Intraductal Papillary Mucinous Neoplasm of the Pancreas

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KEYWORDS

- Intraductal papillary mucinous neoplasm • Pancreas • Biology
- Clinical management

KEY POINTS

- Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are categorized as main-duct (MD) and branch-duct (BD) lesions, with MD-IPMNs associated with a higher risk of malignancy and warranting surgical resection.
- Most BD-IPMNs are biologically indolent, with obstructive jaundice and radiographic features, such as presence of mural nodule or main pancreatic duct dilation greater than 10 mm, indicating higher risks lesions that should prompt consideration for resection.
- IPMN is a disease associated with a field defect. For multilesion disease, every cyst should be risk-stratified individually, and cyst-specific segmental resection performed when indicated. Follow-up after resection should be pursued, even if it was for benign IPMNs, given the risk of recurrence in the remnant gland.
- There are no high-level data supporting the use of adjuvant chemotherapy or radiation for invasive IPMNs. However, IPMNs with even small foci of invasion are associated with lymph node metastasis that poses a significant recurrence risk, suggesting the use of adjuvant therapy is appropriate in selected settings.

INTRODUCTION

The incidence of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas has been on a rise in the past 2 decades, driven mainly by the widespread use of cross-sectional imaging.[1,2] IPMNs are defined as intraductal mucin-producing neoplasms that involve the main pancreatic duct or its side branches and lack the ovarian stroma typically seen in mucinous cystic neoplasms. Most IPMNs are discovered incidentally and remain asymptomatic, making it difficult to estimate their true prevalence, which has been described to be as low as 0.0008%, and as high as 10% in patients

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older than 70 years.[3,4] IPMNs follow a classic spectrum of dysplastic changes and can be classified as low, moderate, or high-grade dysplasia and invasive cancer. Based on experience and clinical evidence from the past 30 years, the International Association of Pancreatology (IAP) released consensus guidelines in 2006 and 2012 providing clinical algorithms based on IPMN features and risk of malignancy.[5,6] In this article, we review the different classifications of IPMNs, their natural history, and clinical management and address recent controversies in the literature.

BIOLOGY OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Duct Involvement

IPMNs are morphologically classified into 2 main subtypes based on the location of pancreatic duct involvement: main duct (MD) and branch duct (BD). This morphologic classification has important biologic implications; MD-IPMNs have been associated with a malignancy rate of 57% to 92%, whereas BD-IPMNs have a more indolent natural history, with a malignancy risk ranging from 6% to 46%.[7–14] However, these malignancy rates are based solely on resected lesions, suggesting that the true malignancy risk is lower for both MD-IPMNs and particularly so for BD-IPMNs.

There is a third group, IPMNs with mixed-duct involvement, which historically has been treated akin to MD involvement with regard to its malignancy risk. This concept has recently been challenged, with the Heidelberg group demonstrating that 29% (n = 512) of suspected BD-IPMNs revealed histologic involvement of the MD that was not evident on preoperative imaging.[15] However, in an analysis of our own data at the Massachusetts General Hospital (n = 404), we found that the risk of high-grade dysplasia and invasive carcinoma in these minimal-mixed IPMNs was 11% and 6%, respectively, which more closely resembles the natural history of BD-IPMNs.[16] This subset of minimal-mixed IPMNs is clearly biologically different from those with grossly mixed involvement, which has been reported to have malignancy rates of up to 72% (**Fig. 1**).[17]

Histologic and Cytologic Classification

In recent years, IPMNs have been further classified into the following categories based on their histologic characteristics and specific mucin expression: intestinal, pancreatobiliary, gastric, and oncocytic subtype (**Fig. 2**). When IPMNs progress to invasive cancer, they can be of the tubular or colloid subtype, and rarely oncocytic.[18–21] These subtypes have important implications and show that IPMN is a heterogeneous disease.

BD-IPMNs have been shown to be most commonly associated with the gastric subtype, which has the least likelihood of tumor invasion (10%) and tumor recurrence (9%) among all subtypes. However, when carcinoma does occur, they are usually of the tubular subtype, which is associated with an increased risk of vascular invasion, perineural invasion, and nodal metastasis, portending a poorer prognosis similar to that of conventional ductal adenocarcinoma.[18,21] Conversely, MD-IPMNs more commonly exhibit intestinal-type epithelium, which has a high likelihood of progressing to carcinoma but generally is of the biologically less aggressive colloid type.[21] The pancreatobiliary and oncocytic subtypes are both less common but very contrasting in their biological behavior. IPMNs exhibiting pancreatobiliary epithelium are associated with the highest rate of tumor invasion (68%) and transformation to tubular carcinoma (82%).[18,21] Oncocytic IPMNs, on the other hand, have a very indolent biology. In a review of 18 patients with oncocytic IPMN, Marchegiani and colleagues[22] reported that most patients (67%) were asymptomatic, and although they had a 10-year recurrence