# Intraductal Neoplasms of the Pancreas

# 10

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**Abstract**

Here described are definitions, epidemiology, etiology, clinical features, radiology, pathology, and treatment and prognosis of intraductal neoplasms of the pancreas, namely, intraductal papillary mucinous neoplasms (IPMNs), intraductal oncocytic papillary neoplasms (IOPNs), and intraductal tubulopapillary neoplasms (ITPNs). IPMNs are grossly visible intraductal epithelial neoplasms of mucin-producing cells. IPMNs are fairly common without known etiologic factors. Imaging studies show cystically dilated ducts involving branch ducts, the main duct, or the both of ducts. Microscopically, the neoplastic cells grow in papillae with various atypical degree ranging from low-grade to high-grade. The papillae show various morphologic features with expression of characteristic mucin proteins, which are classified into gastric, intestinal, and pancreatobiliary types. Mutations in *KRAS* and *GNAS* are frequently found. IPMNs often become invasive, which show adenocarcinoma with ductal or mucinous elements. Disease-specific survivals of patients with surgically resected IPMNs are fairly good in low-grade IPMNs, modest in high-grade IPMNs, however, poor in invasive IPMNs. IOPNs show cystically dilated mucinous ducts with arborizing papillae consist of eosinophilic cells. IOPN is a rare tumor with an average age of patients <65 years. Imaging studies of IOPNs show the same feature as those of IPMNs. Pathologically, IOPNs show high-grade atypia occasionally with invasive elements. IOPNs often harbor fusion genes of *ATP1B1-PRKACB, DNAJB1-PRKACA*, and *ATP1B1-PRKACA*. Disease-specific survival rates of patients with surgically resected IOPNs are reported to be 84% for 5-year and 73% for 10-year. ITPNs are intraductal, grossly visible solid neoplasms arising in the MPD or its branches. ITPN is a rare tumor. Imaging studies show characteristic features called the two-tone duct sign and the cork-in-wine bottle sign. Pathologically, ITPNs show packed tubulopaillary glands consist of cuboidal cells with enlarged atypical nuclei and no visible mucin in cytoplasm. ITPNs often harbor mutations in *PIK3CA, KMT2C, KMT2D*, and *BAP*. ITPNs are often with invasion, and such cases show poor prognosis.

## 10.1 Intraductal Papillary Mucinous Neoplasm (IPMN)

### 10.1.1 Definition

IPMN is a grossly visible, intraductal epithelial neoplasm of mucin-producing cells, found in the main pancreatic duct (MPD), or its branches [1, 2]. The neoplastic epithelium is usually papillary, but may include tubular glands, and the extent of mucin secretion, duct dilatation, and dysplasia can vary [3] (Fig. 10.1). Non-invasive IPMNs are classified into two categories, based on the degree of cytoarchitectural atypia: low-grade and high-grade (carcinoma *in situ*) [4]. If there is a component of invasive carcinoma, these are designated as IPMN with associated invasive carcinoma [4].

### 10.1.2 Epidemiology

IPMNs are fairly common, particularly in the elderly. Incidence was reported to be 1.7–2.8% in consecutive CT scans [5, 6]. The incidence doubled among the patients in their sixties, and tripled in the seventies [6].

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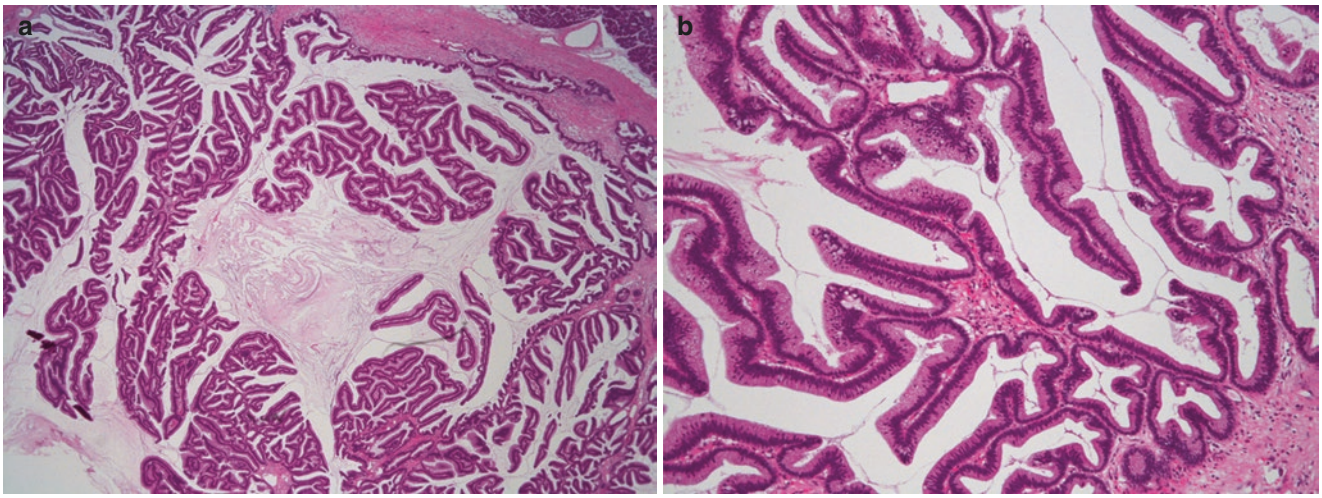


**Fig. 10.1** Histological images of IPMN. (**a**) IPMN shows a cystically dilated duct filled with mucin. Well-formed neoplastic papillae are observed inside the dilated duct. (**b**) The neoplastic papillae are consisted of mucin containing tall columnar cells. Grade of atypia may vary from low-grade to high-grade. Hematoxylin and eosin staining. Original magnifications were × 20 (**a**) and ×100 (**b**)

### 10.1.3 Etiology

No definite etiological environmental factors associated with IPMNs are known. However, patients with Peutz-Jeghers syndrome, familial adenomatous polyposis, and McCune Albright syndrome have a greater risk of IPMNs [7–9]. Individuals with familial predisposition to pancreatic cancer often harbor cystic lesions in their pancreas that are presumably IPMNs [10].

### 10.1.4 Clinical Features

Clinical manifestations of the dilated main duct include epigastric pain, chronic pancreatitis, weight loss, diabetes mellitus, and jaundice [11–15], whereas the dilated branch ducts are often discovered fortuitously during clinical evaluation of some other conditions [16].

### 10.1.5 Radiology

Radiological imaging reveals three distinct types of IPMN, including branch duct-type, main duct-type, and mixed type [16–18]. Branch duct IPMNs show dilated secondary pancreatic ducts of >5 mm size, without the dilatation of the main duct, while the main duct IPMNs show segmental or diffused dilation of the MPD, without any other causes of obstruction. Mixed type IPMNs show the characteristics of both these types of IPMNs [16, 18]. Mural nodules and/or irregular ductal wall thickening can be the sign of high-grade or invasive neoplasms [19, 20].

### 10.1.6 Pathology

#### 10.1.6.1 Macroscopic Appearance

IPMNs show dilated ducts containing mucin. Dilated branch ducts are seen as cysts anywhere in the pancreas. IPMNs involving the main duct can be identified as segmental/fusiform or diffuse/tortuous dilatation of the duct, often accompanied by dilated secondary branch ducts [3], containing mural nodules or polypoid tumors.

#### 10.1.6.2 Microscopic Appearance and Variations

Papillary proliferation of mucin-containing tall columnar cells is a characteristic histopathological feature of IPMNs [1] (Fig. 10.1). Shapes of papillae are diverse, and cellular atypia also vary. According to the shapes of papillae, IPMNs are subdivided into gastric, intestinal, and pancreatobiliary types [21–23]. Gastric-type IPMNs show thick, finger-like papillae, resembling the gastric foveolar cells, or tubular structures of the pyloric glands. Intestinal-type IPMNs show villous papillae mimicking a villous colonic tumor, whereas pancreatobiliary-type show complex, arborizing papillae.

#### 10.1.6.3 Immunohistochemistry

Ductal markers, including cytokeratins 7 and 19, CA19-9, and CEA, are strongly expressed in most of the IPMNs [24, 25]. Mucin glycoproteins MUC1, MUC2, MUC5AC, and MUC6, show subtype-specific expression patterns among IPMNs [21, 26–28]. Gastric-type of IPMNs express MUC5AC and MUC6, while those of the intestinal-type IPMNs contain MUC2 and MUC5AC. Pancretobiliary-type IPMNs express MUC1, MUC5AC, and MUC6 [22, 29].

#### 10.1.6.4 Grading

IPMNs can be low- or high-grade, based on the degree of cytoarchitectural atypia [4]. A high-grade lesion corresponds to carcinoma in situ. Existence of invasive carcinoma with IPMN leads to designation of IPMN with associated invasive carcinoma [4].

#### 10.1.6.5 Differential Diagnosis

Mucinous cystic neoplasm (MCN), oligocystic serous cystic neoplasm (OSC), intraductal tubulopapillary neoplasm (ITPN), lymphoepithelial cyst (LEC), and chronic pancreatitis (CP) with a retention cyst or pseudocyst should be differentially diagnosed from IPMN. MCNs have characteristic ovarian-type stroma in the cyst wall [30]. OSCs are lined by distinct glycogen-rich cuboidal cells [31]. ITPN is a solid intraductal tumor clogging the duct, composed of high-grade cuboidal cells that form tubulopapillae [32]. LECs are lined by keratinized squamous epithelium with lymphoid stroma [33]. When the cysts in CP have flat epithelial lining, they are identified as retention cysts, and when no lining cells are present, they are called pseudocysts [34].

#### 10.1.6.6 Molecular Pathology

Sixty to eighty percent of the IPMNs harbor somatic mutations in *KRAS*, while 50–70% have mutations in *GNAS* [35, 36]. Although *KRAS* mutations are prevalent in the pancreatic ductal adenocarcinomas (PDAC) as well, *GNAS* mutations are rarely found here, which makes them a specific characteristic of IPMN [36–38]. In 14% of the IPMNs, *RNF43* also shows somatic mutations [36, 39, 40]. Overexression of p53, which presumably indicates missense mutations of *TP53*, is found in 10–40% of the high-grade IPMNs and in 40–60% of the associated invasive carcinomas [29, 38, 41, 42]. While loss of SMAD4 is rare [43, 44], nuclear expression of ß-catenin is seen in 18–39% of the IPMNs [38, 45].

#### 10.1.6.7 Treatment and Prognosis

IPMNs with high-grade dysplasia or invasive carcinoma should be surgically resected. According to the international consensus guidelines for management of patients with IPMN [16], surgery is indicated by high-risk stigmata and worrisome features, such as cysts ≥3 cm, enhancing mural nodules <5 mm, thickened enhanced cyst walls, MPD with a size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, lymphadenopathy, elevated serum level of CA19–9, and a rapidly growing cyst at the rate of >5 mm/2 years. High-risk stigmata are usually associated with obstructive jaundice, an enhanced solid component, and MPD with a size ≥10 mm. IPMNs with high-risk stigmata should be resected immediately, while those with worrisome features should be evaluated by endoscopic ultrasound, to further risk-stratify the lesions, whether they have mural nodules or involvement of the MPD. High-grade lesions can be evaluated with cyst fluid or pancreatic juice cytology [16].

Five-year survival rate for patients with surgical resection of the low-grade IPMNs is 100%, and 95–85% with high-grade IPMNs [22, 46, 47]. Survival rate varies between 36–90% when the IPMNs are associated with invasive carcinoma, depending on the stage [22, 46–48]. The morphological subtypes of IPMNs can be a prognostic indicator; 5-year survival rate is 94% for the gastric-type, 90% for the intestinal-type, and 50% for the pancreatobiliary-type [22, 48].

## 10.2 Intraductal Oncocytic Papillary Neoplasms (IOPN)

### 10.2.1 Definition

IOPN is an intraductal neoplasm of eosinophilic epithelial cells that form arborizing papillae [49] (Fig. 10.2). It is categorized as a variant of IPMNs, as it shows a grossly visible intraductal neoplasm with mucin production [21], similar to IPMN. However, a number of studies have reported that IOPNs have distinct molecular features that distinguish them from IPMNs in the current fifth edition of the World Health Organization classification of tumors of the digestive system [50].

### 10.2.2 Epidemiology

IOPNs are fairly infrequent, making up only 4.5–8.4% of the cystic neoplasms of the pancreas [22, 51]. They occur more frequently in men than in women, between 20–80 years of age. With an average age of <65 years, patients with IOPNs are younger than those with IPMNs (> 65 years) [49, 51–53].

### 10.2.3 Etiology

No etiological factor associated with IOPN is known.

### 10.2.4 Clinical Features

Clinical manifestations of IOPN are the same as those of IPMNs, including abdominal pain, weight loss, diabetes mellitus, and jaundice [49, 51].

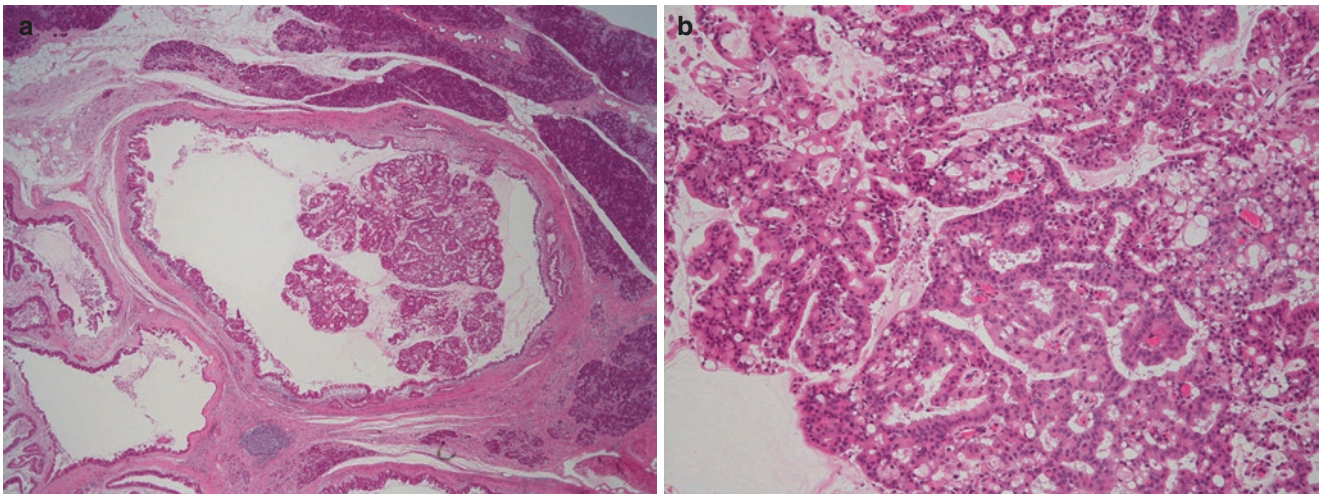


**Fig. 10.2** Histological images of IOPN. (**a**) IOPN shows mucinous dilated ducts. Arborising papillae are seen inside them. (**b**) The neoplastic papillae of IOPN consist of eosinophilic cells with enlarged nuclei and prominent nucleoli, which show high-grade atypia. Intraepithelial lumina are often seen in the cells. Hematoxylin and eosin staining. Original magnifications were × 20 (**a**) and ×100 (**b**)

### 10.2.5 Radiology

Like IPMNs, IOPNs show cystic dilatation of the pancreatic duct, and can be of branch duct type, main duct type, and mixed type. Mural nodules are often seen inside the dilated duct [53].

### 10.2.6 Pathology

#### 10.2.6.1 Macroscopic Appearance

IOPNs show cystic dilation of ducts filled with mucin [49, 53], which is indistinguishable from IPMNs, and may involve branch ducts or the main duct. Polypoid tortuous tumors are often seen inside them.

#### 10.2.6.2 Microscopic Appearance

In IOPNs, the dilated ducts are lined by arborizing papillae, consisting of eosinophilic cells with enlarged nuclei and prominent nucleoli [21, 49], and show high-grade atypia. Intraepithelial lumina are often seen in the neoplastic papillae (Fig. 10.2). Occasionally, the neoplasm invades the parenchymal stroma, resulting in a diagnosis of IOPN with associated invasive carcinoma. The invading mass usually shows clusters of eosinophilic cells in the mucin pools [54].

#### 10.2.6.3 Immunohistochemistry

Neoplastic cells frequently express HepPar1 and mesothelin [54]. The expression of mucin proteins MUC5AC and MUC6 are consistently positive, while MUC1 and MUC2 are infrequently and focally positive [21, 54].

#### 10.2.6.4 Differential Diagnosis

IOPN should be distinguished from cystic neoplasms, including IPMN, mucinous cystic neoplasm, oligocystic serous cystic neoplasm, lymphoepithelial cyst, and solid pseudopapillary neoplasm.

#### 10.2.6.5 Molecular Pathology

IOPNs infrequently show somatic mutations in *KRAS* and *GNAS* unlike IPMNs [36, 40]. Instead, they carry fusion genes of *ATP1B1-PRKACB, DNAJB1-PRKACA*, and *ATP1B1-PRKACA* [55, 56]. Interestingly, these fusion genes upregulate the protein kinase A pathway, which is the main target of *GNAS* that shows frequent gain-of-function mutations in IPMNs, indicating that both IOPNs and IPMNs, are driven by activation of the protein kinase A pathway. Aberrant expression of p53 or SMAD4 is observed in up to 10% of IOPNs [52], and about 30% of these show nuclear accumulation of ß-catenin [48],whereas *RNF43* mutations are not reported [40, 57]. A patient with a germline *SMAD4* mutation was reported to have developed IOPN [58].

#### 10.2.6.6 Treatment and Prognosis

IOPN should be surgically resected. Disease-specific survival rates of patients with surgically resected IOPNs are reported to be 84% for 5-year and 73% for 10-year [22].

## 10.3 Intraductal Tubulopapillary Neoplasms (ITPN)

### 10.3.1 Definition

ITPN is an intraductal, grossly visible solid neoplasm arising in the MPD or its branches [32]. Cystic lesions are infrequent and are only focally and peripherally observed. The neoplastic epithelium has the mixture of tubular and papillary configurations, and the neoplastic cells show uniformly high-grade atypia [32] (Fig. 10.3). The neoplasm is often

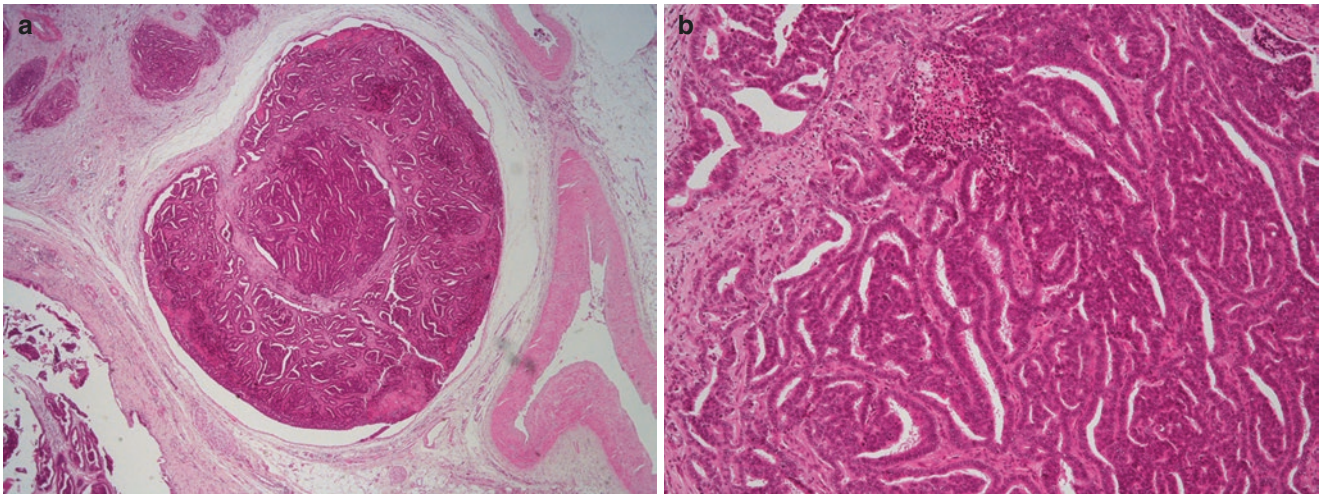


**Fig. 10.3** Histological images of ITPN. (**a**) ITPNs show a solid tumor clogged in dilated pancreatic ducts, without visible mucin. Cystic ducts are occasionally seen in the periphery of a neoplasm-obstructed duct. (**b**) ITPN consist of cuboidal to columnar cells with enlarged nuclei, with little cytoplasmic mucin, exhibiting solid tubulopapillary growth. Necrotic foci are often seen. Hematoxylin and eosin staining. Original magnifications were ×20 (**a**) and ×100 (**b**)

invasive, and is designated as intraductal tubulopapillary neoplasm with associated invasive carcinoma.

### 10.3.2 Epidemiology

ITPN is rare, barely accounting for 0.9% of the exocrine neoplasms and 3% of the intraductal neoplasms of the pancreas [32].

### 10.3.3 Etiology

No definite etiological factors of ITPNs are known.

### 10.3.4 Clinical Features

Clinical manifestations include abdominal pain, nausea, vomiting, jaundice, weight loss, and exacerbation of diabetes mellitus [32, 59]. Some patients have a history of acute pancreatitis [32].

### 10.3.5 Radiology

In CT scan, patients with ITPN show a solid enhanced mass, packed in a dilated duct. Magnetic resonance cholangiopancreatography indicates a filling defect in a dilated duct or an abrupt disruption of the dilated duct. Images of the dilated duct packed with tumor, are known as the two-tone duct sign and the cork-in-wine bottle sign [60]. ITPNs that involve the MPD show a sausage-like image in magnetic resonance imaging [61].

### 10.3.6 Pathology

#### 10.3.6.1 Macroscopic Appearance

ITPNs show a solid tumor packed in dilated pancreatic ducts, without visible mucin. Cystic ducts are occasionally seen in the periphery of a neoplasm-obstructed duct [32, 59].

#### 10.3.6.2 Microscopic Appearance and Variations

Cuboidal to columnar cells with enlarged nuclei, with little cytoplasmic mucin, exhibit solid tubulopapillary growth [32, 59]. Some may consist of tubular glands. The neoplastic cells show uniformly high-grade atypia (Fig. 10.3). Intraductal comedo-like necrosis is often present. Stromal invasion can be seen in the periductal parenchyma, which shows clusters of tubulopapillary glands. Tumor emboli are occasionally evident in the veins [32].

#### 10.3.6.3 Immunohistochemistry

Cytokeratin (CK) 7 and CK19 are consistently positive. Mucin glycoproteins, MUC1 and MUC6 are positive, while MUC2 and MUC5AC are negative [32, 59]. Trypsin, an acinar marker, is negative.

#### 10.3.6.4 Differential Diagnosis

A solid intraductal neoplasm can be observed in the intraductal variant of acinar cell carcinoma and intraductal neuroendocrine tumors [62, 63]. Histologically, neuroendocrine

tumors can be easily differentiated; however, the intraductal variant of acinar cell carcinoma may show solid tubular growth with necrosis, mimicking ITPNs. Acinar cell carcinomas usually express trypsin, an immunohistochemical marker of differentiation [32]. IPMNs occasionally show solid nodules inside the dilated duct. IPMN of the pyloric gland variant may particularly show a polypoid tumor in a dilated duct, mainly consisting of tubular glands. However, it can be distinguished from ITPNs by its well-formed tubular glands with low-grade atypia and the expression pattern of mucin which is negative for MUC1 and positive for MUC5AC [64].

#### 10.3.6.5 Molecular Pathology

ITPNs often show somatic mutations in *PIK3CA, KMT2C, KMT2D*, and *BAP1* [65, 66]. Some tumors also harbor *FGFR2* fusion genes [66]. *KRAS* or *GNAS* mutations that are common in IPMNs, are not seen in ITPNs. Aberrant expression of p16 and p53 is reported in up to 70% of the cases [59], while the atypical expression of SMAD4 is rare [32, 59].

### 10.3.7 Treatment and Prognosis

Surgery is the treatment of choice for patients with ITPN, but some of them may experience a recurrence in the remnant tissue after pancreatectomy [32, 59]. ITPNs diffusely involving the pancreatic duct, need total pancreatectomy [32, 59, 67]. Efficacy of the adjuvant therapy is not known. About 10% of the patients with ITPN die of the disease [32, 59], and all of them are reported to have invasive tumors.

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