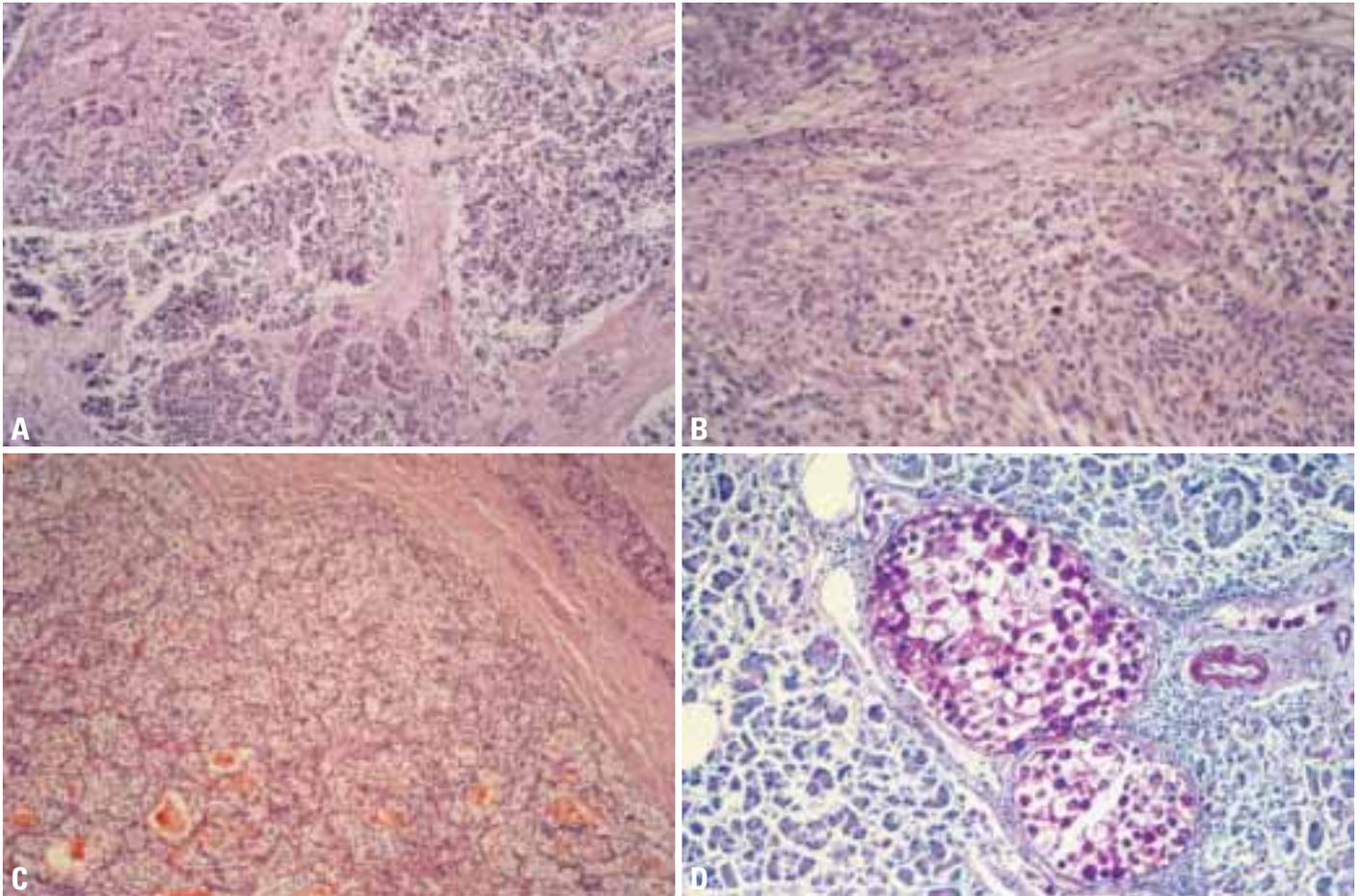
Fig. 10.38 Secondary tumours in the pancreas. **A** Metastatic small cell lung carcinoma. **B** Metastatic melanoma. **C** Metastatic renal cell carcinoma. **D** Metastatic gastric signet ring cell carcinoma.

unique as a primary site since it might give rise to late solitary metastases {1644, 218}.

Histopathology

The main differential diagnostic problem is to distinguish metastases from primary pancreatic neoplasms. The most problematic tumours are metastases from the gastrointestinal tract, renal cell carcinomas, small cell carcinoma, and lymphomas {240, 645, 1781}. Apart from the clinical and radiological signs {934}, multiple tumour foci with an abrupt transition from normal pancreas to the neoplastic tissue without signs of chronic pancreatitis in the surrounding parenchyma support metastatic origin {2089}. Immunohistochemistry specific for certain primary tumours may also be helpful {1190, 1707}.

Prognosis

Since in most cases pancreatic metastases indicate an advanced neoplastic disease, the prognosis is generally poor. In cases of solitary metastases, combined adjuvant therapy and surgical resection might be beneficial {360, 674, 218, 1597}.