Classification of Pancreatic Lesions

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Introduction

The new revised WHO classification of tumors of the pancreas includes both exocrine and endocrine neoplasms in one classification (Table 1.1) [1]. This chapter will briefly review the major exocrine tumors, which are covered in more detail in subsequent chapters. A more detailed discussion of the classification of precursor pancreatic ductal lesions and pancreatic neuroendocrine tumors of the pancreas will also be provided in this chapter.

Classification of Solid Exocrine Tumors of the Pancreas

Ductal Adenocarcinoma

Ductal adenocarcinoma and its variants make up more than 90 % of all malignant exocrine pancreatic tumors. About two thirds of ductal adenocarcinomas occur in the head of the gland; the rest occur in the body or tail, or diffusely throughout the pancreas. They are characterized by an intense desmoplastic reaction in which duct-like structures of varying degrees of differentiation are seen. It comprises extracellular matrix together with a number of different host cell types, including fibroblasts, small endothelial-lined vessels, residual normal epithelia, and a variety of inflammatory cells which are both locally derived and recruited from the circulation [2]. The interplay between all these cells types and the pancreatic cancer cells influences new blood vessel formation, invasion, metastases, and evasion of the host immune system [3]. Because of their proximity to the intrapancreatic portion of the common bile duct, tumors in the head usually produce jaundice since they compress and obstruct the bile duct as they grow. They often obstruct the pancreatic duct as well, and although steatorrhea may result, there may not be any obvious symptoms. Tumors of the head of the pancreas are usually at least 2 cm in diameter when they are first diagnosed. Most tumors that are resected have a median diameter of 2.5–3.5 cm. Tumors of the body and tail commonly are larger (5–7 cm) and more advanced when they are discovered because they do not produce symptoms as early as head tumors do. The symptoms from tumors in the body and tail are usually caused by malignant infiltration of the retroperitoneal structures and nerves, which produces pain. By the time the diagnosis is made, almost all are unresectable. Nevertheless, there is evidence that resectable body tumors have a similar prognosis to resectable tumors in the head of

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Table 1.1 WHO histologic classification of tumors of the exocrine and endocrine pancreas

1. Exocrine
(a) Epithelial tumors
• Benign
– Serous cystadenoma
– Mucinous cystadenoma
– Intraductal papillary-mucinous adenoma
– Mature teratoma
• Borderline (uncertain malignant potential)
– Mucinous cystic neoplasm with moderate dysplasia
– Intraductal papillary-mucinous neoplasm with moderate dysplasia
– Solid-pseudopapillary neoplasm
• Malignant
– Ductal adenocarcinoma
Mucinous noncystic carcinoma
Signet ring cell carcinoma
Adenosquamous carcinoma
Undifferentiated (anaplastic) carcinoma
Undifferentiated carcinoma with osteoclast-like giant cells
Mixed ductal–endocrine carcinoma
– Serous cystadenocarcinoma
– Mucinous cystadenocarcinoma
Noninvasive
Invasive
– Intraductal papillary mucinous carcinoma
Noninvasive
Invasive
– Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Mixed acinar–endocrine carcinoma
– Pancreatoblastoma
– Solid-pseudopapillary carcinoma
– Others
(b) Nonepithelial tumors
• Mesenchymal tumors
– Lymphangioma
– Lipoma
– Solitary fibrous tumor
– Ewing sarcoma
– Desmoplastic small round cell tumor
– Perivascular epithelioid cell neoplasm
• Lymphomas
– Diffuse large B-cell lymphoma (DLBCL)
(c) Secondary tumors
2. Endocrine
(a) Pancreatic neuroendocrine microadenoma
(b) Neuroendocrine tumor G1 (NET G1)/Carcinoid
(c) Neuroendocrine tumor G2 (NET G2)

(continued)

Table 1.1 (continued)

(d) Neuroendocrine carcinoma
• Large cell neuroendocrine carcinoma
• Small cell neuroendocrine carcinoma
(e) Functional PNET
• Gastrinoma, malignant
• Glucagonoma, malignant
• Insulin-producing carcinoma (insulinoma)
• Somatostatinoma, malignant
• Vipoma, malignant

the gland. Approximately 70–80 % of adenocarcinomas of the head of the pancreas have metastasized to regional lymph nodes by the time they are discovered, which worsens the prognosis but does not preclude cure. These tumors also commonly invade lymphatic channels and perineural spaces. The prognosis is also influenced by the degree of tumor differentiation and by the presence of invasion of the retroperitoneal tissues adjacent to the cancer. The best outcome is seen in patients who have well-differentiated neoplasms, without retroperitoneal invasion or lymph node metastases. Distant metastases (e.g., lung) may occur, but pancreatic cancer typically infiltrates locally into the adjacent structures (e.g., stomach, duodenum, colon, transverse mesocolon, portal and superior mesenteric veins, superior mesenteric artery). The liver is the most common site of intraabdominal metastasis, and peritoneal seeding of the tumor is also seen. In patients without distant spread, vascular invasion by tumor is the most common reason for unresectability.

The most widely accepted staging system for pancreatic cancer is the American Joint Committee on Cancer (in cooperation with the TNM committee of the International Union Against Cancer), which is shown in Table 1.2 [4]. Although this system is prognostic for overall survival, it is not particularly useful in guiding treatment, because some patients with advanced-stage disease (i.e., stage IVA) may be candidates for surgical resection, whereas others may not. For this reason, pancreatic cancer patients are generally classified by physicians as having resectable, locally advanced, or metastatic disease. Other histologic variants of pancreatic ductal adenocarcinoma have been described, including mucinous noncystic carcinoma, signet ring cell carcinoma, adenosquamous carcinoma, undifferentiated (anaplastic) carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, and mixed ductal–endocrine carcinoma.

Acinar Cell Carcinoma

Acinar cell carcinomas are uncommon and characterized by acinar arrangement of cells supported by minimal fibrous stoma [5]. They represent 1–2 % of all exocrine pancreatic neoplasms in adults and are considered separate from pancreatic ductal adenocarcinoma. Zymogen granules are present, which may be identified by electron microscopy. Patients may have elevated serum lipase levels and associated nonsuppurative panniculitis of the extremities and bone marrow and manifest subcutaneous nodules and polyarthritis. These tumors usually occur in adults in their sixth to eighth decades of life, and are rare under the age of 40. They have a male predominance, with an M:F ratio of 2:1 [6]. Acinar cell carcinomas are generally well circumscribed and may be multinodular. Areas of necrosis and cystic degeneration may be present and extension into adjacent structure may occur. Metastases most commonly affect the regional lymph nodes and the liver.

Table 1.2 TNM classification of tumors of exocrine and endocrine pancreas

Primary tumor (*T*)			
T0	No evidence of primary tumor		
Tis	in situ tumor		
Tl	Tumor limited to the pancreas, <2 cm in greatest dimension		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension		
T3	Tumor extends directly into duodenum, bile duct, or peripancreatic tissues		
T4	Tumor extends directly into stomach, spleen, colon, or celiac axis vessels		
Regional lymph nodes (*N*)			
N0	Regional lymph nodes not involved		
N1	Regional lymph nodes involved		
N1a	Metastasis in a single regional lymph node		
N1b	Metastases in multiple regional lymph nodes		
Distant metastases			
MX	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases present		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Other Uncommon Solid Pancreatic Tumors

Other solid exocrine tumors of the pancreas include epithelial types such as pancreatoblastoma, a rare malignant epithelial tumor generally affecting young children, composed of well-defined solid nests of cells with acinar formations and squamoid corpuscles, separated by stromal bands. This accounts for 30–50 % of all pancreatic neoplasms in young children [7]. Metastases to the pancreas account for 3–16 % of all pancreatic malignancies, either by direct invasion (stomach, liver, and adrenal gland) or by lymphatic or hematogenous spread, including breast cancer, lung cancer, and renal carcinoma. Renal carcinoma is unique as it may give rise to pancreatic metastases without overt metastases elsewhere. Nonepithelial tumors of the pancreas are rare, including mesenchymal tumors, leimyosarcoma, malignant gastrointestinal stromal tumors, and solitary fibrous tumors. Primary lymphoma of the pancreas is defined as an extranodal lymphoma arising from the pancreas and is usually of B phenotype [including low-grade lymphoma of diffuse small cell type, follicle center cell lymphoma, low-grade MALT lymphoma, and large B-cell lymphoma, seen in immunodeficiency setting (e.g., HIV infection and posttransplant lymphoproliferative disorders following solid organ transplantation)] [8].

Classification of Cystic Exocrine Tumors of the Pancreas

Cystic neoplasms of the pancreas (CNP) were once considered extremely rare (many textbooks perpetuated the notion that most cystic lesions of the pancreas were pseudocysts), and fewer than 10 % were neoplasms [9]. Studies using CT and MRI have shown that the prevalence of pancreatic cysts (in individuals without history of symptoms

Table 1.3 Classification of cystic neoplasms of the pancreas, including lesions that resemble them (clinically common and important diseases highlighted in bold text)

Epithelial neoplasms
Serous cystadenoma
Mucinous cystic neoplasm and MCN-associated carcinoma
Intraductal papillary mucinous neoplasm and IPMN-associated carcinoma
Solid pseudopapillary neoplasm
Pancreatic ductal adenocarcinoma with cystic degeneration
Cystic pancreatic endocrine neoplasm (CPEN)
Acinar cystadenoma and cystadenocarcinoma
Dermoid cyst (cystic teratoma)
Intraductal papillary variant of acinar cell carcinoma
Intraductal tubulopapillary neoplasm
Nonepithelial
Lymphangioma
Epidermoid cyst in intrapancreatic spleen
Cystic pancreatic hamartoma
Mesothelial cyst
Lesions resembling pancreatic cystic neoplasms
Pseudocyst
Lymphoepithelial cyst (epidermoid cyst)
Mucinous nonneoplastic cyst
Enteric duplication cysts
Endometrial cyst
Hydatid cyst
Retention cyst
Accessory splenic cyst
Cystic pheochromocytoma
Cystic gastrointestinal stromal tumor
Retention cyst
Squamoid cyst

of pancreatic disease) is about 2.5 % [10, 11], and that this increases with age to the point that 10 % of persons 70 years or older have a pancreatic cyst [10]. Although the WHO classifies pancreatic cysts based on well-defined neoplastic pathologies, there is a clinical classification which includes both neoplastic and nonneoplastic pancreatic cysts including pseudocysts (Table 1.3) [9].

Serous Cystadenoma

Serous cystadenoma of the pancreas (SCA) is a benign, slow-growing tumor that affects predominantly women (~75 %); the mean age of resected patients has been 62 years [12–15]. This is discussed in further detail elsewhere in this book.

Intraductal Papillary Mucinous Neoplasm

The term "mucinous ductal ectasia" was used for many years to describe an entity characterized by gross dilation of the pancreatic duct due to overproduction of mucus from a proliferative epithelium with papillary growth. This disease is now recognized to be an advanced form of main-duct intraductal papillary mucinous neoplasm (MD-IPMN), and we now recognize that this neoplastic proliferation can involve the side branches of the pancreatic ductal system, either alone (branch-duct IPMN or BD-IPMN) or in combination (mixed or combined IPMN) [16]. This is discussed in further detail elsewhere in this book.

Mucinous Cystic Neoplasm

The mucinous cystic neoplasm of the pancreas (MCN) is a relatively uncommon tumor that comprises about a quarter of all resected cystic neoplasms of the pancreas in large surgical series [17]. This tumor is predominantly seen in women (>95 %) and in the distal pancreas (>95 %), and, unlike branch-duct IPMNs, is always a single lesion [18–20]. This is discussed in further detail elsewhere in this book.

Solid Pseudopapillary Neoplasm

The solid pseudopapillary neoplasm of the pancreas (SPN) is a very uncommon lesion that comprises less than 4 % of resected pancreatic cystic tumors. Prior to its inclusion in the World Health Organization (WHO) classification, it had previously been known by a variety of different names, including papillary epithelial neoplasm of the pancreas, solid and cystic tumor of the pancreas, adenocarcinoma of the pancreas of childhood, papillary-cystic tumor, and solid and papillary epithelial neoplasm [21]. It predominantly affects women (>80 %), and the median age has been between 30 and 38 years, with about 20–25 % of cases being seen in the pediatric population [22–24]. This is discussed in further detail elsewhere in this book.

Classification of Pancreatic Ductal Precursor Lesions

The presumed precursor lesions of pancreatic ductal adenocarcinoma are not discussed in detail in the ICD-10. Pancreatic cancer precursor lesions, also known as pancreatic intraepithelial eoplasia (PanIN), are seen more commonly in patients with pancreatic cancer compared with not (Fig. 1.1) [25, 26]. Pancreatic Intraepithelial Neoplasia (PanIN) precursor lesions can be graded from PanIN-1A (flat mucinous epithelium) to PanIN-2 (columnar epithelium with nuclear atypia) to PanIN-3 (in situ carcinoma) [26]. Normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphophilic cytoplasm, without the features of evolving PanIN such as mucinous cytoplasm, nuclear crowding, and atypia. A transitional squamous metaplasia has also been described, known as squamous metaplasia, in which the normal cuboidal ductal epithelium is replaced by mature squamous or transitional epithelium without atypia (Table 1.4).

In pancreatic intraepithelial neoplasia 1-A (PanIN 1-A), flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin are seen. The nuclei are small and round to oval in shape. When oval, the nuclei are oriented perpendicular to the basement membrane. In pancreatic intraepithelial

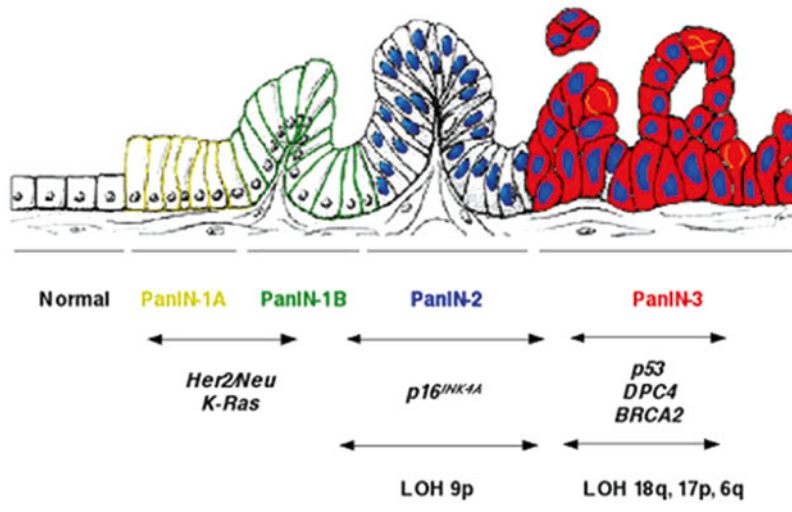

Fig. 1.1 Pancreatic cancer carcinogenesis. Progression of pancreatic intraepithelial lesions (PanIN) from normal to invasive cancer

Table 1.4 Recommended terms for pancreatic intraepithelial neoplasia (Panin)

Recommended WHO term	Previous terminology
Squamous metaplasia	Squamous metaplasia, epidermoid metaplasia, focal epithelial hyperplasia
PanIN-1A	Mucinous cell hypertrophy, mucinous cell hyperplasia, nonpapillary ductal hyperplasia
PanIN-1B	Ductal papillary hyperplasia, adenomatoid ductal hyperplasia, ductular cell hyperplasia
PanIN-2	Any PanIN lesion with moderate dysplasia
PanIN-3	Severe ductal dysplasia, carcinoma-in-situ

neoplasia 1-B (PanIN 1-B), these epithelial lesions have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A. For pancreatic intraepithelial neoplasia 2 (PanIN-2), these mucinous epithelial lesions may be flat or papillary, but with defined nuclear abnormalities, including some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare, but when present are nonluminal (not apical) and not atypical. Pancreatic intraepithelial neoplasia 3 (PanIN-3) typically shows papillary or micropapillary architecture, with true cribriforming, budding off small clusters of epithelial cells into the lumen and luminal necroses. Cytologically, these lesions are characterized by a loss of nuclear polarity, dystrophic goblet cells (goblet cells with nuclei oriented toward the lumen and mucinous cytoplasm oriented toward the basement membrane), mitoses which may occasionally be abnormal, nuclear irregularities, and prominent (macro) nucleoli.

This histologic- and cytologic-based model of pancreatic precursor is supported by molecular analyses (mutational analysis, immunohistochemical analysis, and loss of heterozygosity studies) which have demonstrated most of the molecular changes seen in invasive ductal adenocarcinoma identified in PanIN lesions, with the prevalence of these genetic alterations increasing with increasing degrees of cytologic and architectural atypia in the duct lesions in PanIN.

Classification of Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pancreatic NETs) which arise from the endocrine tissues of the pancreas represent up to 3 % of primary pancreatic tumors. They can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP), associated with a clinical syndrome, so-called functioning pancreatic NET. However, between 50 and 75 % of pancreatic NETs are nonfunctioning (i.e., unassociated with a hormonal syndrome) [27]. This is discussed in further detail elsewhere in this book.

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