A Review of Mucinous Cystic and Intraductal Neoplasms of the Pancreatobiliary Tract

Recent Advances

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• Context.—Although most pancreatic and bile duct neoplasms are solid, mucinous cystic neoplasms and intraductal neoplasms have been increasingly recognized even when clinically silent, thanks to the increased use of sensitive imaging techniques. Cystic and intraductal neoplasms of the pancreas are often resectable and curable and constitute about 5% of all pancreatic neoplasms. Owing to their preinvasive nature and different biology, recognition of these entities remains a major priority. Mucinous cystic neoplasms are histologically and clinically distinct from other cystic pancreatic neoplasms. Pancreatic intraductal neoplasms encompass 3 major entities: intraductal papillary mucinous neoplasm, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm. Intraductal papillary neoplasms of bile ducts are also preinvasive mass-forming neoplasms with both similarities and differences with their pancreatic counterparts. All of these pancreatobiliary neoplasms have diverse and distinctive clinicopathologic, genetic, and prognostic variations.

Objective.—To review the clinical, pathologic, and molecular features of mucinous cystic and intraductal neoplasms of the pancreatobiliary tract.

Data Sources.—Literature review, diagnostic manuals, and guidelines.

Conclusions.—This review will briefly describe well-known clinical and pathologic features and will focus on selected recently described aspects of morphology, grading, classification, and genomic alterations of cystic and intraductal neoplasms of the pancreatobiliary tract.

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Intraductal neoplasms of the pancreas have been more frequently detected in recent years owing to increased use of cross-sectional imaging studies, even if clinically asymptomatic. These tumors are generally cystic on radiologic examination like true cystic neoplasms of the pancreas such as serous or mucinous cystic neoplasm (MCN), although preoperative distinction may be challenging. However, in the absence of invasion, these tumors are often cured by surgery alone. Pancreatic MCN, intraductal papillary mucinous neoplasm (IPMN), intraductal oncocytic papillary neoplasm (IOPN), and intraductal tubulopapillary neoplasm (ITPN) will be reviewed in this article as well as their biliary counterparts.

PANCREATIC MUCINOUS CYSTIC NEOPLASMS

MCNs are defined as cyst-forming and mucin-producing epithelial neoplasms with distinctive ovarian-type subepithelial stroma (Figure 1). Histologically similar neoplasms, also designated MCNs, can arise in the liver, rarely involving the bile ducts or gallbladder, and in other locations such as the peritoneum. In all these locations, there is a striking female predilection, estimated to be 20:1 for those occurring in the pancreas, and they usually affect patients 40 to 50 years of age. Pancreatic MCNs involve the tail of the pancreas in nearly all cases. In contrast to intraductal neoplasms, MCNs do not involve the pancreatic ducts and rather present as a circumscribed multicystic cyst with a mean size of 8.5 cm. MCNs are regarded to be dysplastic preinvasive neoplasms that can have varying degrees of dysplasia in different regions, and invasive carcinomas can arise in 16% of cases, either as a solid nodule or as microscopic foci within the septa of the cyst. The ovarian-type stroma is required for diagnosis and is typically arranged as a highly cellular spindle cell layer immediately beneath the cyst-lining epithelium (Figure 2). Hormone receptors—progesterone receptor more commonly and intensely than estrogen receptor—are expressed immunohistochemically (Figure 3), and clusters of epithelial cells resembling luteinized stroma of the ovary express inhibin and Melan-A (A103). In older patients, the ovarian-type stroma may be less abundant and less cellular (Figure 4), requiring immunolabeling to confirm its presence.

Recent advances related to pancreatic MCNs include recognition of variant morphologies, an update to the
Figure 1. Mucinous cystic neoplasm characterized by unilocular, thick-walled cystic tumor containing hemorrhagic/necrotic material.

Figure 2. Mucinous cystic neoplasm. Epithelial lining of the cyst is predominantly composed of tall, columnar, mucin-containing cells. Underlying stroma is hypercellular and resembles the ovarian stroma (hematoxylin-eosin, original magnification ×100).

Figure 3. Mucinous cystic neoplasm. Progesterone receptor immunohistochemical stain highlights the spindle cells in the stroma (original magnification ×400).

Figure 4. Mucinous cystic neoplasm. In older patients/lesions, the ovarian-type stroma may be less cellular, requiring immunolabeling to confirm its presence. The epithelial lining may also be attenuated (hematoxylin-eosin, original magnification ×200).

Figure 5. The ovarian-type stroma can extend into the adjacent nonneoplastic pancreatic parenchyma (hematoxylin-eosin, original magnification ×100).

Figure 6. Intraductal papillary mucinous neoplasm. The main pancreatic duct is dilated and filled with friable papillary projections.
grading of dysplasia, and new reports on the associated invasive carcinomas and their prognosis.

As implied by the name of the entity (and the World Health Organization [WHO] definition), mucinous epithelium is regarded as a hallmark of MCNs. However, it is becoming more recognized that not all of the epithelium lining the cysts contains evident mucin. In some regions, cysts may be lined by low cuboidal cells without mucin, which resembles the lining of normal ducts (Figure 4).\(^7\)\(^-\)\(^9\) This finding is usually focal within an otherwise conventional MCN that has mucinous cytoplasm elsewhere, and rare cases appear to lack mucin altogether, a phenomenon that is more common in primary hepatic MCNs. Rare cases may even show a nonkeratinizing squamous epithelial lining in some of the cysts. Thus, it is the entity-defining ovarian-type stroma that allows for the diagnosis in such cases. Immunolabeling for hormone receptors in the subepithelial stroma is particularly helpful to confirm it is ovarian-type, but occasionally the stroma becomes hyalinized and loses its obviously hypercellular appearance. Anecdotally, this phenomenon seems to be more common in postmenopausal patients, although definitive data have yet to be published. Another morphologic facet of MCNs that was not initially appreciated is that the ovarian-type stroma can extend into the adjacent nonneoplastic pancreatic parenchyma and surround acini, islets, and small nonneoplastic ductules (Figure 5). Typically, the periphery of MCNs is surrounded by a dense fibrous pseudocapsule, but in some cases the periphery is not microscopically circumscribed. These MCNs can simulate primary spindle cell neoplasms of the pancreas that have entrapment of nonneoplastic parenchyma, such as solitary fibrous tumor.

Another recent change involves the grading of dysplasia in MCNs and also applies to other examples of preinvasive neoplasia in the pancreas such as pancreatic intraepithelial neoplasia (PanIN) and IPMN. Originally, dysplasia was graded in 3 tiers (low grade, intermediate grade, and high grade). However, interobserver reproducibility using the 3-tiered system was suboptimal, and clinical decision-making so that cases with high-grade dysplasia would be limited to the intermediate-grade category in the older system was merged with the low-grade category in the new system, thus the clinical significance of the high-grade category.

A final advance relates to the prognosis of MCNs, in particular those with an associated invasive carcinoma component. Although early reports on MCNs emphasized the potential for malignant behavior even in cases lacking evident invasive carcinoma,\(^11\) multiple reports later demonstrated a universally benign clinical course for cases lacking invasive carcinoma, suggesting that the findings of earlier studies reflected inadequate histologic sampling and failure to detect an invasive component.\(^12\) In fact, in one landmark study, even cases with invasive carcinoma limited to the septa of the cyst seemed to be cured by surgery.\(^13\) However, a large study of completely submitted MCNs from 2015 demonstrated that poor outcomes can occur even with invasive carcinomas limited to the septa and measuring less than 0.5 cm (pT1a).\(^15\) The same study showed a much worse outcome when the invasive carcinomas measured more than 2 cm, with a 5-year survival of 0% compared with nearly 80% for smaller invasive carcinomas. Another interesting observation from that study was that the histology of the invasive carcinomas included tubular, undifferentiated, and papillary patterns, but colloid carcinomas were not seen. This contrasts with the patterns of invasive carcinoma arising in IPMNs, many of which are colloid carcinomas.\(^6\) Presumably the difference in carcinoma subtypes reflects the rarity of intestinal differentiation in MCNs, which is usually limited to scattered goblet cells within the mucinous epithelium.

### PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

**Definition and Clinical Features**

Historically also known as papilomatosis of the pancreatic duct, duct ectatic mucinous cystic neoplasm, mucinous duct ectasia, adenoma of the ducts, and intraductal papillary neoplasms, IPMNs are grossly and radiographically visible intraductal neoplasms with papilla formation and mucin hypersecretion arising in the pancreatic ducts. IPMNs are larger than 5 mm by definition.\(^1\) They are generally cystic owing to ductal dilatation and comprise around 40% of cystic pancreatic neoplasms.\(^13\)\(^,\)\(^14\)

Clinically, IPMNs can be considered in 2 main groups. Main duct–type IPMNs are characterized by dilatation of the major pancreatic duct (Figure 6) and can involve the entire ductal system. Main duct IPMNs are more common in the elderly.\(^15\) IPMNs with involvement limited to the secondary ducts, so-called branch duct–type IPMNs, are generally confined to head and neck regions of the pancreas and have become one of the most commonly detected incidental pancreatic lesions owing to increased use of cross-sectional imaging.\(^16\) They are more frequent in younger patients and less commonly have high-grade dysplasia or invasive carcinoma.\(^17\) Mixed duct–type IPMNs have involvement of both main and secondary ducts. Cystic dilatation of the ducts and mucin spillage into the duodenum are characteristic endoscopic findings for IPMNs, and they can be multifocal.\(^18\)

Radiologic distinction of main duct–type IPMNs from branch duct IPMNs is of clinical importance since the main duct–

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**Current Terminology of Intraductal Papillary Mucinous Neoplasm (IPMN) and Mucinous Cystic Neoplasm (MCN)**

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<tr>
<th>Former Terminology</th>
<th>Current Terminology</th>
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<tr>
<td>IPMN with low-grade dysplasia</td>
<td>IPMN, low-grade</td>
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<td>IPMN with intermediate-grade dysplasia</td>
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<td>IPMN with a subepithelial stroma</td>
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<td>MCN with low-grade dysplasia</td>
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<td>MCN with high-grade dysplasia</td>
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<td>MCN with high-grade dysplasia (carcinoma in situ)</td>
<td>IPMN with an associated invasive carcinoma (carcinoma in situ)</td>
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type has a greater risk of harboring high-grade dysplasia or invasive carcinoma.\textsuperscript{19,20} Close interval surveillance imaging can be used instead of surgery for branch duct IPMNs if they are small (<3 cm) and lack worrisome findings such as mural nodules, irregularities in the duct contours, and main duct dilatation.\textsuperscript{21,23}

Patients with IPMNs generally have nonspecific abdominal symptoms due to ductal obstruction and related pancreatitis. Weight loss, diabetes mellitus, and jaundice may also be seen. There is a slight male predominance.\textsuperscript{23} Documented risk factors for IPMNs are chronic pancreatitis, diabetes (higher risk when insulin dependent), other gastrointestinal tract tumors, and a family history of pancreatic ductal adenocarcinoma (PDAC).\textsuperscript{24,25} There have been reports of increased incidence of extrapancreatic neoplasms in patients with IPMN as well.\textsuperscript{26–28} IPMNs, mostly of branch duct–type, have been more frequently reported in patients with Peutz-Jeghers syndrome, familial adenomatous polyposis, and McCune-Albright syndrome.\textsuperscript{29–32}

**Pathologic Features**

IPMNs can be localized or multicentric and can also involve the entire pancreatic ductal system. Systematic macroscopic evaluation is important to document the intraductal nature of IPMNs.\textsuperscript{33} Extensive sampling of the specimen is also crucial for the detection of an invasive carcinoma component, which can be quite small.\textsuperscript{33,34} The spectrum of cyst and papilla formation and the extent of ductal dilatation vary significantly between cases.

Branch duct–type IPMNs generally manifest as multilocular cystic lesions in otherwise unremarkable pancreatic parenchyma, often in the uncinate process. They can also appear as multiple small cysts separated by normal pancreatic tissue. Connection of these lesions to the ductal system can be difficult to demonstrate. The cyst contents are commonly mucinous or serosanguinous and the lining is often smooth. Papillae, when present, appear as feathery granulations or polyloid, lobulated projections.\textsuperscript{35–38}

Main duct IPMNs are most frequently located in the head of the pancreas but can involve the entire ductal system, as aforementioned. They are characterized by a dilated, tortuous main pancreatic duct, which is generally extensively involved and may be lined by a carpet of velvety, friable, and focally hemorrhagic papillae. As in MCNs, dysplasia in IPMNs is now graded by using a 2-tiered grading system that replaced the former 3-tiered grading scheme. Former categories of IPMN with low-grade dysplasia and IPMN with intermediate-grade dysplasia are now regarded as low-grade IPMN. IPMN with high-grade dysplasia is now considered high-grade IPMN, corresponding to the most dysplastic third of the spectrum (Table).\textsuperscript{10} Histologic features of high-grade IPMNs include irregular branching and budding of the papillae, full-thickness nuclear stratification with loss of polarity, pleomorphism, prominent nucleoli, and frequent mitoses.

Three different morphologic subtypes of IPMNs are described: intestinal-type (Figure 7, A), gastric-type (Figure 7, B), and pancreatobiliary-type (Figure 7, C). Since these subtypes can coexist, they are subclassified by the predominant cell type. The intestinal-type IPMN constitutes about 20% of cases and resembles villous adenomas of the gastrointestinal tract.\textsuperscript{39,40} Intestinal-type IPMNs often harbor high-grade dysplasia.

Gastric-type IPMN is the most common type (~70%) and is characterized by cells resembling gastric foveolar epithelium. This type is frequently seen in branch duct–type IPMNs.\textsuperscript{39} Gastric-type IPMNs usually harbor low-grade dysplasia.\textsuperscript{41} Of note, when cytologic or architectural features of high-grade dysplasia are present, they resemble pancreatobiliary-type IPMNs.\textsuperscript{42}
Pancreatobiliary-type IPMN is the least common (~10%), and most cases have high-grade dysplasia. This type typically involves the main duct. The papillae are more complex and arborizing with cuboidal cells, showing high-grade features like branching papillae, micropapillae, and cribriforming.

Invasive carcinomas arise within IPMNs with varying frequencies, depending on the distribution of the neoplasm, the morphologic subtype, and the degree of dysplasia. When IPMNs are detected incidentally, the incidence of invasive carcinoma is low. Invasive carcinoma is found in up to 15% of branch duct–type and 60% of main duct–type IPMNs. Overall, about one-third of resected IPMNs have invasive carcinoma. When an invasive component is present, it is typically tubular-type in gastric- and pancreatobiliary-type IPMNs (Figure 8) and colloid-type in...
intestinal-type IPMNs (Figure 9).\textsuperscript{41,45,47–49} Owing to high incidence of chronic pancreatitis and fibrosis associated with IPMNs, it may be extremely hard to recognize small foci of carcinoma grossly. Skip lesions and multifocality have also been well documented in IPMNs.\textsuperscript{50} Colloid-type carcinoma is a clinically and biologically distinct entity with a better prognosis than other ductal adenocarcinoma variants.\textsuperscript{48,51} It is characterized by stromal pools of mucin-containing scattered strips or clusters of neoplastic cells and must be distinguished from benign spillage of mucin into the stroma, which does not contain neoplastic cells.\textsuperscript{48} Tubular-type carcinoma shows all conventional histomorphologic features of PDAC.\textsuperscript{45,47,52,53}

The most recent update of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system allows subclassification of the typically small invasive carcinomas in IPMNs into pT1a (\(\leq0.5\) cm), pT1b (\(>0.5\) cm, \(\leq1\) cm), and pT1c (\(>1\) cm) to yield more systematic data for future evaluations.\textsuperscript{22,41}

### Immunohistochemical and Molecular Features

IPMNs have staining patterns related to their different cell types that can be demonstrated by immunohistochemistry. Most IPMNs express ductal markers and keratins like cytokeratin (CK) 7, CK19, CA19-9, carinoembryonic antigen (CEA), AE1/AE3, CAM 5.2, and B72.3.\textsuperscript{34,55} CDX2, a marker of intestinal differentiation, and CK20 are expressed in intestinal-type IPMNs. MUC2 expression is also seen in intestinal-type IPMNs. This immunoprofile of intestinal-type IPMNs has contributed to recognition of an intestinal pathway of carcinogenesis in the pancreas, with progression to colloid-type invasive adenocarcinoma, which shows similar immunohistochemical features.\textsuperscript{52} In contrast, intestinal markers display negativity and MUC1 usually displays positivity in pancreatobiliary-type IPMNs.\textsuperscript{39,42,56–58} Gastric-type IPMNs do not express intestinal markers or MUC1 or MUC2. MUC5AC is expressed in most IPMNs regardless of the cell type.\textsuperscript{30,42,52,56}

Molecular studies have revealed a wide variety of alterations in IPMNs, mostly similar to those seen in PDACs. Whole-exome sequencing of IPMNs revealed a mean of 26 mutations per neoplasm.\textsuperscript{59} The frequency and type of molecular alterations depends on factors like cell type, degree of dysplasia, association with invasive carcinoma, and type of invasive carcinoma.

KRAS, GNAS, and RNF43 are the most frequently mutated genes in IPMNs. Compared to more than 95% frequency in PDACs, KRAS mutation is identified in about 80% of IPMNs and is most frequent in gastric-type.\textsuperscript{60,61} GNAS and RNF43 genes are frequently altered in IPMNs and are relatively specific for this entity, not being altered commonly in ductal adenocarcinomas (although RNF43 mutations can be seen in MCNs).\textsuperscript{39} Hotspot mutations in codon 201 of the GNAS gene are seen in 41% to 66% of IPMNs, and RNF43 is mutated in 75%.\textsuperscript{60,62–64} GNAS mutation strongly correlates with the cell type and appears to be involved in mucin-related pathways. It has been shown that exogenous expression of mutated GNAS upregulates expression of MUC2 and MUC5AC in human pancreatic duct epithelial cell lines and human pancreatic cancer cell lines, through upregulation of intracellular cyclic adenosine monophosphate.\textsuperscript{65} This mutation is detected in almost 100% of intestinal-type IPMNs and in 71% and 51% of pancreatobiliary-type and gastric-type IPMNs, respectively.\textsuperscript{64} When an invasive component is present, GNAS mutation is significantly more frequent in colloid-type carcinomas than tubular-type carcinomas (89% versus 32%, respectively), and KRAS mutations are more common in tubular-type carcinomas than colloid-type carcinomas (89% versus 52%, respectively).\textsuperscript{66} KRAS and GNAS mutations are not significantly related to the degree of dysplasia, suggesting that these mutations occur early in IPMN carcinogenesis.\textsuperscript{66}

Molecular analysis of multilocular IPMNs reveals that each locule is monoclonal and some different locules from the same case harbor different mutations, demonstrating that the IPMNs may consist of multiple neoplastic clones evolving independently. Two adjacent locules are more likely to contain the same KRAS or GNAS mutation than 2 topographically separate nodules.\textsuperscript{69}

Somatic mutations of TP53, and loss of p16/CDKN2A or SMAD4/DPC4, the 3 major altered genes in PDACs besides KRAS, can also be seen in IPMNs, although at a lower frequency.\textsuperscript{60} PIK3CA and AKT1 mutations and loss of PTEN, all members of the PI3K-AKT signaling pathway, are also described in IPMNs.\textsuperscript{65,67,68}

### Differential Diagnosis

The differential diagnoses of IPMNs include MCNs as well as other intraductal neoplasms that can have mucinous epithelium such as PanIN, simple cysts, and retention cysts. Recognition of the characteristic subepithelial stroma helps in the diagnosis of MCNs. IPMNs are distinguished from PanINs by size (PanINs are usually less than 0.5 cm, whereas IPMNs usually measure more than 1.0 cm) and the expression in IPMNs of intestinal differentiation markers, if present, which is rare in PanINs.

A problematic differential diagnosis occurs when simple cysts that contain mucinous epithelium without significant papilla formation are encountered. Simple cysts without mucinous epithelium are considered retention cysts and usually occur secondary to ductal obstruction. They are usually unilocular and lined by a single-layer low cuboidal or flat epithelium, with minimal or no atypia. Flat mucinous epithelium lining a simple cyst has been regarded as PanIN involving a retention cyst, although the appearance is essentially indistinguishable from the more simple regions of an IPMN.\textsuperscript{34} Recently, the term simple mucinous cysts has been proposed for simple cysts measuring greater than 1 cm with a flat mucinous epithelial lining without ovarian-type stroma, papillary architecture, or high-grade dysplasia (Figure 10). Genomic sequencing of simple mucinous cysts revealed that the most commonly altered gene is KMT2C (62%). KRAS and TP53 mutations were detected in 15%, and BRAF, RNF43, CDKN2A, and SMAD4 alterations were present in 8%. In 31%, no mutations were found, and none of the cases harbored GNAS mutations. These findings support the neoplastic nature of most simple mucinous cysts and show that they are not genetically identical to gastric-type IPMNs.\textsuperscript{69}

### Natural History, Clinical Management, and Prognosis

The management of IPMNs is a multifactorial process, and individualized approaches are largely being applied. Most incidentally detected cysts of the pancreas are branch duct–type IPMNs, and as discussed before, close interval surveillance is proposed for branch duct–type IPMNs if smaller than 3 cm and lacking worrisome findings like mural nodules, irregularities in the duct contours, and a dilated main duct.\textsuperscript{21,22,70} When these findings are present, the incidence of associated invasive carcinoma is approximately
15%; however, in one study the specificity of guideline recommendations was found to be low, despite high sensitivity.44,70–72 Therefore, a personalized approach remains the primary model. For main duct-type IPMNs, there is an agreement that resection is indicated, as the incidence of high-grade dysplasia of invasive carcinoma is fairly high.17,73

IPMNs are well established as a precursor for invasive carcinoma, and since they can be radiologically detected, they constitute an archetype of a potentially curable preinvasive neoplasm in the pancreas.47 Appropriate treatment, owing to the often multifocal nature of these neoplasms, remains one major dilemma. A conservative surgical approach is the preferred management of these patients, and therefore assessment of margins remains an important predictor, as demonstrated by multiple researchers. Most patients do not experience local recurrence even if pancreatic ductal margins are involved by IPMNs, although the few studies with true long-term follow-up are beginning to show that a proportion recur.51,73–77 Also, negative margins do not exclude the possibility of recurrence owing to the multifocal nature of these neoplasms. In one study, the highest grade of dysplasia within noninvasive IPMNs was found to be a better predictor of recurrence than the margin status.78 Evaluation of the margin may be problematic when the ductal lining is denuded, especially on frozen section, and deeper sections are suggested until epithelium is seen. If margin evaluation reveals normal ductal epithelium or low-grade dysplasia (either IPMN or associated PanIN), no further surgery is suggested. When high-grade dysplasia (either IPMN or PanIN) is present in the margin, some additional surgical resection can be considered. In any event, close follow-up is warranted for these patients.

The overall 5-year survival rate of patients with IPMN is favorable, even when associated with invasive carcinoma if the carcinoma is the colloid-type.51,78 Invasive carcinomas designated as pT1a have an excellent prognosis.79 On the contrary, when tubular-type adenocarcinoma is present, the clinical course is aggressive, similar to that of a conventional PDAC, although some data suggest it is still less aggressive than PDACs without a preexisting IPMN.80

**PANCREATIC INTRADUCTAL ONCYCYTIC PAPILLARY NEOPLASM**

IOPN of the pancreas is a rare and distinctive cystic epithelial neoplasm first described in 1996.81 Like IPMNs, IOPNs are radiographically or grossly visible neoplasms composed of nodular, papillary projections lined by oncocytic cells within cystically dilated pancreatic ducts.7 In the 2010 World Health Organization (WHO) classification, it was regarded as a subtype of IPMN owing to clinicopathologic similarities.82 However, owing to recent studies illustrating clinicopathologic and molecular differences between IPMNs and IOPNs, they are again categorized as a separate entity in the 5th edition of the WHO classification.3 Recent studies have better characterized the associated invasive carcinomas, outcome, immunophenotype, and molecular features of IOPNs.

**Clinical Features**

IOPNs constitute 4.5% of all pancreatic intraductal neoplasms, and unlike IPMNs, they are slightly more common in females.83,84 No specific symptoms are attributed to IOPNs, and almost half of the cases are discovered incidentally; however, symptoms indicating chronic pancreatitis or obstruction due to mass effect can be encountered.81,85,87 They are mostly (70%) located in the head of the pancreas and main pancreatic duct.81,83,84

**Pathologic Features and Differential Diagnosis**

IOPNs exhibit cystic dilatation of the pancreatic ducts, and involved ducts contain large, tan–brown, and friable nodular projections with little luminal mucin accumulation.86,87 The average size is 5.5 cm.86,88 Careful examination is required to document the intraductal nature of the neoplasm or an associated invasive carcinoma component. Histologically, IOPNs are composed of complex and arborizing papillae with delicate fibrovascular cores, which are lined by multiple layers of cuboidal or columnar cells with oncocytic cytoplasm (Figure 11). Nuclei are generally round, and nucleoli are prominent.86,87 Intracellular mucin-containing lumina and intracellular vacuoles impart a characteristic cribriform appearance (Figure 12). Interspersed goblet cells are present. The cytomorphicologic and architectural features are generally complex; therefore, almost all IOPNs are regarded as having high-grade dysplasia.1 Immunohistochemically, IOPNs generally express MUC6 (Figure 13) and to a lesser extent MUC1, whereas MUC2 and MUC5AC labeling is restricted to goblet cells.86,88,89 Hepatocyte Paraffin 1 (Hep Par-1) staining is also encountered in most cases, which is intriguing in light of the molecular findings in IOPNs (see below).86

An invasive carcinoma component is present in about 30% of IOPNs and tends to be limited in extent when present.81,83,85 An oncocytic appearance, a rare phenotype for invasive carcinomas of the pancreas, is generally retained in these invasive components. The invasive component is generally characterized by small infiltrating tubules or solid nests; however, abundant extracellular mucin reminiscent of colloid-type carcinoma can also be seen (Figure 14).85,83 Pseudoinvasion may mimic invasive carcinoma in IOPNs and can be a major challenge. Owing to ductal obstruction, atrophy of benign glands adjacent to the involved duct can be seen, and these small glandular structures can raise a high suspicion for carcinoma. Other pseudoinvasion patterns include myxoid stromal changes surrounding the massively dilated ducts, which mimics desmoplasia.89

In IOPNs, when the neighboring epithelia of adjacent papillae fuse, a distinctive solid pattern results, raising a concern for acinar cell carcinoma or oncocytic pancreatic neuroendocrine tumor. Immunohistochemical studies for neuroendocrine or acinar markers can be used in this distinction, as IOPNs generally do not express these.

**Molecular Features**

IOPNs lack the major molecular alterations related to IPMNs or ductal adenocarcinomas. KRA and GNAS mutations are absent in IOPNs and RNF43 mutation is only seldom described.86 TP53 mutations and loss of p16/CDKN2A or SMAD4/DPC4 are also not described in IOPNs.86,89 Targeted next-generation sequencing of 13 tumor samples from 11 patients revealed recurrent mutations in ARHGAP26, ASXL1, EPHA8, and ERBB4.89 Two recent studies have analyzed pancreatic and biliary IOPNs by RNA-based targeted sequencing and demonstrated a specific variant fusion of DNAJB1-PRKACA, which was previously thought to be specific for fibrolamellar hepatocellular carcinomas.90,92 ATP1B1-PRKACA and ATP1B1-PANCREATOBILIARY CYSTIC AND INTRADUCTAL NEOPLASMS—OZCAN & KLIMSTRA

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PRKACB fusions were also identified, and these fusions are now regarded as entity defining in the appropriate clinicopathologic setting.91,92

Natural History, Clinical Management, and Prognosis

Virtually all IOPNs have high-grade dysplasia; however, high-grade dysplasia does not seem to impact the prognosis following resection.83,85 Local recurrence can occur as long as 10 years after resection in about 45% of the patients, but additional resection is usually curative.81,83,85

IOPNs are associated with invasive carcinomas in about 30% of cases. Even in these cases, the 5-year disease-specific survival is nearly 100%.81,83,85,87,93 It has been suggested that the absence of major molecular driver mutations that characterize PDACs might account for the much better clinical behavior of IOPNs,81,83,86

**PANCREATIC INTRADUCTAL TUBULOPAPILLARY NEOPLASM**

IOPN of the pancreas is a predominantly tubule-forming, intraductal epithelial neoplasm of ductal-type with high-grade dysplasia.94 There is minimal apparent mucin production by these neoplasms.94 Originally described by Tajiri et al95 in 2004 as “intraductal tubular carcinoma” and renamed as *intraductal tubulopapillary neoplasm* by Yamaguchi et al96 in 2009, ITPN was included in the recent 2 WHO classifications as a distinct entity.1,82 Recent reports have clarified the clinical course, immunophenotype, and molecular features of ITPNs.

**Clinical Features**

ITPNs are rare neoplasms and account for 3% of intraductal neoplasms of the pancreas.96 Mean age at the time of diagnosis is 55 years (range, 25–79), and they are slightly more common in females. The most common presentation is chronic pancreatitis-related symptoms such as vague abdominal pain, vomiting, weight loss, steatorrhea, and diabetes mellitus.94 Almost half of ITPNs are located in the head of the pancreas and about 30% of ITPNs involve the gland diffusely.94

**Pathologic Features and Differential Diagnosis**

Grossly, ITPNs average 4.5 cm (range, 0.5–15 cm).94 ITPNs form solid or cystic masses and cause dilatation of pancreatic ducts; however, the intraductal nature of these tumors can be difficult to demonstrate in some cases (Figure 15).96–99 They are generally fleshy on gross examination.94 Multifocality has been reported.100 Microscopically, ITPNs form circumscribed nodules composed of back-to-back tubular glands, which gives the tumor a cribriform appearance (Figure 16).94–96 ITPNs, especially when solid, obstruct the ductal lumen; thus, the surrounding stroma is generally fibrotic. When the neoplastic epithelium shows continuity with nonneoplastic ductal epithelium, there is solid evidence for the intraductal location of these tumors, although in many regions the neoplastic epithelium completely fills the dilated ducts, mimicking an invasive, solid neoplasm.96 Rarely, papillae can be seen, but they are usually only focal when present (Figure 17).96 ITPNs are architecturally complex and therefore are considered to have high-grade dysplasia. The tumor cells are predominantly cuboidal or sometimes columnar, with a modest amount of eosinophilic or amphophilic cytoplasm. Nuclei are generally small and uniform, round to oval, with some atypical forms. Mitotic figures are readily identifiable and intraluminal secretions can be seen; however, intracellular mucin is not present. Foci of necrosis, generally with a comedo-like pattern within the intraductal tumor nodules, are encountered in more than half of the cases. Some rare changes such as clear cell change (Figure 18), or cartilaginous or osseous metaplasia, have been reported.94,101,102

ITPN-associated invasive carcinoma occurs in about 70% of cases. The invasive component is generally limited in extent; however, the invasive component predominates in 10% of cases.94,96,99 The diagnosis of an associated carcinoma component can be highly challenging because many of...
Figure 16. Intraductal tubulopapillary neoplasm. The tumor is characterized by nodules composed of back-to-back tubular glands, resulting in a cribriform appearance. The tumor cells are cuboidal with a modest amount of cytoplasm and reveal frequent mitotic activity (inset) (hematoxylin-eosin, original magnifications ×10 and ×400 [inset]).

Figure 17. Intraductal tubulopapillary neoplasm. Although a tubular growth pattern is predominant, rare cases may reveal focal papillae formations (hematoxylin-eosin, original magnification ×20).

Figure 18. Intraductal tubulopapillary neoplasm. Clear cell change (hematoxylin-eosin, original magnification ×200).

Figure 19. Intraductal tubulopapillary neoplasm associated with invasive carcinoma. Since most of the tumor nodules lack a peripheral rim of native ductal epithelium, recognizing an invasive component may be difficult. Individual malignant cells or small, angulated glands extending away from the tumor nodules into desmoplastic stroma represent invasion (hematoxylin-eosin, original magnification ×100).

Figure 20. Intraductal papillary neoplasm of bile ducts. A papillary, friable tumor within dilated intrahepatic bile ducts.

Figure 21. Intraductal papillary neoplasm of bile ducts. Most cases reveal a predominantly papillary growth pattern (hematoxylin-eosin, original magnification ×10).
the tumor nodules lack a peripheral rim of native ductal epithelium (Figures 16 and 19). When an unequivocal diagnosis of associated invasive carcinoma is established, determination of the extent remains as another diagnostic challenge. Invasive carcinoma is characterized by individual malignant cells or small, angulated nonmucinous glands, extending away from the tumoral nodules into desmoplastic stroma (Figure 19).

### Immunohistochemical and Molecular Features

Immunohistochemically, ITPNs express CK7 and CK19 in most cases (89%). Most ITPNs are also immunoreactive for CA19.9, a marker of ductal origin. The MUC expression profile of ITPN is distinctive, with labeling for MUC1 and MUC6 in 88% and 68% of cases, respectively. MUC2 staining, mainly seen in intestinal-type IPMNs, and MUC5AC staining, seen in all other intraductal tumors of the pancreas, are consistently absent in ITPNs. The pancreatic enzyme and neuroendocrine markers also display negativity. When overlapping features of pancreatobiliary-type IPMN are present and a differential diagnosis between IPNBs constitute a significantly higher proportion of bile ducts in Asian populations (10%–38%) than in North American and European countries (7%–12%). Controversy on the most frequent localization also remains. Intrahepatic bile ducts have been found to be the most frequent site (80%) in some studies, whereas others reported the most prevalent localization as extrhepatic bile ducts (70%). Multicentricity is well documented in IPNBs, and tumors can involve both intrahepatic and extrahepatic bile ducts. Imaging features of IPNB are distinctive and vary according to the location of the tumor and degree of mucin production. Cholangiography generally shows luminal filling defects.

IPNB is slightly more common in males and most frequent in the sixth and seventh decades of life. Recurrent and intermittent abdominal pain and cholangitis-related symptoms are the most frequent clinical presentations.

### Pathologic and Immunohistochemical Features

IPNBs present as a polypoid mass in the bile duct (Figure 20) and lead to fusiform, cylindrical, or cystic dilatation of the affected segment. The median size of involved ducts is 4.1 cm and the tumor size is usually 5 to 20 mm. Occasionally, extensive mucin secretion into the duct lumen can be seen, similar to pancreatic IPMNs, but this appears to occur more frequently in Asian patients.

IPNBs show predominantly papillary structures with delicate fibrovascular cores. Tubular and glandular components may be seen in combination (Figure 21), and some have a markedly complex tubular architecture that can be difficult to recognize as intraductal (versus invasive), based on bile duct biopsies. IPNBs show different degrees of dysplasia and, like their pancreatic counterparts, they are graded in a 2-tiered scheme; high grade is used for the most dysplastic third of the spectrum. They also have similar cell lineages as pancreatic intraductal neoplasms and exhibit intestinal, gastric, pancreatobiliary, and oncocytic differentiation (Figure 22, A through D). Often, however, more than 1 pattern is apparent within the individual neoplasm. When 2 or more cell lineages are seen, classification is based on the predominant pattern. The frequency of these patterns shows geographic variation. Intestinal- and gastric-type differentiation are more common in Asian patients, and pancreatobiliary-type is more common in European and North American patients. At the time of diagnosis, 40% to 80% of IPNBs have at least focal invasive carcinoma, and when present, the neoplasm is diagnosed as intraductal papillary neoplasm with associated invasive carcinoma.

The pancreaticobiliary-type accounts for about 70% of IPNBs and shows consistent labeling with MUC1 and CK7. MUC2 and MUC5AC can also be expressed in 23% and 54% of cases; MUC6 positivity is usually not reported. Ten percent of IPNBs are gastric-type and the histomorphologic features resemble the pancreatic counterpart, with a tubular growth pattern, tall columnar epithelium, and scattered goblet cells. Immunohistochemical expression of MUC1, MUC5AC, and MUC6 is frequently seen. When an associated invasive carcinoma is present in either gastric or pancreaticobiliary IPNBs, it is almost always tubular-type.

The intestinal-type is the least common pattern of IPNB, accounting for 5% of cases. Immunohistochemically, MUC2 is frequently expressed, but MUC1 is also commonly detected. Invasive carcinomas arising in association with intestinal-type IPNBs are often colloid-type (Figure 22, D), accounting for the very rare mucinous adenocarcinoma...
primary in the liver. An oncocytic pattern morphologically similar to pancreatic IOPNs can occur in the bile ducts as well and can also be designated IOPN. Cases arising in the intrahepatic bile ducts form large multicystic masses that are difficult to recognize as intraductal. MUC1, MUC2, and MUC6 immunoreactivity is commonly encountered in biliary IOPNs.

When the architecture of the intraductal neoplasm is predominantly tubular and mucin production is absent, it resembles ITPNs of the pancreas and is designated intraductal tubular/tubulopapillary neoplasm of the bile ducts. These neoplasms always express MUC1 and MUC6 and have distinctive molecular features.

Molecular Features

IPNBs follow the stepwise progression from low-grade to high-grade dysplasia and to invasive adenocarcinoma, and this process involves somatic mutations of TP53, inactivation of p16/CDKN2A, and activating mutations of KRAS as early events; loss of SMAD4/DPC4 is a late event in carcinogenesis. Histologic examination of bile ducts in a genetically engineered animal model carrying KRAS and TP53 mutations revealed the presence of preinvasive lesions, further supporting the importance of these genes in the early phases of carcinogenesis.

The specific altered genes and their frequency depends on the histologic subtype of IPNB. All gastric-type intraductal papillary neoplasms harbor an alteration in the Wnt signaling pathway, and the MAPK pathway is involved in 78%. APC and KRAS mutations are more common in the gastric-type than in other histologic subtypes (55.5% versus 44.4%, respectively) (preliminary institutional data). SMAD4, GNAS, and RNF43 mutations are more common in intestinal-type IPNBs, and pancreatobiliary-type harbors frequent alterations in tumor suppressor genes such as TP53 (43%), CDKN2A/B, and ARID2 (36% each).

Natural History, Clinical Management, and Prognosis

When possible, resection is the primary treatment, as these neoplasms commonly harbor high-grade dysplasia and invasive carcinoma. The presence of high-grade dysplasia or associated invasive carcinoma remains the major predictor of prognosis. The prognosis of IPNB-associated cholangiocarcinomas is significantly better than de novo intrahepatic/extrahepatic cholangiocarcinomas, perhaps in part because early obstruction of major bile ducts leads to clinical intervention before the carcinoma becomes deeply invasive. The multifocal nature of IPNBs is well established, and cholangiocarcinomas derived from IPNBs have a recurrence rate as high as 47%. Associated invasive carcinoma is more frequent in gastric

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Figure 22. A, Intraductal papillary neoplasm of bile ducts, intestinal-type. B, Intraductal papillary neoplasm of bile ducts, gastric-type. C, Intraductal papillary neoplasm of bile ducts, pancreatobiliary-type. D, Intraductal papillary neoplasm of bile ducts, oncocytic-type (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B], ×50 [C], and ×100 [D]).

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and pancreaticobiliary types than in intestinal and oncocytic types, but as of yet no established prognostic relevance of the IPN subtypes has been proven. When an invasive component is present, the disease-specific survival strongly correlates with the depth of invasion, and the prognosis is more favorable after complete resection.112

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References


Intraductal papillary mucinous neoplasms of the pancreas have heterogeneous somatic mutations. The GNAS activating mutation is the earliest genetic alteration detected in IPMN, preceding the other detected mutations. This mutation leads to increased production of adenyl cyclase, causing activating GNAS mutations in IPMN to induce a cascade of signaling events. The presence of GNAS mutations in IPMN is associated with a higher risk of malignancy and a worse prognosis. It is also important to note that the pancreas is a highly heterogenous organ, and IPMN can exhibit variable degrees of differentiation, ranging from noninvasive to invasive neoplasms. The presence of stromal invasion, lymphatic permeation, and vascular invasion are important indicators of the aggressive potential of IPMN. The functional implications of these mutations in IPMN pathogenesis may be important for understanding the molecular mechanisms of pancreatic carcinogenesis.

In conclusion, the GNAS activating mutation is a key genetic alteration in the development of IPMN, and its presence is associated with a higher risk of malignancy and a worse prognosis. Further research is needed to better understand the functional implications of these mutations in IPMN pathogenesis and to develop targeted therapies for the treatment of this disease.

References:


