Ductal Adenocarcinoma

9

9.1 Definition and Terminology

Ductal adenocarcinoma is a malignant epithelial neoplasm arising in the pancreas, which exhibits glandular differentiation and does not contain a predominant component of another type of neoplasia (see Chap. 20).

The name 'ductal adenocarcinoma' implies that the neoplasm originates from the pancreatic duct system. Although the exact cellular origin is still debated, current data indicate that ductal adenocarcinoma is likely to develop from a cell type in the peripheral ramifications of the duct system. Therefore, topographical association of ductal adenocarcinoma with the main pancreatic duct or large caliber branch ducts is more likely to reflect secondary tumor involvement than the site of cancer origin, except in the context of intraductal papillary neoplasia (see Chap. 17).

Tubular adenocarcinoma, infiltrating duct carcinoma, and duct cell carcinoma are occasionally used as synonyms for ductal adenocarcinoma. The term mucinous adenocarcinoma refers to ductal adenocarcinoma of the pancreas with intracellular or intraluminal mucin production and should not be confounded with colloid carcinoma (syn. mucinous noncystic carcinoma), which is a subtype of ductal adenocarcinoma characterized by large extracellular mucin pools containing suspended neoplastic cells (see Sect. 9.14.2).

In clinical practice, and also throughout this chapter, the term 'pancreatic cancer' is used as a shorthand for ductal adenocarcinoma. The term 'pancreatic head cancer' is ambiguous, as it either indicates ductal adenocarcinoma of the pancreas arising in the pancreatic head or can be used as a more generic term for adenocarcinoma of ampullary, common bile duct, or pancreatic origin.

9.2 Epidemiology

Ductal adenocarcinoma accounts for 85–90% of all pancreatic neoplasms. It is a fairly common cancer, although its incidence varies between different parts of the world. Overall, pancreatic cancer is more common in higher-income than in lower-income countries (age-adjusted incidence rate for both sexes 6.2 versus 1.5 cases per 100,000 person-years), which may reflect a difference in both genuine cancer incidence and pancreatic cancer reporting due to unequal accessibility to advanced medical diagnostics. A further reason for the geographical variation in incidence is the possible existence of racial differences. Epidemiological data show, for instance, that native Hawaiians, Alaskans, and African-Americans are more frequently affected than white Americans, and that the incidence in the Maori population is higher than in the remainder of the population in New Zealand. How far these differences between various population groups can be explained by differences in expo-

F. Campbell, C. S. Verbeke, *Pathology of the Pancreas*,
https://doi.org/10.1007/978-3-030-49848-1_9

sure to etiological factors such as tobacco smoking, is yet to be determined. Studies of migrant populations moving from low- to high-risk regions suggest an important role of environmental exposure, because after 15–20 years the risk of the first generation migrants has increased above the level of the country of origin.

Between the 1950s and the 1980s, the incidence rates of pancreatic cancer rose in high-income countries but leveled off or slightly declined thereafter, particularly in men. In 2007, the highest mortality rates in men were observed in the Baltics, the Nordic, and some Eastern European countries (over 9/100,000), while the lowest rates were recorded in Latin America and Hong Kong [1]. Recent reports indicate an increasing incidence rate in Europe and North America, which may be the result of ageing populations and increasing risk factors, in particular obesity. It has been predicted that by 2030, pancreatic cancer will become the second-leading cause of cancer-related death in the Western world, which is mainly due to the continued improvement of prognosis for cancers in other organs.

Due to its poor prognosis, ductal adenocarcinoma of the pancreas is one of the few cancers for which the incidence nearly equals the mortality rate. It ranks as the 7th leading cause of cancer-related death worldwide but takes up position 4 in the Western world.

Pancreatic cancer affects mainly the middle-aged to elderly, age being an important risk factor. It is rare before the age of 40 and extremely uncommon before age 20. There is only a mild male predilection (male:female ratio: 1.1–1.3:1.0).

9.3 Etiology

Our knowledge of the etiology of pancreatic cancer is limited. However, intense research in recent years, both in the epidemiological and molecular biological fields, has brought to light a number of extrinsic and genetic risk factors, as well as a possible interaction between both.

Hereditary risk factors for ductal adenocarcinoma of the pancreas, believed to play a role in an estimated 10% of patients, are covered in the chapter on hereditary disease (see Chap. 6, Sect. 6.4). In addition to the relatively rare, inherited diseases and syndromes, the ABO blood type has been shown to be related to the risk of pancreatic cancer (lower in individuals with O blood type compared to type A or B).

Only a small number of extrinsic risk factors have been convincingly identified. Tobacco smoking is by far the strongest risk factor, the risk for current smokers compared to never smokers being increased 2- to 3-fold. Heavy (but not mild or moderate) alcohol consumption is a possible, weak etiological factor, which may have genetic and epigenetic effects in addition to potentiating other risk factors such as smoking, poor nutrition, and the inflammatory pathways that are related to chronic pancreatitis. The role of diet-related factors in the development of pancreatic cancer has been studied intensely, but the results are conflicting. Overall, the consumption of red or processed meat, especially when cooked at high temperatures, the intake of N-nitrosamines or nitrates, high intake of (saturated) fats, low consumption of fruits and vegetables, and a low dietary folate intake are associated with an increased risk. Several occupational exposures have also been linked to ductal adenocarcinoma of the pancreas, in particular those connected to industrial areas such as car manufacturing, coal gas industries, hide tanning, and metalworking.

Chronic pancreatitis, particularly if hereditary, is the most important medical condition that is associated with an increased risk of ductal adenocarcinoma (see Chap. 6, Sect. 6.4 and Chap. 7, Sect. 7.2.10). Longstanding diabetes type 2 and obesity, in particular obesity during adolescence, are likely further risk factors, although the associated increase in risk is estimated at only 1.5- to 2-fold. The risk associated with previous cholecystectomy or partial gastrectomy has not been confirmed by all studies.

The link between these established or possible risk factors and the morphologically defined precursor lesions of invasive ductal adenocarcinoma (pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasia, mucinous cystic neoplasia) is left largely unexplored, except for familial pancreatic cancer, in which precursor

lesions are the target of screening and surveillance programmes for high-risk individuals (see Chap. 6, Sect. 6.6).

9.4 Clinical Features

Recent studies indicate that—at least in some patients—pancreatic cancer may already have been present for close to a decade before the disease becomes clinically manifest [2]. As the initial clinical symptoms are frequently nonspecific, the diagnosis of pancreatic cancer may be delayed even further. Weight loss and epigastric pain, often radiating towards the back, are the most common symptoms. Some patients may also develop nausea and symptoms of biliary obstruction, that is, pruritus, dark urine, and clay-colored stools. However, in the majority of patients, it is only painless jaundice that will be sufficiently alarming to lead them to seek medical advice. Diabetes mellitus type 2 is a further known clinical manifestation of pancreatic cancer that may precede the cancer diagnosis by 24 months. The sudden onset of this type of diabetes as well as the association with weight loss rather than weight gain differ from the usual type 2 diabetes that is common in the elderly age group and should alert the clinician to the possibility of pancreatic cancer-associated diabetes [3]. Two further clinical signs related to ductal adenocarcinoma usually develop at a later disease stage and only in a proportion of patients: Trousseau syndrome (migratory thrombophlebitis) and the Sister Mary Joseph nodule. The latter refers to a palpable periumbilical nodule, which represents a subcutaneous metastasis of pancreatic cancer. Other, less common presentations include acute pancreatitis, hypoglycemia, hypercalcemia, metastatic carcinoma of unknown origin, and endocarditis.

The clinical presentation depends on the location of the tumor. While painless jaundice is the main presenting sign of cancer arising in the pancreatic head, there is no comparable sign for tumors developing in the body or tail of the pancreas. Consequently, ductal adenocarcinoma in the body or tail often presents at an even more advanced stage than pancreatic head cancer. General symptoms such as weight loss and fatigue, pain, and possibly a palpable tumor mass are the main alarming features for this group of pancreatic cancers.

The mainstay of pancreatic cancer diagnostics nowadays is abdominal imaging, in particular computerized tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS). Pancreatic ductal adenocarcinoma is usually identified as a hypodense mass that may deform or expand the pancreatic outlines and often involves the peripancreatic soft tissue or other surrounding structures. Dilatation and abrupt cut-off of the main pancreatic duct, common bile duct, or both (the so-called double duct sign) are highly suggestive of cancer of the pancreatic head. The degree of local and regional tumor extension, which is paramount to decisions regarding the resectability of the cancer, can be assessed with the three modalities. EUS offers the additional advantage of fine needle aspiration (FNA) or biopsy (FNB) from the lesion. FNA/FNB is particularly important for the management of patients with unresectable pancreatic cancer, whose cytotoxic treatment usually requires a positive tissue diagnosis (see Chap. 24). Endoscopic retrograde cholangiopancreatography (ERCP) is more invasive and associated with the risk of acute pancreatitis, which makes it less attractive as a first-line diagnostic investigation but may be required for stent insertion to relieve biliary obstruction.

Serum carcinoembryonic antigen (CEA) and CA19.9 have insufficient sensitivity and specificity to be useful as screening markers. However, they are used for follow-up to monitor treatment effect and identify tumor recurrence.

9.5 Macroscopy

Ductal adenocarcinoma of the pancreas usually presents as a poorly circumscribed tumor mass with an ill-defined, highly infiltrative margin (Fig. 9.1), although occasionally, tumors may be more sharply demarcated (Fig. 9.2). It has a characteristic firm, ‘wooden’ consistency. The tumor is most commonly of a pale greyish-white color, and occasionally a yellow-orange tinge may be seen where the cancer infiltrates adipose tissue.

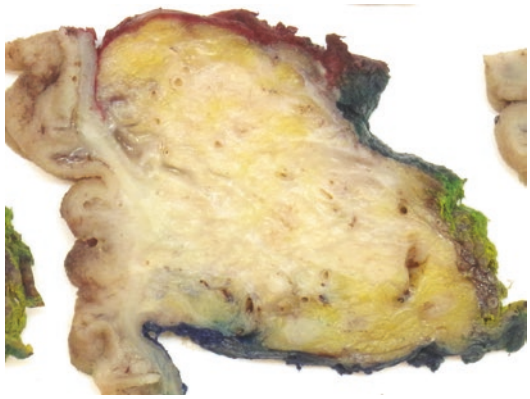


Fig. 9.1 Macroscopy: the tumor consists of pale tissue and is poorly circumscribed

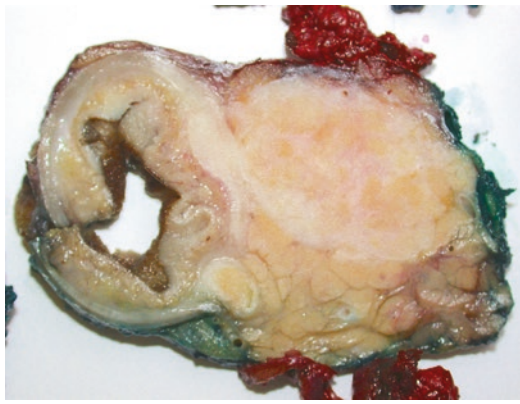


Fig. 9.2 Macroscopy: white tumor tissue is relatively well demarcated from the lobulated, ochre-colored pancreatic parenchyma

The tumor is usually of an irregular spherical shape and can reach a size of up to or over 10 cm. Most commonly, the tumor size ranges between 2 and 4 cm. Ductal adenocarcinomas smaller than 1 cm are highly uncommon, except for those arising in the context of intraductal papillary mucinous neoplasia, mucinous cystic neoplasia, tumors picked up during screening of high-risk patients, or so-called incidentalomas (see Fig. 9.38). Ductal adenocarcinoma of the body and tail is usually larger in size than that arising in the pancreatic head, because obstructive jaundice is a common, earlier presenting sign of the latter (Fig. 9.3). Due to the characteristically ill-defined outlines of ductal adenocarcinoma, the tumor size is often underestimated on naked-eye inspection, and microscopic assessment is required to establish the tumor dimensions and identify the correct tumor stage (see Chap. 3, Sect. 3.3.8).

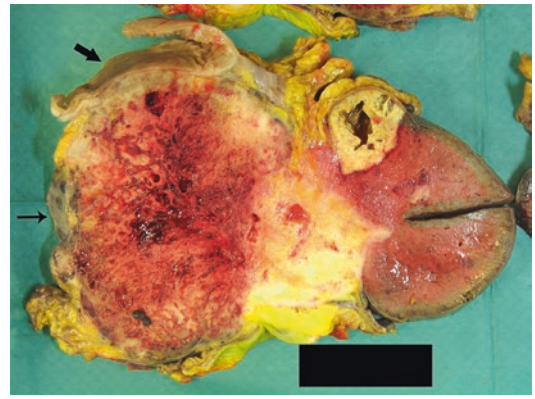


Fig. 9.3 Macroscopy: a large tumor of the pancreatic body and tail infiltrates the spleen, gastric wall (*arrow*), and colon (*block arrow*). Note the unusual hemorrhagic sponge-like appearance of the tumor where it infiltrates the retroperitoneal soft tissue (same tumor as shown in Figs. 2.6 and 9.63)

Ductal adenocarcinomas are solid tumors. A cystic component due to tumor necrosis may be present. However, in most tumors necrosis is too limited in extent to cause gross cavitation (Fig. 9.4). Smaller cystic areas, measuring up to several millimeters in size, may be seen in subtypes of ductal adenocarcinoma, such as large duct adenocarcinoma or colloid carcinoma (see Sects. 9.8.3 and 9.14.2), in which large tumor glands or mucinous collections, respectively, can reach a macroscopically visible size. Not infrequently associated with pancreatic cancer are small retention cysts, that is, native pancreatic ducts that are cystically dilated due to tumor-related outflow obstruction (see Chap. 19, Sect. 19.3.2). The presence of significant cystic areas in a ductal adenocarcinoma, in particular if containing mucin, should raise the suspicion of underlying mucinous cystic neoplasia or intraductal papillary mucinous neoplasia (see Chaps. 16 and 17).

Hemorrhage is an uncommon finding in pancreatic cancer, with the exception of undifferentiated carcinoma with osteoclast-like giant cells, a subtype of ductal adenocarcinoma, which differs from the typical macroscopic morphology of pancreatic cancer in several aspects (see Sect. 9.14.8).

Ductal adenocarcinoma is commonly associated with marked fibrosis of the surrounding

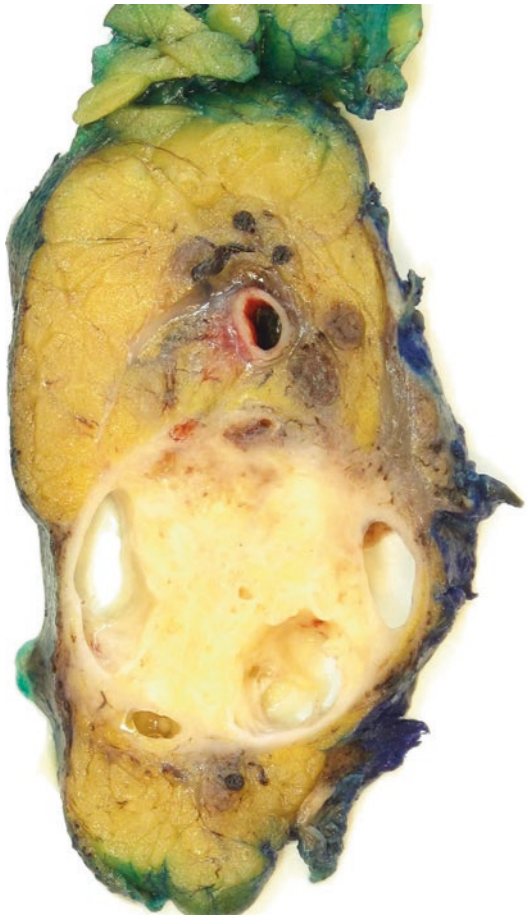


Fig. 9.4 Cystic degeneration: this ductal adenocarcinoma of the pancreatic body contains multiple irregular cystic areas due to tumor necrosis

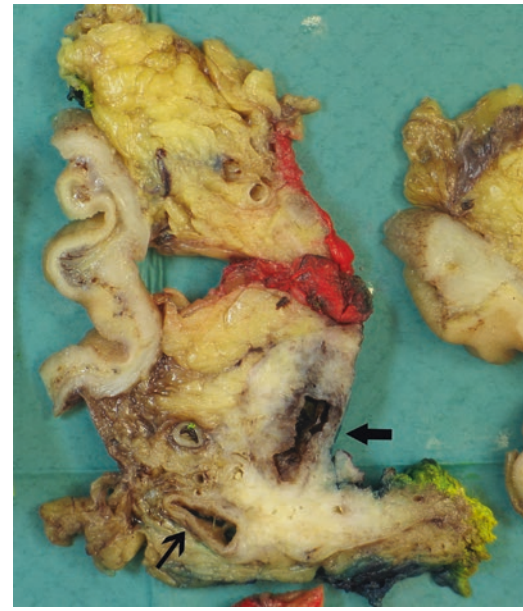


Fig. 9.5 Double duct dilatation: a ductal adenocarcinoma seated in the cranial part of the pancreatic head causes obstruction and prestenotic dilatation of the extrapancreatic common bile duct (*arrow*) and the main pancreatic duct (*block arrow*) close to the pancreatic neck transection margin

pancreas. This phenomenon further obscures the ill-defined invasive tumor front and renders the macroscopic identification of the tumor extent even more difficult. Fibrosis of the pancreas is often associated with a degree of parenchymal atrophy around and upstream from the tumor site, and this characteristic combination of features is often referred to as obstructive pancreatitis or peritumoral pancreatitis (see Chap. 7, Sects. 7.2.4 and 7.2.6.4). Dilatation of the main pancreatic duct due to tumor obstruction is common (Fig. 9.5). Dilatation of the common bile duct, in isolation or in combination with pancreatic duct dilatation is a frequent finding. A metal or plastic stent may be introduced to alleviate the biliary obstruction (see Chap. 3, Sect. 3.3.3).

The vast majority of ductal adenocarcinomas extend beyond the confines of the pancreas and infiltrate surrounding structures such as the duodenal wall, ampulla, common bile duct, peripancreatic soft tissue, and the adjacent large vessels, that is, the superior mesenteric, portal, or splenic vein (Fig. 9.6). Especially when located in the very top (i.e., most cranial) part of the pancreatic head, ductal adenocarcinoma, even of fairly small size, commonly involves multiple neighboring structures, that is, the common bile duct, portal vein, or gastroduodenal artery (Fig. 9.7). Pancreatic cancer developing in the pancreatic body or tail may infiltrate the spleen, stomach, (meso-)colon, small bowel, adrenal gland, Gerota's fascia, perirenal fat, renal hilum, or renal parenchyma (Fig. 9.3). Metastatic deposits in peripancreatic lymph nodes are not uncommonly macroscopically visible (see Fig. 3.17).

Ductal adenocarcinoma of the pancreas is usually a solitary lesion, but multifocal tumors have been reported. Diffuse cancer involvement of the pancreas is exceedingly rare. The majority of pancreatic cancers develop in the pancreatic

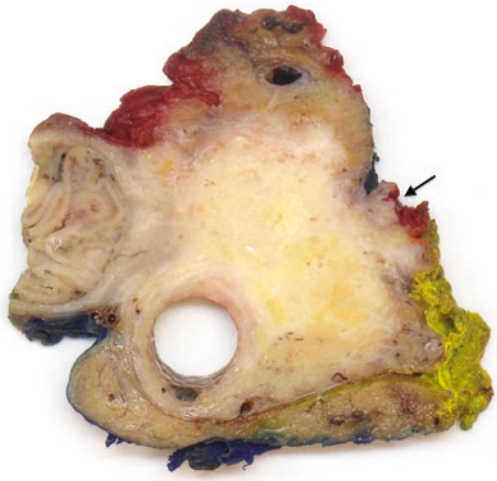


Fig. 9.6 Duodenal invasion: tumor tissue spans the full width of the pancreatic head and infiltrates both the duodenal wall and SMV groove, necessitating a small resection of the SMV (*arrow*)

Fig. 9.7 Invasion of bile duct and portal vein: the tumor is located in the cranial part of the pancreatic head. The invasive front of the tumor shows segmental invasion of the common bile duct (*short arrows*) and focal infiltration of a segment of resected portal vein (*long arrow*)

head (60–70%). As carcinoma in this location is more often resectable than adenocarcinoma arising in the pancreatic body or tail, it is usually overrepresented in surgical series.

Adenocarcinoma in the pancreatic head with macroscopic features as outlined above is not always of pancreatic origin but may have arisen from the ampulla, distal common bile duct, or duodenum. Distinction between these cancers, which are often collectively referred to as 'periampullary cancers', is of paramount significance, and detailed macroscopic assessment of the tumor location, epicenter, and extension is key to correct cancer origin attribution (see Sect. 9.12.3).

9.6 Microscopy

Ductal adenocarcinoma of the pancreas consists of highly infiltrative neoplastic epithelial tumor cells, which show a degree of gland formation and are embedded in a prominent desmoplastic stroma. The tumor glands are distributed haphazardly, irrespective of the lobular architecture of the pancreas and the organized spatial distribution of ducts and muscular blood vessels. This is an important diagnostic feature, which is particularly helpful in distinguishing pancreatic cancer from reactive glandular structures (see Sect. 9.12.1).

9.6.1 Pancreatobiliary Type

The vast majority of ductal adenocarcinomas are of the so-called pancreatobiliary type, which is characterized by the formation of small to medium-sized simple or branched glands (Fig. 9.8). The glands often have irregular and angulated contours and may seem incomplete or

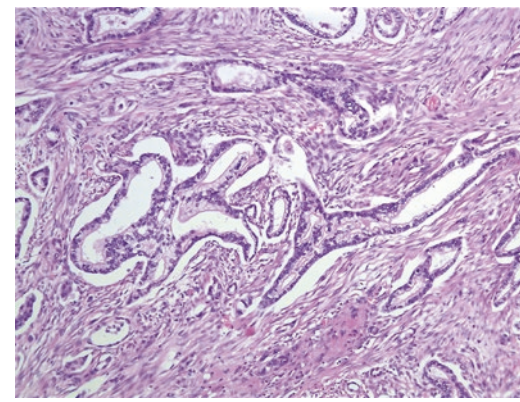


Fig. 9.8 Microscopy: pancreatobiliary type ductal adenocarcinoma typically consists of simple or branching glands, which are lined by columnar epithelium with pale-staining cytoplasm and a roundish basally located nucleus. Note the presence of dense desmoplastic stroma

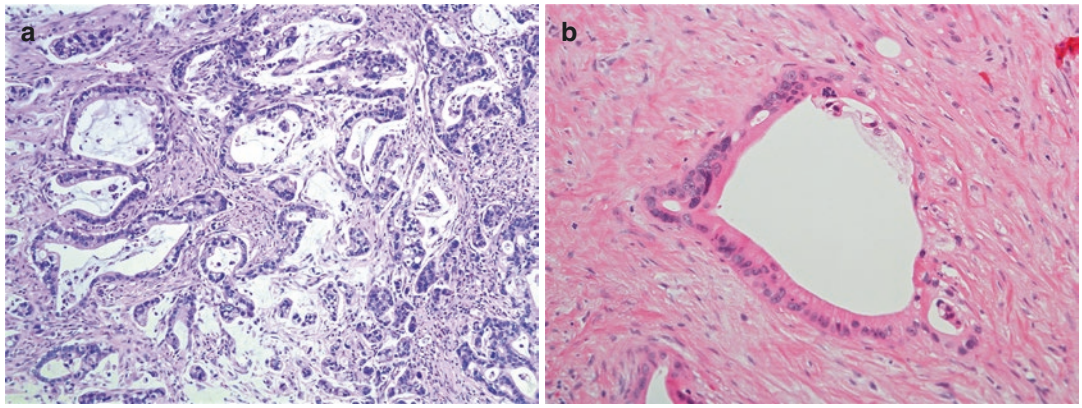


Fig. 9.9 Microscopy: pancreatobiliary type ductal adenocarcinoma consists of irregularly spaced glands, many of which show spillage of mucus into the stroma (so-called ruptured glands) (**a**). This tumor gland has an incomplete appearance, as part of the neoplastic epithelium consists of significantly flattened tumor cells (**b**)

'ruptured', when a part of the glandular wall is composed of highly flattened tumor cells or is focally apparently missing (Fig. 9.9). Complex glandular or cribriform patterns may occasionally be seen as well as intraluminal micropapillary projections (see Fig. 9.17). The lumen of the tumor glands is usually empty, and collections of mucus or cellular detritus admixed with neutrophils—so-called dirty necrosis—are not common. Intracellular mucin production is present to a varying degree, and if prominent, the cytoplasm may be copious. Consequently, the nuclear to cytoplasmic ratio may not always be high. Extracellular mucin, if present, is usually found within the lumina of the tumor glands and confined to a focus or limited area of the tumor, whereas extensive pool-like extracellular mucin collections are considered a feature of a special subtype of ductal adenocarcinoma, the so-called colloid (or mucinous noncystic) carcinoma (see Sect. 9.14.2). The term mucinous adenocarcinoma, which refers to a conventional ductal adenocarcinoma with intracellular and intraluminal mucin, should be avoided, as it may cause confusion with colloid carcinoma or pancreatic cancer arising in a mucinous cystic neoplasm.

The tumor cells are usually cuboidal to low columnar in shape, but irregular to bizarre cell shapes may be observed in poorly differentiated cancers. Nuclear morphology is commonly characterized by enlargement and a varying degree of pleomorphism. As a rule of thumb, a four-fold variation in nuclear size between cells lining the same gland can be regarded as diagnostic of carcinoma. However, the absence of this finding does not exclude carcinoma, because well-differentiated tumors may show markedly uniform, round, and basally orientated nuclei with one or two inconspicuous nucleoli. The cytoplasm may vary in tinctorial quality from pale eosinophilic to slightly basophilic or clear.

Ductal adenocarcinoma is characterized by a highly invasive growth pattern. Infiltration by tumor cell singletons, a single tumor gland, or a small number of tumor cell clusters is commonly present at a considerable distance from the main tumor mass. Tumor glands often extend along interlobular septa deeply into otherwise uninvolved pancreatic parenchyma and intermingle with islets, acini, and nonneoplastic pancreatic ducts (Fig. 9.10). A similar pattern of tumor infiltration may be observed along interlobular septa of the peripancreatic adipose tissue (Fig. 9.11).

The desmoplastic stroma that accompanies ductal adenocarcinoma is nearly as characteristic as the cancer proper. It is composed of fibroblasts, collagen fibers, and a scattering of inflammatory cells, mainly lymphocytes and histiocytes. The tumor stroma can vary from rather cellular with more densely packed tumor glands (Fig. 9.12), to collagen-rich and less cellular. The latter is often present in the tumor periphery,

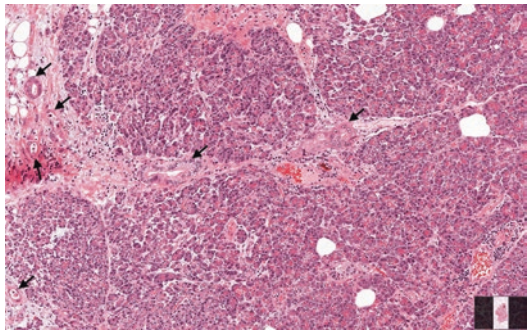


Fig. 9.10 Infiltrative growth: single tumor glands spread along interlobular septa (*arrows*)

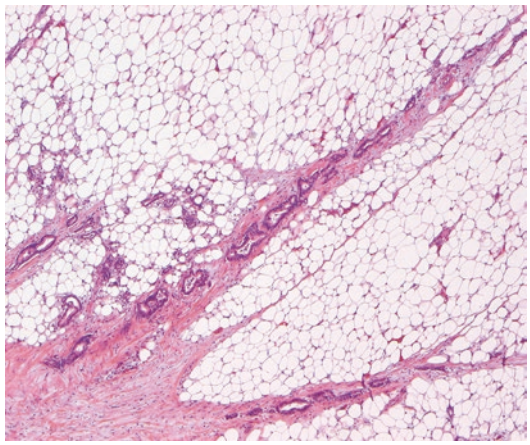


Fig. 9.11 Infiltrative growth: tumor glands spread along septa of the peripancreatic adipose tissue

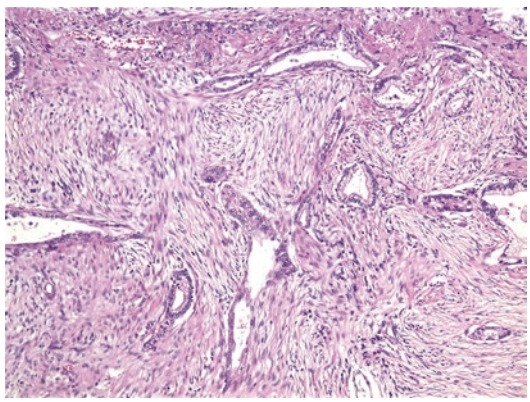


Fig. 9.12 Tumor stroma: branching tumor glands of pancreatobiliary type are embedded in a cellular desmoplastic stroma

where the cancer glands tend to be spaced more widely (Fig. 9.13). Especially at the invasive front, tumor glands may be separated from each

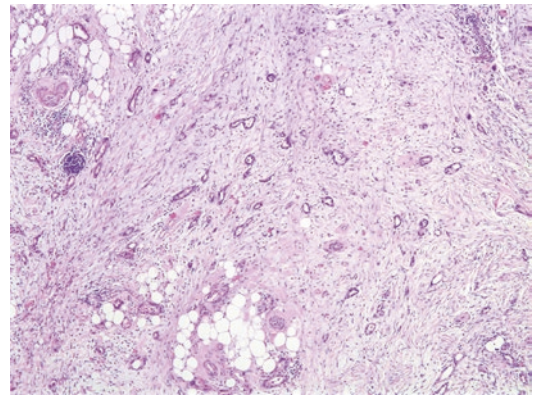


Fig. 9.13 Tumor stroma: tumor glands at the cancer periphery are widely spaced in a vast expanse of desmoplastic stroma, which is collagen-rich and less cellular

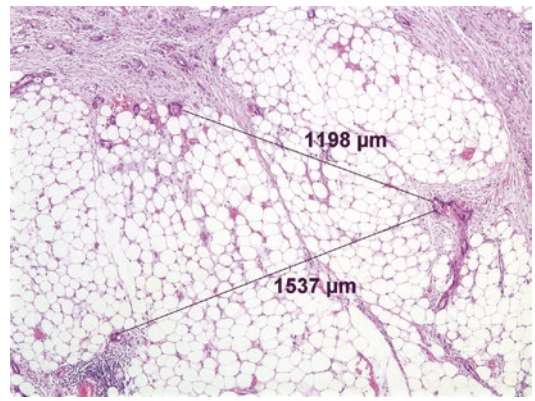


Fig. 9.14 Dispersed growth: infiltrating glands at the tumor periphery grow at a marked distance from each other (exceeding 1.5 mm in this figure)

other by considerable distances—1.5 mm or more—and therefore they can be easily missed on cursory microscopic examination (Fig. 9.14). The desmoplastic reaction extends in a carpet-like fashion along with, and often slightly ahead of, the invasive cancer, entrapping residual acini, islets, and pancreatic ducts along its way. The prominent stromal component of pancreatic cancer accounts for the characteristic macroscopic appearance of the tumor, its grey-white color, and wooden consistency. However, invasive tumor glands are not always accompanied by the desmoplastic stroma. The presence of 'naked' tumor glands, which are often found within pristine peripancreatic adipose tissue without evidence of a stromal reaction, is a well-recognized feature at

the invasive front of ductal adenocarcinoma (Fig. 9.15). Lacking an associated stromal reaction and occurring in small numbers, these naked glands escape macroscopic inspection or radiographical imaging and account amongst other factors for the frequent underestimation of tumor size and extent in pancreatic cancer.

9.6.2 Intestinal Type

Up to 5–10% of ductal adenocarcinomas have been reported to exhibit an intestinal type morphology. As indicated by the name, the morphology of these tumors resembles that of intestinal cancer. Compared to the pancreatobiliary type of ductal adenocarinoma, the glands of the intestinal type are usually larger and well defined. Moderately or poorly differentiated tumors of this type may show a cribriform growth pattern. The glandular lumina can contain 'dirty necrosis', and they are lined by a high-columnar epithelium with cigar-shaped, often pseudo-palisaded nuclei (Fig. 9.16).

While several recent reports claim a more favorable outcome for intestinal type compared to pancreatobiliary type ductal adenocarcinoma, this observation awaits definitive confirmation. For this reason and the fact that the diagnostic criteria lack validation in terms of reproducibility, the intestinal type has not been included in the WHO classification 2019 of pancreatic tumors [4].

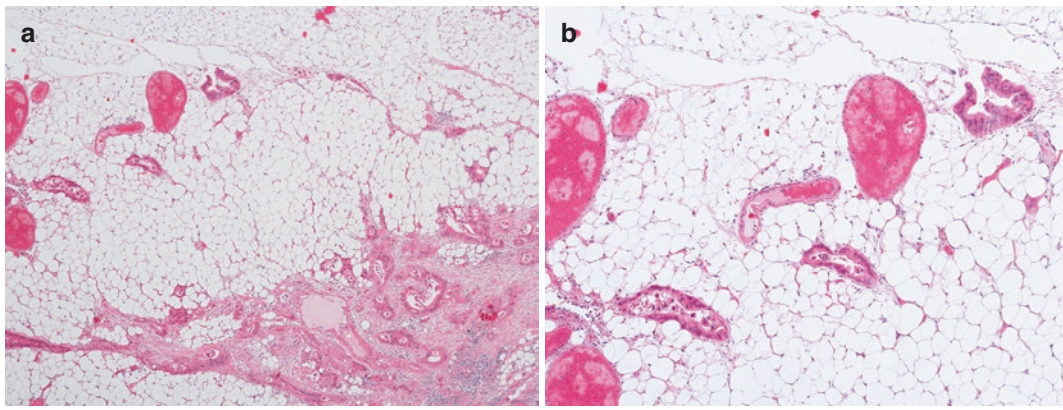


Fig. 9.15 Naked glands: at the invasive tumor front, a few single tumor glands infiltrate the peripancreatic fat (**a**). They are not associated with a stromal reaction, and tumor cells are flanked by adipocytes (**b**)

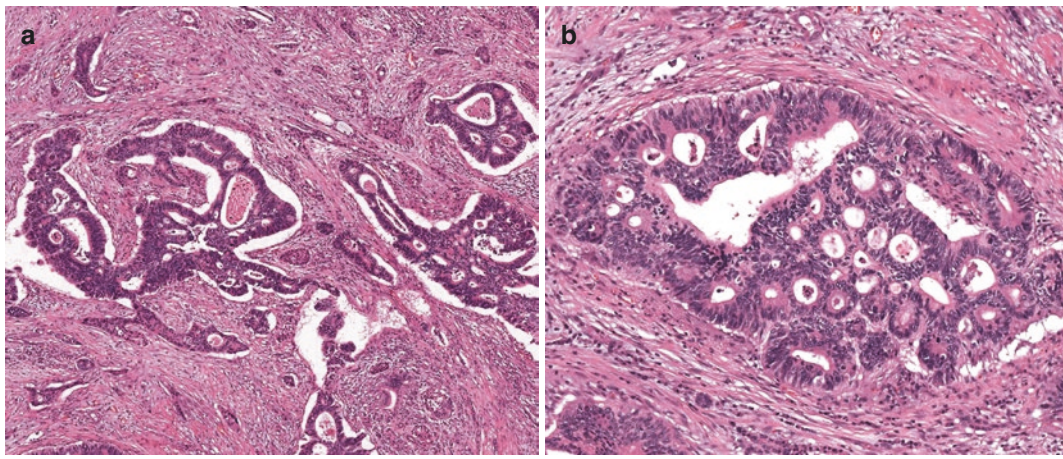


Fig. 9.16 Intestinal type: tumor glands are large and often of a complex or cribriform architecture (**a**). The neoplastic epithelium is high columnar and has cigar-shaped nuclei, which are orientated perpendicularly to the basement membrane (**b**). Note the presence of small amounts of necrotic detritus in some lumina

9.6.3 Intratumor Heterogeneity

The histomorphology of invasive ductal adenocarcinoma is not uncommonly characterized by a marked degree of intratumor heterogeneity, such that a variety of growth patterns and cytological appearances may be seen in different parts of the same tumor (Fig. 9.17). The morphology of both the carcinoma proper and the associated tumor stroma may differ, resulting in a wide range of different morphological phenotypes that are not represented in the WHO classification 2019 (see Fig. 9.23) [5]. In addition, in many pancreatobiliary type cancers, there is a tendency towards a more intestinal morphology in areas where the tumor involves the duodenum. When infiltrating the duodenal muscularis propria, tumor glands commonly become larger and elongated, align with the smooth muscle bundles, show a more intestinal-type cytomorphology, and appear moderately to well-differentiated (Figs. 9.18 and 9.19). Furthermore, when infiltrating the mucosa of the duodenum or papilla of Vater, the cancer cells may grow along the basement membrane of the native crypts and villi, creating the impression of in situ neoplasia (Fig. 9.20). In endoscopic biopsy material this intestinal mimicry may occasionally lead to an erroneous diagnosis of a primary duodenal carcinoma (see below). On occasion, the tumor glands infiltrating the duodenal wall may enlarge to the point of being macroscopically visible cysts (Fig. 9.21), a finding that may erroneously raise the suspicion of paraduodenal (groove) pancreatitis (see Chap. 7, Sect. 7.2.8 and Fig. 7.75).

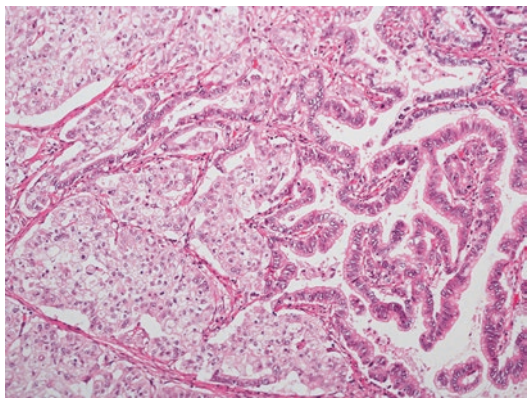


Fig. 9.17 Intratumor heterogeneity: ductal adenocarcinoma changes abruptly from a solid to a papillary growth pattern. The tumor cells have a clear cell appearance only in the solid area

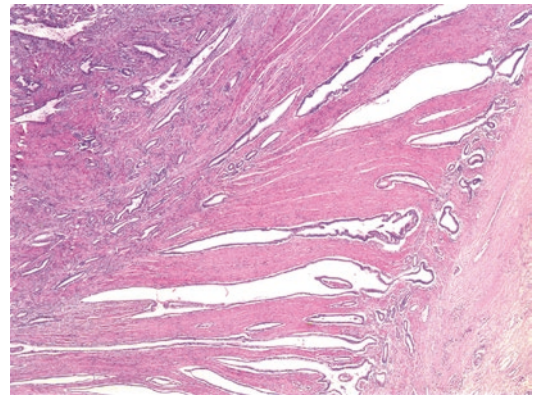


Fig. 9.18 Intestinal mimicry: when infiltrating the duodenal muscularis propria, the usually small angulated or branching glands of pancreatobiliary type ductal adenocarcinoma become large and elongated, and align with the muscle bundles. Note the lack of prominent desmoplasia

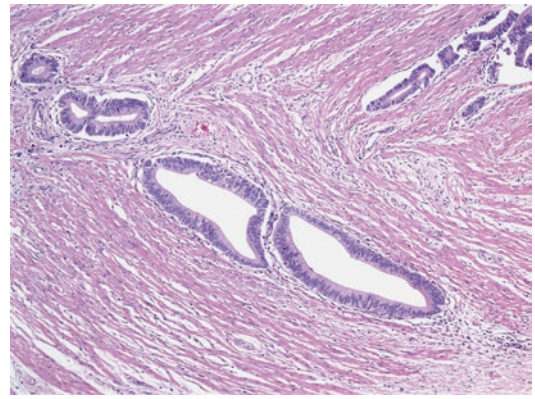


Fig. 9.19 Intestinal mimicry: pancreatobiliary type carcinoma can acquire an intestinal phenotype when infiltrating the duodenal muscle layer. Glands are larger, elongated, and lined by high-columnar cells with cigar-shaped, slightly pseudostratified nuclei. Note the lack of prominent desmoplasia

9.7 Grading

Different systems have been proposed for the grading of ductal adenocarcinoma of the pancreas. Grading according to TNM UICC (eighth

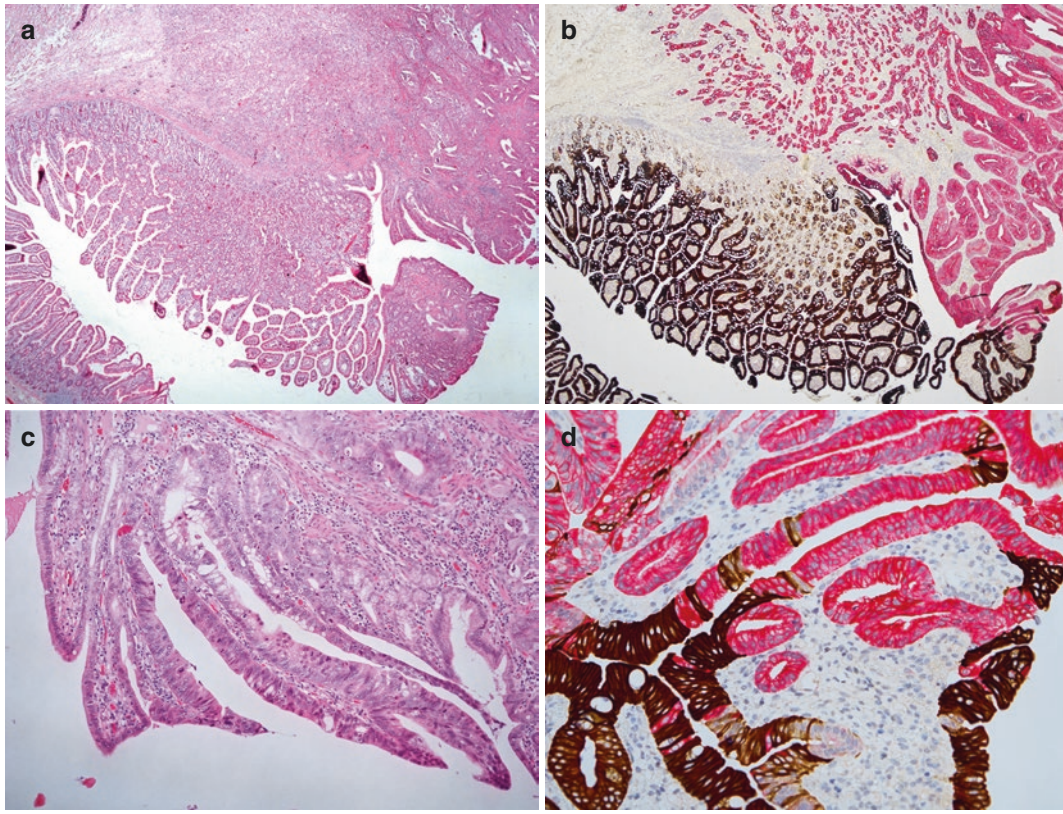


Fig. 9.20 Intestinal mimicry: pancreatobiliary type ductal adenocarcinoma infiltrates the duodenal wall and reaches the mucosal surface (**a**). Immunohistochemical double staining shows a sharp demarcation between invasive ductal adenocarcinoma (*red*; MUC1) and duodenal mucosa (*brown*; MUC2). Note the change in size and shape of the tumor glands as they reach the mucosa (**b**). Invasive tumor cells grow along the basement membrane of duodenal villi and crypts, mimicking in situ neoplasia (**c**). Immunostaining shows clear distinction between tumor cells (*red*; MUC1) and native epithelium (*brown*; MUC2) (**d**)

edition) follows a general four-tiered system, which is also applicable to other gastrointestinal adenocarcinomas (Table 9.1) [6]. The grading system proposed by the WHO classification is based on the degree of glandular differentiation, mucin production, nuclear atypia, and the mitotic activity (Table 9.2) [4]. It is more elaborate and therefore more onerous to apply than the grading system proposed by TNM UICC. Grading is highly concordant between both systems and has a similar predictive value [7].

Most tumors exhibit a range of histopathological grades, in which case the highest grade should be reported, irrespective of its extent. In practice, the majority of ductal adenocarcinomas comprise a poorly differentiated component, which consists of a rather inconspicuous population of tumor cell singletons or small solid clusters, which contain little mucin and may show marked nuclear atypia (Fig. 9.22).

9.8 Morphological Patterns

Conventional ductal adenocarcinoma may include areas with variant growth patterns, which are of no known biological, genetic, or clinical relevance. The significance of these patterns lies mainly in their distinction from benign structures, that is, normal pancreatic ducts or precursor lesions such as pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasia (see Chaps. 8 and 17). In addition to the patterns that are included in the WHO classi-

Fig. 9.21 Paraduodenal pancreatitis-like invasion of the duodenal wall: occasionally, ductal adenocarcinoma infiltrating the duodenal muscularis propria may assume a cystic appearance, which may mimic paraduodenal (groove) pancreatitis

Table 9.1 Histological grading of ductal adenocarcinoma of the pancreas according to the UICC TNM classification (8th edition) [6]

Grade of differentiation	
Grade X	Grade of differentiation cannot be assessed
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated
Grade 4	Undifferentiated

fication and further described below, there is a wide range of histomorphologies that have been neither assigned a nomenclature nor further characterized (Fig. 9.23) [5].

9.8.1 Foamy Gland Pattern

Tumor cells of this variant pattern of ductal adenocarcinoma acquire a foamy appearance due to their microvesicular mucin-rich cytoplasm. The luminal border of the tumors cells is often particularly well defined by linear cytoplasmic condensation, which resembles the enterocytic brush border. The nuclei are typically basally

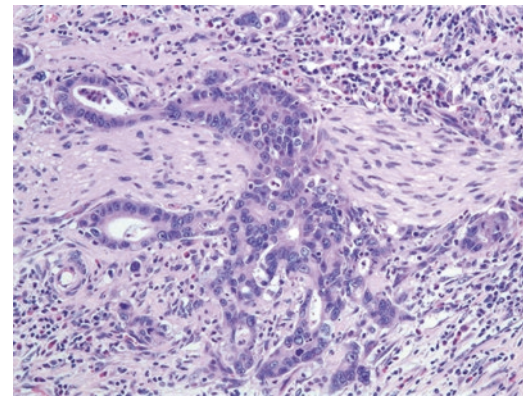


Fig. 9.22 Grading: fairly well formed tumor glands are admixed with complex, nearly solid tumor cell groups showing moderate nuclear pleomorphism. In addition, there are scattered small solid tumor cell clusters and a few single cells, some of which exhibit marked nuclear atypia. Note the presence of mitotic activity. The tumor is graded as poorly differentiated (grade 3)

Table 9.2 Histological grading of ductal adenocarcinoma of the pancreas according to the WHO classification 2019 [4]

Grade of differentiation	Glandular differentiation	Mucin production	Mitoses/10 HPF	Nuclear features
Grade 1	Well-differentiated glands	Intensive	5	Little pleomorphism, polar arrangement
Grade 2	Moderately differentiated ductular or tubular glands	Irregular	6–10	Moderate pleomorphism
Grade 3	Poorly differentiated glands, abortive mucoepidermoid and pleomorphic structures	Abortive	>10	Marked pleomorphism and increased size

Abbreviation: *HPF* high power fields

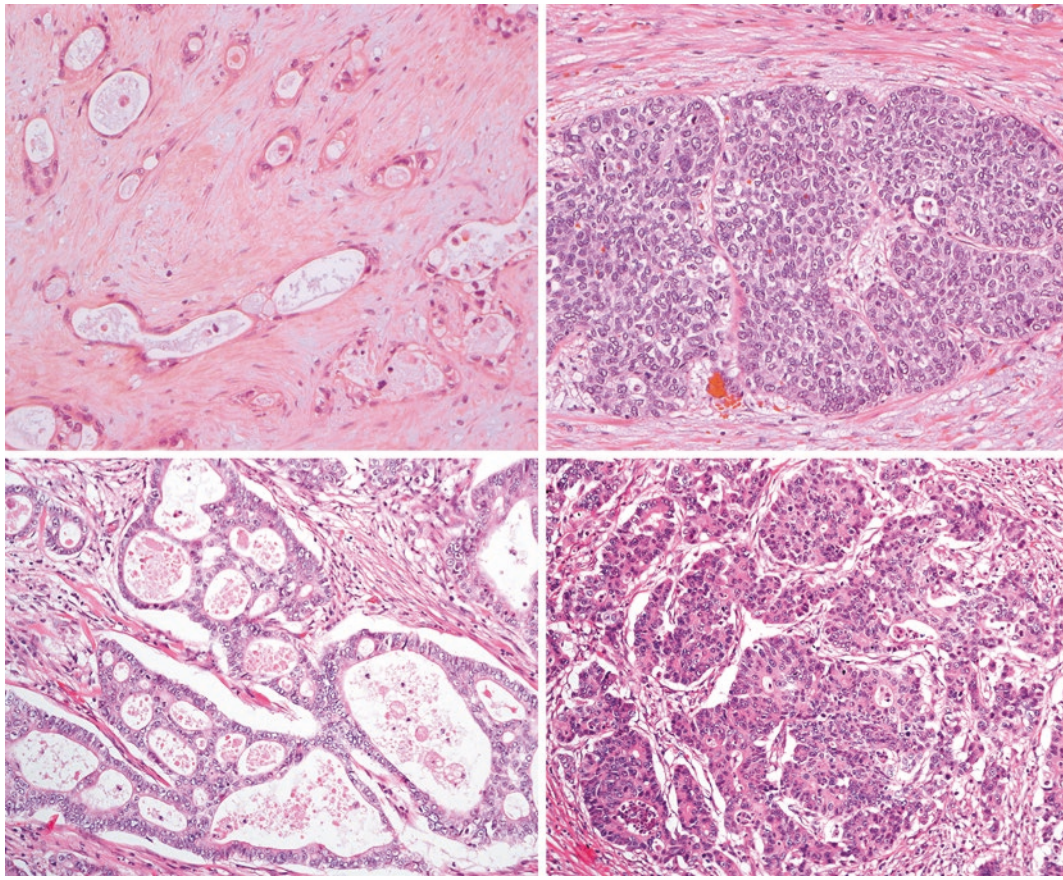


Fig. 9.23 Morphological heterogeneity: ductal adenocarcinoma *not otherwise specified* encompasses a wide range of growth patterns and histomorphological appearances, four examples of which are shown

located, round, hyperchromatic, and often raisinoid in shape. Ductal adenocarcinoma with foamy gland features is usually well differentiated to the point that the deceptively bland tumor glands may be misinterpreted as benign ducts (Fig. 9.24).

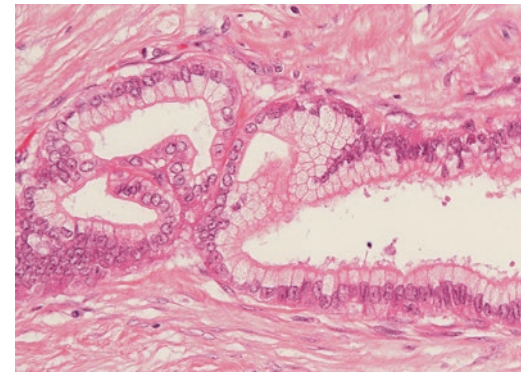


Fig. 9.24 Foamy gland pattern: the presence of cytoplasmic mucin-filled microvesicules gives the tumor cells a foamy appearance. The apical cell border is well delineated by linear cytoplasmic condensation. Round or raisinoid nuclei showing little pleomorphism are basally located

9.8.2 Clear Cell Pattern

Some ductal adenocarcinomas have abundant clear cytoplasm, which differs from that of the foamy gland pattern, because it is homogeneous and non-vesicular (Fig. 9.25). Given the fact that these tumors often display a solid growth pattern, ductal adenocarcinoma with clear cell features may resemble metastatic renal cell carcinoma,

from which it can be distinguished with the aid of immunohistochemistry (see Chap. 12, Sect. 12.5). Clear cell ductal adenocarcinoma stains positively for mucin and for other immunohistochemical markers of ductal adenocarcinoma (see Sect. 9.9).

9.8.3 Large Duct Pattern

In this variant, tumor glands are dilated (> 0.5 mm) up to a size that may be macroscopically apparent as small cysts (Fig. 9.26). While the tumor cells may show a mild degree of intraluminal tufting, this is never a prominent feature. Devoid of prognostic significance, the importance of this variant lies in the occasional difficult distinction between single such large invasive tumor glands and native pancreatic ducts with or without pancreatic intraepithelial neoplasia. Because these large glands are often deceptively bland-looking, their abnormal localization outwith the normal lobular architecture or within the duodenal wall may help reaching the correct diagnosis.

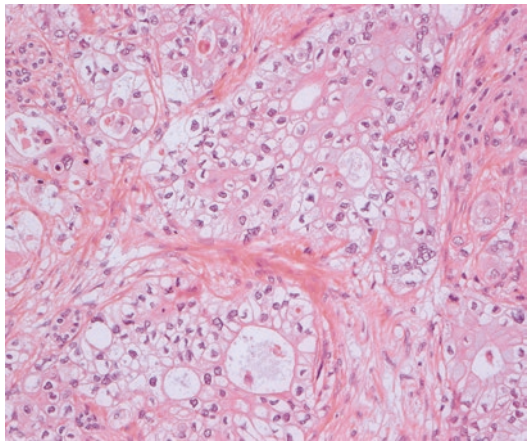


Fig. 9.25 Clear cell pattern: tumor cells are characterized by abundant, homogeneously clear cytoplasm. The clear cytoplasm and solid growth pattern bear resemblance with renal cell cancer of clear cell type

9.8.4 Cystic Papillary Pattern

This variant is characterized by large-caliber neoplastic glands, which—in contrast to the large duct variant—show prominent and often complex intraluminal papillary projections. The neoplastic tumor cells are high-columnar and contain intracellular mucin. The lumina of the large tumor glands contain mucin and can be dilated, occasionally reaching grossly cystic dimensions (Fig. 9.27). This variant pattern shows resemblance with intraductal papillary mucinous neoplasia, but the neoplastic proliferation is stroma-invasive and not intraductal, as evidenced by the absence of elastin fibers around the neoplastic glands (see Chap. 1, Sect. 1.4.3). Furthermore, the distribution of the neoplastic glands is haphazard, independent of the branching architecture of the pancreatic duct system. The presence of the cystic papillary

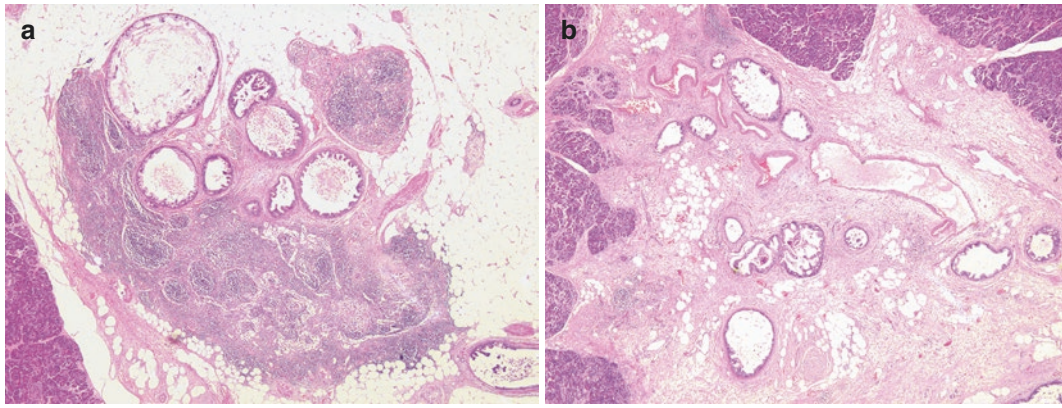


Fig. 9.26 Large duct pattern: this tumor forms large glands with mild intraluminal tufting and mild to moderate atypia. While the invasive nature of the glands is obvious when found within a lymph node (**a**), the distinction from pancreatic intraepithelial neoplasia is more difficult within the confines of the pancreas. The proximity of the suspicious glands to muscular blood vessels indicates the invasive nature (**b**)

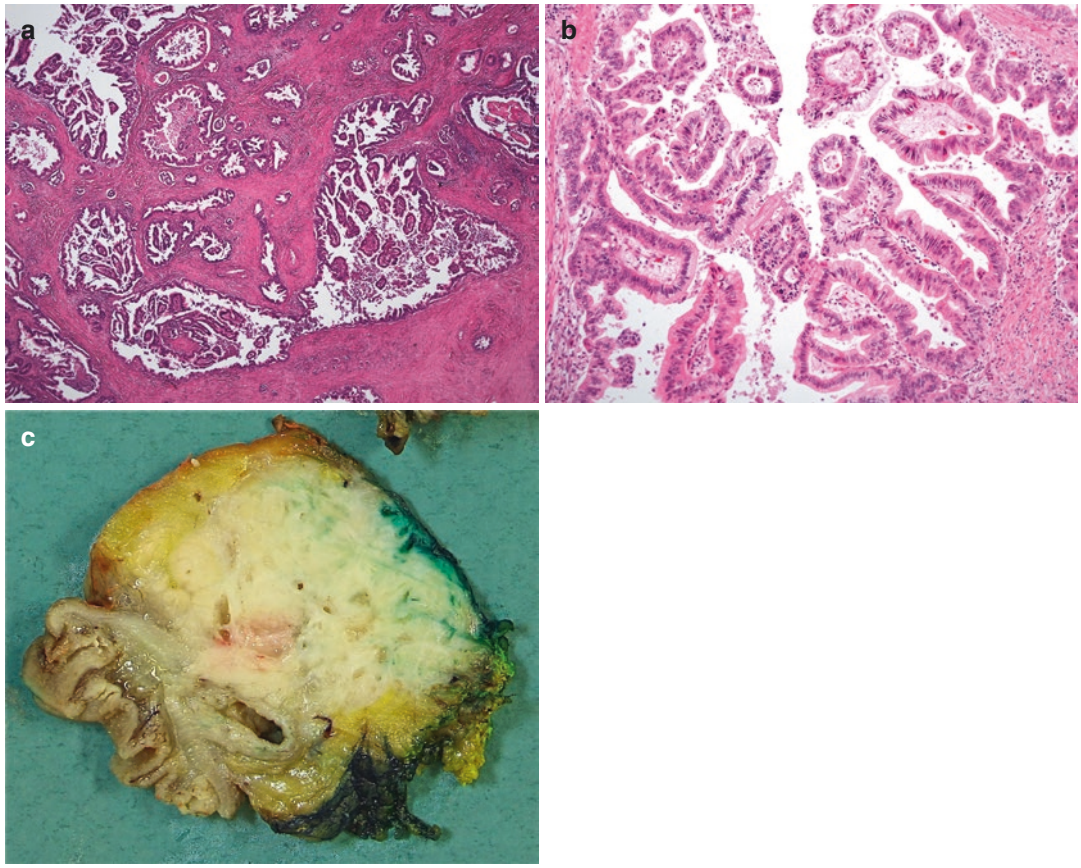


Fig. 9.27 Cystic papillary pattern: the tumor grows as large duct-like structures with prominent intraluminal papillary projections (**a**). The tumor cells are high-columnar and contain mucus (**b**). Macroscopically, the tumor is mainly solid but contains small, slightly mucinous, cystic areas (**c**)

neoplastic formations within the duodenal wall, lymphovascular channels, or perineural clefts further indicates their invasive nature. Tumors with this variant microscopic pattern usually contain areas of conventional ductal adenocarcinoma, although these may be less prominent.

9.9 Immunohistochemistry

Intensive research in recent years has uncovered a rapidly expanding range of markers—over 2500—that are aberrantly expressed in pancreatic cancer [8]. However, not all of these are specific for pancreatic cancer, and for many the diagnostic value in distinguishing invasive ductal adenocarcinoma from nonneoplastic pancreatic ducts, other primary pancreatic neoplasms, or extrapancreatic cancer has not been validated. Data on the few markers that have been tested are not uncommonly divergent, if not conflicting, due to—amongst several other factors—differences in the immunoscoring system that has been used. In this section, the discussion is limited to markers that may be of some proven diagnostic value.

9.9.1 Immunohistochemical Profile

Ductal adenocarcinoma expresses the same keratins as normal pancreatic duct epithelium, that is, cytokeratins (CK) 7, 8, 18, and 19. Expression of CK20 is absent or less extensive than that of CK7, except in pancreatic cancer of intestinal type or in certain subtypes of ductal adenocarcinoma, for example, colloid carcinoma. However,

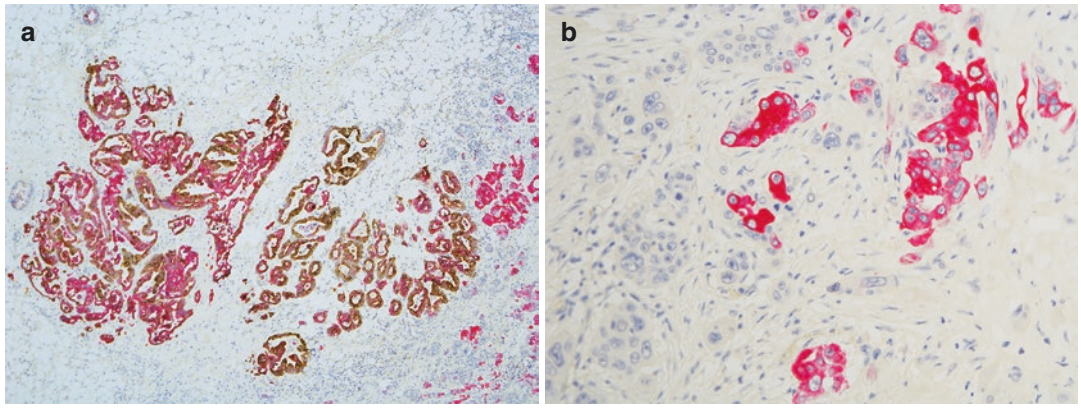


Fig. 9.28 Cytokeratin immunostaining: this pancreatobiliary type tumor shows staining for both CK7 (*red*) and CK20 (*brown*) (**a**). Some of the poorly differentiated tumor cells are negative for both markers (**b**)

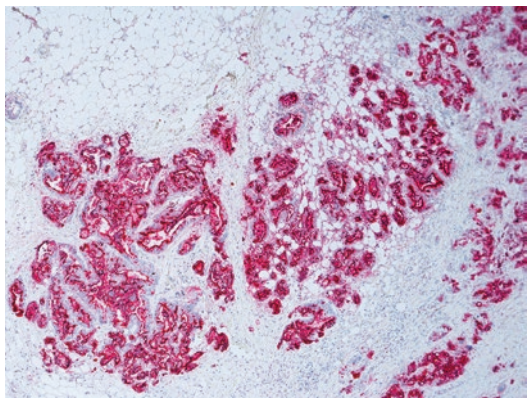


Fig. 9.29 Mucin immunostaining: the entire tumor cell population shows immunolabeling for MUC1 (*red*), while MUC2 (*brown*) expression is absent (same tumor as in Fig. 9.28)

expression of both CK7 and 20 can be lacking in poorly differentiated ductal adenocarcinoma (Fig. 9.28). Over 50% of tumors also stain for CK4.

Most ductal adenocarcinomas express mucin (MUC) 1 and 5AC, while 20–25% are positive for MUC6. Immunostaining for MUC2 is observed in less than 10% of ductal adenocarcinomas, mainly those with an intestinal or colloid morphology (Fig. 9.29). The vast majority of ductal adenocarcinomas also express CEA, CA19-9, and maspin, whereas CA125 and mesothelin are found in approximately 50% and 49–71% of cases, respectively [9–11]. Vimentin is usually absent, except in the undifferentiated subtypes (see Sects. 9.14.7 and 9.14.8). Immunolabeling for synaptophysin and chromogranin A highlights scattered endocrine cells that may be present in a proportion of ductal adenocarcinomas. If more than 30% of the cancer cells stain positively, the tumor is to be regarded as a pancreatic mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) (see Chap. 20, Sect. 20.10). Immunostaining for neuroendocrine markers may also pick up a small number of entrapped nonneoplastic endocrine cells. Ductal adenocarcinoma is usually negative for the pancreatic exocrine enzymes trypsin, chymotrypsin, amylase, lipase, and the acinar marker BCL10. Nuclear staining for SMAD4 (DPC4) is lost in approximately 55% of pancreatic cancers, while staining is positive for p53 in 50–75% of cases. Overexpression of a number of other markers has been reported recently, including EGF and its receptor ERRB2, TGFα, TGFβ, PDGF, VEGF, CD44v6, claudin 4 and 18, B72.3, IMP-3, members from the S100 group of proteins (S100A4, S100A6, S100P), and many more.

9.9.2 Distinction from Other Pancreatic or Extrapancreatic Neoplasms

Despite the abundance of information on the immunohistochemical staining patterns in ductal adenocarcinoma, there is as yet not a single

marker or an immunohistochemical signature that can be used to unequivocally diagnose pancreatic ductal adenocarcinoma and distinguish it from nonneoplastic reactive ductular pancreatic structures or adenocarcinoma of ampullary and bile duct origin. The use of immunohistochemistry for the distinction of ductal adenocarcinoma from other primary pancreatic neoplasms and metastasis from extrapancreatic malignant tumors is discussed elsewhere (see Chaps. 12 and 20, Sects. 12.5 and 20.9, Tables 12.1 and 20.5).

9.9.3 Distinction from Reactive Pancreatic Ductules

In some cases, immunohistochemistry for CEA, CA125, mesothelin, S100P, SMAD4, and p53 may be helpful in the distinction between invasive ductal adenocarcinoma and reactive pancreatic ductules. However, results should be interpreted with great caution, because—as outlined above—immunostaining for the first three markers is neither entirely sensitive nor specific. The absence of immunostaining for CEA, CA125, S100P, or mesothelin does not definitively exclude a diagnosis of ductal adenocarcinoma, especially if applied to only a small number of glandular structures, for example, on biopsy material. Furthermore, a normal nuclear immunolabeling pattern for p53 and SMAD4 may be found in 25–50% of ductal adenocarcinomas. Conversely, reactive ducts may occasionally show focal positivity for CEA, CA125, mesothelin, S100P, or p53. However, absence of nuclear staining for SMAD4 is not observed in reactive glands.

9.10 Tumor Propagation

Ductal adenocarcinoma is characterized by a highly infiltrative growth pattern and a propensity for propagation along preformed channels, be it perineural clefts, lymphatics, blood vessels, pancreatic ducts, or preformed structures such as fibrous septa between lobules of the acinar parenchyma or the peripancreatic adipose tissue (Figs. 9.10 and 9.11).

The vast majority (>90%) of tumors show evidence of *perineural tumor propagation* (Fig. 9.30). This may be especially prominent in pancreatic cancers that infiltrate the peripancreatic soft tissue, in particular the tissue plane facing the superior mesenteric artery and the soft tissue sheath around the extrapancreatic common bile duct, because these areas contain numerous peripheral nerves of various calibers (see Chap. 1, Figs. 1.25 and 1.28). Perineural tumor propagation is commonly also seen in the periarterial neural plexus (see Chap. 1, Figs. 1.26 and 1.27) that surrounds the gastroduodenal and splenic artery (Fig. 9.31), or the celiac trunk and superior

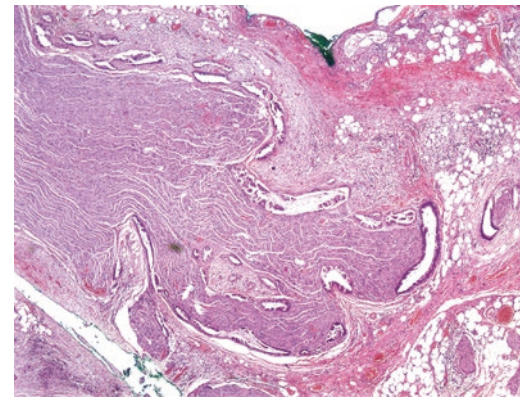


Fig. 9.30 Perineural invasion: numerous tumor glands involve a large peripheral nerve in peripancreatic adipose tissue flanking the superior mesenteric vessels

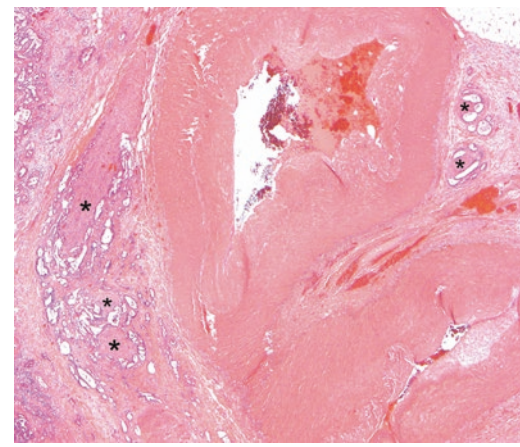


Fig. 9.31 Perineural invasion: the neural plexus surrounding the splenic artery shows multifocal perineural tumor propagation (*asterisks*)

mesenteric artery in the rare case that these large arteries are resected. Benign glandular inclusions have been described in peripheral nerves in and around the pancreas (see Chap. 1, Fig. 1.29), but these are so extremely rare that they hardly represent a differential diagnosis. Maybe more problematic is the rare occurrence of pseudoneural inclusion of nonneoplastic islet cells in chronic pancreatitis (see Chap. 7, Sect. 7.2.4, Fig. 7.30), a finding that in combination with other atypical features in this setting may raise the suspicion of invasive adenocarcinoma.

Tumor *invasion of lymphatic channels* is also common in ductal adenocarcinoma of the pancreas, and this may be found both within and outside the pancreas. The duodenal wall and ampullary region are particularly rich in lymph vessels, and therefore, these areas must be scrutinized with great care to identify lymphatic tumor propagation (Fig. 9.32). Immunostaining for podoplanin/D2-40, a marker of lymphatic endothelium, may be helpful, in particular in distinguishing lymphatic from vascular tumor invasion (Fig. 9.33). However, in pancreatic cancers that have metastasized to the lymph nodes—over 70% of all cases—the histological identification of lymphatic tumor propagation provides no additional prognostic information.

Vascular tumor propagation is another frequent mode of tumor spread. It is of particular prognostic importance, as distant metastasis—most commonly to the liver—is the cause of death in the majority of pancreatic cancer patients (see Sect. 9.13). Vascular invasion may be less easy to identify than perineural tumor propagation. Because arterial branches are paired with the venous ramifications of the vasculature and tumor invasion usually affects the latter, it may be helpful to search for arterial blood vessels that are not accompanied by a venous counterpart (‘orphan arteries’), but instead are flanked by a tumor cell cluster that is located within and thereby obscures the accompanying vein (Fig. 9.34). Detailed inspection of the tumor

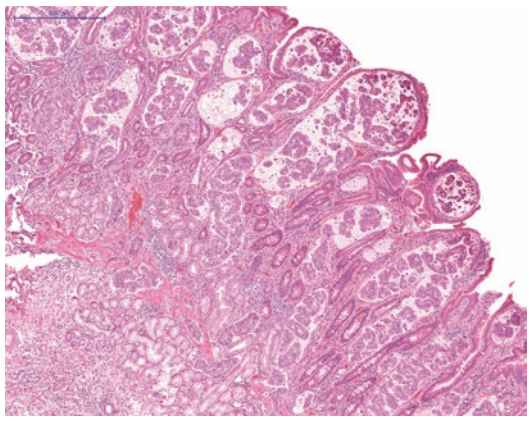


Fig. 9.32 Lymphatic channel permeation: countless lymphatic channels in the duodenal lamina propria are dilated and filled with invasive adenocarcinoma

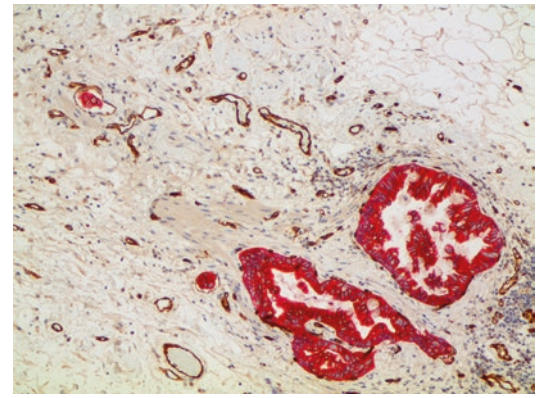


Fig. 9.33 Lymphatic channel permeation: immunohistochemical double-staining for D2–40 (*brown*) and CK7 (*red*) reveals the presence of numerous lymphatic channels, two of which contain a small tumor cell cluster. In addition, there are two larger stroma-invasive tumor glands

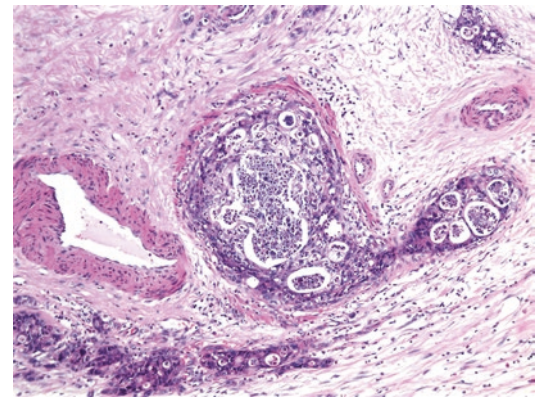


Fig. 9.34 Vascular invasion: a medium-sized vein is completely occluded by adenocarcinoma. Note the unaltered flanking artery, whose presence aids in identifying venous tumor occlusion

focus may reveal residual structures of the venous wall, and elastica van Gieson staining is most valuable in identifying residua of both elastin and smooth muscle fibers within and around such intravascular tumor foci (Fig. 9.35). Occasionally, the invasive tumor cells seem to replace the endothelial cells such that the vascular lumen is surrounded by neoplastic cells, resulting in a mimicry of a nonneoplastic duct or, if atypia is more pronounced, a pancreatic duct involved by pancreatic intraepithelial neoplasia (see Chap. 8). The presence of a smooth muscle layer surrounding the structure, detected on van Gieson staining or by immunohistochemistry, leads to the correct diagnosis of vascular invasion (Fig. 9.36). It should be borne in mind that a collar of elastin fibers can be seen in association with both blood vessels and pancreatic ducts (see Chap. 1, Sect. 1.4.3). Immunostaining for endothelial markers (e.g., CD31) allows identification of intravascular tumor cell clusters in a smaller proportion of affected blood (and lymphatic) vessels, whose wall and endothelial lining have remained intact. Thrombosed veins deserve particular attention, as thrombosis is commonly the result of intravascular tumor spread. While blood vessels are obviously present throughout the entire pancreas and surrounding tissues, they are particularly

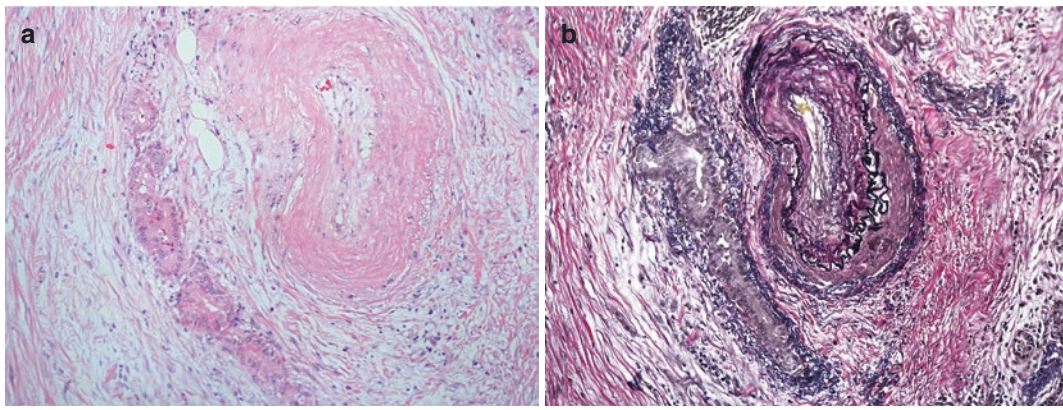


Fig. 9.35 Vascular invasion: an orphan artery is flanked by a tumor gland cluster (**a**). Elastica van Gieson staining reveals residua of the elastin membrane and smooth musculature of the tumor-occluded associated vein (**b**)

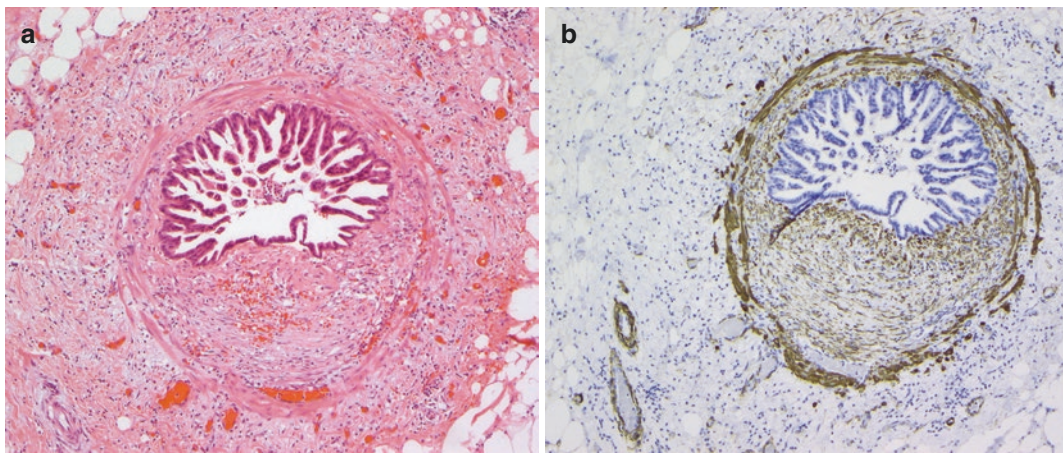


Fig. 9.36 Vascular invasion mimicking PanIN: invasive adenocarcinoma growing along the luminal surface of a vein resembles high-grade PanIN (**a**). The presence of a smooth muscle layer encircling the neoplastic epithelium confirms that the latter is present within a vein, not a pancreatic duct (**b**, immunohistochemical stain for smooth muscle actin)

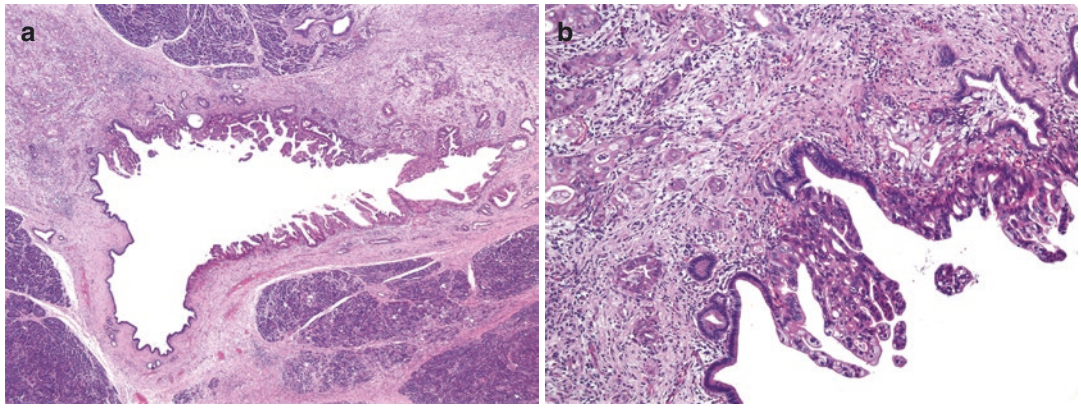


Fig. 9.37 Duct cancerization: this large interlobular duct is partially involved by intraductal tumor propagation (**a**). The abrupt transition between the highly atypical epithelium and the normal epithelial lining, together with the presence of invasive adenocarcinoma around the duct, allow the distinction from high-grade PanIN (**b**)

prominent and therefore easier to examine near the anterior and posterior pancreatoduodenal crevices, in the anterior adipose tissue, and in the soft tissue facing the superior mesenteric artery. For tumors involving any of these areas, the search for vascular invasion may be most promising here.

Intraductal tumor propagation is a further common mode of pancreatic cancer spread, which is found in up to 70% of tumors and may result in tumor spread up to several centimeters beyond the main tumor mass [12]. It is often a multifocal finding, and ducts of any caliber, in particular medium-sized interlobular ducts, can be involved. Occasionally, intraductal tumor spread or so-called duct cancerization may also be seen along the common bile duct or ampulla. At times, the distinction between duct cancerization and high-grade PanIN may be problematic (see Chap. 8, Sect. 8.6.2). Overall, the presence of invasive tumor glands in the vicinity of the pancreatic duct in question, and the abrupt transition from atypical to normal epithelium are clues in favor of duct cancerization (Fig. 9.37).

9.11 Staging

The UICC TNM (eighth edition) staging system [6] applies to cancer derived from the exocrine pancreas, that is, ductal adenocarinoma and its subtypes as well as acinar cell carcinoma. It may also be used for staging of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) with a ductal adenocarcinoma or acinar cell carcinoma as the exocrine tumor component (see Chap. 10, Sect. 10.10.3 and Chap. 20, Sect. 20.10), for intraductal papillary mucinous neoplasia and mucinous cystic neoplasia with high-grade dysplasia or invasive carcinoma, for pancreatoblastoma, and solid pseudopapillary neoplasia. In 2018, the eighth edition of the UICC TNM classification of tumors published a revised version of the staging of primary tumor (pT) and lymph node (pN) status. The reason to change staging criteria for pT1–3 from tumor size and extent (seventh edition) [13] to tumor size only (eighth edition) [6] was prompted by the following observations and concerns. First, extension beyond the pancreas was found to be a criterion with suboptimal reproducibility, because the pancreas has no capsule and the outline of the gland may not always be well defined. In addition, tumor infiltration of the common bile duct was also interpreted differently by individual pathologists and national guidelines. Second, extrapancreatic tumor extension occurs in more than 80% of tumors that are smaller than 20 mm in size, and yet, there is no associated decrease in survival compared to size-matched tumors without extrapancreatic extension. Third, extrapancreatic extension is present in up to 90% of cases, such that the vast majority of pancreatic cancers fall into the same stage category of pT3. The

implementation of exclusively size-based criteria for pT1–3 in the eighth edition of UICC TNM results in a more even stratification of patients across stages without sacrificing prognostic accuracy and with a presumed improved reproducibility [14]. When it comes to staging of the lymph node status, an N2 category has been added, similar to the pN-staging for other gastrointestinal cancer sites. Several studies have validated the eighth edition of the UICC/AJCC staging systems and found the revised N-stage to be highly prognostic, while only a modest improvement is observed for the revised T-stage, which still remains a fairly weak predictor of survival [14–17].

The prefix 'p' indicates that staging is based on pathology findings. The descriptors L, V, Pn, and R can be used to report the cancer stage in terms of lymphatic, vascular, and perineural tumor propagation as well as residual disease.

Staging is an essential part of the diagnostic work-up and key to the patient management. The pathology report on resection specimens should therefore always explicitly state the staging for pT, pN, and the various other descriptors.

The staging system for pancreatic cancer issued by the American Joint Committee on Cancer (AJCC) [18] is identical to the UICC TNM system, with exception of the assignment of celiac lymph nodes (see Sect. 9.11.2).

Table 9.3 Staging of carcinoma of the exocrine pancreas according to the UICC TNM classification (8th edition) [6]

Stage	Staging criteria
T-primary tumor	
• TX	• Primary tumor cannot be assessed
• T0	• No evidence of primary tumor
• Tis	• Carcinoma in situ[a]
• T1	• Tumor 2 cm or less in greatest dimension
– T1a	– Tumor 0.5 cm or less in greatest dimension
– T1b	– Tumor greater than 0.5 cm and no more than 1 cm in greatest dimension
– T1c	– Tumor greater than 1 cm but no more than 2 cm in greatest dimension
• T2	• Tumor more than 2 cm but no more than 4 cm in greatest dimension
• T3	• Tumor more than 4 cm in greatest dimension
• T4	• Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery
N-regional lymph nodes	
• NX	• Regional lymph nodes cannot be assessed
• N0	• No regional lymph node metastasis
• N1	• Metastasis in 1–3 regional lymph node(s)
• N2	• Metastasis in 4 or more regional lymph nodes
M-distant metastasis	
• M0	• No distant metastasis
• M1	• Distant metastasis

[a]Includes high-grade pancreatic intraepithelial neoplasia (PanIN)

9.11.1 Staging of the Primary Tumor

The criteria for staging of the primary tumor (pT-stage) are based on tumor size and extent (Table 9.3), the latter criterion pertaining only to stage pT4. Incorrect pT-assessment, and in particular underestimation of tumor size, is the main pitfall in staging of ductal adenocarcinoma. This is likely to happen, if macroscopic size measurement is not checked and corrected by microscopic assessment. As explained above, the highly infiltrative pattern of pancreatic cancer, its markedly dispersed growth, and the occurrence of 'naked glands' can only be appreciated on histology. Because these phenomena are particularly prominent at the tumor periphery, their identification is important for accurate assessment of tumor size (and extent) and, consequently, for assignment to the correct T-stage.

The majority of ductal adenocarcinomas are stage pT2, that is, measure between 2 cm and 4 cm in size. Outside the context of intraductal papillary mucinous neoplasia or mucinous cystic neoplasm, ductal adenocarcinoma smaller than 2 cm, that is, stage pT1, is rarely diagnosed because of the lack of specific symptoms (Fig. 9.38).

While tumor invasion of the wall of the superior mesenteric vein (SMV) or portal vein does not affect the T-stage, accurate microscopic assessment of the relationship of the tumor to the vein is nevertheless important, because several—but not all—studies observed that tumor invasion of the named veins (Fig. 9.39) (see Figs. 3.8, 3.23, and 3.24) portends worse patient outcome [19–22] and that the depth of invasion into the vessel wall (tunica adventitia, media, intima, or vascular lumen) is prognostically relevant [23,

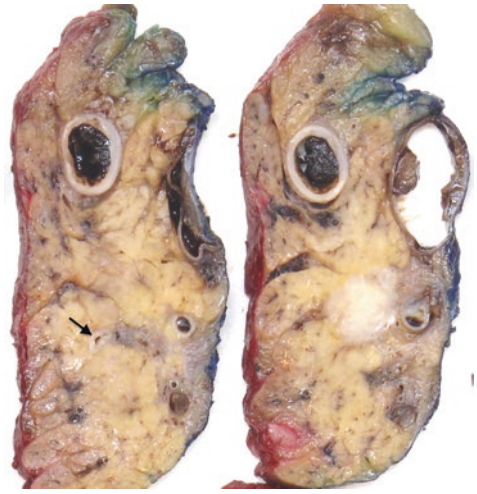


Fig. 9.38 Ductal adenocarcinoma detected at an early stage: this ductal adenocarcinoma measuring 11 mm in maximum diameter occludes the main pancreatic duct (*arrow*), which resulted in recurrent attacks of acute pancreatitis and early detection of the small cancer

24]. Furthermore, accurate pathology reporting on the presence or absence of tumor invasion of the large veins is important for correlation with preoperative imaging and intraoperative surgical assessment during multidisciplinary case discussion (see Chap. 4). As discussed in Chap. 3, the entire fragment of resected vein should be subjected to microscopic examination, and the depth of tumor invasion into the vein—adventitia, media, intima or lumen—should be recorded. Because the tunica adventitia blends with the surrounding soft tissue, it has been defined by some as the layer of fibrous tissue within 1 mm from the outer limit of the tunica media. Assessment of the resection margins of the resected fragment of vein and the adjacent margin at the SMV groove is described below (see Sect. 9.11.4).

Ductal adenocarcinoma located in the anterior-cranial part of the pancreatic head may surround

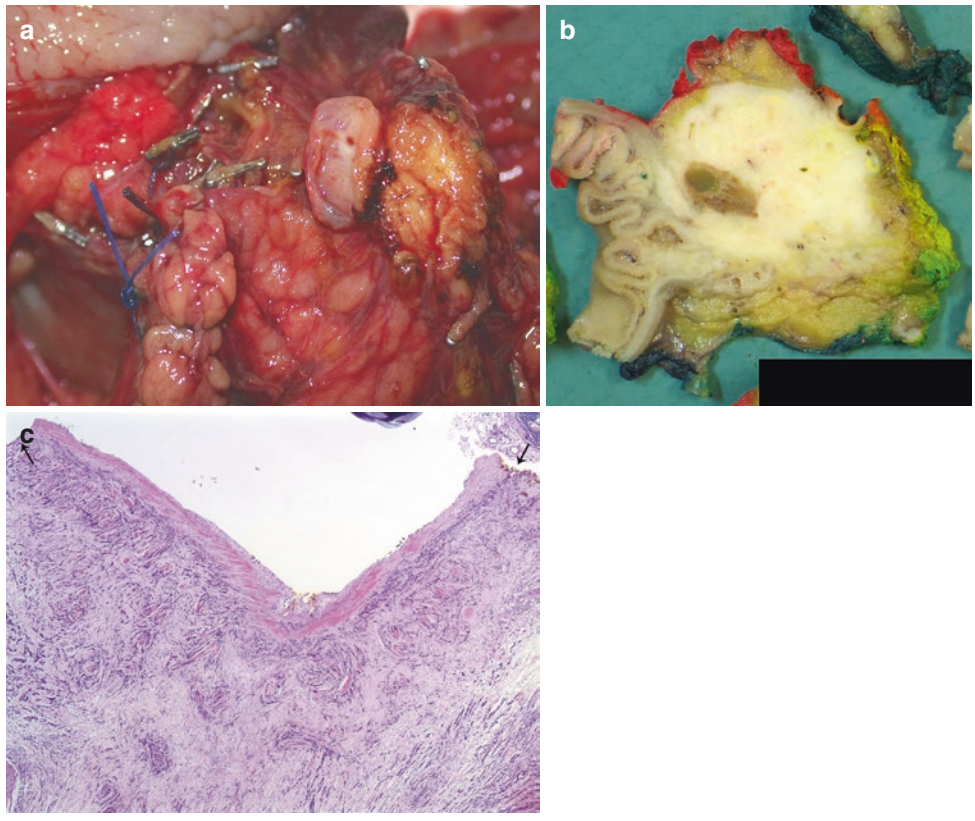


Fig. 9.39 Invasion of SMV: an ellipse of the superior mesenteric vein (SMV) is tightly adherent to the SMV groove opposite to the pancreatic transection margin (with blue suture; **a**). Axial specimen slicing reveals a large tumor, which invades the SMV wall (inked orange; **b**). Microscopically, poorly differentiated adenocarcinoma infiltrates the full thickness of the SMV wall and reaches the transection margins of the vein (*arrows*, **c**)

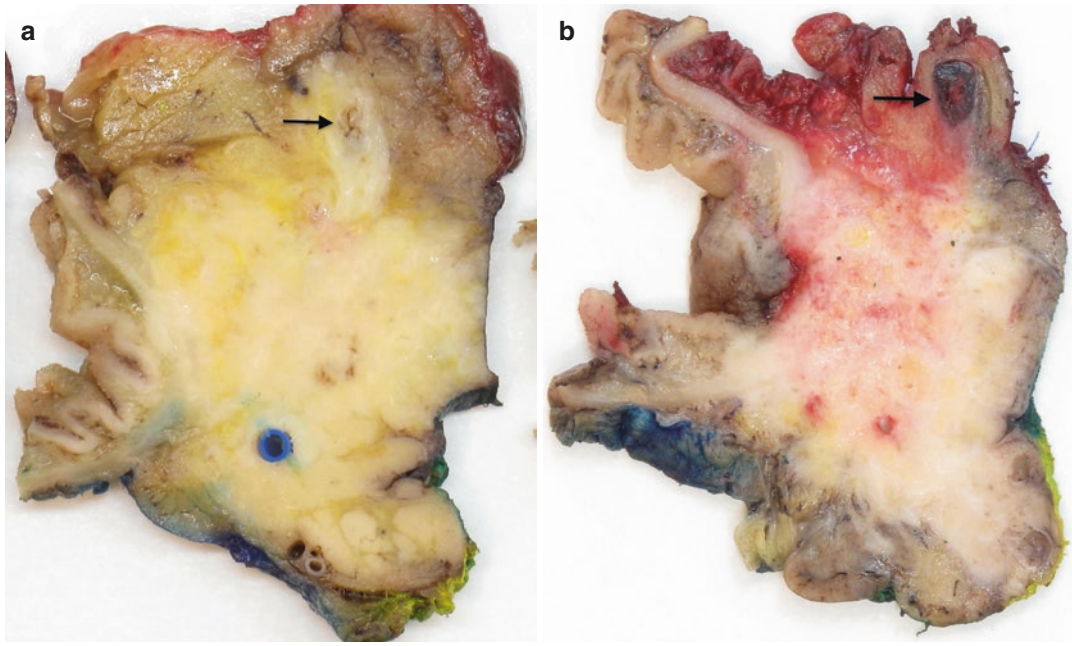


Fig. 9.40 Involvement of the gastroduodenal artery: tumor infiltrates the anterior peripancreatic adipose tissue and surrounds the gastroduodenal artery (*arrow*, **a**). In this case, tumor involvement of the gastroduodenal artery has resulted in thrombosis (*arrow*, **b**)

the gastroduodenal artery and occasionally lead to thrombosis of that blood vessel (Fig. 9.40).

9.11.2 Staging of Lymph Node Metastasis

Tumor involvement of one or more regional lymph nodes, either by metastatic seeding or direct tumor invasion, is observed in 70% or more of resected ductal adenocarcinomas and is present even when the primary tumor is small (<2 cm). Lymph node status is one of the strongest predictors of survival for ductal adenocarcinoma of the pancreas. Based on outcome data, node-positive disease has now been subdivided in pN1 (1–3 positive regional lymph nodes) and pN2 (4 or more positive regional lymph nodes) [6, 14–16].

The lymph node stations that are regarded by UICC TNM (eighth edition) as regional for pancreatic cancer arising in the pancreatic head and neck or body and tail are listed in Table 9.4, and their position is explained in Fig. 3.27 and Table 3.2. It should be mentioned that the UICC and AJCC (eighth edition) staging systems differ regarding the assignment of celiac lymph nodes [6, 18]. While UICC considers these as regional lymph nodes for cancer in the head of the pancreas, they are regarded as regional lymph nodes exclusively for tumors in the body and tail of the pancreas by the AJCC. Current knowledge about the topographic distribution of lymph node metastases depending on the site of the primary cancer within the pancreas is limited. Overall, tumors arising in the pancreatic head metastasize most frequently to the anterior and posterior pancreatoduodenal lymph nodes and those along the superior mesenteric artery. Pancreatic cancer in the uncinate process spreads most frequently to the latter group of lymph nodes. Carcinoma of the body and tail metastasizes mainly to the lymph nodes along the splenic artery and celiac trunk. Lymph node grouping according to the Japan Pancreas Society is discussed in Chap. 3.

Tumor metastasis to other, more distant lymph node stations, for example, the aortocaval lymph

Table 9.4 Regional lymph nodes for carcinoma of the head/neck and body/tail of the pancreas according to the UICC TNM classification (eighth edition) [6]

Anatomical localization	For tumors of pancreatic
Common bile duct	Head/neck
Common hepatic artery	Head/neck and body/tail
Portal vein	Head/neck
Pyloric	Head/neck
Infrapyloric	Head/neck
Subpyloric	Head/neck
Anterior pancreatoduodenal vessels	Head/neck
Posterior pancreatoduodenal vessels	Head/neck
Superior mesenteric vein	Head/neck
Right lateral wall of superior mesenteric artery	Head/neck
Celiac	Head/neck and body/tail
Proximal mesenteric	Head/neck
Retroperitoneal	Body/tail
Lateral aortic	Body/tail
Splenic artery	Body/tail
Hilum of spleen	Body/tail

nodes, is to be reported as distant metastasis, stage pM1.

The accuracy of the pN-stage depends on the lymph node yield [25, 26], which according to UICC TNM (eighth edition) is set at an average of 10 lymph nodes in pancreatoduodenectomy specimens [6]. The AJCC requires a minimum of 12 lymph nodes [18]. A higher lymph node yield of 15 lymph nodes has been suggested and is meanwhile accepted as a national pathology standard in some countries [27]. There are currently no recommendations for the lymph node yield from distal pancreatectomy specimens.

The clinical significance of lymph node micrometastasis is controversial, although an increasing body of literature suggests that the presence of micrometastatic spread is an adverse prognostic factor. One reason for the divergence in observations between studies is the existence of controversial definitions of lymph node micrometastasis. The UICC introduced the concept of isolated tumor cells, which are defined as single tumor cells or small cell clusters that measure no more than 0.2 mm in greatest extent and can be detected on routine H&E staining or by immunohistochemistry [6]. It is proposed to classify lymph nodes with isolated tumor cells as negative, but to indicate the presence of isolated tumor cells by adding a specific suffix, i.e., pN0(i+). At present there is insufficient evidence regarding the clinical significance of micrometastasis to recommend the examination of multiple section levels, or the use of immunohistochemical or molecular analysis for the identification of isolated tumor cells within lymph nodes.

Lymph node metastasis should be distinguished from benign glandular lymph node inclusions, which are extremely rare in peripancreatic lymph nodes, but not so uncommon in abdominal lymph nodes of females (see Chap. 13, Sect. 13.6).

9.11.3 Lymphatic, Vascular, and Perineural Tumor Spread

The presence of tumor within lymphatic channels, blood vessels, or perineural clefts is staged as pL1, pV1, or pPn1. These descriptors are binary, hence they describe only the presence or absence of the particular mode of tumor spread, but do not reflect whether this is a common or rare finding within a given tumor. The accuracy of reporting depends on multiple factors, including the number of sections examined and whether ancillary techniques (elastica van Gieson staining or immunohistochemistry for CD31, D2-40, or S100) are used to identify blood and lymphatic vessels or peripheral nerves. These modes of tumor propagation are not as strong prognostic factors as tumor stage. On occasion, tumor growth within a large vessel, most commonly the splenic vein, may be visible macroscopically and should then be reported as pV2 (Fig. 9.41).

9.11.4 Resection Margin Status

The R descriptor refers to the presence or absence of residual disease. However, in clinical practice, the R-stage is usually regarded as synonymous to the resection margin status. To date there is no

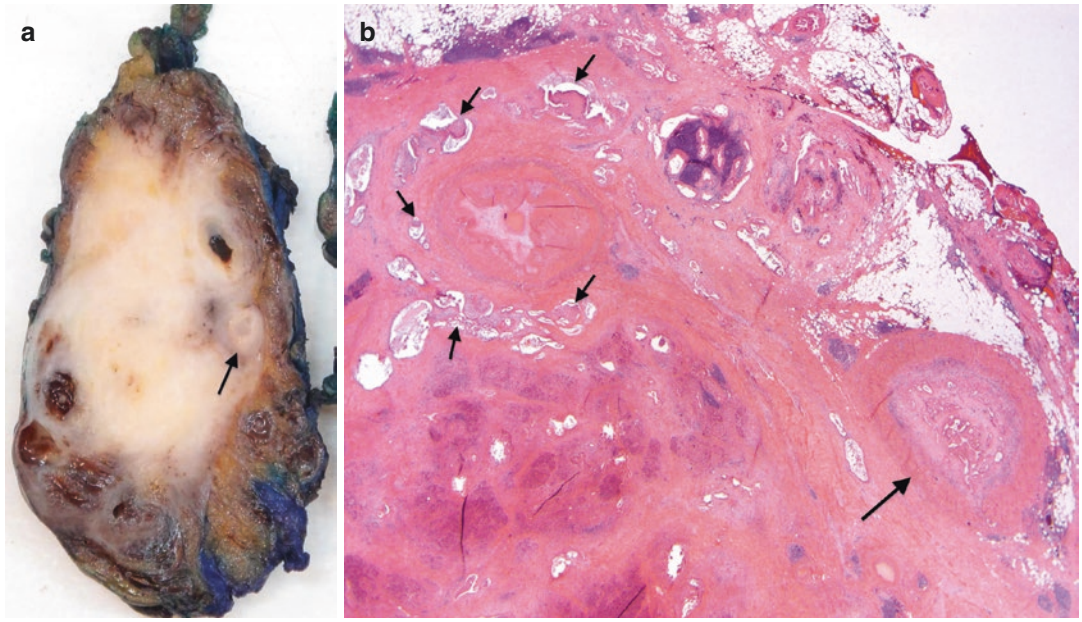


Fig. 9.41 Tumor occlusion of the splenic vein: the splenic vein is occluded by tumor (*arrow*, **a**). Histology confirms venous tumor occlusion (*long arrow*). Note the presence of a small lymph node metastasis and extensive tumor propagation along the neural plexus surrounding the splenic artery (*short arrows*, **b**)

universally accepted, evidence-based definition of microscopic margin involvement (pR1) in pancreatic cancer. In most countries, pR1 is defined as the presence of tumor cells within 1 mm of a margin (Fig. 9.42). However, this '1 mm rule' is a mere adoption from rectal cancer, for which clinicopathological correlation studies have shown a significant association between a clearance of up to 1 mm and an increased risk of local tumor recurrence. Such studies have not been performed for pancreatic cancer, and consequently, the minimum clearance appropriate for this malignancy is not known. In view of the more dispersed growth pattern in pancreatic compared to rectal cancer, the 1 mm rule may underestimate the presence of microscopic residual disease [28].

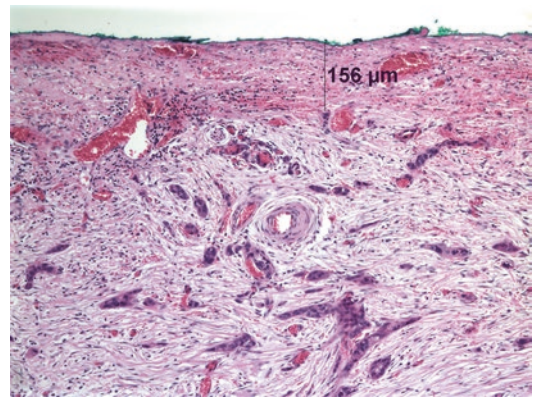


Fig. 9.42 Microscopic margin involvement: invasive adenocarcinoma lies within 1 mm of the inked circumferential resection margin

Further controversy exists as to whether microscopic margin involvement relates only to direct tumor growth or whether it can also be applied to tumor cells within lymphovascular channels or perineural clefts that are present within 1 mm to the margin. Regarding lymph node metastasis, it seems sound to record microscopic margin involvement only if there is extranodal tumor growth within 1 mm of the margin (Fig. 9.43). In practice, however, microscopic margin involvement will be identified in the majority of cases (over 75%), even if based exclusively on direct tumor growth, provided the specimen has been properly dissected and sampled.

Tumor involvement of the transection margins of the pancreatic neck or common bile duct is often assessed intraoperatively by frozen section examination (see Chap. 23, Sect. 23.3). In con-

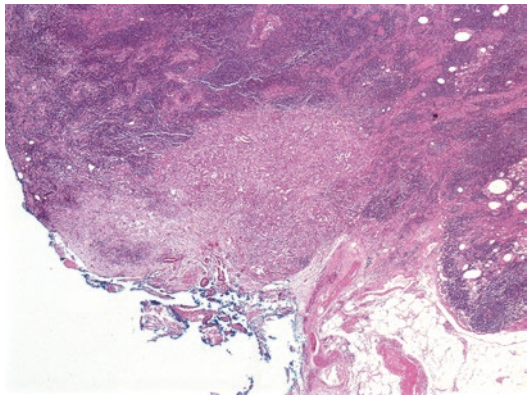


Fig. 9.43 Microscopic margin involvement: a lymph node metastasis with tumor extension into the perinodal fat is present at the inked circumferential resection margin

trast, there is no clear indication for assessment of the circumferential resection margins, because involvement of any of these margins has usually no surgical implication, since the resection in these areas cannot be extended, provided the surgery is performed according to current standards [29]. Microscopic tumor involvement is reported most frequently at the posterior margin and the margins facing the superior mesenteric vein (SMV) and artery (SMA) (see Fig. 3.5). Amongst the various circumferential resection margins, the SMA-facing margin is the only true resection margin, that is, the only area where the surgeon transects tissue, in this case the soft tissue adjacent to the SMA. The posterior margin and the margins at the SMV and around the extrapancreatic bile duct are so-called dissection margins, where the surgeon bluntly dissects tissue along an anatomical plane. It remains to be seen whether involvement of either type of margin—resection or dissection—is of similar prognostic significance [30].

Involvement of the anterior surface is rather uncommon, but occasionally it may be suspected already during macroscopic inspection, when the tumor protrudes and is visible on the anterior surface of the pancreas (Fig. 9.44). In pancreatoduodenectomy specimens, involvement of the anterior surface is often detected at the anterior pancreatoduodenal crevice, the anatomical narrow where the anterior surface curves inward before reaching the anterior duodenal wall (see Fig. 3.26). Because the anterior surface is a true anatomical surface rather than a surgical resection margin, reporting of R1 should be based on a clearance of 0 mm, i.e., tumor cells should be present at the surface (Fig. 9.45).

Special attention should be given to the margins of tangential or segmental resections of the superior mesenteric or portal vein. While the transection margin of the venous tissue is usually clear of tumor, microscopic tumor infiltration up to the specimen surface where the vein is adherent to the SMV groove is commonly seen (Figs. 9.46 and 9.47) [31].

According to the UICC definition, R2 denotes the presence of macroscopic residual disease. However, in clinical practice R2 is usually interpreted as macroscopic margin involvement. An R2 surgical resection usually suggests underestimation of local tumor extent and resectability on preoperative imaging. Discussion sometimes arises as to who should make the diagnosis of R2—the surgeon or the pathologist—and where the difference between microscopic and macroscopic margin involvement exactly lies. The distinction between R1 and R2 seems indeed to be important, as the prognosis is significantly worse after R2 resection. In many pancreatic cancer centers it has been agreed that a diagnosis of R2 resection depends on the surgeon's assessment. In practice, it may be more objective and informative if the pathologist refrains from using the R2 terminology, but instead simply states the extent over which the specimen surface is involved by tumor (Fig. 9.48).

9.12 Differential Diagnosis

The diagnosis of ductal adenocarcinoma of the pancreas may on occasion require differential diagnostic considerations to distinguish it from reactive pancreatic changes (especially in the context of chronic pancreatitis) and from primary pancreatic or metastatic tumors. Distinction of ductal adenocarcinoma from this variety of lesions is of paramount importance, because the treatment, follow-up, and prognosis for the various entities differ significantly. Immunohistochemistry may be helpful on many

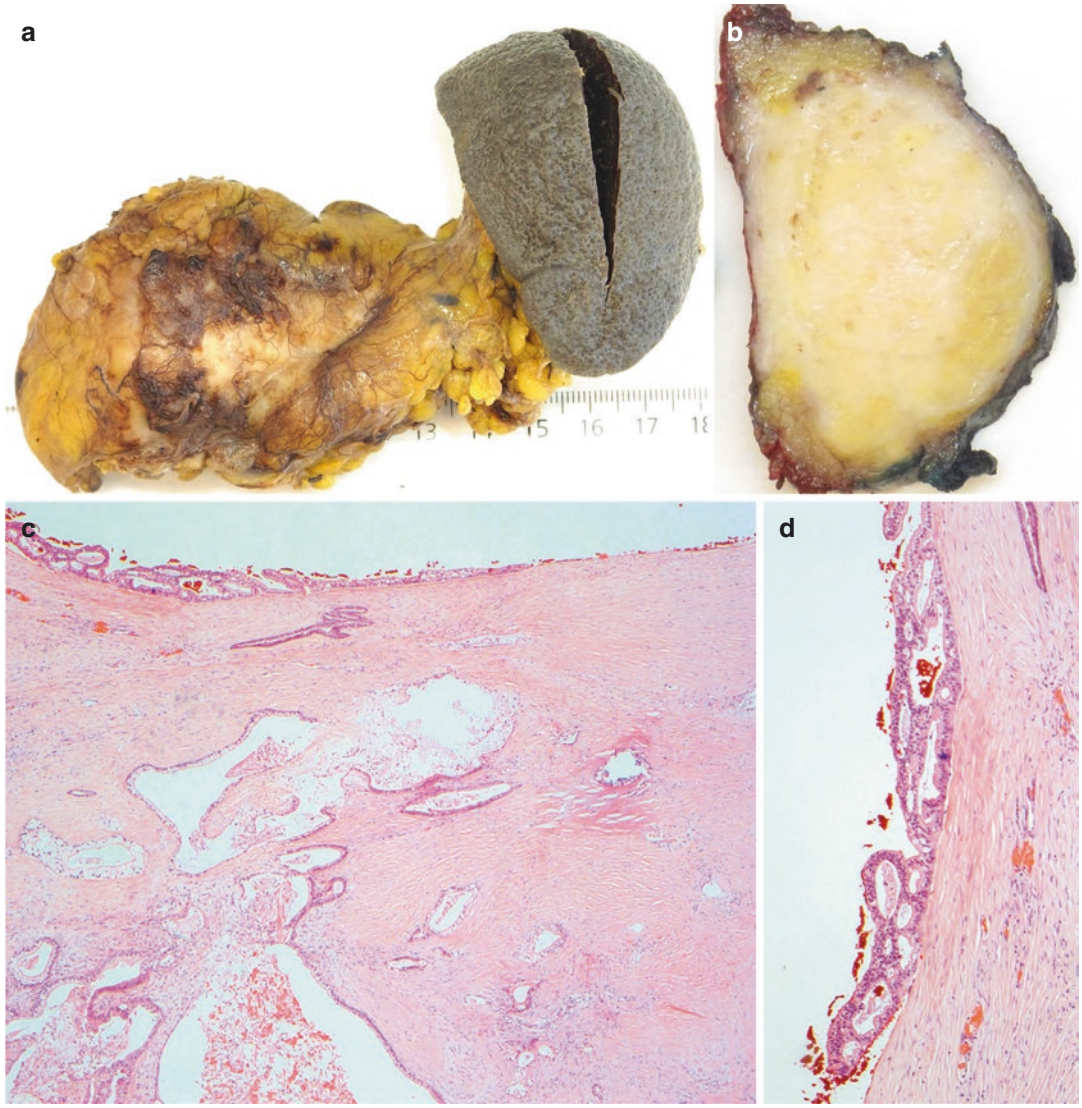


Fig. 9.44 Involvement of the anterior pancreatic surface: a large tumor protrudes from the anterior pancreatic surface (**a**). On cut section, tumor tissue lies directly underneath the red-inked anterior surface (**b**). Histologically, the well-differentiated ductal adenocarcinoma grows extensively on the anterior surface (**c**). Note the red ink on the anterior specimen surface (**d**)

occasions, but meticulous macroscopic and microscopic examination remains the backbone of the differential diagnosis.

9.12.1 Chronic Pancreatitis and Reactive Duct Changes

The distinction between ductal adenocarcinoma and reactive ducts, for example, in the context of chronic pancreatitis, can be problematic, especially in biopsy material or on frozen section. However, even in surgical resection material from patients with known chronic pancreatitis, definitive exclusion or diagnosis of ductal adenocarcinoma may be difficult, as both diseases can share multiple microscopic features. In chronic pancreatitis, gradual atrophy and fibrosis of the gland result in a vast fibrous stroma with a small number of scattered ductular structures, some of

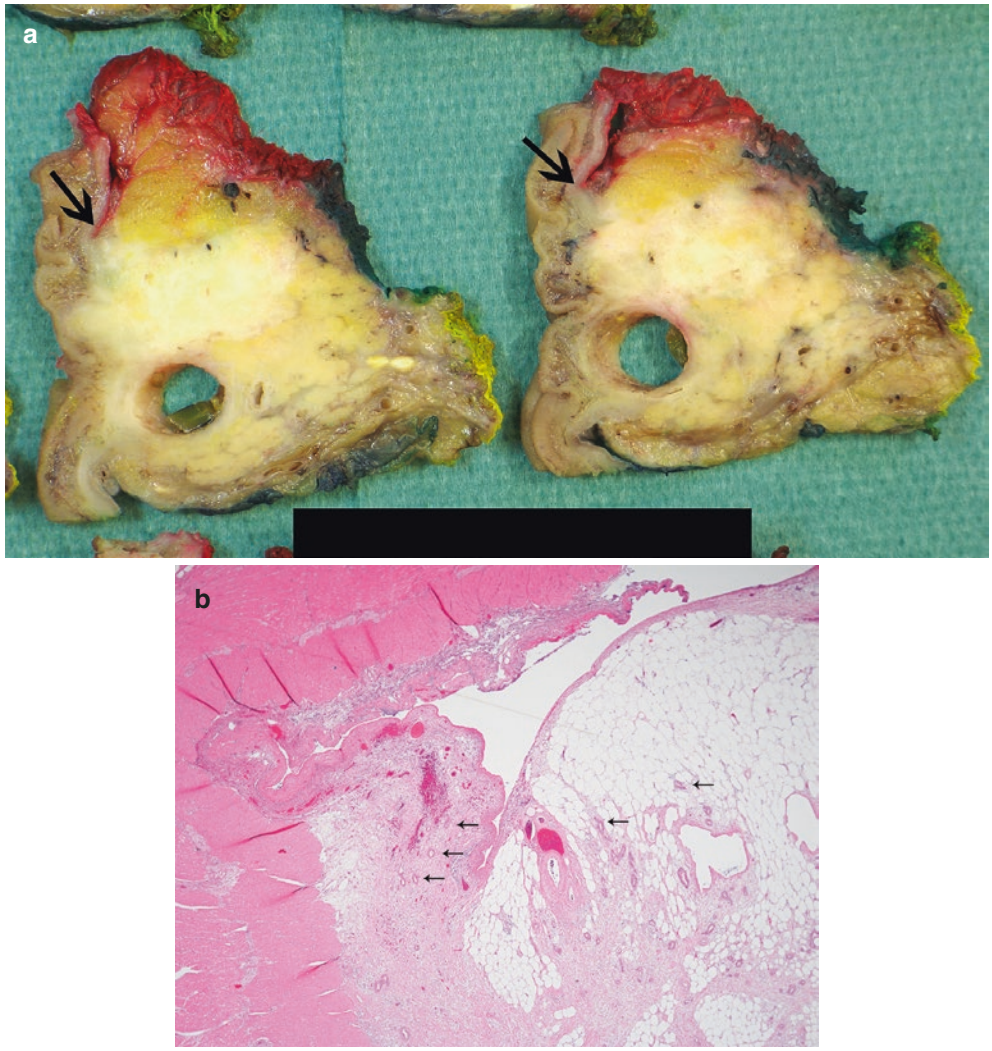


Fig. 9.45 Microscopic involvement of anterior surface: ductal adenocarcinoma located in the anterior part of the pancreatic head infiltrates the anterior peripancreatic fat and extends close to the anterior pancreatoduodenal crevice (*arrows*; **a**). Microscopically, tumor glands (*arrows*) lie close to, but do not breach the anterior surface (pR0; **b**)

which may show architectural and cytological atypia (see Chap. 7, Sect. 7.2.4, Fig. 7.36). This microscopic picture is not dissimilar from that of ductal adenocarcinoma, in which invasive tumor glands, exhibiting only mild atypia in case of a well-differentiated tumor, are spread out in the desmoplastic tumor stroma. Interspersed residual islets, acini, and unequivocal normal pancreatic ducts may be found in both chronic pancreatitis and ductal adenocarcinoma.

The resolution of this differential diagnosis is first and foremost based on the assessment of two architectural features: lobular architecture and segregation of blood vessels and pancreatic ducts. Lobular architecture is mainly preserved in chronic pancreatitis. Even if acinar atrophy is advanced, the outline of the lobules can remain identifiable by the distinct quality of the intralobular stroma, which is looser and slightly more basophilic than the dense collagen-rich fibrous stroma that surrounds the lobules (see Chap. 7, Sect. 7.2.4, Fig. 7.32). In contrast, in ductal adenocarcinoma, tumor glands are haphazardly distributed, across lobular boundaries, and irrespective of the branching system of the pancreatic ducts (Fig. 9.49).

In the normal pancreas, muscular blood vessels and pancreatic ducts take a different course

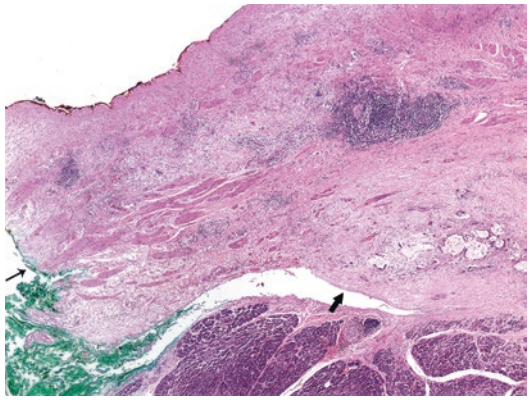


Fig. 9.46 Microscopic margin involvement around SMV resection: adenocarcinoma infiltrates the SMV groove and tunica adventitia of the SMV. While the transection margin of the vein is clear (*arrow*), tumor is present within 1 mm of the SMV margin (*block arrow*)

and are separated by acinar parenchyma (see Chap. 1, Sect. 1.4.5, Fig. 1.23). Therefore, the finding of a ductular structure in close approximation of a muscular blood vessel is highly suggestive of invasive adenocarcinoma (Figs. 9.50 and 9.51a). While this architectural feature is usually retained well into later stages of chronic pancreatitis, due to the gradual acinar atrophy and subsequent collapse, the separation of residual pancreatic ducts and muscular blood vessels will ultimately become reduced [32, 33]. Therefore, the use of this architectural feature should be circumspect in cases with advanced acinar atrophy (Fig. 9.51b) (see Figs. 7.33, 7.34, and 7.35). In contrast, even in advanced fatty infiltration of the

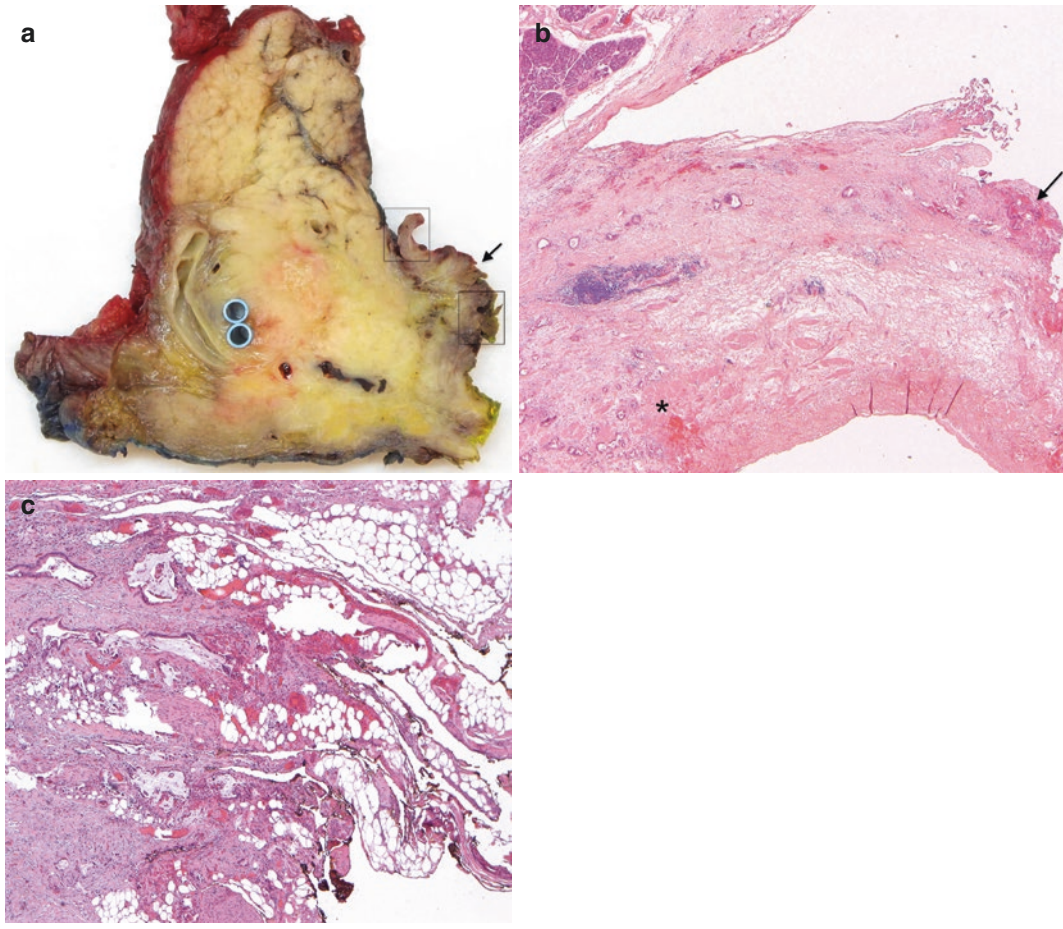


Fig. 9.47 Microscopic margin involvement around SMV resection: an ill-circumscribed ductal adenocarcinoma infiltrates the uncinate process. Note the irregular soft tissue flanking one side of the venous resection (*arrow*). The *boxes* indicate the areas that are shown at higher magnification in (**b**) and (**c**). Microscopically, tumor infiltrates the tunica media (*asterisk*) and adventitial soft tissue up to the transection margin of the venous sleeve (*arrow*, **b**). There is broad tumor infiltration of the irregular peripancreatic soft tissue that flanks the SMV-resection, with involvement of the overlying, inked margin (**c**)

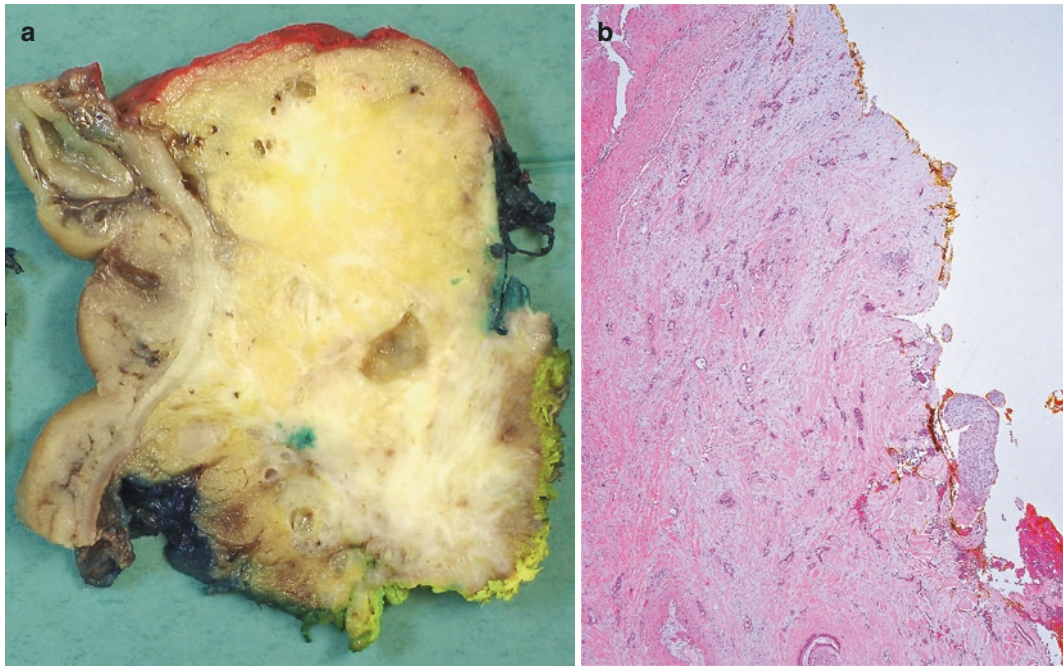


Fig. 9.48 Extensive microscopic margin involvement: there is broad tumor growth onto the SMA margin, which is inked yellow (**a**). Microscopically, there is extensive tumor growth within 1 mm to that margin (**b**)

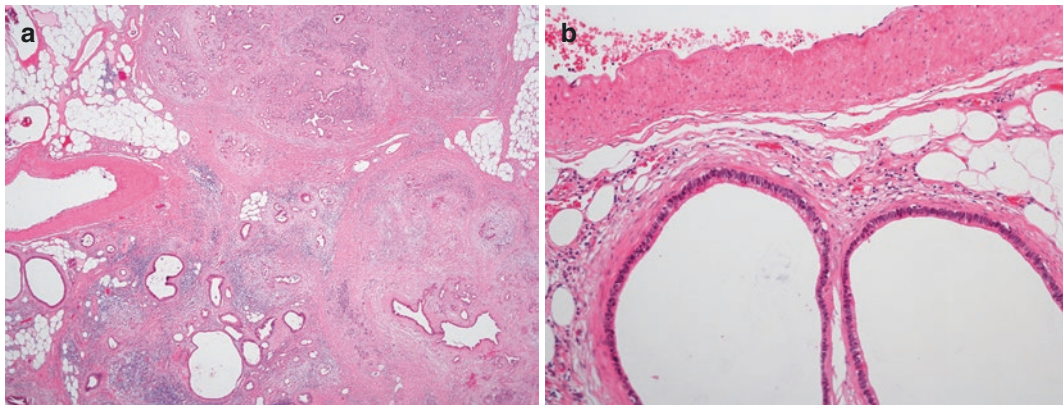


Fig. 9.49 Loss of normal tissue architecture: lobular boundaries are clearly outlined in the upper-right of the picture, whereas in the lower-left corner, large ductular structures efface the lobular architecture (**a**). Despite the rather bland cytology of some ducts, their presence adjacent to a muscular artery confirms this is adenocarcinoma (**b**)

pancreas, individual glands in chronic pancreatitis are usually surrounded by a small amount of stroma, whereas so-called naked glands, devoid of any associated stroma, can be seen at the invasive front of ductal adenocarcinoma (see Sect. 9.6.1).

Cytological features are also important in the distinction between pancreatic cancer and reactive ductular structures, and these criteria are discussed in detail in Chap. 23. The use of immunohistochemical staining has been discussed earlier in this chapter (see Sect. 9.9.3).

Chronic pancreatitis also causes changes to the endocrine compartment that may require careful consideration. Islet cells may exhibit marked nuclear atypia, which may raise the sus-

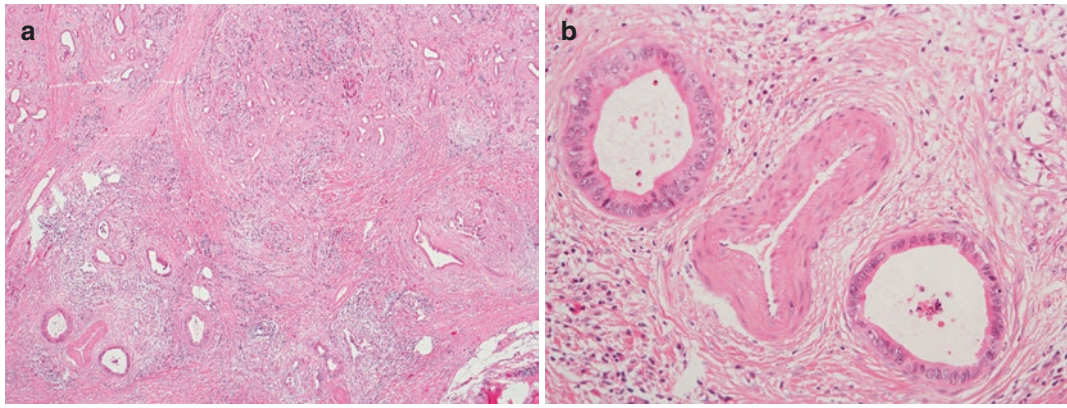


Fig. 9.50 Loss of normal tissue architecture: the loss of lobular architecture, presence of glandular structures next to a muscular artery (**a**), and cytological atypia (**b**) confirm that this is invasive ductal adenocarcinoma

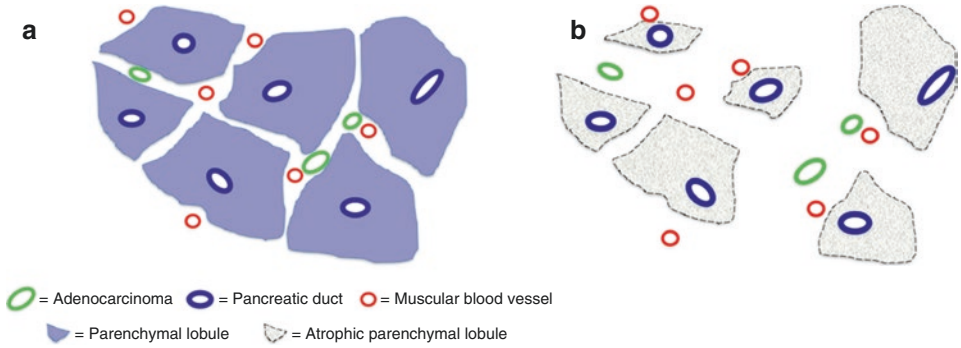


Fig. 9.51 Altered spatial relationship between intralobular ducts and muscular blood vessels following acinar atrophy: in normal pancreas, intralobular ducts and muscular blood vessels are separated by acinar parenchyma. Ductlike structures flanking muscular blood vessels are therefore suspicious of invasive carcinoma (**a**). As acinar atrophy progresses and lobules become smaller, gradual collapse of the tissue architecture may result in the proximity of intralobular ducts and muscular blood vessels, which should not be mistaken as evidence of malignancy (**b**)

picion of ductal adenocarcinoma if these atypical islet cells are present in any of the three following scenarios: (i) if islets are fragmented and small solid nests and strands of residual islets cells are scattered in dense fibrous stroma (Fig. 9.52); (ii) if islets are intimately associated with nonneoplastic glands; (iii) if, on rare occasion, islet cells associate intimately with peripheral nerves and thus mimic perineural invasion (see Fig. 7.30).

9.12.2 Other Pancreatic Neoplasms

A summary of the main differential diagnostic features of the primary solid pancreatic neoplasms is presented in Table 20.5.

9.12.2.1 Acinar Cell Carcinoma

The distinction between acinar cell carcinoma and ductal adenocarcinoma is usually straightforward. A lobulated appearance, high cellularity, scanty stroma within the tumor lobules, and an acinar growth pattern are features of acinar cell carcinoma. In addition, cytological detail and preserved nuclear uniformity, despite a high proliferative activity, are further findings in favor of acinar cell carcinoma (see Chap. 10). Careful consideration should be given to cancers with a signet ring or clear cell morphology, as these can be variants of both ductal adenocarcinoma and acinar cell carcinoma. Immunostaining for the enzymes trypsin and chymotrypsin and for the acinar cell marker BCL10 is the most useful

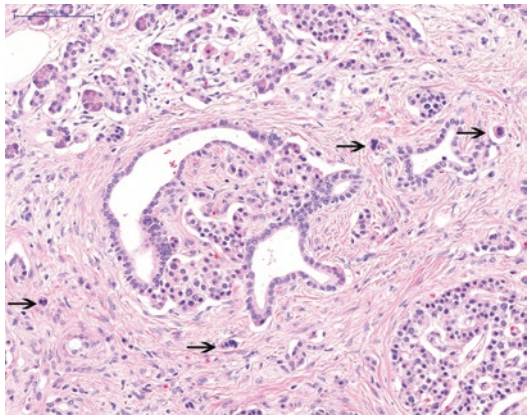


Fig. 9.52 Altered islets mimicking ductal adenocarcinoma: fragmented residual islets composed of small endocrine cell clusters showing nuclear atypia (*arrows*) should not be confounded with poorly differentiated adenocarcinoma

ancillary test to make the distinction, while immunolabeling for CEA can be focally present, and expression of cytokeratins 7 and 19 can also be seen in a proportion of acinar cell carcinomas.

9.12.2.2 Pancreatic Neuroendocrine Neoplasia

Pancreatic neuroendocrine tumors grade 1–3 (PanNETs) are always to be included in the differential diagnosis of ductal adenocarcinoma, as the former may assume a tubular, glandular, or cribriform growth pattern. The stroma of PanNETs can vary, but may be extensive and hyaline, and as such not entirely different from the desmoplastic stroma in ductal adenocarcinoma. With the exception of the pleomorphic variant, PanNETs usually exhibit less cytological atypia than ductal adenocarcinoma, and the uniformity of their centrally placed nuclei, the stippled chromatin pattern, and the absence of prominent nucleoli are distinguishing features. Because the mitotic activity in ductal adenocarcinoma may vary considerably, this is not usually a reliable criterion to distinguish ductal adenocarcinoma from PanNETs. Further morphological and immunohistochemical criteria on which to base this important differential diagnosis are discussed in detail in Chap. 20, Sect. 20.9.

Less obvious may be the distinction between adenocarcinoma and pancreatic neuroendocrine carcinoma (PanNEC) of large cell type, which usually lacks the above-described distinctive morphological features of grade 1–3 PanNETs. Immunostaining for neuroendocrine markers is usually needed to ascertain the correct diagnosis.

Special attention is required for the distinction between ductal adenocarcinoma and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), as by definition, these neoplasms exhibit ductal differentiation in at least one third of the tumor mass. The confirmation of neuroendocrine differentiation in the remainder of the tumor will indicate the correct diagnosis.

9.12.2.3 Solid Pseudopapillary Neoplasm

While solid pseudopapillary neoplasms have a strong predilection for young females, they may also be found in males and at an older age. However, both the macroscopic and microscopic features of these tumors are usually distinct from ductal adenocarcinoma, and both tumors have different immunohistochemical profiles (see Chap. 18 and Table 20.5). The rare solid pseudopapillary neoplasms that exhibit prominent cytoplasmic vacuolization may mimic the signet ring cell subtype of ductal adenocarcinoma (see Sect. 9.14.3). However, the intracytoplasmic vacuoles are—unlike those in adenocarcinoma—devoid of mucin. Poorly differentiated tumor areas lacking the characteristic features of solid pseudopapillary neoplasm have been reported in a few patients with an unusually short survival (see Chap. 18). While, in isolation, these areas may be more difficult to distinguish from (poorly differentiated) ductal adenocarcinoma, they are usually found in only a part of the tumor mass, the remainder of which exhibits features characteristic of solid pseudopapillary neoplasia.

9.12.3 Adenocarcinoma of Ampullary, Distal Bile Duct, or Duodenal Origin

Pancreatic, ampullary, and distal bile duct cancer are often collectively denoted as periampullary cancers or pancreatic head cancers. The reason for this grouping is the anatomical proximity of

the parent tissues, which can render pathological identification of the cancer origin difficult, especially in tumors of a large size. Some authors define periampullary cancer as a carcinoma arising within 2 cm of the major duodenal papilla. While this term may be useful as a clinical working diagnosis, it is inaccurate and should be avoided in pathology reports.

Duodenal adenocarcinoma can usually be excluded from the group of pancreatic head cancers based on its extensive, not uncommonly circumferential, involvement of the bowel wall, which is highly unusual in primary pancreatic, ampullary, or distal bile duct carcinoma. Because duodenal carcinoma may show a range of morphologies, including pancreatobiliary and gastric-like features, in addition to the intestinal type [34], microscopic and immunohistochemical examination may be of limited help to distinguish it from primary pancreatic cancer. Furthermore, pancreatic cancer may occasionally mimic duodenal carcinoma at a microscopic level, as it can acquire a more intestinal phenotype when infiltrating the duodenal wall, and it may simulate duodenal intramucosal neoplasia by spreading within the lamina propria (see Sect. 9.6.3; see Figs. 9.19 and 9.20).

Rigorous distinction between the different pancreatic head cancers is of direct relevance to individual patient management. First and foremost, clinical evidence suggests that these cancers differ in prognosis. Hence, careful distinction is essential for accurate prediction of outcome. Second, cancer origin determines to a major extent the indication for and selection of adjuvant treatment as well as the patient's participation in clinical trials. Furthermore, accurate identification of the tumor origin is important for correct staging, as the T-staging criteria differ between the pancreatic head cancers. In the long term and irrespective of individual patient management, exact diagnostic distinction between the cancer groups is a prerequisite for identification of possible differences in epidemiology, etiology, and molecular biology.

Identification of the cancer origin is based on (i) the anatomical relationship of the center of the tumor mass to the ampulla, common bile duct, and pancreas, and (ii) the presence of a neoplastic precursor lesion. The localization of the center of the tumor is the most important diagnostic criterion, as precursor lesions are often lacking or may be present fortuitously (see below). Careful gross examination of the three-dimensional relationship of the cancer to the key anatomical structures as outlined in Chap. 3 is of paramount importance and cannot be substituted by histomorphological or immunohistochemical investigations, because the microscopic features and immunoprofiles are largely shared among the three cancer groups (Fig. 9.53). While intestinal type adenocarcinoma is more common in the group of ampullary cancers compared to primary pancreatic and common bile duct carcinoma, the difference in relative incidence is not helpful for the correct diagnosis in the individual case. Furthermore, the suggested immunohistochemical signature to distinguish between intestinal and pancreatobiliary type ampullary adenocarcinomas based on a panel, including MUC1, MUC2, CDX2, and CK20 [35], may at times be useful, although subtyping is not always straightforward, and a significant proportion of carcinomas has hybrid features [36].

In *adenocarcinoma arising from the ampulla*, the center of the tumor will be located at mid-level of the craniocaudal length of the pancreatic head. As the tumor increases in size, it will involve the adjacent duodenal wall and pancreatic parenchyma and eventually extend into the peripancreatic soft tissue of the anterior and/or posterior pancreatoduodenal crevice (Figs. 9.54 and 9.55). In contrast, due to the location of the common bile duct in the posterior aspect of the pancreatic head (see Chap. 1, Sect. 1.3.2), *cancer developing from the intrapancreatic common bile duct* will predominantly involve the posterior part of the pancreatic head and peripancreatic soft tissue in the cranial half of the pancreatic head (Fig. 9.56). In *adenocarcinoma arising in the extrapancreatic common bile duct*, tumor involvement will be found mainly in the soft tissue sheath around the common bile duct stump and in the superior part of the pancreatic head (Fig. 9.57). As ductal adenocarcinoma can originate anywhere within the pancreatic head, it may involve any part of the pancreas and/or surrounding tissues (Fig. 9.53), including the common bile duct,

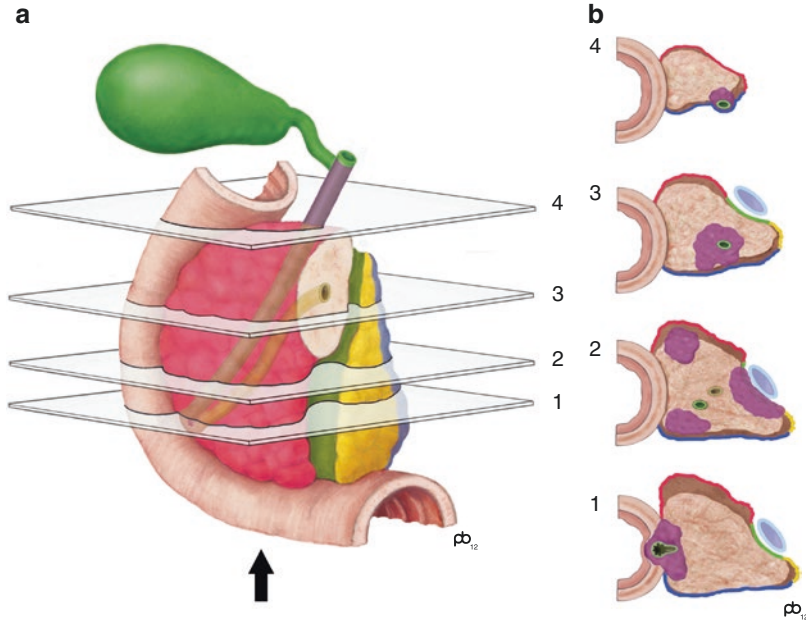


Fig. 9.53 Localization of periampullary cancers: the craniocaudal localization of a tumor (**a**) and its position within the axial specimen slices (**b**) is key to identification of the cancer origin. Ampullary carcinoma is located at and around the ampulla at mid craniocaudal height (1). Pancreatic carcinoma can be located anywhere within the pancreatic head (2). Cancer of the intrapancreatic bile duct is seated in the posterior part of the pancreatic head, above the level of the ampulla (3). Carcinoma arising from the extrapancreatic common bile duct is located in the cranial part of a pancreatoduodenectomy specimen and centers on the short extrapancreatic bile duct stump (4). (Image courtesy and copyright of Paul Brown, The Leeds Teaching Hospitals NHS Trust, Leeds, UK)

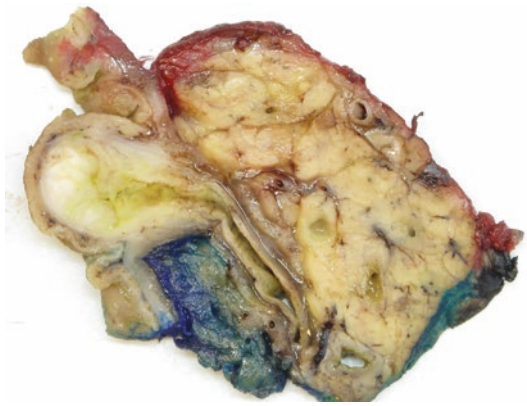


Fig. 9.54 Ampullary carcinoma: a well-circumscribed carcinoma involves the ampulla of Vater. Note the dilated main pancreatic duct

which is then secondarily involved and therefore does not lie in the center of the tumor mass (Fig. 9.58). If a tumor is located caudal to the level of the ampulla and in the part of the pancreatic head that is close to the superior mesenteric artery, origin from the ampulla, duodenum, or common bile duct can be excluded.

Meticulous assessment of the local anatomical landmarks is also important for the correct identification of the localization of precursor lesions. The latter are most frequently found in association with ampullary cancer, the reported incidence amounting to over 80%. In contrast, precursor neoplasia of the bile duct is much less commonly observed in association with distal bile duct carcinoma (10%–33%), and it usually presents as flat dysplasia rather than an adenomatous polypoid lesion. The diagnostic usefulness of pancreatic intraepithelial neoplasia (PanIN) as evidence of the pancreatic origin of an adenocarcinoma is limited, because low-grade PanIN is a common finding in the general population, especially over the age of 40, and it can be fortuitously coexistent with non-pancreatic cancer (see Chap. 8). If PanIN changes are high-grade, distinction from secondary duct cancerization may be problematic (see Fig. 9.37).

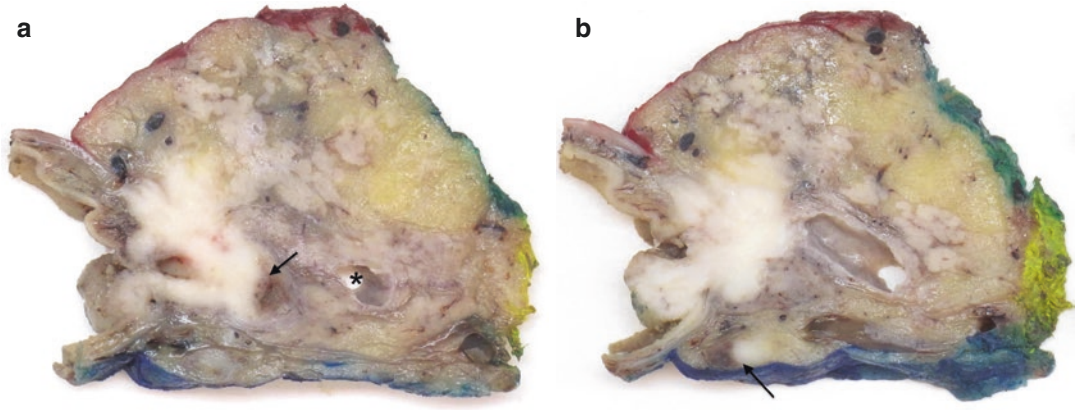


Fig. 9.55 Ampullary carcinoma: a locally advanced carcinoma infiltrates the ampulla of Vater and extends into the dilated distal common bile duct (*arrow*). Note the dilated main pancreatic duct (*asterisk*, **a**). There is also tumor invasion of the duodenal papilla and early infiltration of the pancreas. Note the presence of a peripancreatic lymph node metastasis (*arrow*, **b**)

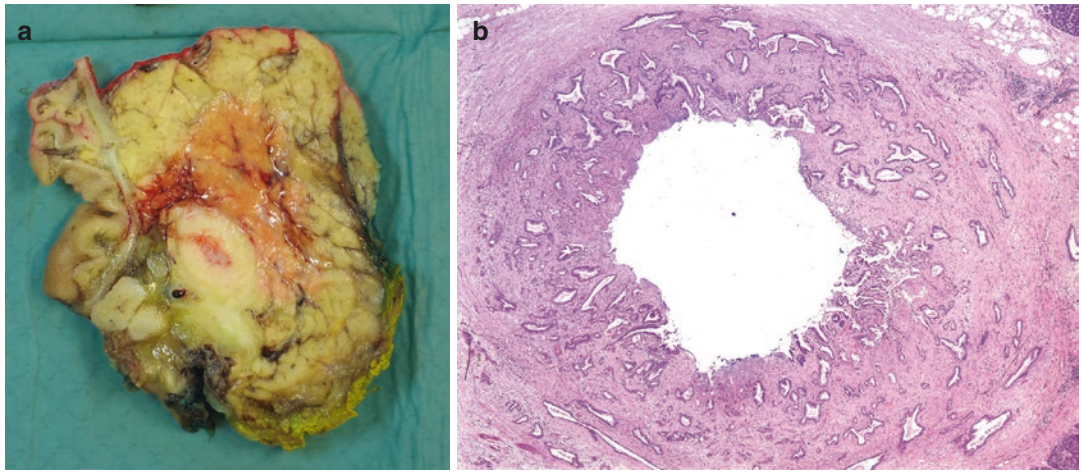


Fig. 9.56 Carcinoma of the intrapancreatic bile duct: the wall of the bile duct is thickened and its lumen narrowed by tumor, which extends into the surrounding pancreatic tissue (**a**). Microscopically, adenocarcinoma encircles the bile duct wall and infiltrates the periductal stroma (**b**)

9.12.4 Metastasis from Extrapancreatic Primaries

The distinction between ductal adenocarcinoma of the pancreas and metastasis from extrapancreatic primary cancers is discussed in Chap. 12.

9.13 Treatment and Prognosis

Ductal adenocarcinoma is fatal in almost all patients. This dire outcome is the combined result of the intrinsic aggressiveness of the cancer, the lack of effective cytotoxic treatment, and the late stage at which these tumors are usually detected. In line with the carcinogenesis model of ductal

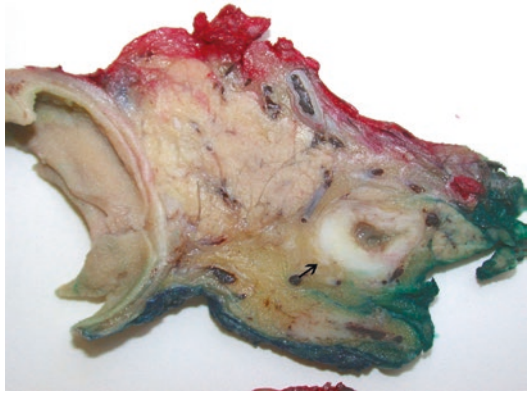


Fig. 9.57 Carcinoma of the extrapancreatic bile duct: white tumor tissue shows segmental infiltration of the extrapancreatic common bile duct. Note early tumor extension into the periductal soft tissue (*arrow*) and the proximity to the periductal circumferential margin (inked green)

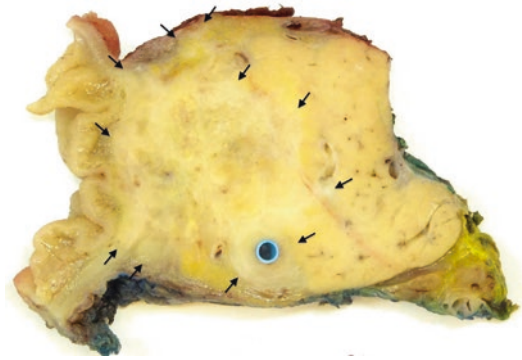


Fig. 9.58 Pancreatic cancer with secondary involvement of the common bile duct: this large pancreatic cancer involves mainly the anterolateral part of the pancreatic head and the duodenal wall (*arrows*). At its periphery, the tumor also infiltrates half of the circumference of the (stented) common bile duct

adenocarcinoma that is based on a linear progression through the various stages of pancreatic intraepithelial neoplasia (PanIN) and the concomitant accumulation of mutations (see Chap. 8), it has been estimated that more than a decade has elapsed between the occurrence of the initiating mutations and the establishment of the first metastasis. According to this computational model, patients die on average 2 years thereafter [2]. While in theory this offers a large window of opportunity for diagnosis of pancreatic cancer at a curative stage, the early and rapid metastatic spread that characterizes the disease as well as the fact that even small tumors (< 2 cm) have already metastasized, argue against gradual pancreatic cancer progression. Recently, an alternative "cataclysmic" model has been suggested, according to which large-scale and complex, simultaneous rather than sequential, genomic errors occur that lead within a short time span to aggressive invasive and metastasizing tumors [37]. Further knowledge about the progression of ductal adenocarcinoma is essential to guide more effective screening and treatment strategies.

Surgical resection is currently the only potentially curative treatment option. However, only 15–20% of patients are eligible for surgery at the time of diagnosis. In the remaining 80% of patients, the tumor is locoregionally too advanced to be resected or has metastasized to distant sites, mainly to the liver. Despite recent advances in surgical techniques allowing, for example, safe resection of ductal adenocarcinomas with a degree of involvement of the superior mesenteric vessels or portal vein, the mean survival after surgical resection is only 10–20 months [38]. In comparison, for patients who do not undergo surgical resection, the mean survival is 3 to 5 months. Even after successful surgical resection with curative intent, the majority of patients (70–90%) develop disease recurrence, most within 2 years after surgery. Correspondingly, the 5-year survival rate for patients following surgical resection is approximately 10–25%, compared to 8% for patients with inoperable disease [38]. Distant metastasis—in decreasing order to the liver, peritoneum, and lung—and local recurrence develop with a similar frequency [39]. However, patients rarely die of the latter but rather of distant metastasis, which usually exerts its fatal effect before local tumor recurrence becomes the determinant of outcome.

Since most pancreatic cancers that are surgically resected show a full house of adverse prognostic factors—the typical stage being pT2N1L1V1Pn1R1—it is difficult to assess the prognostic impact of each individual factor. Furthermore, many published data are based on retrospective analysis of series that date back to

before the late 1990s, when specimen handling and microscopic reporting were not standardized and pathology assessment was less meticulous than what is currently regarded as good practice. Hence, not surprisingly, key pathology data from various centers differ significantly. Overall, however, pT-, pN-, and pM-stage are strong prognostic factors, while vascular and perineurial invasion, and the grade of differentiation seem to be of weaker predictive value.

Adjuvant treatment has become part of the standard therapy for ductal adenocarcinoma of the pancreas; its survival benefit is statistically significant but limited, increasing the median survival by a few months. The discussion of whether adjuvant treatment should be based on chemotherapy or chemoradiotherapy is still ongoing [38].

Despite adjuvant treatment, most patients die of distant metastasis, and some do after such a short postoperative time interval that the presence of occult metastasis at the time of surgery must be assumed. Since pancreatic disease seems to be a systemic disease at presentation in most patients, moving chemo(radio)therapy to the preoperative setting seems to be appropriate. Indeed, neoadjuvant chemo(radio)therapy offers systemic treatment at the earliest possible moment rather than at a later time point (if and) when the patient has recovered from surgery, which offers ultimately only a local form of treatment. In addition, patients may manifest clinically detectable metastasis or an aggressive disease course during the neoadjuvant treatment period, that is, before unnecessary surgery is undertaken. Finally, with preoperative chemo(radio)therapy, the risk of R1 resection may be reduced, and treatment is delivered to tissues that are not yet rendered less receptive to cytotoxic treatment due to surgery-induced inflammation and hypoxia.

In recent years, chemo(radio)therapy is also considered for patients with locally advanced pancreatic cancer with the intention to reduce tumor size and extent, such that the cancer becomes resectable. For the approximately 20% of patients whose tumor can be surgically removed, survival improves to a level that is comparable with that of patients with primary operable disease [38].

Limited data are available regarding the prognosis and response to (neo-)adjuvant treatment of the subtypes of ductal adenocarcinoma, which are discussed in the next section. While most subtypes have an equally poor or even worse outcome, colloid and medullary carcinoma seem to portend a better prognosis.

9.14 Histological Subtypes of Ductal Adenocarcinoma

This diagnostic group encompasses tumors that are regarded as subtypes of pancreatic cancer, because they exhibit significant other features of differentiation in addition to the morphology of conventional ductal adenocarcinoma. These subtypes do not only exhibit a distinct morphological appearance but differ also clinically and in terms of patient outcome. Staging of the variant tumors follows the TNM UICC system (eighth edition) for carcinoma of the exocrine pancreas (Table 9.3). The subtypes of ductal adenocarcinoma are rare tumors, which overall account for up to 3–4% of all malignancies of the exocrine pancreas. Colloid carcinoma may be slightly less uncommon, as it can develop in association with intraductal papillary mucinous neoplasia (see Chap. 17). Occasionally, ductal adenocarcinomas with a distinct histomorphology—for example, oncocytic—that differs from the below-described subtypes, have been reported. However, because their clinical and biological features are currently not well defined, they are currently not considered separate subtypes by the WHO classification.

9.14.1 Adenosquamous Carcinoma and Squamous Cell Carcinoma

This subtype shows significant ductal and squamous differentiation. The latter should represent at least 30% of the entire tumor mass. While this cut-off is arbitrary, it is useful in distinguishing this subtype from the occasional presence of small foci of squamous differentiation within otherwise conventional ductal adenocarcinoma, a

finding that is of no clinical significance. Tumors with predominant squamous differentiation and only focal evidence of ductal differentiation should also be reported as adenosquamous carcinoma. True squamous cell carcinoma with pure squamous differentiation is extremely rare in pancreatic cancer, and if ductal differentiation is not identified despite thorough tumor sampling, metastasis from an extrapancreatic primary (e.g., lung cancer) should be excluded. Adenosquamous carcinoma does not usually differ from conventional ductal adenocarcinoma in its clinical presentation and macroscopic appearance. There is no known association with any specific clinical syndrome.

Microscopically, the areas of squamous differentiation are usually intimately admixed with those of conventional ductal adenocarcinoma. They show the usual characteristic features of squamous cell carcinoma, including a growth pattern of solid sheets and clusters with often a layered or swirling cellular arrangement, and polygonal tumor cells with distinct cellular borders, intercellular junctions, deeply eosinophilic cytoplasm, and a varying degree of keratinization (Fig. 9.59). Immunostaining for the markers p63, p40, and cytokeratins (CKs) 5/6 and 14 may be helpful in confirming the presence and evaluating the extent of squamous differentiation. Immunolabeling for CK7, CK20, and CA19-9 is usually limited to the ductal component, which may also be highlighted by mucin stains. The molecular signature and immunohistochemical profile of adenosquamous carcinoma showing loss of p16 and SMAD4, and strong nuclear staining for p53 are similar to those found in conventional ductal adenocarcinoma. Limited evidence suggests that adenosquamous carcinoma falls into the basal-like subtype of the transcription-based classification of pancreatic ductal adenocarcinoma (see Sect. 9.18) [40].

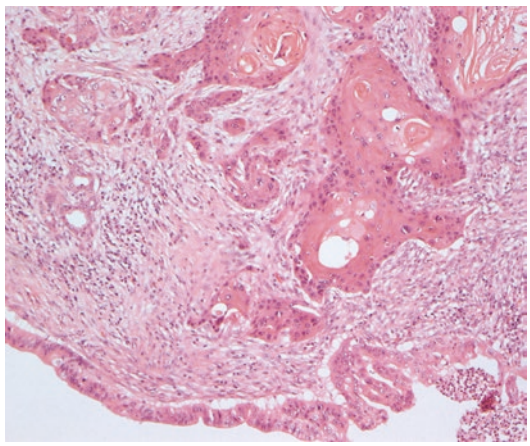


Fig. 9.59 Adenosquamous carcinoma: the carcinoma is mainly composed of solid cell sheets with squamoid features and contains, in addition, foci of glandular differentiation

In addition to metastatic spread from extrapancreatic adenosquamous carcinoma, the differential diagnosis also includes pancreatoblastoma. The latter contains squamoid nests and may include areas of ductal differentiation, but is predominantly composed of acinar cell neoplasia, which stains for pancreatic enzymes (see Chap. 10, Sect. 10.11.3).

Patients with resected adenosquamous carcinoma have a poorer prognosis (median survival less than 1 year) than those with a conventional, pure ductal adenocarcinoma. Both the ductal and squamous components of this variant may be found in metastatic deposits.

9.14.2 Colloid Carcinoma

This subtype, also denoted as mucinous noncystic carcinoma, has been defined by the WHO classification as a ductal adenocarcinoma containing features of a colloid carcinoma, that is, large extracellular mucin pools, in at least 80% of the tumor mass (Fig. 9.60). The latter are partially lined with neoplastic epithelium and contain free-floating tumor cells, which are often fairly well differentiated and have a prominent mucin content. Tumor cells suspended in the mucin pools can acquire signet ring morphology. Colloid carcinoma should be distinguished from mucinous adenocarcinoma, which is a conventional ductal adenocarcinoma containing abundant intracellular or intraluminal mucin collections, but lacking the extracellular mucin pools characteristic of colloid cancer.

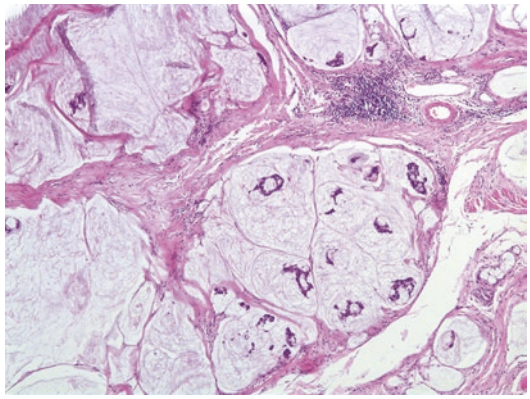


Fig. 9.60 Colloid carcinoma: the tumor is composed of large extracellular mucin pools containing free-floating strips of tumor cells

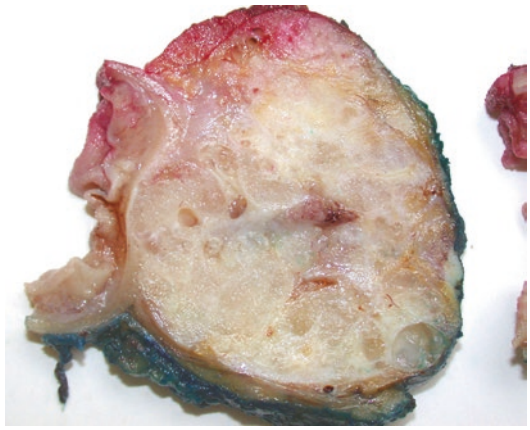


Fig. 9.61 Colloid carcinoma: the tumor shows a glistening mucinous cut surface, contains small cystic areas, and has pushing type margins

Macroscopically, colloid carcinomas are usually large and well circumscribed. They consist, at least in some parts, of friable solid tumor tissue with a gelatinous appearance (Fig. 9.61). Mucin is abundant and of a viscous, jelly-like consistency. Colloid carcinomas occur almost exclusively in association with intraductal papillary mucinous neoplasia (IPMN), which may be identifiable macroscopically as cystically dilated ducts (see Chap. 17). In this context, it is important to distinguish invasive colloid carcinoma from spillage of mucin into the stroma following rupture of a pancreatic duct involved by IPMN. The presence of free-floating neoplastic cells within the mucin pools or in abnormal location, for example, in perineural clefts, may help in making the distinction. The location of the mucin pools proper is a further diagnostic feature, as these are found in the periductal stroma in case of duct rupture, whereas in colloid carcinoma they can be present at a distance from the duct system. Furthermore, the inflammatory reaction is usually more prominent in duct rupture than in invasive colloid carcinoma. A further differential of colloid carcinoma is mucinous cystic neoplasia, which occurs almost exclusively in women and has a characteristic ovarian-type stroma (see Chap. 16).

Immunohistochemically, colloid carcinoma cells express markers of intestinal differentiation, in particular CDX2 and MUC2, in addition to cytokeratins (including CK20), CEA, and CA19-9. Immunostaining for MUC1 is usually negative. Unlike conventional ductal adenocarcinoma, nuclear staining for p53 is positive in only a quarter of cases, and expression of SMAD4 is usually retained.

Colloid carcinoma is rare in the pancreas and occurs more commonly in the ampulla and duodenum. Therefore, the diagnosis of colloid carcinoma of the pancreas requires careful exclusion of a tumor origin in the GI tract.

Colloid carcinoma is reported to portend a more favorable prognosis compared to conventional ductal adenocarcinoma, despite the overall larger tumor size of this subtype. Pseudomyxoma peritonei is a rare complication of colloid carcinoma.

9.14.3 Signet-Ring Cell (Poorly Cohesive Cell) Carcinoma

This is a very rare subtype with histomorphological features similar to signet ring cell carcinoma originating in the stomach. Infiltration by individual, poorly cohesive rounded tumor cells containing a large intracytoplasmic mucin vacuole and a peripherally placed, flattened nucleus is characteristic of these tumors (Fig. 9.62). A com-

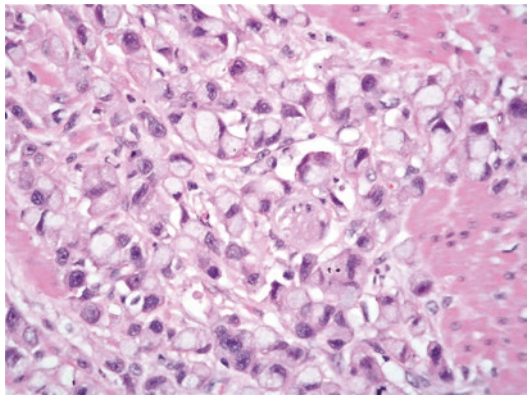


Fig. 9.62 Signet ring cell carcinoma: the tumor cells are poorly cohesive and grow in ill-defined clusters. Many cells have a signet ring appearance

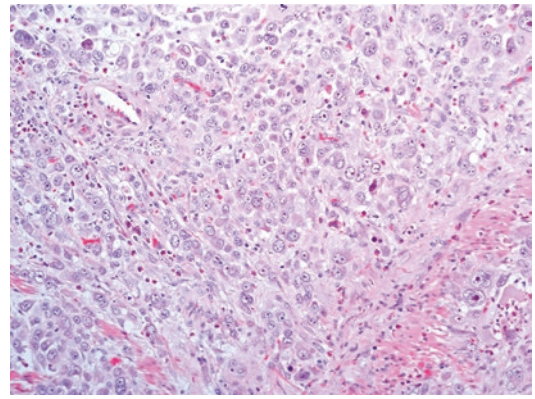


Fig. 9.63 Medullary carcinoma: large tumor cells with ill-defined borders grow in a syncytium-like solid sheet. The macroscopy of this pancreatic cancer is illustrated in Figs. 2.6 and 9.3

ponent of conventional ductal adenocarcinoma is usually present, and it has been recommended to report this variant only if at least 50% of the tumor mass shows signet ring cell differentiation. While extracellular mucin collections can be present, they do not form the large pools that are characteristic of colloid carcinoma. Individual tumor cells, or small clusters, infiltrating the stroma are a feature of signet ring cell carcinoma that is not observed in colloid carcinoma. Unlike the latter, signet ring cell carcinoma is not associated with intraductal papillary mucinous neoplasia.

While survival data for this rare subtype are limited, prognosis seems to be extremely poor. The differential diagnosis includes metastatic carcinoma from the stomach or breast (see Chap. 12, Table 12.1). In addition, signet ring morphology due to non-mucinous cytoplasmic accumulations may occasionally be seen in pancreatic endocrine neoplasia with rhabdoid features, acinar cell carcinoma with signet ring change, and rare lymphomas with signet ring morphology. Prominent cytoplasmic vacuolization mimicking signet ring morphology may also be seen in solid pseudopapillary neoplasia, but the lack of highly infiltrative tumor cell growth and desmoplastic stroma, along with a distinct immunohistochemical profile, allow an unequivocal distinction between both tumors (see Chaps. 10, 18 and 20, Table 20.5).

9.14.4 Medullary Carcinoma

This rare subtype of ductal adenocarcinoma shares some, but not all, morphological features with medullary carcinoma of the large bowel. The tumor is characterized by poor differentiation with limited glandular differentiation and the appearance of a syncytial growth pattern, due to the indistinct borders of individual tumor cells (Fig. 9.63). Tumor-infiltrating T lymphocytes may be numerous and at least focal necrosis is commonly observed. A Crohn's-like lymphoid reaction is usually not present in pancreatic tumors, which also lack the mucinous component that has been described in colonic medullary tumors. Unlike conventional ductal adenocarcinoma, medullary carcinoma is macroscopically characterized by soft tumor tissue with well-demarcated pushing type borders.

Medullary carcinoma can occur sporadically or in patients with Lynch syndrome (see Chap. 6, Sect. 6.4). Many but not all tumors are wild-type for the *KRAS* gene and microsatellite instable (MSI+), and immunostaining for one or more of the mismatch repair proteins is lost in some of these cancers. The diagnosis of medullary carcinoma of the pancreas may be a clue to an inherited cancer syndrome, including Lynch syndrome, and may justify genetic counseling of the patient. Pancreatic ductal adenocarcinoma with Epstein-Barr virus infection of the

cancer cells may morphologically mimic medullary carcinoma [41].

The differential diagnosis of medullary carcinoma includes poorly differentiated acinar cell carcinoma and conventional ductal adenocarcinoma. Immunohistochemistry is usually helpful, in particular the loss of nuclear staining for MLH1 or MSH2, and the absence of labeling for trypsin, other acinar enzymes, and BCL10.

Prognosis for medullary carcinoma of the pancreas seems more favorable than that for conventional ductal adenocarcinoma (mean survival 62 months versus 10–20 months in surgically resected patients). In analogy with medullary colorectal carcinoma, pancreatic tumors may not respond to 5-fluouracil treatment, while immunotherapy may be effective.

9.14.5 Hepatoid Carcinoma

This extremely rare subtype shows morphological and immunohistochemical evidence of hepatocellular differentiation in >50% of the tumor mass. The tumor is composed of large polygonal cells with abundant eosinophilic cytoplasm that show immunolabeling for HepPar1 (Hepatocyte-Paraffin 1). The tumor cells have a centrally placed nucleus with a single nucleolus, and they are arranged in a trabecular pattern, often with a sinusoidal type of vascularization. Some cases may exhibit a canalicular pattern of staining for CEA (polyclonal) and CD10. Bile production may be present in well-differentiated tumors. Periodic acid-Schiff (PAS)-positive diastase-resistant hyaline globules, similar to those seen in liver parenchyma, may occasionally be present. Alpha-fetoprotein (AFP) is expressed in some but not all tumors. Hepatoid differentiation occurs not only in pancreatic cancer with ductal differentiation, but also in association with neuroendocrine neoplasia (see Chap. 20, Sect. 20.5.1, Fig. 20.11). The macroscopic appearance of hepatoid carcinoma is non-distinct, although some tumors have been reported to exhibit an unusual tan to red-brown color.

The main differential diagnosis is the pancreatic metastasis of an occult hepatocellular carcinoma, which should be excluded primarily on clinical grounds. Acinar cell carcinoma can mimic hepatoid carcinoma morphologically and may also express AFP and markers of hepatocellular differentiation, including HepPar1 and glypican 3. Immunostaining for arginase 1 and FISH for albumin are likely more specific markers of hepatocellular differentiation. Positive immunostaining for AFP can also be seen in a minority of ductal adenocarcinomas, pancreatic endocrine neoplasms, and pancreatoblastomas as well as in extrapancreatic malignancies, including germ cell tumors. Therefore, immunolabeling for AFP is by itself insufficient evidence for a diagnosis of hepatoid carcinoma. Moreover, HepPar1 expression may also be seen in intraductal oncocytic papillary neoplasia (see Chap. 17, Sect. 17.3).

Information on the prognosis for hepatoid carcinoma of the pancreas is currently too limited to allow a confident statement.

9.14.6 Invasive Micropapillary Carcinoma

The micropapillary component in this subtype is characterized by small clusters of cancer cells that closely adhere to each other and are located in a distinct empty space that may resemble a dilated lymphatic channel (Fig. 9.64). Invasive micropap-

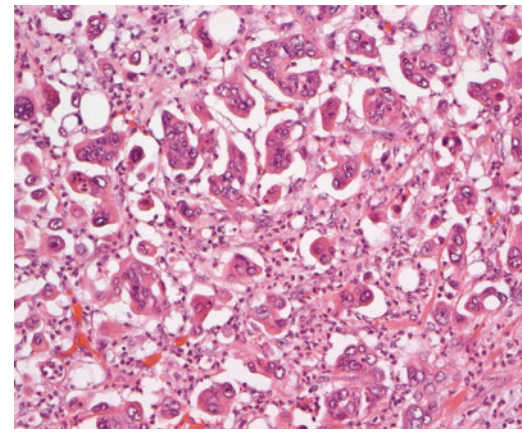


Fig. 9.64 Invasive micropapillary carcinoma: small cohesive cancer cell clusters are surrounded by an empty space. Note the presence of scattered neutrophils

illary carcinoma is defined by the occurrence of micropapillae in >50% of the tumor mass, which is a rare finding. Slightly more frequently, micropapillary morphology may be seen focally in conventional ductal adenocarcinoma. Invasive micropapillary carcinoma is often associated with dense intraepithelial infiltration of neutrophils and shows a more aggressive behavior. It should be noted that invasive micropapillary carcinoma is slightly more common in the ampulla [42].

9.14.7 Undifferentiated Carcinoma

Undifferentiated carcinoma has also been denoted as anaplastic carcinoma, pleomorphic large cell carcinoma, spindle cell carcinoma, sarcomatous carcinoma, and carcinosarcoma. It is defined as a malignant epithelial neoplasm in which a significant tumor component does not show a definitive direction of differentiation. Necrosis and hemorrhage are commonly present and may be extensive. Most tumors are large and widely invasive and exhibit lymphovascular and perineural propagation.

Undifferentiated carcinomas exhibit a spectrum of morphological features. Three patterns can be distinguished, but individual tumors may contain a combination of patterns. *Anaplastic undifferentiated carcinoma* consists at least to 80% of pleomorphic mononuclear cells admixed with bizarre, often multinucleated giant cells showing copious eosinophilic cytoplasm. Cell cannibalism of tumor cells, erythrocytes, or inflammatory cells may be seen. Nuclear pleomorphism is usually prominent, and mitotic figures, including atypical ones, are numerous. The neoplastic cells are usually non-cohesive, and desmoplastic stroma is scanty (Fig. 9.65).

In *sarcomatous undifferentiated carcinoma*, neoplastic cells are mainly spindle-shaped and may be arranged in a vague fascicular or herringbone pattern in at least 80% of the tumor. While cytological atypia is usually less prominent than in anaplastic giant cell carcinoma, pleomorphism is nonetheless significant (Fig. 9.66).

Carcinosarcomas contain in addition to the atypical spindle cell component, areas of unequivocal adenocarcinomatous differentiation. Arbitrarily, either component should represent at least 30% of the tumor mass.

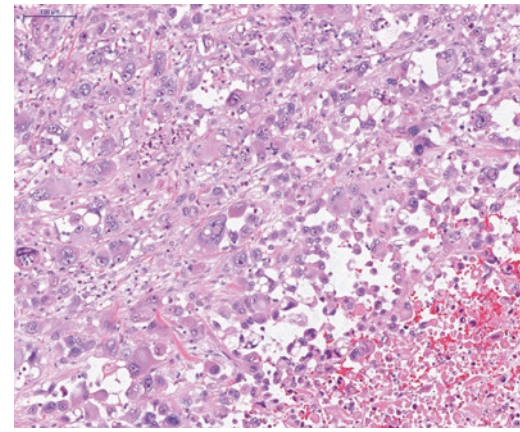


Fig. 9.65 Undifferentiated carcinoma, anaplastic giant cell variant: large, highly pleomorphic tumor cells grow in poorly cohesive solid sheets. Note the scanty tumor stroma and presence of an atypical mitotic figure

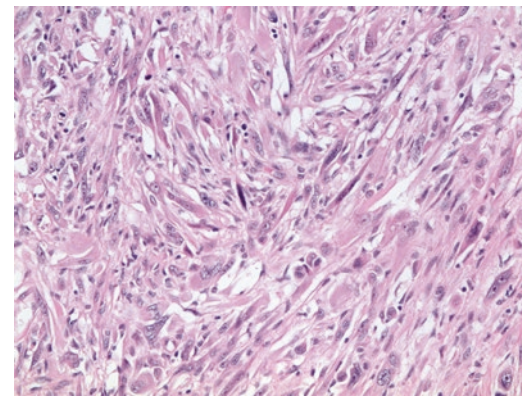


Fig. 9.66 Undifferentiated carcinoma, sarcomatoid variant: tumor spindle cells with pleomorphic nuclei are arranged in vague short bundles

Mesenchymal tumor differentiation in the latter two variants may sometimes lead to the presence of heterologous stromal elements, including bone, cartilage, or skeletal muscle. Squamous differentiation and rhabdoid features have also been reported.

Immunohistochemical evidence of an epithelial histogenesis is found in all undifferentiated carcinomas, although labeling for epithelial markers may be very focal. CK7, 8, 18, and 19

are among the cytokeratins that can be expressed. Immunolabeling for E-cadherin is typically absent. Most tumors also express vimentin, CEA, MUC1, and CA19-9. Spindle cells may stain for actin but usually not desmin. Immunolabeling for neuroendocrine markers is absent in most tumors.

The differential diagnosis of this group of neoplasms is wide and depends on the morphological features of the individual tumor. Overall, metastatic melanoma, poorly differentiated germ cell tumors, and hematopoietic neoplasms should be included in the differential diagnosis. Immunostaining for melanocytic markers (HMB45, melan-A, S100), human chorionic gonadotropin-beta (β-HCG) and leukocyte common antigen or other leukocyte markers may be helpful. Primary sarcomas of the pancreas are extremely rare, and the absence of a specific line of mesenchymal differentiation (morphologically and/or immunohistochemically), the marked degree of cytological atypia, and the positive staining for cytokeratins, even if only focal, favor carcinosarcoma. However, it has to be noted that keratin positivity can occur in the rare case of pancreatic synovial sarcoma (see Chap. 11, Sect. 11.1.12). Undifferentiated carcinoma metastatic to or originating from the pancreas cannot be distinguished immunohistochemically. However, the presence of extensive and high-grade PanIN or the association with a mucinous cystic neoplasm may make a pancreatic primary more likely (see Chap. 16). Distinction from undifferentiated carcinoma with osteoclast-like giant cells is discussed below.

The prognosis for undifferentiated carcinoma of the pancreas is extremely poor. Metastasis is often already present at the time of diagnosis. The reported mean survival is less than 6 months.

9.14.8 Undifferentiated Carcinoma with Osteoclast-Like Giant Cells

This subtype of ductal adenocarcinoma is composed of round or spindle-shaped, highly pleomorphic neoplastic tumor cells that are non-cohesive. In addition, it contains a second population of nonneoplastic multinucleated histiocytic giant cells (Fig. 9.67). The latter are believed to represent an unusual stromal reaction and are often found in areas of necrosis or hemorrhage (Fig. 9.68). They typically have 20 or more uniform small nuclei and may occasionally contain hemosiderin or other phagocytosed material within their copious eosinophilic cytoplasm.

Immunohistochemistry highlights the different character of both cell populations. Most of the pleomorphic neoplastic cells stain for vimentin, while some show labeling for epithelial markers (MNF116, cytokeratins, AE1/AE3, EMA, CEA). Nuclear staining for p53 may be found in some tumors, while Ki67 labeling

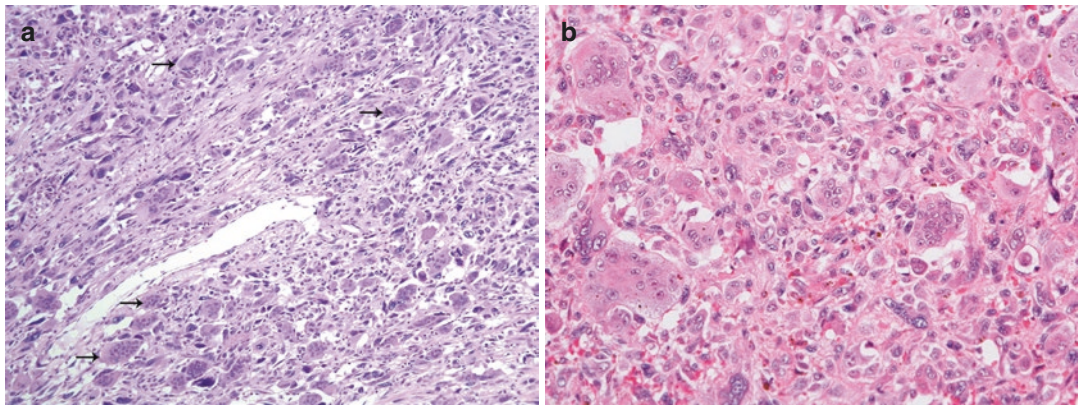


Fig. 9.67 Undifferentiated carcinoma with osteoclast-like giant cells: cellular tumor tissue is composed of large, highly pleomorphic tumor cells admixed with multinucleated osteoclast-like cells (*arrows*; **a**). The latter contain copious cytoplasm and numerous uniform vesicular nuclei with a single nucleolus (**b**)

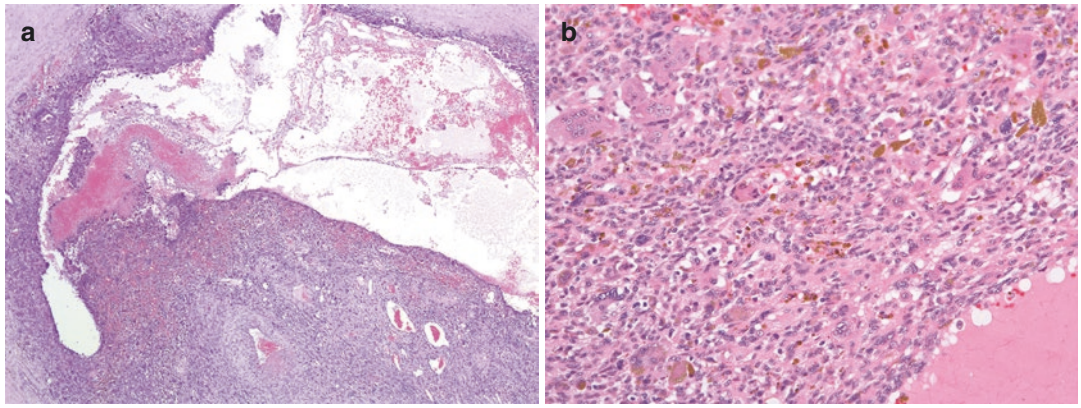


Fig. 9.68 Undifferentiated carcinoma with osteoclast-like giant cells: hemorrhage and necrosis result in gross pseudocystic change (**a**). Osteoclast-like giant cells are particularly numerous in areas of hemorrhage (**b**)

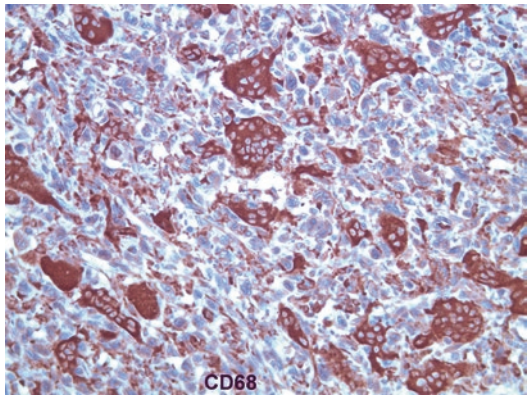


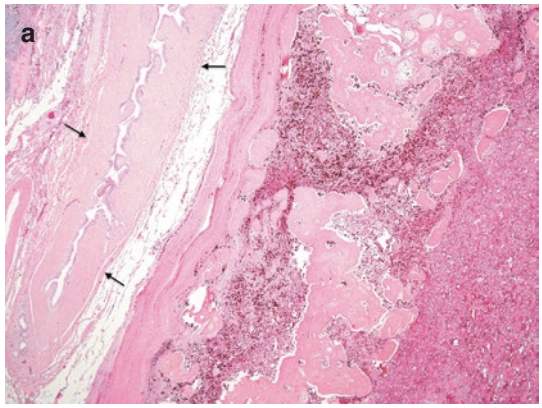
Fig. 9.69 Undifferentiated carcinoma with osteoclast-like giant cells: immunostaining for CD68 labels the osteoclast-like giant cells while the tumor cells remain negative

always reflects a high proliferation rate. In contrast, the osteoclast-like giant cells do not express epithelial markers, have a low proliferative activity, lack nuclear immunolabeling for p53, and stain for markers of leukocytic/histiocytic differentiation (CD45, CD68) (Fig. 9.69). The nonneoplastic nature of the osteoclast-like giant cell population has also been confirmed by molecular analysis: in contrast to the pleomorphic tumor cells, these are diploid and do not contain *KRAS* mutations. Expression of osteonectin and cathepsin K by the osteoclast-like giant cells has been reported in areas of osteoid or bone formation, which may be present in some tumors (Fig. 9.70). Focal chondroid differentiation has also been described.

A significant proportion of undifferentiated carcinomas with osteoclast-like giant cells include areas of conventional ductal adenocarcinoma, which is a further line of evidence supporting the classification of the former as a rare subtype of the latter. While the components of undifferentiated carcinoma and adenocarcinoma are intimately admixed, the transition between the two is usually abrupt (Fig. 9.71), and the characteristic osteoclast-like giant cells are limited to the areas of undifferentiated carcinoma. Some tumors have been reported to arise in association with high-grade PanIN or mucinous cystic neoplasia (see Chap. 16).

The presence of the benign-appearing osteoclast-like giant cells allows distinction of this rare subtype of ductal adenocarcinoma from other neoplasms with pleomorphic tumor cells, first and foremost undifferentiated carcinoma. Multinucleated osteoclast-like histiocytic giant cells may also be present in other malignant tumors, including trophoblastic neoplasia, malignant fibrous histiocytoma, and various forms of Hodgkin or non-Hodgkin lymphoma.

The gross appearance of undifferentiated carcinoma with osteclast-like giant cells differs significantly from that of conventional ductal adenocarcinoma and indeed other primary pancreatic neoplasms. The tumors are usually large



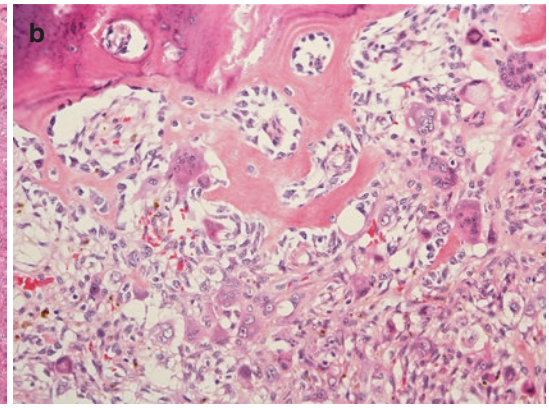


Fig. 9.70 Undifferentiated carcinoma with osteoclast-like giant cells: extensive osteoid and bone formation are present within the tumor. Note the expansile border of the tumor, which is sharply demarcated from the adjacent common bile duct (*arrows*, **a**). Tumor cells are intimately associated with the tumor osteoid and bony formations (**b**)

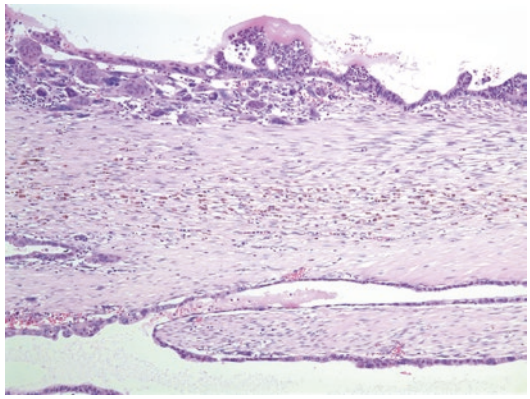


Fig. 9.71 Undifferentiated carcinoma with osteoclast-like giant cells: the transition to conventional ductal adenocarcinoma is abrupt

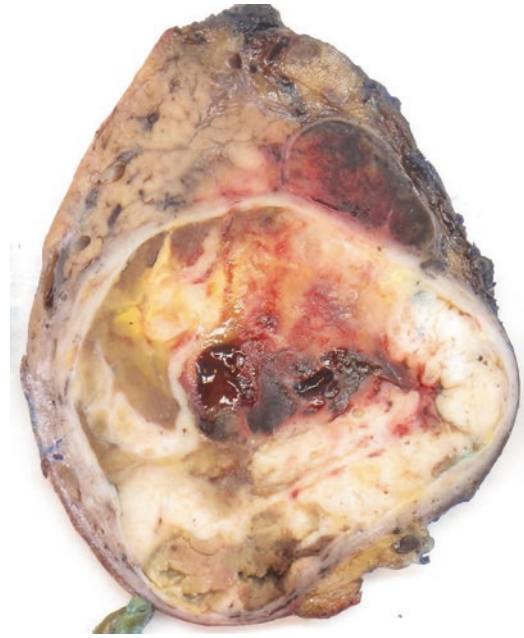


Fig. 9.72 Undifferentiated carcinoma with osteoclast-like giant cells: this large tumor with sharply demarcated expansile margins shows prominent hemorrhage and cystic change

at the time of presentation. They have well-defined pushing borders, and despite the considerable tumor size, the flanking pancreatic parenchyma is often remarkably well preserved. The tumor is essentially solid, but cystic cavities, often of considerable dimensions, are common and may occasionally be the dominant macroscopic feature. Hemorrhage is usually extensive but patchy in distribution (Fig. 9.72). The tumor tissue is of an unusually soft consistency and may show areas of necrosis. In rare cases, bone formation may be extensive to the point of being macroscopically visible as irregular whitish 'spiky' formations (Fig. 9.73). The tumors have a propensity to extend in a polypoid fashion along the main pancreatic duct, branch ducts, or exceptionally, the distal common bile duct (Figs. 9.74 and 9.75).

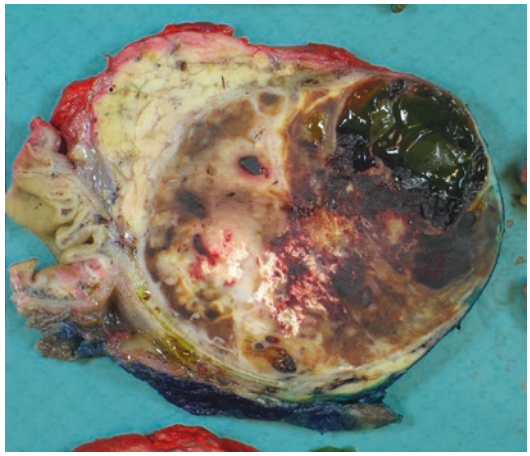


Fig. 9.73 Undifferentiated carcinoma with osteoclast-like giant cells: this large tumor has sharply defined expansile margins and shows extensive hemorrhage. Note the spiky white bone depositions. The adjacent pancreas is well preserved

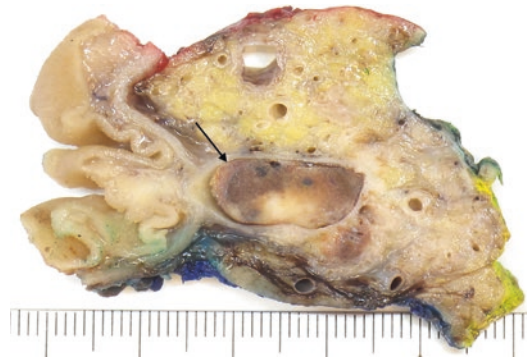


Fig. 9.75 Undifferentiated carcinoma with osteoclast-like giant cells: the tumor extends in a polypoid fashion into the dilated main pancreatic duct (*arrow*)

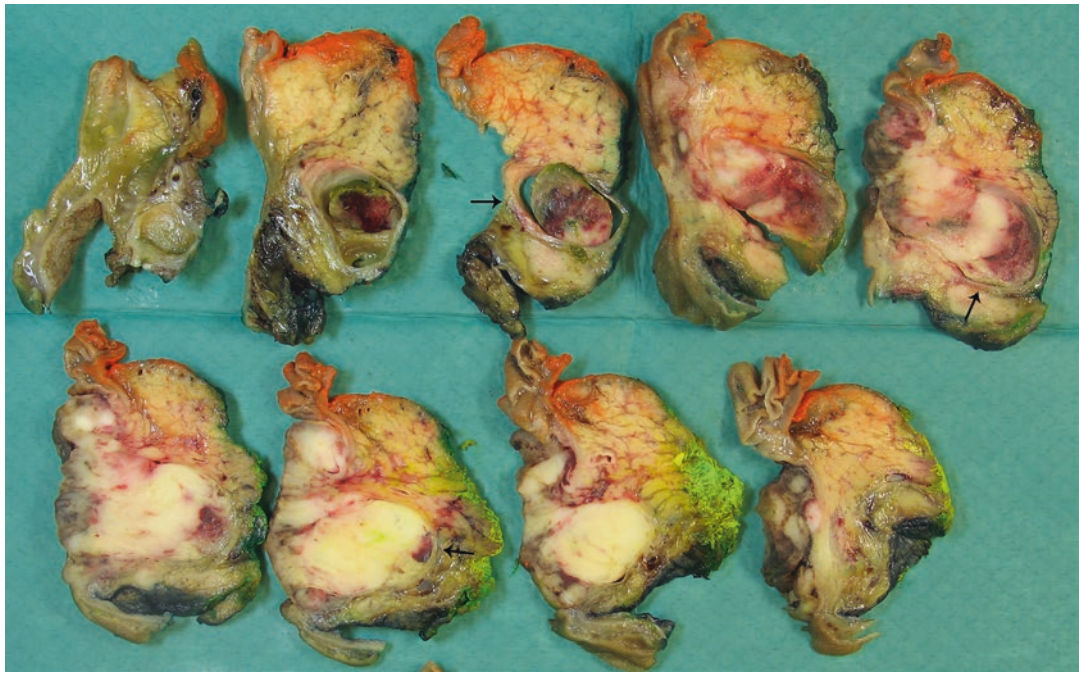


Fig. 9.74 Undifferentiated carcinoma with osteoclast-like giant cells: the bulk of this tumor grows within and dilates the common bile duct (*arrows*)

The prognosis of this subtype seems to be unpredictable, with a protracted clinical course and in some cases survival beyond 5 years being recorded. It has been suggested that the extent of conventional ductal adenocarcinoma in these tumors has an adverse prognostic impact, but this correlation awaits confirmation [43].

9.15 Carcinoma with Mixed Differentiation

Carcinomas with mixed differentiation are defined as malignant epithelial neoplasms of the pancreas containing significant components of more than one distinct direction of differentiation. In addition to ductal adenocarcinoma, these mixed carcinomas may contain a component with neuroendocrine or acinar differentiation. Extremely rare is a combination of all three lines of differentiation within a single pancreatic cancer. By definition, each component of the mixed carcinoma should comprise at least 30% of the overall tumor mass, and there should be an intimate admixture of the various components. The so-called collision tumors, in which the components are topographically separated within the common tumor mass, are not included in this category.

9.15.1 Mixed Neuroendocrine—Non-Neuroendocrine Neoplasm (MiNEN)

These tumors are among the rarest pancreatic neoplasms. They should be carefully distinguished from the rather common finding of pancreatic neuroendocrine tumors with entrapped nonneoplastic ductules, or of ductal adenocarcinomas containing scattered endocrine cells or enlarged nonneoplastic islets. The diagnosis and clinical implications of these tumors are discussed in more detail in Chap. 20, Sect. 20.10.

9.16 Mixed Acinar-Ductal Carcinoma

Mixed carcinomas can also show a combination of ductal and acinar differentiation (see Chap. 10). The diagnosis is usually based on immunohistochemical identification of either component, unless the ductal adenocarcinoma part presents as a colloid carcinoma, for which no ancillary diagnostic investigations are required.

9.17 Ductal Adenocarcinoma Following Neoadjuvant Treatment

In recent years, neoadjuvant chemo(radio)therapy has become an established treatment option. The theoretical advantages of this form of treatment are discussed elsewhere (see Sect. 9.13). For the pathologist, the reporting of pancreatic resection specimens from patients who have undergone neoadjuvant treatment can pose a diagnostic challenge. The main difficulties in the macroscopic and microscopic assessment of such specimens are directly linked to the intended therapeutic effect. When the cancer has responded to preoperative treatment, the number of tumor cells has been reduced, but this process of tumor regression often occurs in a non-uniform fashion, affecting some parts of the tumor more than others. Tumor regression is usually associated with inflammation and fibrosis, although the former may be mild and patchy at the time of surgical resection. The net result of the treatment-induced changes is usually the presence of a reduced number of tumor cells within an expanded fibrous stroma.

This section discusses in more detail the issues that are of particular importance and the problems that may arise when reporting on pancreatic resection specimens following neoadjuvant treatment.

9.17.1 Macroscopic Examination

The combination of treatment-induced changes affecting both the carcinoma and the nonneoplastic pancreas renders the macroscopic assessment of these specimens even more difficult than is the case for tumors that have not undergone neoadjuvant treatment (Fig. 9.76). Reliable macroscopic distinction between (viable) tumor tissue and areas of fibrosis is sometimes not possible, and therefore the key principles of pancreatic specimen dissection—thin axial slicing, close-up photography, and extensive, that is, subtotal, sampling—are even more important.

Due to the seemingly random regression of the cancer, its relationship with the key anatomical

Fig. 9.76 Effect of neoadjuvant treatment: macroscopic examination can be problematic due to marked tissue shrinkage and distortion of the local anatomy. Fibrosis and residual tumor are often indistinguishable. Note the gross distortion of the specimen contours and irregularity of the circumferential margins

structures and the exact location of the center of the tumor mass may no longer be unequivocally recognizable. Hence, exact identification of the tumor origin—pancreatic, ampullary, or common bile duct—may occasionally be problematic. The effect of neoadjuvant treatment on precursor lesions has not been systematically studied.

9.17.2 Microscopic Examination

As a consequence of the effect of treatment, the density of the tumor cells will be reduced, that is, even lower than that typically found in untreated ductal adenocarcinoma (Fig. 9.77). Some tumor cells may show marked atypia, including occasional bizarre nuclei and cell shapes, whereas others may be cytologically deceivingly bland (Figs. 9.78 and 9.79). As treatment can have a significant effect on the tumor morphology, the grade of tumor differentiation is not reported in pancreatic cancer following neoadjuvant chemo(radio)therapy.

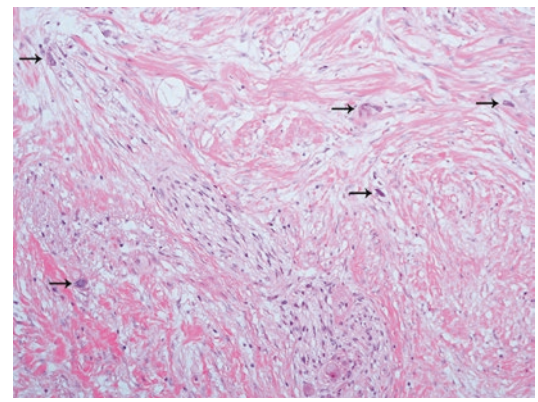


Fig. 9.77 Effect of neoadjuvant treatment: tumor cells may be present as inconspicuous singletons (*arrows*) lying widely dispersed in a desmoplastic stroma

In some cases, tumor regression may result in lake-like accumulations of mucin within the fibrous stroma (Fig. 9.80). Individual cells or small

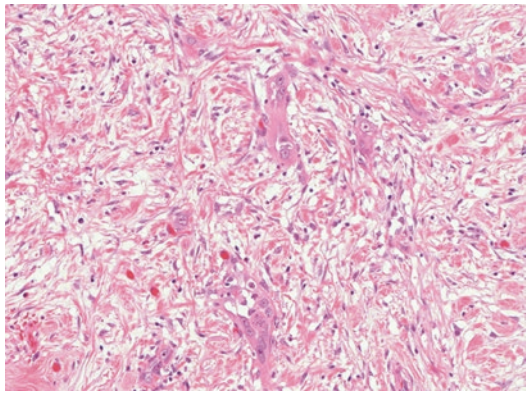


Fig. 9.78 Effect of neoadjuvant treatment: tumor cells may acquire bizarre shapes and nuclear features, which should not be mistaken as an indication of poor tumor differentiation. Note the abundant cellular stroma

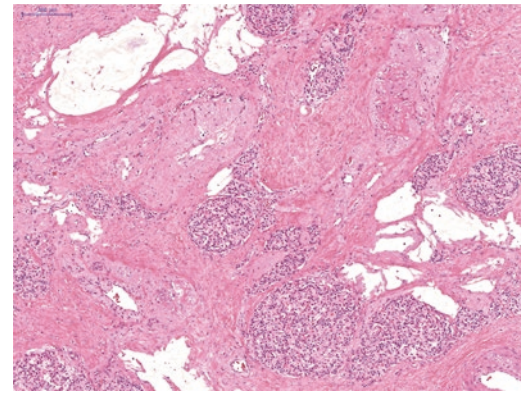


Fig. 9.80 Effect of neoadjuvant treatment: acellular mucin lakes indicate areas of tumor regression. Note the marked degenerative vascular changes and islet aggregation

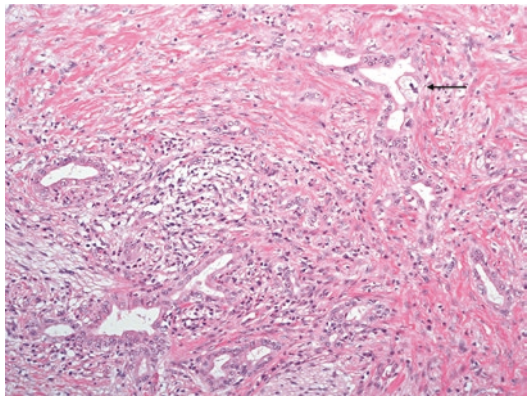


Fig. 9.79 Effect of neoadjuvant treatment: treatment-induced cytomorphological changes are patchy. A single bizarre tumor cell is present within relatively bland-looking tumor glands (*arrow*)

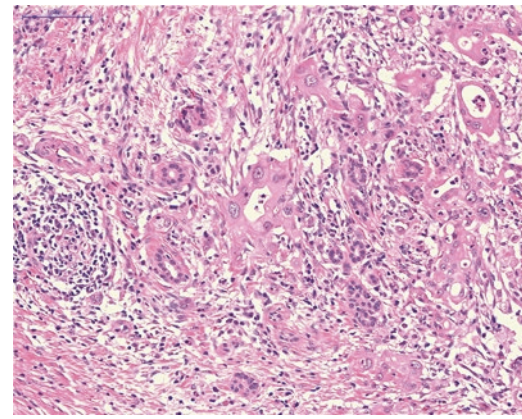


Fig. 9.81 Effect of neoadjuvant treatment: residual tumor glands are intimately admixed with nonneoplastic ducts

cell clusters may float in these pools, and occasionally distinction between viable tumor cells or macrophages may be difficult and require immunohistochemistry, particularly in case this represents the only focus of possible residual tumor.

Microscopic assessment is often hindered by the fact that tumor regression tends to be patchy and unpredictable in distribution. Hence, residual tumor foci may be found at a considerable distance from each other, scattered between areas of nonneoplastic pancreatic parenchyma (Fig. 9.81). The latter often exhibits marked atrophy and fibrosis with effacement of the lobular architecture, fragmentation or aggregation of islets, and reactive epithelial atypia, which in summation can make the distinction between nonneoplastic ductular structures and scanty residual tumor glands problematic. This is compounded by the fact that the morphology of the cancer can vary considerably throughout the specimen, such that comparison with microscopic appearances in areas of unequivocal residual cancer is not always helpful when having to decide on the nature of an individual focus showing atypical features. The presence of glandular structures flanking large blood vessels (Fig. 9.82), in lymphovascular or perineural spaces, or in structures adjacent to the pancreas (e.g., the duodenal wall, ampulla, common bile duct, or peripancreatic soft tissue) allows a confident diagnosis of residual cancer.

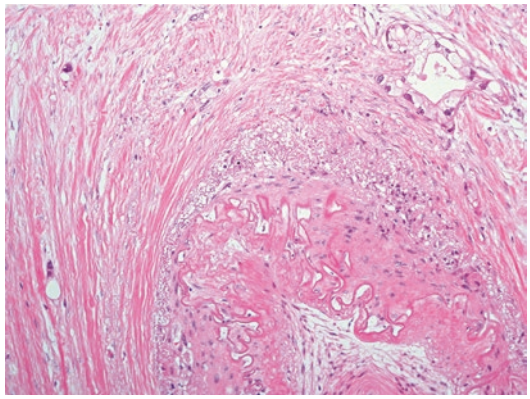


Fig. 9.82 Effect of neoadjuvant treatment: the presence of small ducts and atypical cell clusters adjacent to a muscular artery confirms their malignant nature

The usefulness of immunohistochemistry for the distinction between tumor glands and reactive ductules in posttreatment pancreatic resection specimens has not been well studied, and observations from untreated pancreatic cancer cases may not always be applicable to tumors that underwent neoadjuvant treatment.

9.17.3 Vascular Resection

Opinions on the indications for neoadjuvant therapy differ. While in some pancreatic cancer centers, patients with primarily resectable tumors are also offered preoperative treatment, this is usually limited to patients with borderline resectable tumors, with the intention to shrink the tumor such that it becomes resectable. Borderline resectability is defined, amongst other factors, by the involvement of the superior mesenteric vein or portal vein. Hence, venous resection is commonly included in the surgical procedures following neoadjuvant treatment. As outlined elsewhere (see Chap. 3, Sects. 3.3.5.2 and 3.3.8), the venous tissue should be carefully examined. Preliminary reports indicate that involvement of the wall of the resected vein predicts a shorter disease-free and overall survival.

In recent years, patients with locally advanced pancreatic cancer are also considered for chemotherapy, with the aim to reduce the size and extent of the tumor such that the cancer becomes resectable. These cases often present with involvement of one or several arteries (superior mesenteric artery, hepatic artery, celiac trunk), possibly in combination with venous involvement and/or tumor growth into neighboring viscera. Consequently, an extended surgical procedure is often required, and the resulting specimen may include, in addition to a venous resection, resection of an artery and/or (part of) the stomach, left adrenal, or colon (Figs. 9.83 and 9.84). As outlined in Chap. 3, the relationship of the (residual) cancer and these structures should be examined, together with the associated resection margins and surfaces.

9.17.4 Staging

Staging for the full set of descriptors (T N L V Pn R) requires meticulous scrutiny of all tissue sections. The prefix 'yp' should be used to indicate that staging was performed following neoadjuvant treatment. Because stages T1–3 are defined by tumor size according to the eighth edition of UICC/AJCC TNM [6, 18], exact measurement of the size of the residual cancer is essential to correct staging. However, following neoadjuvant treatment, measurement of the tumor dimensions may be difficult, especially because the residual cancer is often present in the form of two or more separate foci rather than a single residual tumor mass. Currently, there are two different approaches: (i) measurement of the length of the line that connects the tumor foci that lie furthest away from each other, including intervening noncancerous tissue, or (ii) measurement of the size of each separate residual cancer focus (excluding intervening nonneoplastic tissues) and addition of these sizes to obtain the overall tumor dimensions [44]. While the first approach is easier, it may result in considerable overestimation of tumor size in case there are only a few small residual cancer foci that are lying at larger distances from each other. The disadvantage with the second approach is that it may be difficult if not impossible to distinguish contiguous from separate tumor foci in multiple tissue sections through the tumor bed and to make the

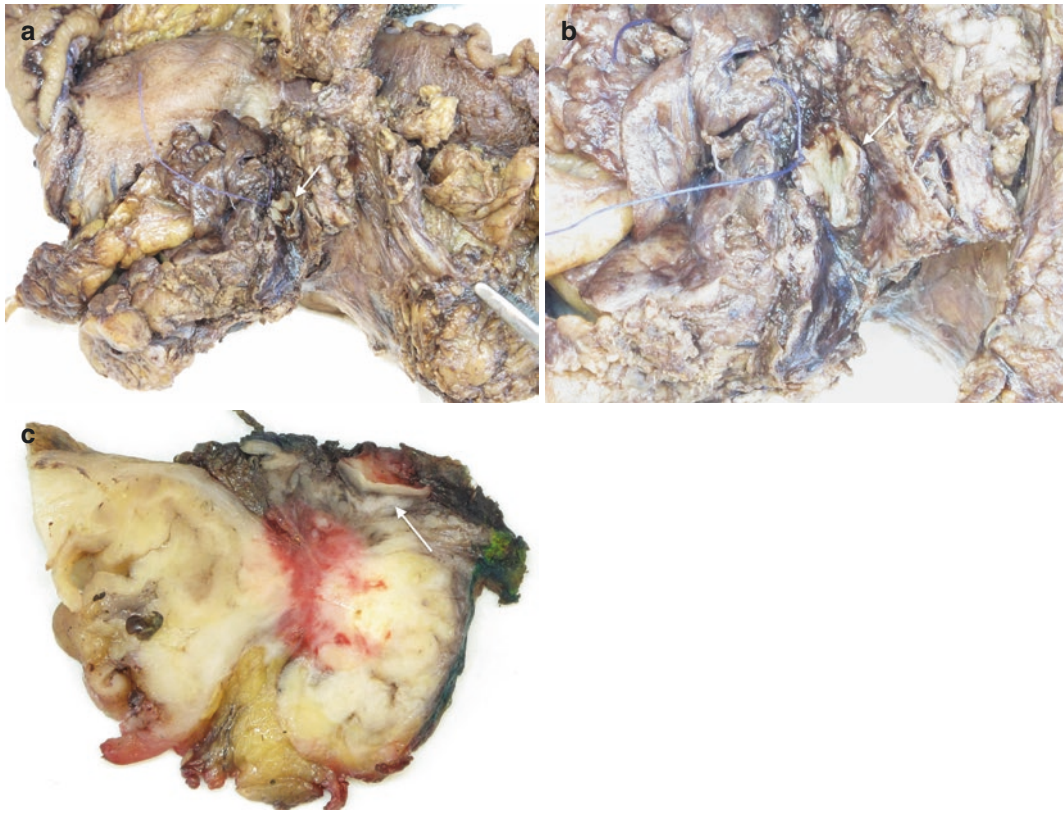


Fig. 9.83 Resection of hepatic artery following neoadjuvant treatment: a 1 cm long segmental resection of the hepatic artery is firmly adherent to the cranial part of the pancreatic head. Note the surgical marker suture (*arrow*; **a** and **b**). An axial specimen slice shows a longitudinal section through the small arterial resection (*arrow*), which is drawn into a large ductal adenocarcinoma that infiltrates the duodenal wall and the peripancreatic soft tissue (**c**)

measurements in two or more directions to identify the largest tumor dimension. To date, there is no consensus as to how measurement should best be done, and the decision is left at the discretion of the pathologist, depending on local practice, personal experience, and the individual case. While further studies to evaluate the prognostic significance of T-staging following neoadjuvant therapy are awaited, first reports suggest that T-staging according to the eighth edition of AJCC/UICC is not an independent predictor of patient survival [45]. In contrast, lymph node status following neoadjuvant treatment seems to remain a strong predictor of outcome. Treatment-induced regression of lymph node metastasis has hardly been studied, but seems to occur, because the overall rate of lymph node metastasis is lower in series following neoadjuvant therapy. However, in the individual case, tumor regression with associated fibroinflammatory changes is not a common finding in regional lymph nodes. The prognostic value of the lymph node rate following neoadjuvant treatment needs further validation, especially because the lymph node yield in preoperatively treated specimens is often lower. A minimum lymph node yield to ensure reliable assessment of the ypN-stage has not been identified yet.

While the margin status should be included in the pathology report, the assessment of the resection margins following neoadjuvant treatment is not without its problems. As preoperative treatment causes tumor cells to regress in a haphazard fashion, the absence of tumor cells within 1 mm of the specimen surface—the admittedly somewhat arbitrary, currently proposed definition of R1 used in treatment-naïve tumors—does not

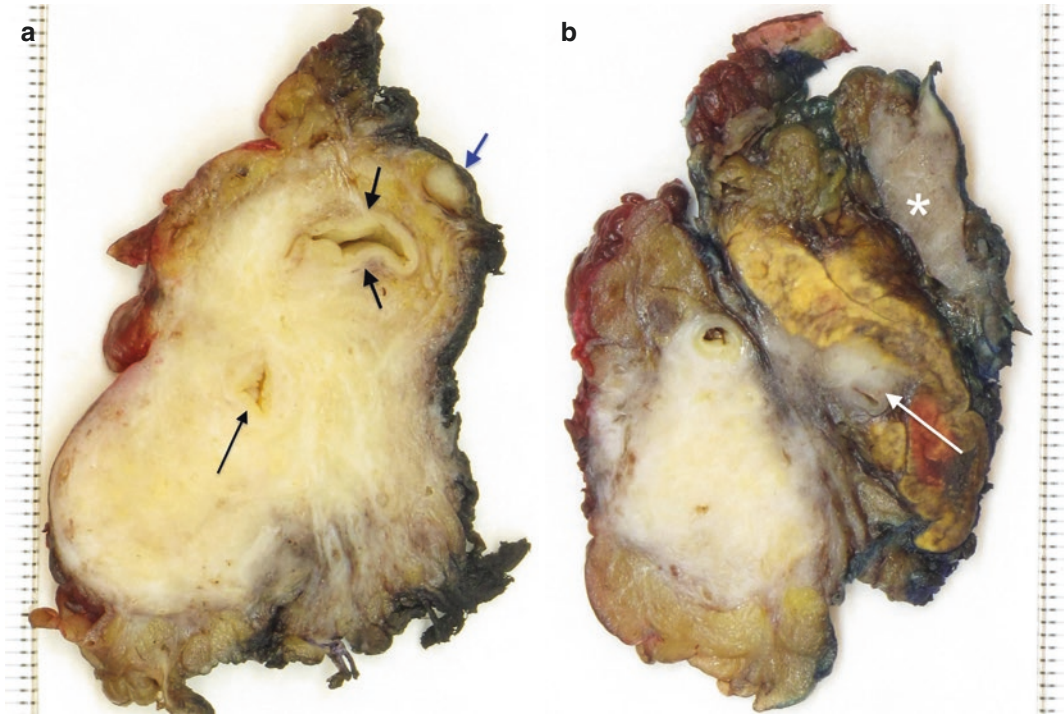


Fig. 9.84 Resection of celiac trunk and left adrenal gland following neoadjuvant treatment: a large ductal adenocarcinoma originating in the pancreatic body shows extensive infiltration of soft tissue posterior to the pancreas with 180 degrees involvement of the celiac trunk (*short arrows*). Note the high-grade tumor occlusion of the splenic artery (*long arrow*) and a small lymph node metastasis (*blue arrow*, **a**). There is direct tumor extension around the superior adrenal artery and invasion of the adrenal gland (*arrow*). Note the large aggregate of neural ganglia posterior to the adrenal gland (*asterisk*, **b**)

reliably predict that tumor cells were not left behind in the surgical bed (Fig. 9.85). Application of the current definition of microscopic margin involvement (see Sect. 9.11.4) is bound to underestimate the presence of microscopic residual disease following neoadjuvant treatment. Perhaps not surprisingly, preliminary reports seem to indicate that margin status following neoadjuvant treatment is of no prognostic value [45], but further studies are awaited.

9.17.5 Tumor Regression Grading

In recent years, various schemes for the histological grading of the degree of tumor regression have been proposed (Table 9.5) [44]. Most are based on an estimation of the proportion of tumor cells that have been destroyed or, conversely, cancer cells that have remained viable compared to the original tumor bulk or with respect to the extent of (treatment-induced) fibrosis. The scoring systems are typically three- or four-tiered. The main problem with these systems is that the original tumor bulk is neither known to the pathologist, nor can it be reliably identified in the surgical specimen. Furthermore, fibrosis is both common and extensive in pancreatic cancer, and there are no diagnostic features that allow distinction of treatment-induced fibrosis from fibrosis of other causes. Hence, a scoring system based exclusively on the amount of residual cancer—which is the only reliably assessable parameter—seems to be the most sound and is recommended by the College of American Pathologists [48]. A further advantage of this system is that it is based on semi-quantitative criteria rather than numeric cut-off values, which are both arbitrary and difficult to use in practice. Further adding to the difficulty of scoring tumor regression is the fact that the effect of treatment is often heterogenous within

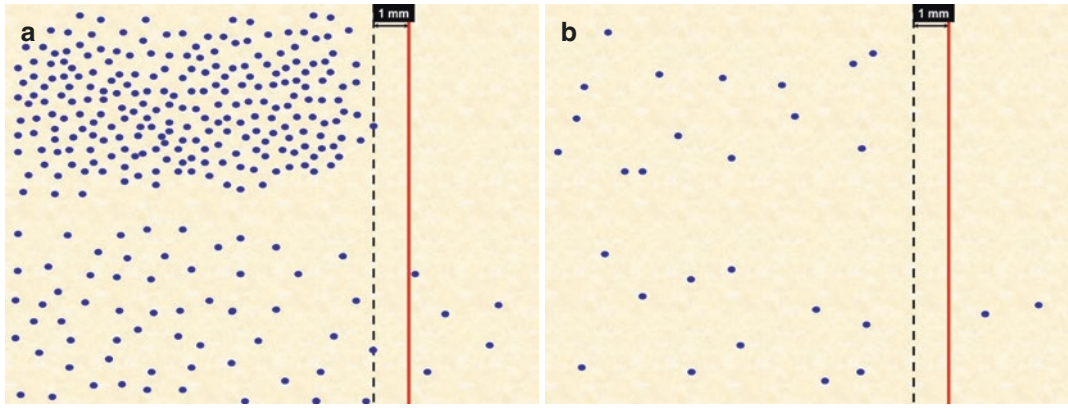


Fig. 9.85 Effect of neoadjuvant treatment: prediction of the presence or absence of residual tumor at the resection margin is determined by the tumor growth pattern. In the tumor with a less compact growth pattern (*lower half*), a clearance of 1 mm does not guarantee the absence of residual disease (**a**). As the growth pattern is altered by neoadjuvant treatment and tumor cells lie at greater distances from each other, the usual definition of R1 (<1 mm clearance) leads to underestimation of residual tumor (**b**) (*blue dots*: tumor cells, *red line*: resection margin, *dotted line*: 1 mm from margin)

Table 9.5 Tumor regression grading for ductal adenocarcinoma of the pancreas

	Evans et al. [46]	Chatterjee et al. [47]	College of American Pathologists [48]
Criterion	Percentage tumor cell destruction/viable cancer cells	Extent/percentage viable cancer cells	Extent residual cancer
Grade	I = 0–9% tumor cell destruction IIa = 10–50% tumor cell destruction IIb = 51–90% tumor cell destruction III = <10% viable cancer cells IV = 0% viable cancer cells	0 = No residual tumor 1 = Minimal residual tumor (<5%) 2 = ≥5% residual tumor	0 = Complete response (no residual cancer cells) I = Near-complete response (single cancer cells or rare small groups of cancer cells) II = Partial response (residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells) III = Poor or no response (extensive residual cancer with no evident tumor regression)

a tumor. Not surprisingly, interobserver agreement is low [49], and therefore a simplified, 3-tiered scoring system has been suggested, which discriminates only between complete regression, near-complete regression, and non-near-complete regression, the latter being defined as >5% residual cancer cells [47]. While interobserver agreement is better, the simplified system introduces an arbitrary, difficult to use numeric threshold value based on the unrealistic comparison of the residual cancer burden with the original cancer bulk. Moreover, as (near-) complete tumor regression is rare, the vast majority of patients fall in the same category, such that it has no predictive value in most cases. On the whole, at present, the tumor regression grading system that is recommended by the College of American Pathologists seems the better approach, despite the above-described shortcomings.

9.18 Diagnostic Molecular Pathology

Ductal adenocarcinoma is caused by a wide range of somatic and germline mutations. The latter are discussed in Chap. 6. The most common genetic

abnormalities in ductal adenocarcinoma are oncogenic mutations of *KRAS* and the loss-of-function and/or deletions of the tumor suppressor genes *TP53, SMAD4 (DPC4),* and *CDKN2A (P16)*. In addition, a large number of other genomic alterations are found at low prevalence. Of the vast knowledge that has been acquired over the past decades, little is currently of direct diagnostic application. Because the loss of expression of *SMAD4* is cancer-specific, immunohistochemistry may be of help to distinguish invasive carcinoma from reactive ducts in a pancreatic biopsy (see Sect. 9.9.3).

In recent years, expression profiling has resulted in several classification systems of ductal adenocarcinoma, which on the whole distinguish between two subtypes—classic and basal-like—that are characterized by distinct molecular signatures and differences in therapeutic response and patient outcome [50, 51]. Similarly, two subtypes of tumor stroma—normal and activated—have been proposed [52]. Ductal adenocarcinomas combining a basal-like cancer cell population with an activated stroma show a poorer response to chemotherapy and a worse survival compared to tumors of classic subtype with normal-type stroma. Development of improved taxonomy systems, especially in the face of marked intratumor heterogeneity, is awaited.

To date, detection of microsatellite instability (MSI+) and mutations of *BRCA* and related genes are the only analyses that, in a hitherto experimental setting, may be undertaken to identify patients who may benefit from immunotherapy or treatment with platinum-based chemotherapy and PARP (poly ADP ribose polymerase) inhibitors, respectively [53].

9.19 Reporting Checklist

Table 9.6 provides a summary of the data items that are to be included in the pathology reporting of ductal adenocarcinoma of the pancreas. A more detailed checklist for the reporting of the macroscopic examination is provided in Chap. 3 (see Table 3.3).

Table 9.6 Reporting checklist for ductal adenocarcinoma of the pancreas (including subtypes)

Macroscopic assessment
• Specimen type (e.g., pancreatoduodenectomy, distal/total pancreatectomy) – Type – Dimensions of main anatomical constituent parts – Other anatomical structures (e.g., venous resection)
• Appearance of tumor – Consistency, color, well/poorly circumscribed – Presence of cystic change, hemorrhage, necrosis
• Tumor size – Craniocaudal dimension – Axial dimensions
• Tumor site and extension – Localization in craniocaudal (specimen slices involved), mediolateral, and anteroposterior direction – Relationship to key anatomical structures – Invasion of other structures included in the specimen (e.g., venous resection) – Minimum distance to nearest resection margin(s)
• Other findings
• Background pancreas

Table 9.6 (continued)

Microscopic assessment
• Type, pattern, or subtype of ductal adenocarcinoma – Type: pancreatobiliary or intestinal – Pattern: foamy gland, clear cell, large duct, cystic papillary – Subtype: adenosquamous/squamous, colloid, signet ring cell, medullary, hepatoid, invasive micropapillary, undifferentiated, undifferentiated with osteoclast-like giant cells
• Grade of differentiation[a]
• Tumor size: corrected by microscopic measurement – Craniocaudal dimension – Axial dimensions
• Tumor extent – Confined to pancreas or infiltration of extrapancreatic tissues – Involvement of additionally resected tissues or organs, e.g., superior mesenteric/portal vein – Depth of tumor invasion
• Lymph nodes: number of involved lymph nodes/total number of lymph nodes – Regional (number and position of lymph nodes according to UICC TNM or JPS system) [6, 54] – Extraregional
• Tumor propagation – Lymphatic – Vascular – Perineural – Duct cancerization
• Resection margins – Transection margins: pancreatic neck, common bile duct, stomach/duodenum – Circumferential margins: facing SMV, facing SMA, posterior, anterior, around extrapancreatic common bile duct – Resection margins of additionally resected structures or organs (e.g., venous resection)
• Tumor regression grading[b]
• Tumor stage: (y[b])pT N M L V Pn R
• Precursor lesions: – Pancreatic intraepithelial neoplasia – Intraductal papillary mucinous neoplasia – Mucinous cystic neoplasia
• Background pancreas: – E.g., chronic pancreatitis
• Other findings

Abbreviations: *JPS* Japan Pancreas Society, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein
[a]Not applicable to pancreatic ductal adenocarcinoma following neoadjuvant therapy
[b]For pancreatic ductal adenocarcinoma following neoadjuvant therapy

References

1. Bosetti C, Bertuccio P, Negri E, La Vecchia C, Zeegers MP, Boffetta P. Pancreatic cancer: overview of descriptive epidemiology. Mol Carcinog. 2012;51:3–13.
2. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature. 2010;467:1114–8.
3. Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, Chari ST, Abbruzzese JL. Diabetes, pancreatogeneic diabetes, and pancreatic cancer. Diabetes. 2017;66:1103–10.
4. Lokuhetty D, White V, Watanabe R, Cree IA, editors. Digestive system of malignant tumours. WHO classification of tumours. 5th ed. Lyon, France: IARC Press; 2019.
5. Verbeke C. Morphological heterogeneity in ductal adenocarcinoma of the pancreas—does it matter? Pancreatology. 2016;16:295–301.

6. Brierley JD, Gospodarowicz MK, Wittekind C, editors. UICC: TNM classification of malignant tumours. 8th ed. Oxford: Wiley-Blackwell; 2017.
7. Giulianotti PC, Oggi U, Fornaciari G, Bruno J, Rossi G, Giardino D, Di Candio G, Mosca F. Prognostic value of histological grading in ductal adenocarcinoma of the pancreas. Klöppel vs TNM grading. Int J Pancreatol. 1995;17:279–89.
8. Harsha HC, Kandasamy K, Ranganathan P, Rani S, Ramabadran S, Gollapudi S, et al. A compendium of potential biomarkers of pancreatic cancer. PLoS Med. 2009;6:e1000046.
9. Dennis JL, Hvidsten TR, Wit EC, Komorowski J, Bell AK, Downie I, et al. Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. Clin Cancer Res. 2005;11:3766–72.
10. Liu H, Shi J, Anadan V, Wan HL, Diehl D, Blansfield J, Gerhard GI, Lin F. Reevaluation and identification of the best immunohistochemical panel (pVHL, maspin, S100P, IMP-3) for ductal adenocarcinoma of the pancreas. Arch Pathol Lab Med. 2012;136:601–9.
11. Winter JM, Tang LH, Klimstra DS, Brennan MF, Brody JR, Rocha FG, et al. A novel survival-based tissue microarray of pancreatic cancer validates MUC1 and mesothelin as markers. PLoS One. 2012;7:e40157.
12. Ishii M, Kimuar Y, Sugita S, Imamura M, Ito T, Nobuoka T, Meguro M, Hasegawa T, Mizuguchi T, Hirata K. Surgical and oncological impact of main pancreatic duct spread in invasive ductal adenocarcinoma: a clinicopathological study of 184 resected cases. Pancreatology. 2015;15:681–7.
13. Sobin LH, Gospodarowicz MK, Wittekind C, editors. UICC: TNM classification of malignant tumours. 7th ed. Oxford: Wiley-Blackwell; 2009.
14. Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint Commission on Cancer (8th edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg. 2017;265:185–91.
15. van Roessel S, Kasumova GG, Verheij J, Najarian RM, Maggino L, de Pastena M, et al. International validation of the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg. 2018;153:e183617.
16. Park MY, Shin SH, Song KB, Hwang D, Lee JH, Lee YJ, Kim SC. Validation of the eighth edition of the American Joint Committee on Cancer staging system and proposal of an improved staging system for pancreatic ductal adenocarcinoma. Ann Hepatobiliary Pancreat Surg. 2019;23:46–55.
17. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with pancreatic adenocarcinoma: a surveillance, epidemiology and end results (SEER) analysis. Ann Surg Oncol. 2017;24:2023–30.
18. Amin MB, Edge SB, Green FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC Cancer staging manual. 8th ed. New York: Springer; 2017.
19. Wang J, Estrella JS, Peng L, Rashid A, Varadhachary GR, Wang H, et al. Histologic tumor involvement of superior mesenteric vein/portal vein predicts poor prognosis in patients with stage II pancreatic adenocarcinoma treated with neoadjuvant chemoradiation. Cancer. 2012;118:3801–11.
20. Beltrame V, Gruppo M, Pedrazzoli S, Merigliano S, Pastorelli D, Sperti C. Mesenteric-portal vein resection during pancreatectomy for pancreatic cancer. Gastroenterol Res Pract. 2015;2015:659730.
21. Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastroinstest Surg. 2004;8:935–49.
22. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, et al. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: preoperative outcome and long-term survival in 136 patients. Ann Surg. 2008;247:300–9.
23. Fukuda S, Oussoultzoglou E, Bachellier P, Rosso E, Nakano H, Audet M, Jaeck D. Significance of the depth of portal vein wall invasion after curative resection for pancreatic adenocarcinoma. Arch Surg. 2007;142:172–9.
24. Ravikumar R, Sabin C, Abu Hilal M, Aroori S, Bond-Smith G, Bramhall S, et al. Impact of portal vein infiltration and type of venous reconstruction in surgery for borderline resectable pancreatic cancer. Brit J Surg. 2017;104:1538–48.
25. Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, Choti MA, Pawlik TM. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol. 2008;15:165–74.
26. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006;13:1189–200.
27. Campbell F, Cairns A, Duthie F, Feakins R. Dataset for the histopathological reporting of carcinoma of the pancreas, ampulla of Vater and common bile duct. 2019. https://www.rcpath.org. Accessed 01 Oct 2019.
28. Verbeke CS, Knapp J, Gladhaug IP. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer—implications for resection margin assessment. Histopathology. 2011;59:1111–21.
29. Verbeke C, Frankel W. Pathology. Operative standards for cancer surgery presented by the American College of Surgeons and the Alliance for Clinical Trials in Oncology. Volume I: Breast, lung, pancreas, colon. Edited by Katz MH, Posner M. Philadelphia, PA: Lippincott Williams & Wilkins; 2015, p. 181–272.
30. Jamieson NB, Foulis AK, Oien KA, Going JJ, Glen P, Dickson EJ, Imrie CW, McKay CJ, Carter R. Positive immobilization margins alone do not influence survival following pancreatico-duodenectomy

for pancreatic ductal adenocarcinoma. Ann Surg. 2010;251:1003–10.
31. Kleive D, Labori KJ, Line PD, Gladhaug IP, Verbeke CS. Pancreatoduodenectomy with venous resection for ductal adenocarcinoma rarely achieves complete (R0) resection. HPB (Oxford). 2020;22:50–7.
32. Sharma S, Green KB. The pancreatic duct and its arteriovenous relationship. An underutilized aid in the diagnosis and distinction of pancreatic adenocarcinoma from pancreatic intraepithelial neoplasia. A study of 126 pancreatectomy specimens. Am J Surg Pathol. 2004;28:613–20.
33. Wachtel MS, Miller EJ. Focal changes of chronic pancreatitis and duct-arteriovenous relationships. Avoiding a diagnostic pitfall. Am J Surg Pathol. 2005;29:1521–3.
34. Xue Y, Vanoli A, Balci S, Reid MM, Saka B, Bagci P, et al. Non-ampullary-duodenal carcinomas: clinicopathologic analysis of 47 cases and comparison with ampullary and pancreatic adenocarcinomas. Mod Pathol. 2017;30:255–66.
35. Ang DC, Shia J, Tang LH, Katabi N, Klimstra DS. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of Vater. Am J Surg Pathol. 2014;38:1371–9.
36. Xue Y, Reid MM, Balci S, Quigley B, Muraki T, Memis B, et al. Immunohistochemical classification of ampullary carcinomas. Critical reappraisal fails to confirm prognostic relevance for recently proposed panels, and highlights MUC5AC as a strong prognosticator. Am J Surg Pathol. 2017;41:865–76.
37. Notta F, Chan-Seng-Yue M, Lemire M, Li Y, Wilson GW, Connor AA, et al. A renewed model of pancreas cancer evolution based on genomic rearrangement patterns. Nature. 2016;538:378–82.
38. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic development in pancreatic cancer: current and future perspectives. Nature Rev Gastroenterol Hepathol. 2018;15:333–48.
39. Tanaka M, Mihaljevic AL, Probst P, Heckler M, Klaiber U, Heger U, et al. Meta-analysis of recurrence pattern after resection for pancreatic cancer. Brit J Surg. 2019;106:1590–601.
40. Kalimuthu SN, Wilson GW, Grant RC, Seto M, O'Kane G, Vajpeyi R, Notta F, Gallinger S, Chetty R. Morphological classification of pancreatic ductal adenocarcinoma that predicts molecular subtypes and correlates with clinical outcome. Gut. 2019;69:317–28.
41. Wilentz RE, Goggings M, Redston M, Marcus VA, Adsay NV, Sohn TA, et al. Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas. A newly described and characterized entity. Am J Pathol. 2000;156:1641–51.
42. Guzinska-Ustymowicz K, Niewiarowska K, Pryczynicz A. Invasive micropapillary carcinoma: a distinct type of adenocarcinoma in the gastrointestinal tract. World J Gastroenterol. 2014;20:4597–606.
43. Muraki T, Reid MD, Basturk O, Jang K-T, Bedolla G, Bagci P, et al. Undifferentiated carcinoma with osteoclastic giant cells of the pancreas: clinicopathological analysis of 38 cases highlights a more protracted clinical course than currently appreciated. Am J Surg Pathol. 2016;40:1203–16.
44. Verbeke C, Häberle L, Lenggenhager D, Esposito I. Pathology assessment of pancreatic cancer following neoadjuvant treatment: time to move on. Pancreatology. 2018;18:467–76.
45. Klaiber U, Schnaidt ES, Hinz U, Gaida MM, Heger U, Hank T, Strobel O, Neoptolemos JP, Mihaljevic AL, Büchler MW, Hackert T. Prognostic factors of survival after neoadjuvant treatment and resection for initially unresectable pancreatic cancer. Ann Surg. 2019; https://doi.org/10.1097/SLA.0000000000003270. Online ahead of print.
46. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, Chamsangavej C, Fenoglio CJ, Ames FC. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127:1335–9.
47. Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H, et al. HIstologica grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. Cancer. 2012;118:3182–90.
48. Kakar S, Shi C, Adsay NV, Fitzgibbons P, Frankel WL, Klimstra DS, et al. Protocol for the examination of specimens from patients with carcinoma of the pancreas: College of American Pathologists (CAP).
49. Kalimuthu SN, Serra S, Dhani N, Hafezi-Bakhtiari S, Szentgyorgyi E, Vajpeyi R, Chetty R. Regression grading in neoadjuvant treated pancreatic cancer: an interobserver study. J Clin Pathol. 2017;70:237–43.
50. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531:47–52.
51. Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S, et al. Subtypes of pancreatic ductal adenocarcinoma and their different responses to therapy. Nat Med. 2011;17:500–3.
52. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47:1168–78.
53. Singh RR, Goldberg J, Varghese AM, Yu KH, Park W, O'Reilly EM. Genomic profiling in pancreatic ductal adenocarcinoma and a pathway towards therapy individualisation: a scoping review. Cancer Treat Rev. 2019;75:27–38.
54. Japan Pancreas Society. Classification of pancreatic carcinoma. 4th ed. (English). Tokyo: Kanehara; 2017.