Reporting precursors to invasive pancreatic cancer: pancreatic intraepithelial neoplasia, intraductal neoplasms and mucinous cystic neoplasm

Roeland F de Wilde
Ralph H Hruban
Anirban Maitra
G Johan A Offerhaus

Abstract

Invasive ductal adenocarcinoma of the pancreas remains an almost universally lethal disease. Despite strenuous research efforts, the prognosis of the disease has not improved in the past decades. However, knowledge of pancreatic tumorigenesis and the identification and characterization of the precursor lesions that give rise to invasive pancreatic cancer have dramatically improved. This, coupled with the finding that it takes almost two decades for a pancreatic cell with an initial mutation to develop into a metastatic pancreatic cancer provides hope for the early detection of curable pancreatic neoplasms. We present a review of established precursor lesions of pancreatic cancer, including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms (including intraductal oncocytic papillary neoplasm and intraductal tubulopapillary neoplasm), and mucinous cystic neoplasm.

Keywords cyst fluid; intraductal oncocytic papillary neoplasm; intraductal papillary mucinous neoplasm; intraductal tubulopapillary neoplasm; mucinous cystic neoplasm; pancreatic ductal adenocarcinoma; pancreatic intraepithelial neoplasia

Roeland F de Wilde *MD is at the Departments of Pathology and Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; and the Department of Pathology at The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA. Conflicts of interest: none declared.*

Ralph H Hruban *MD the Departments of Pathology and Oncology at The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA. Conflicts of interest: none declared.*

Anirban Maitra *MBBS the Departments of Pathology and Oncology at The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA. Conflicts of interest: none declared.*

G Johan A Offerhaus *MD MPH PhD Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands. Conflicts of interest: none declared.*

Introduction

Invasive pancreatic ductal adenocarcinoma (PDAC, i.e. pancreatic cancer), is the fourth leading cause of cancer-related deaths in the USA.[1] In 2008, an estimated 161,800 world-wide deaths were attributed to pancreatic cancer in the developed world, and the mortality rate approaches its incidence (10–12:100,000).[2] The 5-year survival rate of pancreatic cancer is a bleak <6% which is due, at least in part, to the fact that the vast majority of patients (~80%) are diagnosed with locally advanced or metastatic disease.[1] Chemo- and/or radiation therapies are only marginally effective, increasing survival by only a few months for only a subset of patients.[3] Therefore, it is crucial that pancreatic neoplasia be detected earlier, before an invasive cancer develops, while the disease is still curable.

It is now recognized that invasive pancreatic cancer arises from histologically well-defined noninvasive precursor lesions. This, combined with the recent finding that it takes many years for a pancreatic cell with an initial mutation to progress to a metastatic cancer, highlights a significant window of opportunity for early detection.[4]

The first step in developing an early detection test is to identify curable precursor lesions and to understand their biology.[5,6] Herein, we present a review of the literature on four recognized precursor lesions of pancreatic cancer, beginning with the microscopic pancreatic intraepithelial neoplasia (PanIN) followed by the macroscopic intraductal papillary mucinous neoplasm (IPMN) including intraductal oncocytic papillary neoplasm (IOPN), then briefly covering intraductal tubulopapillary neoplasm (ITPN), and fourth a discussion of the mucinous cystic neoplasm (MCN).[7] Finally, recent advances in cyst fluid analysis and its potential use in diagnosis (for biomarker detection) will be discussed, highlighting findings that could be of potential benefit for the detection and treatment of precursors to PDAC.

Pancreatic intraepithelial neoplasia

Clinical appearance and morphology of PanINs

Microscopic intraductal lesions believed to be precursors to invasive pancreatic cancer have been recognized for more than a century.[8] It was only in the past 2–3 decades that molecular studies helped establish that these small lesions, now called PanINs, are definitely precursors to PDAC.[9–12]

Like PDAC itself, PanINs are encountered mostly in the head of the pancreas and less in the body and/or tail. In one large autopsy study, the overall prevalence of PanINs was approximately 19% (Table 1).[12] In addition, the prevalence of PanINs has been found to increase with age; 6.7% of patients aged ≤50 years, 28% of patients aged 50–65 and 37% of patients aged ≥65 harbour PanIN lesions. Cubilla and Fitzgerald reported that PanIN-2 (which they had designated as intermediate-grade ductal papillary hyperplasia) was three times more prevalent in pancreata with an associated invasive cancer than in those without, and the highest grade lesions (i.e. PanIN-3) were only found in pancreata with an associated PDAC.[11] Similarly, Andea et al. reported that PanINs were more common in pancreata harbouring PDAC (82%), than in pancreata with pancreatitis (60%) and normal pancreata

General characteristics of precursor lesions of pancreatic cancer

	PanIN	IPMN	MCN	ITPN
Sex ratio (female:male)	1:1	2:3	20:1	1:1
Predominant age of diagnosis	Increasing with age	60–70	40–50	56 (mean)
Intrapancreatic location	Head>body/tail	Head>body/tail	Body/tail	Head>body>tail
Relation with pancreatic duct(s)	Occur in small ducts	Occur in main and/or branch ducts	None	Occur in dilated ducts
Diagnostic features by imaging techniques	Chronic pancreatitis-like changes in very few patients	Dilated pancreatic duct, filling defects, cyst(s)	Cystic mass with thick walls that compresses/ displaces duct	Resemble pancreatobiliary-type IPMNs
Macroscopic features	Mostly not grossly visible (<5 mm)	Dilated pancreatic ducts with abundant mucin	Well-defined cysts with thick walls containing mucin or hemorrhagic material	Solid nodular masses within ducts, no mucin
Microscopic features	Columnar/papillary mucinous epithelium, adjacent parenchymal atrophy may be present	Flat, micro/grossly papillary epithelium, parenchymal atrophy may be present	Mucin-producing columnar cells with associated ovarian-like stroma	Cribriform or solid with necrosis

PanIN, pancreatic intraepithelial neoplasia; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; ITPN, intraductal tubulopapillary neoplasm.

Table 1

(16%).[9] Thus, PanINs, particularly high-grade PanINs, increase with age and are associated with PDAC.[13]

Pancreatic intraepithelial neoplasia occurs in smaller pancreatic ducts and are <5 mm in diameter which makes PanINs generally not grossly detectable. In fact, size is one of the features used to distinguish PanINs from IPMNs which, by definition, are usually >1 cm. PanINs are characterized by the replacement of the normal cuboidal ductal epithelium by columnar mucinous cells, either flat or papillary, with various degrees of dysplasia. PanINs are divided in three grades based on the degree of cytonuclear and architectural atypia (Figure 1).[14,15] Typically, low-grade or PanIN-1A lesions have a flat epithelium consisting of columnar mucinous cells with basally located round to oval uniform nuclei (containing supranuclear mucin) which are perpendicularly oriented to the basement membrane. In contrast to PanIN-1A, PanIN-1B lesions have a (micro)papillary architecture. PanIN-2 lesions feature greater architectural complexity, including early loss of nuclear polarity, pseudostratification and hyperchromasia (i.e. darker nuclei), all consistent with intermediate-grade dysplasia. In PanIN-3 lesions (high-grade dysplasia or carcinoma-*in situ*), significant cytological atypia is present and includes complete loss of nuclear polarity, hyperchromasia, conspicuous nucleoli and the presence of mitotic figures (occasional abnormal mitotic figures). Architectural changes in PanIN-3 lesions include (micro)papillary rather than flat epithelium, sometimes luminal necrosis, and cribriform architecture, the phenomenon of so-called Roman bridge formation between tufts. Of note, PanIN-3 lesions are still confined within the basement membrane and there is no invasive growth of the neoplastic epithelial cells.

The clinical significance of a PanIN at the margin of an otherwise R0 resection for PDAC was recently examined. In contrast to the negative effect of invasive cancer at a margin, PanIN, even high-grade PanIN-3 at a margin appears to have no clinical significance for patients with an invasive cancer.[16]

PanINs are often surrounded by lobular parenchymal atrophy (i.e. lobulocentric atrophy) (Figure 1f).[17–19] Observations in humans suggest that PanIN lesions obstruct exocrine outflow in the ducts and the subsequent release of acinar enzymes to the parenchyma leads to autodigestion, thus creating localized pancreatitis-like atrophy. By contrast, observations in genetically engineered animal models suggest that genetic changes in acinar cells drive acinar-ductal metaplasia imparting the appearance of lobulocentric atrophy. Patients with a strong family history of pancreatic cancer sometimes have multiple PanIN lesions which produce multifocal lobulo-centric atrophy and radiological changes similar to those seen in chronic pancreatitis. This suggests that a specific at-risk population can be screened for the presence or absence of PanINs by looking for theses changes.[19]

A number of intraductal lesions should be considered in the differential diagnosis of PanINs. First, repeated ductal epithelium injury can lead to the replacement of normal cuboidal cells by mature stratified or pseudostratified squamous epithelium, commonly referred to as squamous metaplasia. Squamous metaplasia is distinguished from PanINs by the direction of differentiation of the cells, and the absence of significant atypia in squamous metaplasia. Second, duct inflammation and repair can produce reactive atypia with enlarged nuclei and nucleoli. The inflammation helps distinguish reactive atypia from PanINs. Third, 'cancerization of ducts' can occur as invasive cancer grows from the stroma back into and along previously non-neoplastic ducts. Two features distinguish PanINs from this "cancerization." Cancerization is almost always associated with an invasive carcinoma in the stroma next to the lesion in