Intraductal Neoplasms of the Pancreas: An Update

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ABSTRACT

With improvements in imaging to detect silent pancreatic lesions and increases in the number of centers now performing pancreatic surgery, more surgeries have been performed for indications other than invasive carcinoma. This has enormously added to our knowledge of the intraductal neoplasms of the pancreas. In addition, our understanding of the genetics of these lesions has expanded with the introduction of routine molecular genetic analyses. In this review, we provide an update into the most common intraductal neoplasms, namely intraductal papillary mucinous neoplasm and intraductal tubulopapillary neoplasm. We first focus on their clinicopathologic and molecular features of relevance to the practicing pathologist and then discuss their differential diagnoses.

Key Words: Pancreatic intraductal tumors, IPMN, ITPN

INTRODUCTION

Intraductal neoplasms of the pancreas have become increasingly more common as recent developments in imaging techniques have led to increased detection of clinically silent tumors, many of which are detected incidentally during work-up for other diseases (1-5). Therefore, within the last decade, their histomorphologic, and especially molecular features have been studied in detail.

This article reviews the currently available information on the clinicopathological/molecular features, differential diagnosis, and biological behavior of intraductal neoplasms of the pancreas namely; intraductal papillary mucinous neoplasm (IPMN) (including intraductal oncocytic neoplasm) as well as intraductal tubulopapillary neoplasm (ITPN).

Intraductal Papillary Mucinous Neoplasms

Definition

The term intraductal papillary mucinous neoplasm (IPMN) was first described by Klöppel et al. in 1994 as grossly visible, mucin-producing, predominantly papillary, epithelial neoplasm arising from the main pancreatic duct or branch ducts, with varying degrees of duct dilatation (6). As per the international guidelines (7), which was also endorsed by the 2010 WHO Classification System (8), greater than 1 cm diameter by radiologic/gross examination is required to distinguish IPMNs from large pancreatic intraepithelial neoplasms (PanINs).

Clinical Features

IPMNs occur slightly more frequently in men than in women with a male to female ratio of 3 to 2. The mean age at the time of diagnosis ranges between 62 and 67 years (8-12). Most patients diagnosed with IPMNs are asymptomatic (13,14) and when associated with symptoms, it can mimic chronic pancreatitis (11,15-18). The etiology of IPMNs is not so clear, however, a previous history of diabetes, especially with insulin use, smoking, and a family history of pancreatic ductal adenocarcinoma are regarded as risk factors (10,19). Interestingly, the rate of extrapancreatic malignant tumors (colonic, gastric, bile duct, breast and prostate carcinoma) is reported to be higher in patients with IPMN than in those with pancreatic ductal adenocarcinoma (PDAC) (11,12,20-24).

Diagnostic Imaging Techniques

Typical signs on computed tomography (CT) are a diffusely distended pancreatic duct with filling defects and cystic lesions with connection to the pancreatic duct system (12,25-27). However, magnetic resonance imaging (MRI) seems superior to CT in terms of characterizing the lesion (28). Endoscopic retrograde cholangiopancreatography (ERCP) also usually reveals a dilated pancreatic duct with filling defects (12,29,30).

Classification

IPMNs are currently classified based on their radiologic (and also macroscopic) appearance, cell type, and grade

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of dysplasia (31). Most IPMNs are localized, but they can diffusely involve the entire gland.

Radiologic (and Also Macroscopic) Classification

All IPMNs connect to larger pancreatic duct(s); however, not all IPMNs arise in the main pancreatic duct. Therefore, they are classified as branch duct-type and main duct-type (12).

Branch duct-type IPMN (BD-IPMN) is one of the most common "incidentalomas" due to the recent widespread use of imaging modalities (32). It arises in younger patients and is more likely to involve the uncinate process (12,16,33). BD-IPMN manifests either as a cyst or a cluster of cysts without dilation of the main pancreatic duct. The cysts are usually not larger than 1-2 cm with smooth and glistening cyst lining (Figure 1A) (10,15,26,31). Many BD-IPMNs lack nodular formation and commonly contain inspissated mucinous material (34).

Main duct-type IPMN (MD-IPMN) is usually located in the head of the pancreas. It is characterized by a markedly dilated (average diameter, 4.1 cm), tortuous main pancreatic duct that may be filled with mucin or solid but friable mass (12,31,35,36) (Figure 1B).

Microscopic Classification

IPMNs differ in the cell type that composes the papillary epithelium, allowing their classification into gastric, intestinal, pancreatobiliary, and oncocytic subtypes (37) based on the histomorphologic features and the immunohistochemical characteristics. Although the oncocytic-type was originally described as a separate entity (intraductal oncocytic papillary neoplasm) (See below)

(38), the current (2010) WHO puts this neoplasm under the general category of IPMNs, due to overlap between the clinicopathologic features of IOPNs and other subtypes of IPMNs (39).

In gastric-type, the papillae are lined by simple epithelium that resembles gastric foveolar epithelium. BD-IPMNs often show gastric foveolar differentiation (12,40-42) (Figure 2A). The tumor cells have low proliferative activity, and rarely exhibit malignant transformation. Intestinal-type IPMNs have papillae lined by pseudostratified columnar cells with cigar-shaped nuclei and apical goblet like mucin resembling colonic villous adenomas (Figure 2B). Most main duct IPMNs are of intestinal type (12, 41, 43, 44). Pancreatobiliary-type IPMNs usually involve the main pancreatic duct and are characterized by more complex, interconnecting papillae lined by atypical cuboidal cells that have little intracellular mucin, enlarged round nuclei, and prominent eccentric nucleolus (Figure 2C) (10,41). This type epithelium is often seen in an intimate association with less atypical gastric type epithelium, and for this reason, some observers believe that it represents the high-grade dysplastic version of gastric type rather than a specific type of its own (42). Of note, both intestinal- and pancreatobiliary-types of IPMN may have areas lined by gastric-type epithelium; however, it is extremely uncommon to find both intestinal- and pancreatobiliary-type papillae within the same IPMN.

Microscopically, IPMNs also exhibit various degrees of dysplasia. Based on the degree of architectural and cytological atypia, the current (2010) WHO classification system subclassifies these neoplasms as IPMN with low-grade, intermediate-grade, and high-grade dysplasia (8). In
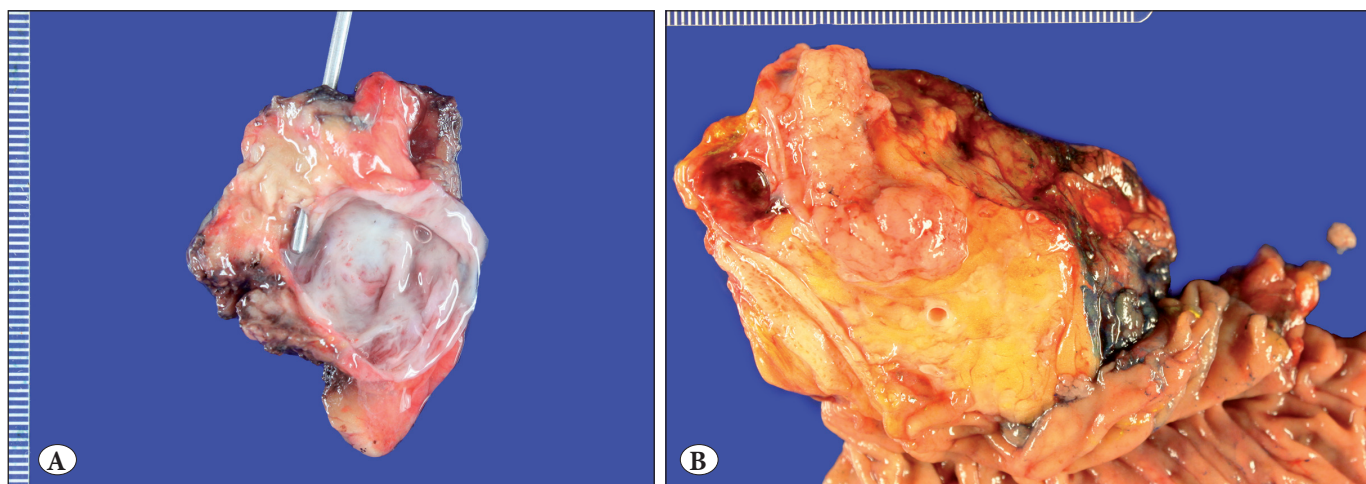

Figure 1: A) Branch duct-type IPMN with smooth and glistening cyst lining. **B)** Main duct-type IPMN involving the main pancreatic duct with friable papillary projections.

this 3-tiered grading system, low-grade dysplasia is defined as neoplastic cells that form a single layer of well oriented, have small and uniform nuclei, lack of nucleoli and mitoses (Figure 3A). Intermediate-grade dysplasia is defined as tumor cells with nuclear stratification, high nuclear to cytoplasmic ratio, loss of polarity, enlarged nuclei and pleomorphism, but papillae still have fibrovascular cores. High-grade dysplasia has more complex architecture with nuclear pleomorphism, increased mitotic figures, atypia, and cribriforming additional to these features (Figure 3B) (43). In a given case, the final grade of IPMN is based on the highest grade, no matter how small it is (45).

However, lately it has been shown that IPMNs with low-grade or intermediate-grade dysplasia have low progression rate compared to ones with high-grade dysplasia (45-51). Also, the goal of clinical management is to observe low-grade and intermediate-grade precursor lesions and to resect high-grade precursor lesions in order to decrease the risk of invasive cancer. Therefore, at a recent international consensus meeting held in Baltimore to revise the grading system and reporting of precursor lesions in pancreas, a 2-tiered classification scheme was felt to be more in line with practical consequences: low-grade and intermediate-grade dysplasia likely has no immediate clinical consequences, whereas high-grade dysplasia usually requires clinical attention. According to this new 2-tiered grading system, intermediate-grade is now categorized as low-grade, and high-grade is used only for most advanced dysplastic lesions (52).

Invasive Carcinoma Associated with IPMNs

The most important determinant of outcome in the management of patients with IPMNs is whether an associated invasive carcinoma is present or not (1,11,13,16,53-57). Approximately 40-60% of resected IPMNs have had an associated invasive carcinoma, either of the colloid-type or ductal-type (11,58). Various authors have reported that MD-IPMNs have a higher potential of having invasive disease, compared to BD-IPMNs (13,43,59,60).

Gastric-type IPMNs rarely have an invasive carcinoma (61); however, when a carcinoma develops, it is typically ductal-type and has aggressive behavior (62). Intestinal-type IPMNs tend to be large, complex, and prone to have invasive carcinoma, and when they are associated with an invasive carcinoma, it is typically of colloid type (Figure 4A) characterized by nodules of stromal mucin that contain relatively scant clusters of carcinoma cells (10,41,63-65). This form of invasive carcinoma has to be distinguished from benign spillage of mucin into the stroma called pseudoinvasion. In contrast to invasive carcinoma, benign spillage of mucin does not contain neoplastic cells and is usually associated with an inflammatory response at the periphery. In some cases, it can be very difficult to distinguish pseudoinvasion from true invasive colloid carcinoma. For such cases, the diagnosis of "indeterminate for invasion" may have to be rendered (45). Invasive carcinoma associated with pancreatobiliary-type IPMNs is usually tubular type, characterized by infiltrating small
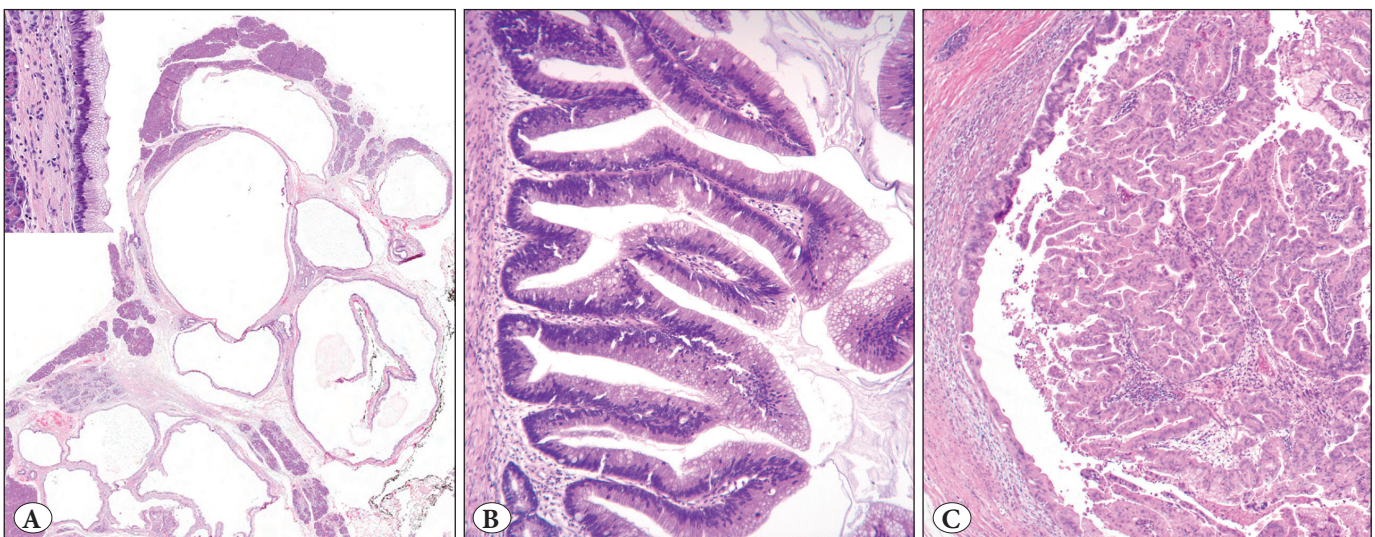
Figure 2: A) IPMN of gastric type. The papillae are lined by simple epithelium that resembles gastric foveolar epithelium (H&E; x100). **B)** IPMN of intestinal type. The papillae lined by pseudostratified columnar cells with cigar-shaped nuclei, apical goblet like mucin resembling colonic villous adenomas (H&E; x200). **C)** IPMN of pancreatobiliary type with more complex, interconnecting papillae lined by atypical cuboidal cells that have little cytoplasmic mucin and enlarged round nuclei (H&E; x100).

to medium tubular units separated by desmoplastic stroma with all the morphologic features of PDAC (Figure 4B) (10,16,24,54,66-68).

Grossing

First of all, every attempt should be made to measure the diameter of the main pancreatic duct. Then, for unifocal but multilocular lesions, overall size of locules; for multifocal lesions, the range of the foci should be documented (45). Some IPMNs have very thin-walled cysts that can rupture during gross examination. Therefore, for such IPMNs,

the true size needs to be determined by close correlation with radiologic findings. Documenting the gross size of any solid or gelatinous component is also required as invasive carcinomas are often solid or gelatinous and this component often corresponds to "mural nodule" detected by imaging preoperatively (69). More importantly, it should be kept in mind that an invasive carcinoma arising in association with an IPMN can only be definitely excluded by thorough evaluation of not only the entire lesion but also the uninvolved pancreas as well (45,70,71).
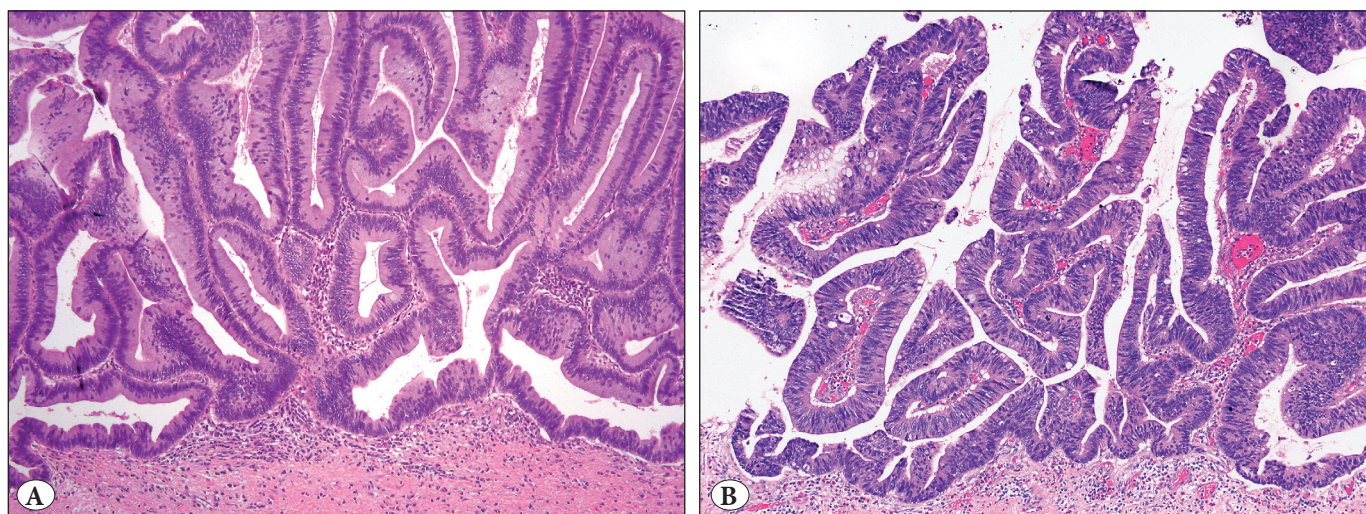

Figure 3: A) IPMN with low grade dysplasia. The neoplastic cells form a single layer of well oriented, small and uniform nuclei and lack of frequent mitoses (H&E; x100). **B)** IPMN with high grade dysplasia has more complex architecture with cribriform pattern, nuclear pleomorphism, and increased mitotic figures (H&E; x100)
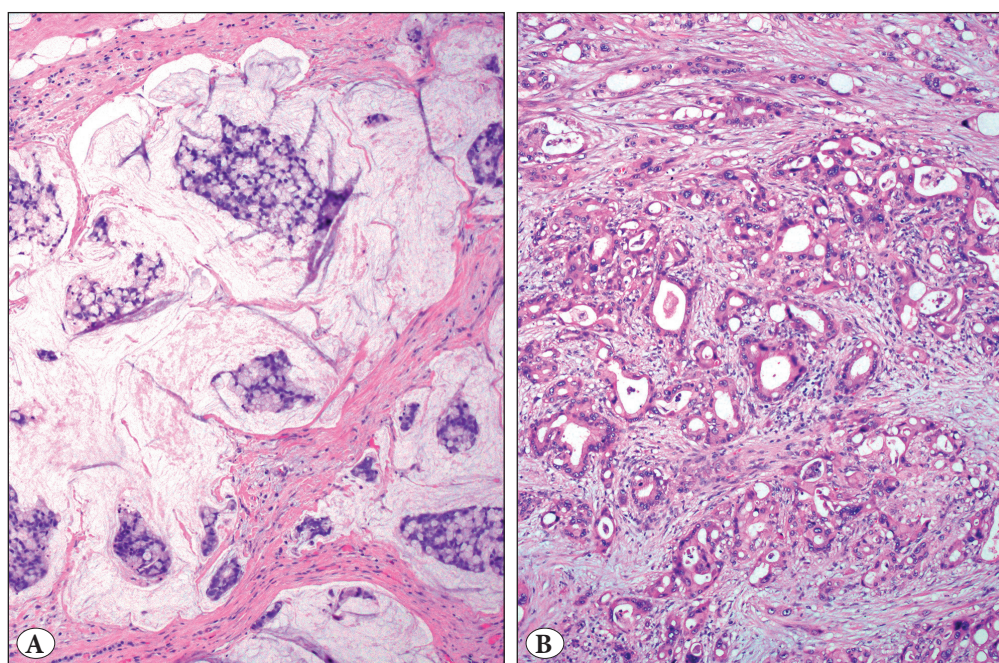

Figure 4: A) Invasive carcinoma of colloid type characterized by abundant mucin with floating epithelial cells and (H&E; x40),
B) Tubular type, characterized by infiltrating small to medium tubular units separated by desmoplastic stroma (H&E; x40).

Frozen Section

Evaluation of margins by frozen section may be indicated in some cases of IPMNs. The presence of low-grade dysplasia at the resection margin does not need further resection, while involvement by high-grade dysplasia or invasive carcinoma is important as it usually means more aggressive surgery (72-74). Although intestinal- and oncocytic-type IPMNs are easy to distinguish from PanIN, gastric- or pancreatobiliary-type IPMNs are virtually indistinguishable from PanIN. For this reason, it is recommended that low-grade intraductal mucinous lesions in pancreatic margins be reported as "No high-grade dysplasia or invasive carcinoma is identified; low-grade mucinous epithelium is present (differential diagnoses include low-grade PanIN or low-grade IPMN)." Similarly, high-grade intraductal mucinous lesions should be reported as "High-grade mucinous epithelium is present (differential diagnoses include high-grade PanIN or high-grade IPMN).

Evaluation of denuded duct epithelium is also problematic on frozen section. For such cases, deeper sections are suggested to find whether any adherent epithelium is present. If deeper sections are also similar, the case may be reported as "denuded epithelium, cannot assess for neoplastic process" (45,53)

Reporting

In reporting IPMNs, if there is no associated invasive carcinoma, it is recommended that the diagnosis should start with the name of the precursor lesions, followed by the grade, morphologic subtype and size (i.e. IPMN with low-grade dysplasia, intestinal type, 2 cm). If there is any associated invasive carcinoma, the pathology report should separately document the characteristics of both precursor and invasive lesions. The term "IPMN with invasive carcinoma" or "invasive carcinoma with an associated IPMN" may be used. The terms "malignant IPMN" or "minimally invasive IPMN" should not be used as these terms are non-specific and potentially misleading. If the invasive carcinoma is unifocal, the largest diameter of the invasive focus should be measured. If it is multifocal, it is recommended that both the diameter of the largest invasive focus and the overall estimated size of all foci in aggregate be provided in the comment of the report (45, 52).

Immunohistochemical Features

All IPMNs express cytokeratin (AE1/AE3, CAM5.2, CK7, 8,18,19), and except for the intestinal type, all are negative for CK20 (75,76). Different patterns of MUC expression are seen in IPMNs and correlate with morphologic differentiation (Table I) (24,41,44). MUC5AC is detected in most IPMNs, regardless of the type. The gastric-type just labels with MUC5AC, while the pancreatobiliary-type IPMNs also label with MUC1 and is negative for MUC2 (12,41,42,44,77-80). Intestinal-type IPMNs express the intestinal lineage markers such as MUC2, and CDX2 that are not expressed in the normal pancreas or other IPMN types (11,12,24,41,44,78). When pancreatobiliary- and intestinal-type IPMNs are associated with invasive carcinoma, the invasive component also expresses the same markers as non-invasive component does. It should be noted that scattered goblet cells can be seen in non-intestinal types of IPMNs rendering the tumor focal positivity for MUC2, CDX2, and CK20 (34). Immuno labeling can also reveal scattered chromogranin positive cells at the base of the neoplastic epithelium (81).

Molecular Features

Whole-exome sequencing of IPMNs revealed about 26 mutations per IPMN (82,83). The most common mutations seen in IPMNs are *KRAS, GNAS* and *RNF43* genes. *KRAS* mutation is identified in approximately 80% of IPMNs, while *GNAS* mutation is seen in approximately 60%, and *RNF43* in approximately 75%. *KRAS* mutation is most commonly seen in gastric-, and secondly in pancreatobiliary-type (84-86). *GNAS* mutation is commonly identified in intestinal-type of IPMNs and if the neoplasm is associated with invasive carcinoma this mutation is seen in both invasive and non-invasive component (87). Although *KRAS* mutation is

Table I: Immunohistochemical profile of IPMNs (including IOPNs)

	CK7/8/18/19	MUC1	MUC2	CDX2	CK20	MUC5AC	MUC6
IPMNs							
Gastric type	+	-	-	-	-	+	-
Intestinal type	+	-	+	+	+	+	-
Pancreatobiliary type	+	+	-	-	-	+	+
IOPNs	+	+	-	-	-	+	+

IPMN: Intraductal papillary mucinous neoplasm. **IOPN:** Intraductal oncocytic papillary neoplasm

common in both IPMN and PDAC, *GNAS* mutation is not identified in PDAC and the frequency of *RNF43* mutation in PDAC is not known (84). Less common alterations seen in IPMNs involves *PIK3CA, AKT1, CDKN2a/p16, SMAD4, TP53, BRAF, CTNNB1/β-catenin, IDH1, STK11, PTEN, ATM, CDH1,* and *FGFR3* genes (54,82,88,89).

Treatment

Nowadays, IPMNs represent the 10-30% of all resectable pancreatic tumors and the treatment of MD-IPMNs has not changed much over the past three decades. Most patients with MD-IPMNs who fit for surgery, undergo tumor resection. BD-IPMNs measuring >3 cm in diameter, even without mural nodules is also recommended for resection according to Sendai guidelines although Fukuoka guidelines include more conservative criteria for resection (7)

Prognosis

Malignant progression is more closely associated with older age (>70 years) and female gender (90). Not surprisingly, invasive carcinoma stage is the most significant predictor of survival followed by the invasive carcinoma histological subtype (55, 91-93) and half of those with an associated invasive carcinoma die of the disease (15,66) (94-98). In a relatively recent study comparing stage matched IPMN-associated colloid carcinoma, IPMN-associated tubular carcinoma, and conventional pancreatic adenocarcinoma, the colloid carcinoma was found to have a more favorable survival outcome than the tubular carcinoma (The 5-year estimated survival rates for colloid carcinoma and tubular carcinoma were 87% and, 55%, respectively (p=0.01)). Also, patients with invasive tubular IPMN had no statistically

Figure 5: Mucinous cystic neoplasm characterized by mucin producing columnar epithelium surrounded by ovarian type stroma (H&E; x100).

significant difference in survival as matched patients with conventional ductal pancreatic carcinoma (The 3-year estimated survival rates were 61% and, 21%, respectively (p=0.87)) (99).

Series from large centers also allow the conclusion that non-invasive IPMNs recur in up to 13% after resection. The recurrence rate is higher (28-60%) for IPMNs with invasive component (100,101). Invasive carcinoma may also develop in the remnants after partial pancreatectomy for IPMNs. This is likely related to the multicentricity of IPMNs (102) that is why careful examination of the remaining pancreas by the surgeon is as important as extensive, if not total, sampling of the resected pancreas by the pathologists.

Differential Diagnosis

The most common problem is to distinguish IPMNs from MCNs. IPMNs are defined as mucin producing tumors arising from the main or branch pancreatic ducts (8), while MCNs are characterized by de-novo mucin-producing tumors with ovarian-type type stroma (Figure 5) (i.e. MCNs don't have any communication with pancreatic ductal system) (103). They have different clinical, gross and microscopic findings (Table II). For example, MCNs generally involve the tail of the pancreas in perimenopausal women, while IPMNs are seen in older men and involve the head of the pancreas. Grossly, the most important finding that favors MCN over IPMN is the lack of communication with pancreatic duct system (11,14,77,103-105). Microscopically, both neoplasms are lined by mucinous epithelium, but MCNs have distinct ovarian-type stroma, which is positive for estrogen, and progesterone receptors as well as smooth muscle actin (SMA), inhibin and calponin (12,103-113). The cyst lining of both lesions might be papillary or flat, and sometimes be almost entirely denuded, which makes rendering the diagnosis difficult. In this situation, additional sectioning is recommended to identify the epithelial lining (104,114,115). The epithelial cells of MCNs label with CK7, 8, 18, 19, CAM 5.2, as well as MUC5AC. MUC6 expression is also reported (114,116). MUC1 expression can be identified in the invasive component. Unlike IPMNs, MCNs do not show intestinal differentiation, so they generally do not express CDX2 and CK20 (115,117).

The other problematic issue is to distinguish IPMNs from PanIN. If the IPMN is gastric- or pancreatobiliary-type, it may be impossible to distinguish IPMNs extending to smaller ducts from independent, incidental PanIN (43,54). If the tumor is grossly and microscopically less than 0.5 cm,
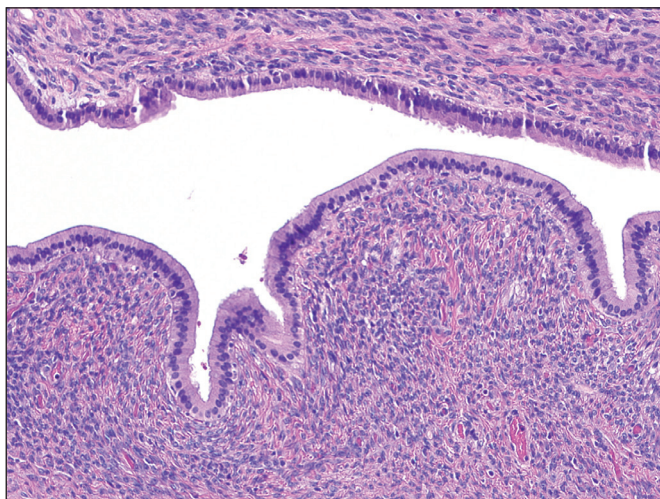
Table II. The comparison of IPMNs and MCNs

	MCNs	IPMNs
Age	40-50 yrs	60s
Gender	F>M	M>F
Location of the tumor	Body/Tail	Head
Relation with pancreatic duct	No	Yes
Mucin extrusion from ampulla	No	Often
Stroma	Ovarian type	Collagenous
Multifocality	Rare	20-30%
CK7/8/18/19	+	+
MUC5AC	Rarely +	+
MUC6	Rarely +	+ (pancreatobiliary type)
CDX2	-	+ (Intestinal type)
CK20	-	+ (Intestinal type)
ER,PR	+ (stroma)	-

IPMN: Intraductal papillary mucinous neoplasm, **MCN:** Mucinous cystic neoplasm.

PanIN is favored as IPMN is, by definition, larger than 1 cm in size (10,43,73). Also, the papillae of IPMNs are taller and more complex than those of PanIN, and the tumors cells may express MUC2 in IPMNs, while they are negative in PanIN (43). Some PDACs with large invasive glands, a.k.a large duct-type PDAC, may also resemble IPMNs, but the irregular contours and flat epithelial lining of the glands and presence of necrotic debris within their lumen favor PDAC (118,119).

Of note, larger than 1 cm pancreatic cysts lined by non-papillary mucinous epithelium without ovarian-type stroma (i.e. mucinous cysts that do not have characteristic features of intraductal papillary mucinous neoplasms or mucinous cystic neoplasms) may pose diagnostic challenges (120). The term "simple mucinous cyst" was recently proposed for these lesions (52). Since *KRAS* mutations can be detected in these typically bland cysts, and in rare instances, focal high-grade dysplasia may be present, these cysts should be viewed as neoplastic and treated similarly to other neoplastic mucinous pancreatic cysts (120).

Intraductal Oncocytic Papillary Neoplasm

Definition

The term intraductal oncocytic papillary neoplasm (IOPN) was first described by Adsay et al in 1996, as a grossly cystic epithelial neoplasm composed of oxyphilic cells that grow within the pancreatic ducts (38). However, the current (2010) WHO classification puts this neoplasm under the general IPMN category (39).

Clinical Features

IOPN is usually seen during the seventh decade of life (58, 121,122) with equal male to female ratio (58,121,122). Patients are either asymptomatic or have non-specific symptoms, similar to IPMNs.

Pathologic Features

Macroscopically, IOPNs usually involve the head of the pancreas and present as cystic lesions with soft friable papillary structures involving the main pancreatic duct. The mean tumor size is 6 cm (38,122-124).

Microscopically, they are characterized with papillary projections lined by stratified cuboidal or columnar cells. The cells have distinctive oncocytic cytoplasm and nuclei with single, prominent, nucleoli (58,121) (Figure 6A,B). Intracellular lumens are also seen (38, 121-123, 125, 126). Despite highly complex morphology and atypical cytology, most examples are devoid of invasive carcinoma, and, if present, invasion is usually limited in amount (121, 124). The invasive component can be oncocytic, mucinous (colloid-like), sarcomatoid/undifferentiated, or even neuroendocrine type (38,123,125,127,128). Similar to IPMNs, features of both invasive and non-invasive components should be documented separately (121).

Immunohistochemical Features

The tumor cells usually express MUC1 and MUC6 (61,77,121,129,130), while are negative for MUC2, and CDX2. More importantly, neuroendocrine and acinar differentiation markers are both negative.

Molecular Features

Recent molecular studies showed that IOPNs have distinct molecular features compared to IPMNs as they do not reveal *KRAS, GNAS, or RNF43* mutations, which are commonly seen in IPMNs (131).

Prognosis and Treatment

The long-term follow-up of patients with IOPN reveals that the recurrence rate is high (up to 40%) (132). However, survival outcomes are still favorable despite the second resection. Also, even though these intraductal neoplasms may develop invasive carcinoma, usually in the form of invasive oncocytic or mucinous (colloid-like) carcinoma, they still have more indolent course than conventional PDAC (16,31,38,40,71,121,124,126,133).

Intraductal Tubulopapillary Neoplasm

Definition

First reported by Tajiri et al in 2004 (134), intraductal tubulopapillary neoplasm (ITPN) was classified by WHO as a distinct type of pancreatic intraductal neoplasm in 2010 (8).

Clinical Features

ITPNs are rare neoplasms seen at an average age of 53 years, with equal female to male ratio (31,135). The patients usually present with non-specific symptoms such as abdominal pain, vomiting, weight loss, and steatorrhea. Unlike PDAC, there is no jaundice (135). The tumor is usually characterized by solid and cystic areas on imaging; pre-operative diagnosis of IPMN might be rendered for some cases.

Pathologic Features

On gross examination, the tumors are multinodular, with the mean tumor size of 4.5 cm and one might see soft, polypoid masses within dilated pancreatic ducts (135). About 50% of the ITPNs involve the head of the pancreas, and 30% involves the entire gland. Cyst formation is generally uncommon, and the adjacent pancreatic tissue is usually sclerotic (136). Because of their intraductal growth pattern, it is difficult to differentiate ITPNs from IPMNs grossly (8,137).

Microscopically, these neoplasms have a nodular growth pattern (Figure 7A). Intraductal location of at least some of the tumor nodules is identified in every case as there is continuity of the neoplastic epithelium with histologically normal-appearing ductal epithelium. However, many tumor nodules show no residual non-neoplastic ductal epithelium at the periphery (135). The nodules are composed of either back to back tubular glands or punctuated sheets of tumor cells (Figure 7B) (54,134,138). Despite the entity's name, the predominant growth pattern is tubular in ITPNs with papilla formation seen only focally in rare cases (135,139). Although small foci of necrosis are common, rare cases might even reveal comedo-like necrosis as shown here within the nodules. The cuboidal tumor cells have modest amount of cytoplasm without
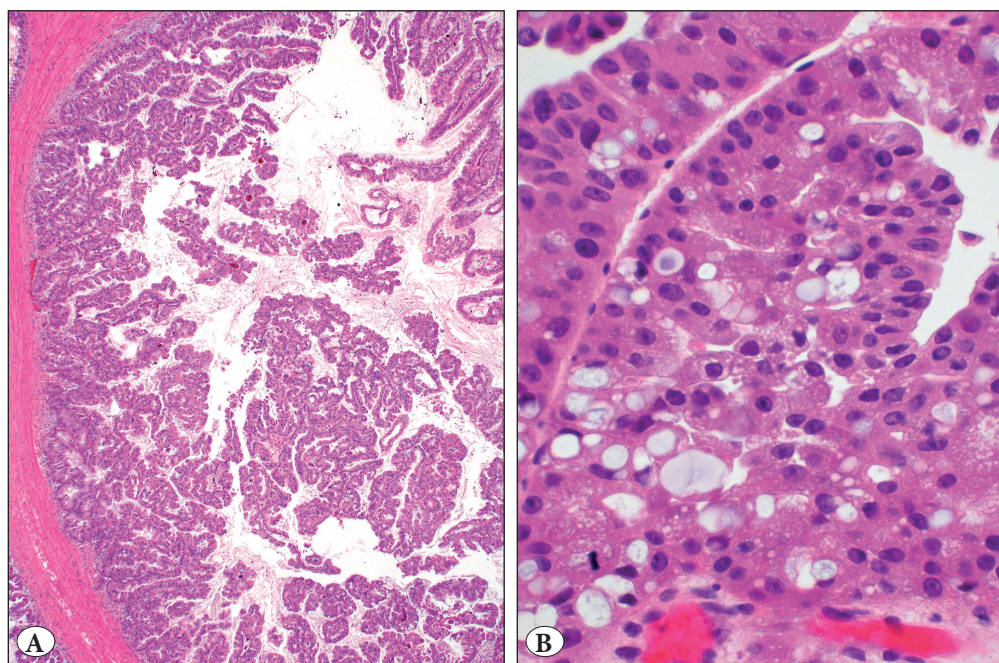

Figure 6: A) The characteristic appearance of IOPN with complex papillae and distinctive granular cytoplasm (H&E; x100) and **B)** Nuclei with single prominent, eccentric nucleoli. Intracellular lumens are also present (H&E; x200).
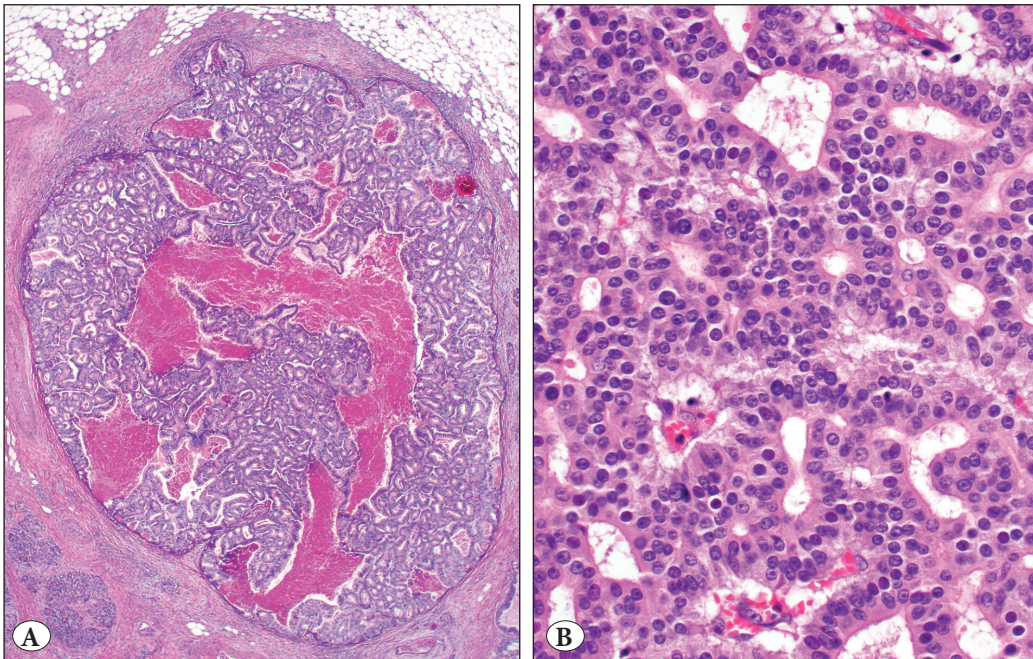
Figure 7: A) Intraductal tubulopapillary neoplasm with a nodular growth pattern within the fibrotic stroma (H&E; x100), and **B)** The nodule is composed of back to back tubular glands or punctuated solid areas (H&E; x200).

obvious intracellular mucin content. The nuclei are small, round to oval, and moderately to markedly atypical with readily identifiable mitotic figures (135).

Approximately 70% cases have invasive carcinoma component ranging from minute (representing less than 10% of the tumor) to extensive (more than 50% of the tumor) (135). However, because (7,134) many of the individual tumor nodules lack a peripheral rim of non-neoplastic ductal epithelium, it is often very difficult to determine whether invasive carcinoma is present (24,138). Foci in which there are thin strands of cells extending away from the edges of the nodules are regarded to represent stromal invasion (Figure 8). In some cases, there are individual malignant glands clearly infiltrating into the stroma (135).

Immunohistochemical Features

The immuno profile for ITPNs is interesting. The tumor cells are positive with CK7,8,18,19, and MUC1 and MUC6, while MUC2 and MUC5AC are generally negative. Most cases also express CA19.9, which is typically expressed in ductal epithelial cells and ductal neoplasms (135).

Molecular Features

Although their intraductal nature and some of clinicopathological feature similar to those of IPMNs, ITPNs appear to have distinguishing molecular characteristics. For example, in a recent study based on targeted next-generation sequencing for a panel of 51 cancer-associated

genes, no mutations were identified in three ITPNs analyzed (88). Similarly, in another study analyzing eleven ITPNs by targeted next-generation sequencing for a panel of 300 cancer-associated genes, our group showed that ITPNs do not harbor the majority of the previously reported IPMN-related mutations. In fact, only three specific genes were mutated in more than one ITPN: *MLL2*, *MLL3*, and *BAP1* (chromatin remodeling genes) (140). Further analysis of genetic alterations in biologically distinct pathway(s) will likely shed new light on the mechanisms of intraductal tumor formation in the pancreas.
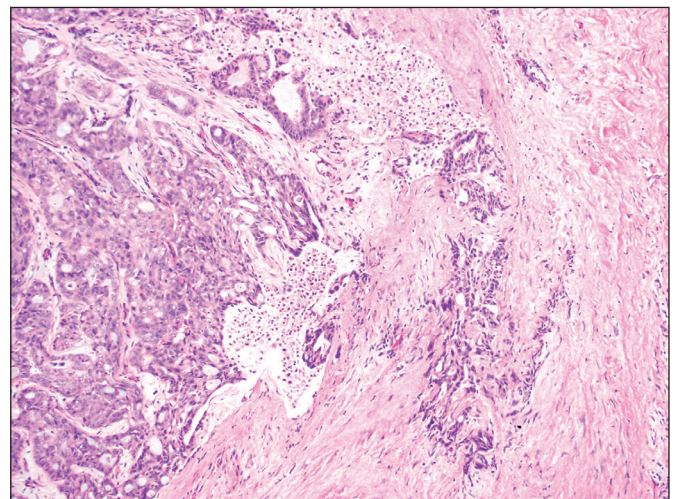

Figure 8: Foci in which there are thin strands of cells extending away from the edges of the nodules are regarded as stromal invasion (H&E; x40).

Prognosis

Although ITPN is relatively newly defined entity, preliminary data suggest that the overall clinical course of these neoplasms was indolent. Interestingly, there seems to be no clinical course and invasion correlation (135,139). However, this is most likely, due to sampling phenomenon. Therefore, careful sampling and evaluation is warranted.

Differential Diagnosis

The differential diagnosis includes other fundamentally intraductal tumors such as IPMNs as well as other pancreatic neoplasms that may rarely grow within the ducts (acinar cell carcinoma and pancreatic neuroendocrine neoplasm). Although IPMNs may have some limited tubular growth, especially at the periphery of the involved ducts, all show extensive intraductal papilla formation, and complete obliteration of the ductal profiles is distinctly unusual.

The back-to-back tubules of intraductal tubular carcinoma, each of which has a relatively small lumen, closely simulate the pattern of acinar neoplasms of the pancreas. Most acinar cell carcinomas are large solid lesions and demonstrate no involvement of the native pancreatic ducts. However, rare cases have been described in which an intraductal growth pattern is present either focally or extensively. Some in fact show papillary formations within the native ducts (137,141,142). Acinar cell carcinomas with intraductal spread can be difficult to distinguish from ITPN by routine microscopy, but immunohistochemistry is very helpful. Acinar cell carcinomas consistently express pancreatic enzymes such as trypsin, chymotrypsin, and lipase and generally lack expression of CK19 (141-144).

Finally, pancreatic neuroendocrine neoplasms can rarely show an intraductal growth pattern. Usually, these are solid neoplasms, although gland formation can occur in pancreatic neuroendocrine neoplasms. Again, immunohistochemistry is extremely helpful, as there is diffuse positivity for chromogranin and/or synaptophysin in pancreatic neuroendocrine neoplasms. In should be kept in mind that some ITPNs have a minor population of neuroendocrine cells (as can be seen in any type of exocrine pancreatic neoplasm), but these are generally arranged individually, and diffuse labeling for neuroendocrine markers is not found (135,139).

SUMMARY and CONCLUSION

Intraductal neoplasms of the pancreas are precursor lesions for pancreatic ductal adenocarcinoma and IPMNs are the most common type among these. The most important determinant of outcome in the management of patients with these intraductal neoplasms is whether an associated invasive carcinoma is present or not and the tumor size/ stage is the most significant predictor of survival followed by the histological subtype. That is why the careful and extensive, if not complete, sampling is necessary (8,13,16, 53,55-57).

Differential diagnoses of IPMN include PanIN, IOPN, ITPN, MCN, and large duct type PDAC. In addition to imaging and histomorphologic findings, immunohistochemistry and even genetic tests summarized in this article might be used to establish the final diagnosis.

CONFLICT of INTEREST

The authors declare no conflict of interest.

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