NEOPLASTIC PRECURSOR LESIONS OF THE PANCREAS

A Patient's Guide

Jeffrey A. Van Lier Ribbink, M.D., FACS

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CONTENTS

I) What are neoplastic precursor lesions of the pancreas?

II) What is Pancreatic Intraepithelial Neoplasia (PanIN)

III) What is an Intraductal Papillary Mucinous Neoplasm (IPMN) of the pancreas?

IV) What are the poor prognostic indicators for malignancy in Branch Duct IPMNs (BD-IPMNs)?

V) How are IPMNs of the pancreas managed

VI) What are Mucinous Cystic Neoplasms of the pancreas?

I

WHAT ARE NEOPLASTIC PRECURSOR LESIONS OF THE PANCREAS

Neoplastic precursor lesions of the pancreas are lesions that have an increased risk of developing into pancreas cancer. These include Pancreatic Intraepithelial Neoplasia (PanIN), Intraductal Papillary Mucinous Neoplasm (IPMN), and Mucinous Cystic Neoplasm (MCN) of the pancreas.

II

What is Pancreatic Intraepithelial Neoplasia (PanIN)?

Many PDACs appear to arise from noninvasive epithelial precursor lesions. One of these lesions consists of proliferations of cells lining the pancreatic ducts called Pancreatic Intraepithelial Neoplasm (PanIN). These epithelial cell proliferations in the past were categorized as PanIN-1A, PanIN-1B, PanIN-2, and PanIN-3 lesions. These are less than or equal to 5mm in size. They are microscopic and can only be seen through the microscope. They cannot be seen by CT scan, MRI, or ultrasound.

The PanIN-1A lesion consists of flat epithelial cell proliferations with no architectural or cytologic atypia. The PanIN-1B lesions had no nuclear cytologic atypia, but the proliferations did show architectural atypia with the epithelial cells forming intraluminal papillae. The PanIN-1A and PanIN-1B lesions were considered to be low-grade dysplastic lesions.

The PanIN-2 lesions consist of architectural and nuclear atypia. The architectural atypia consists of the epithelial cells forming intraluminal papillae. The nuclear atypia consists of nuclear hyperchromasia, nuclear pseudostratification, enlarged nuclei, crowding of nuclei, and a mild loss of polarity. Mitoses are rarely seen, and when seen a located basally. These PanIN-2 lesions were considered as intermediate grade dysplastic lesions.

The PanIN-3 lesions are characterized by significant architectural and cytologic atypia. Architecturally the lesions are papillary with small clusters of cells budding off into the ductal lumen. The cytologic atypia consists of enlarged, overlapping nuclei that show a loss of orientation so that they are no longer oriented perpendicular to the basement membrane. Nucleoli can be prominent and mitosis can be found. These PanIN-3 lesions were considered a high grade dysplastic lesion, also known as carcinoma in-situ.

The Baltimore Consensus Meeting for Neoplastic Precursor Lesions of the Pancreas in 2015 reclassified these lesions to better correlate with their potential to progress to pancreatic ductal adenocarcinoma. PanIN-1A, PanIN-1B, and PanIN-2 lesions were recategorized as low-grade PanIN with low potential of progression to invasive PDAC. PanIN-3 was revised to high grade PanIN with significant propensity to progress to invasive PDAC.

III

WHAT IS AN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN) OF THE PANCREAS?

An IPMN is a complex mucinous cystic lesion of the pancreas. This is not a simple cyst filled with fluid, but is composed of solid and liquid components. It can have thickened walls, nodular walls, and septations. The contained fluid is quite thick and mucinous. These are 10mm or more in size, and originate in the pancreatic ductal system as papillary growths. The IPMNs are benign tumors that have an increased risk for malignant transformation.

50% of IPMNs occur in the head of the pancreas, 4% in the uncinate process, 7% in the tail, and 39% are spread throughout the pancreas.

In the past, IPMNs were classified by the degree of epithelial dysplasia. Those with low-grade dysplasia were called adenomatous IPMNs. Those with intermediate grade dysplasia were termed borderline IPMNs. IPMNs with high-grade dysplasia were termed carcinoma in-situ. Finally, those with invasive carcinoma were termed IPMNs with an associated invasive carcinoma.

In 2015, the above nomenclature was changed. IPMNs with low grade dysplasia are now termed low grade IPMN. IPMNs with intermediate grade dysplasia are now termed low grade IPMNs. IPMNs with high-grade dysplasia (carcinoma in situ) are now termed high grade IPMNs. IPMNs with an associated invasive carcinoma are still referred to in the same manner.

IPMNs are also classified relative to which pancreatic ducts are involved. A main duct IPMN (MD-IPMN) involves the main pancreatic duct only, and is associated with diffuse dilation or segmental dilation of the main pancreatic duct. IPMNs that involve only the branch pancreatic ducts are termed branch duct IPMNs (BD-IPMNs) Those IPMNs that involve both the main and branch pancreatic ducts are termed mixed duct IPMNs.

IPMNs are also classified according to their histopathology. These are changes in the cells of the IPMN papillary growths that extend from the wall of the pancreatic duct into the lumen of the pancreatic duct. These include gastric (44-63%), intestinal (18-36%), pancreatobiliary (7-18%) and oncocytic (1-8%) IPMNs.

The risk of malignancy in MD-IPMNs has been reported to be as high as 57%-92%. BD-IPMNs have a lower reported risk of malignancy in the range of 6-46%.

IV

What Are the Poor Prognostic Indicators for Malignancy in BD-IPMN's

"Worrisome features" for BD-IPMNs include:

1. Cyst size ≥ 3cm
2. Thickened enhancing cyst walls
3. 5-9 mm dilated MPD
4. Non-enhancing mural nodules
5. Abrupt change in MPD caliber
6. Distal pancreatic atrophy
7. Lymphadenopathy

"High risk stigmata" for malignancy in BD-IPMNs include:

1. Obstructive jaundice
2. Enhancing mural nodules
3. MPD dilatation ≥ 10mm

The above represent two-layer criteria to predict malignancy in IPMNs. The "high risk" stigmata are an indication for resection of BD-IPMN, and the "worrisome features" warrant endoscopic ultrasound examination (EUS).

V

How Are IPMNs of the Pancreas Managed?

In 2012, an IPMN guideline conference in Fukuoka, Japan made the following recommendations:

1. Surgical resection was recommended for all MD-IPMN's
2. Surgical resection was recommended for symptomatic BD-IPMN's
3. Surgical resection was recommended for BD-IPMN's with any "high risk stigmata" of malignancy. These include: obstructive jaundice, an enhancing solid component, or main pancreatic duct dilatation $\geq$ 10mm
4. Observation was recommended for BD-IPMNs with cyst size >3cm without "high risk stigmata" or "worrisome features."
5. Observation was recommended for BD-IPMNs with "worrisome features" such as cyst size $\geq$3cm, thickened enhanced cyst walls, 5-9 mm main pancreatic duct, non-enhanced mural nodules, abrupt change in main pancreatic duct caliber with distal pancreatic atrophy, or lymphadenopathy . This observation involves an EUS examination.
6. Resection was recommended for BD-IPMNs with a definite mural nodule, main pancreatic duct involvement, or suspicious/positive cytology for malignancy.

VI

What are Mucinous Cystic Neoplasms of the Pancreas?

Mucinous Cystic Neoplasms (MCNs) are complex cystic lesions of the pancreas. They are not simple cysts just filled with thin fluid. Rather, they may have septations, a thickened wall, and a nodular wall. The fluid is very thick and mucinous. In contrast to IPMNs and pseudocysts, MCNs are not in communication with the pancreatic duct.

95% of MCN's occur in women and 5% in men. They are usually diagnosed between 40 and 70 years of age. They commonly occur in the body and tail of the pancreas. Most are greater than 4.0 cm in size.

Surgical removal is recommended for larger MCN's . 17.5% of those MCNs that are removed prove to be malignant. Small MCNs can be observed.