Pathology of Pancreatic Cancer Precursor Lesions

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KEYWORDS

• Pancreatic ductal adenocarcinoma • Precursor lesions • Carcinogenesis • Histopathology
• Molecular pathology • Intraductal papillary mucinous neoplasm
• Pancreatic intraepithelial neoplasia • Mucinous cystic neoplasm

Key points

- Pancreatic cancer develops from 3 well-established precursor lesions: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN).
- PanINs are the most common precursor lesion of pancreatic ductal adenocarcinoma (PDAC) and are by definition less than 0.5 cm in diameter.
- PanINs are characterized by cuboid to columnar cells with gastric foveolar differentiation and varying degrees of cytologic and architectural atypia.
- IPMNs are most often located in the proximal pancreas and are by definition greater than or equal to 1.0 cm in diameter.
- IPMNs are classified as main-duct type IPMNs, branch-duct type IPMNs, or mixed type IPMNs, and are further subclassified according to the predominant direction of differentiation as gastric, intestinal, pancreatobiliary, or oncocytic.
- Evidence is accumulating for the existence of 2 distinct pathways in the evolution of IPMN into pancreatic adenocarcinoma.
- Intraductal tubulopapillary neoplasm is considered a variant of IPMN, with a high prevalence of *PIK3CA* mutations.
- MCNs almost exclusively occur in female patients, are mainly located in the pancreatic body and tail, do not communicate with the pancreatic duct system, and are characterized by ovarian-type stroma.
- Recently, new guidelines were formulated for reporting pancreatic precursor lesions, improving reproducibility by encouraging a 2-tiered grading system for dysplasia.

ABSTRACT

To better understand pancreatic ductal adenocarcinoma (PDAC) and improve its prognosis, it is essential to understand its origins. This article describes the pathology of the 3 well-established pancreatic cancer precursor lesions: pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm, and mucinous cystic neoplasm. Each of these precursor lesions has unique clinical findings, gross and microscopic features, and molecular aberrations. This article focuses on histopathologic diagnostic criteria and reporting guidelines. The genetics of these lesions are briefly discussed. Early detection and adequate treatment of pancreatic cancer precursor lesions has the potential to prevent pancreatic cancer and improve the prognosis of PDAC.

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OVERVIEW

Noninvasive precursor lesions in the pancreas have been recognized for more than a century.[1] They have the ability to progress to pancreatic ductal adenocarcinoma (PDAC). However, it was not until 1999 that an international consensus meeting formed the basis for the current classification and definition of these precursor lesions.[2] Since then, multiple consensus meetings have been organized, updating the classification system with new insights.[3,4] Three precursor lesions are recognized: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN). All of these meet the criteria for precursor lesion, as defined by a consensus conference, sponsored by the National Cancer Institute.[5] These precursors show a unique multistep morphologic and genetic progression to invasive carcinoma.

PANCREATIC INTRAEPITHELIAL NEOPLASIA

CLINICAL FEATURES

PanIN is the most common precursor lesion of PDAC. These lesions were first described a century ago by Hulst.[1] Both men and women are equally affected and the incidence tends to increase with age.[6–8] PanINs can be found in 82% of pancreata with invasive carcinoma, in 60% of pancreata with chronic pancreatitis, and in 16% of normal pancreata.[7] PanINs occur multifocally in patients with a family history of pancreatic adenocarcinoma.[9,10] Because of their small size (by definition <0.5 cm), these lesions cannot be seen on noninvasive abdominal imaging and they are not associated with clinical signs or symptoms. However, lobular atrophy and fibrosis can be clues for their presence. PanINs are typically found incidentally in resections or biopsy specimens.[6,11,12]

PATHOLOGIC FEATURES

PanINs are noninvasive, microscopic, epithelial neoplasms and by definition involve pancreatic ducts less than 0.5 cm in diameter.[2–4] PanINs are characterized by cuboid to columnar cells with varying amounts of apical cytoplasmic mucin and varying degrees of cytologic and architectural atypia. PanINs almost always show gastric foveolar differentiation.[4]

Hruban and colleagues[2] described the generally accepted PanIN scheme to classify these lesions in 2001. Three grades are discriminated in this scheme, based on the degree of epithelial atypia: PanIN-1, PanIN-2, and PanIN-3. PanIN-1 lesions are characterized by minimal nuclear atypia, inconspicuous nucleoli, and absent mitotic figures and can be further subdivided into flat (PanIN-1A) and micropapillary (PanIN-1B) types. Moderate nuclear atypia, pseudostratification, loss of polarity, hyperchromasia, and rare mitotic figures are features of PanIN-2. PanIN-3 lesions have marked atypia; contain (atypical) mitotic figures; show loss of polarity; and have a papillary, micropapillary, or occasional flat architecture (**Fig. 1**). Cribriform structures, necrosis, and tufting of epithelial cells in the lumen may be present. PanIN-3 is almost exclusively found in association with invasive PDAC.[6,7] This feature is so striking that, in pancreata without a PDAC, a PanIN-3 lesion may serve as a surrogate marker for invasion elsewhere.[7,13] Another pitfall is the extension of an infiltrating carcinoma in pancreatic ducts (ie, ductal cancerization) mimicking a PanIN-3 lesion. The close proximity of an invasive carcinoma to a ductal lesion, the abrupt transition from highly atypical epithelium to normal ductal epithelium, luminal obstruction, and ductal destruction are clues to consider ductal cancerization.[2,3,14]

The clinical significance of PanIN-1 and PanIN-2 has been questioned by studies, because these lesions show little progression to PDAC.[7,15] Grading the lesions also showed poor interobserver agreement.[16] For these reasons, the latest consensus meeting advised the use of a 2-tiered grading system with low-grade PanIN (formerly PanIN-1A, PanIN-1B, and PanIN-2) and high-grade PanIN (formerly PanIN-3). Moreover, the presence of PanIN lesions of any grade at the surgical margin of pancreata resected for invasive PDAC does not influence patient prognosis and additional surgery is not required.[17]

PanINs show an increased expression of MUC 1 (Mucin 1) and MUC5AC (Mucin 5AC) in higher grades of dysplasia.[18–21] The opposite is seen for MUC6 (Mucin 6), showing reduced expression in higher grades of dysplasia.[19,22]

MOLECULAR FEATURES

The early lesions with minimal cytologic atypia were not originally regarded as neoplastic, but instead were designated as hyperplasia or metaplasia.[23] After finding *KRAS* mutations, these lesions were considered neoplastic and the term pancreatic intraepithelial neoplasia was proposed.[2,13,24–27] It has been established that progression from low-grade PanIN to high-grade PanIN requires accumulation of genetic

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