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Review Article

Comprehensive Characterization of Intraductal Oncocytic Papillary Neoplasm of the Pancreas: A Systematic and Critical Review

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ABSTRACT

Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is a recently recognized pancreatic tumor. Here, we aimed to determine its most essential features with the systematic review tool. PubMed, Scopus, and Embase were searched for studies reporting data on pancreatic IOPN. The clinicopathologic, immunohistochemical, and molecular data were extracted and summarized. Then, a comparative analysis of the molecular alterations of IOPN with those of pancreatic ductal adenocarcinoma and intraductal papillary mucinous neoplasm from reference cohorts (including The Cancer Genome Atlas) was conducted. The key findings from 414 IOPNs were as follows: 1) The male-to-female ratio was 1.5:1. Pancreatic head was the most common site (131/237; 55.3%), but a diffuse tumor extension involving more than one pancreatic segment was described in about 1 out of 5 cases (49/237; 20.6%). The mean size was 45.5 mm. An associated invasive carcinoma was present in 50% of cases (168/336). In those cases, most tumors were pT1 or pT2 and pN0 (>80%), and vascular invasion was uncommon (20.6%). Regarding survival, more than 90% of patients were alive after surgical resection. 2) Immunohistochemical and molecular features were as follows. The most commonly expressed mucins were MUC5AC (110/112; 98.2%) and MUC6 (78/84; 92.8%). Compared with pancreatic ductal adenocarcinoma and intraductal papillary mucinous neoplasm, the classic pancreatic drivers *KRAS*, *TP53*, *CDKN2A*, *SMAD4*, and *GNAS* were less altered in IOPN ($P < .01$). Moreover, fusions involving *PRKACA* or *PRKACB* gene were detected in all of the 68 cases examined, with *PRKACB::ATP1B1* being the most common (27/68 cases; 39.7%). These genomic events emerged

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as an entity-defining molecular alteration of IOPN ($P < .01$). Thus, such fusions represent a promising biomarker for diagnostic purposes. Recent evidence also suggests their role in influencing the acquisition of oncocytic morphology. IOPN is a distinct pancreatic neoplasm with specific clinicopathologic and molecular features. Considering the clinical or prognostic implications, its recognition is essential for pathologists and, ultimately, patients' management

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Introduction

Intraductal oncocytic papillary neoplasm (IOPN) was initially defined in 1996[1] as a distinct tumor type in the pancreas, characterized by cyst-forming epithelial neoplasm composed of oncocytic cells with a complex architecture and branching papillae growing within the pancreatic ductal tree.[1,2] For a while, this tumor type was regarded as a subset of intraductal papillary mucinous neoplasms (IPMNs).[3] Later, its distinctive clinical, pathologic, and molecular features that distinguish them from the regular IPMNs began to be appreciated[4-13] and, in the current (2019) World Health Organization (WHO) classification, is now listed as a separate category from the other pancreatic intraductal neoplasms, including IPMNs and intraductal tubulopapillary neoplasms (ITPNs).[1,14-18] However, because they have mainly been analyzed together with other tumor types, the salient characteristics of IOPNs are not fully appreciated.

Given the growing and composite body of literature regarding this topic and its complexity, we aim to provide a comprehensive and quantitative summary of pancreatic IOPNs through the systematic review tool. We also present the most challenging issues regarding this tumor entity, discussing pearls and pitfalls in histology and immunohistochemistry (IHC) and highlighting molecular peculiarities with potential practical implications for clinical practice.

Materials and Methods

This systematic review complied with the Meta-analysis of Observational Studies in Epidemiology guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[19,20] without language restrictions (Supplementary Table S1).

Inclusion and Exclusion Criteria

Criteria for eligibility were as follows: (1) original study on human IOPN; (2) documented pancreatic origin of the lesion; (3) presence of histologic demonstration of IOPN; and (4) publication in a peer-reviewed journal. Exclusion criteria were as follows: (1) preclinical or mouse models of IOPN; (2) nonpancreatic (eg, biliary) origin of the lesion; and (3) published abstract with preliminary data only. Cases that met the WHO diagnostic criteria for IOPN[1] but were described before its recognition as a separate entity were also included in this review.

Data Sources and Literature Search Strategy

A literature search was carried out up to October 27, 2023. Two investigators (G.P. and C.L.) independently searched PubMed, Scopus, and Embase using the following keywords: ("intraductal" OR "intra-ductal" OR "ductal" OR "duct" OR "ducts" OR "Wirsung"), ("oncocytic" OR "oxyphilic" OR "oxyphile"), and ("pancrea*"). Reference lists of all retrieved articles and previous reviews were also considered. The one comprising the most cases and related data was included in the case of doubled cohorts.

Whenever available, the following data were extracted from each included article: authors, country of origin of the analyzed cohort, number of patients, age and sex of patients, primary symptoms, main radiologic findings, involved pancreatic region, tumor size, type of ductal involvement, presence of an associated invasive cancer, size of the invasive component, pTNM, presence of lymphovascular and perineural invasion, resection marginal status, and survival outcomes. Information about the IHC expression of mucins (MUCs) commonly used in routine diagnostic practice, such as MUC1, MUC2, MUC5AC, and MUC6, as well as information regarding the genomic alterations of IOPNs, was analyzed and summarized in different tables.

Fisher exact test and/or χ^2 test were used to assess for any specific difference in the molecular landscape of IOPN vs conventional pancreatic ductal adenocarcinoma (PDAC) and IPMN. This method was utilized to juxtapose the findings of IOPN with data from, which we used as a reference cohort.[21]

Results

The literature search identified a total of 206 articles. After applying our inclusion criteria, 74 articles were included in our systematic review[1,4-12,22-85] (Supplementary Fig. S1), in which the following findings were elucidated.

Definition of Intraductal Oncocytic Papillary Neoplasm

Although initially described as a distinct tumor type in 1996,[1] before its true nature was appreciated with confirmatory studies, IOPN was for a while regarded as a "variant" or "subset" of IPMN in the 2010 WHO classification.[3] However, as more studies focusing on this tumor type were published,[4-13] the distinguishing characteristics of this entity were elucidated. As a result, IOPN is now recognized as a separate category by histopathology, molecular profile, and behavior (see the section below), within this family with a designated International Classification of Diseases for Oncology code of 8455/2.[2]

Clinical Features

The most critical clinicopathologic features are summarized in the Table (details in Supplementary Table S2). The entire cohort was composed of 409 patients. The total number of lesions was 414 as 5 patients experienced a local or pancreatic relapse, developing a secondary IOPN. Sex information was

Table
A table summarizing the most important clinicopathologic parameters of pancreatic IOPN

No.C/No.L	Sex	Mean age at diagnosis	Site in the pancreas	Associated cancer	Mean tumor size	pT[b]	pN[b]	Vascular invasion[b]	Perineural invasion[b]	Involved duct(s)	Symptoms	Main radiological findings
409/ 414[a]	M: 59.9%; F: 40.1%	58.2 y (24-86 y)	H: 55.3%; B: 10.1%; T: 13.1%; ML: 21.5%	Yes: 50%; No: 50%	5.5 mm (2-240 mm)	T1: 67.5%; T2: 15%; T3: 17.5%; T4: 0%	N0: 81.8%; N1: 13.6%; N2: 4.5%	Yes: 20.7%; No: 79.3%	Yes: 6.9%; No: 93.1%	Ma: 38.2%; BR: 38.2 %; MX: 23.6%	NS (34.2%); AP (29.1%); PT (13.9%); others (22.8%)	C: 63.2%; S: 18.4%; SC: 13.2%; DD: 5.2%

AP, abdominal pain; B, body; BR, branch duct; C, radiologic cystic appearance; DD, duct dilation; F, female; H, head; IOPN, intraductal oncocytic papillary neoplasm; M, male; Ma, main duct; ML, involvement of multiple pancreatic regions; MX, mixed; No.C, total number of cases; No.L, total number of lesions; NS, no symptoms; pN, pathologic nodal stage; pT, pathologic tumor stage; PT, pancreatitis; S, radiologic solid or mass-forming lesion; SC, radiologic mixed cystic-solid appearance; T, tail.

Notes:

[a] In 5 patients, data for local disease recurrence have also been reported; thus, the overall number of patients is 409, whereas the overall number of described pancreatic IOPN is 414.

[b] Data regarding IOPN with associated cancers and available information on pT (n = 40), pN (n = 44), vascular (n = 29), and perineural (n = 29) invasion.

available for 317 patients and showed a slight predominance in male (190/317; 59.9%) vs female (127/317; 40.1%) patients. The mean age at diagnosis was 58.2 years ($\sigma = 8.80$; range, 24-86 years). Regarding general symptoms, a significant percentage of cases were diagnosed in asymptomatic patients, often during follow-up for other reasons (27/79; 34.2%). The most common symptom was abdominal pain (23/79; 29.1%), followed by pancreatitis (11/79; 13.9%).

Tumor location within the pancreatic gland was specified in 237 cases and showed the pancreatic head as the most common site (131/237; 55.3%), followed by the tail (33/237; 13.9%) and body (24/237; 10.1%).

Preoperative Diagnosis and Management

Regarding imaging presentation, there was a predominance of cystic appearance (24/38; 63.2%), followed by solid (7/38; 18.4%) and solid/cystic (5/38; 13.2%) lesions. Owing to the complexity of the lesions, the cases were most commonly diagnosed as "cystadenocarcinoma." Duct dilation alone was explicitly reported in 2 cases (5.2%). It was emphasized in many studies that although it is in the category of intraductal neoplasms (and the term "intraductal" is in its name), the intraductal nature of IOPNs was not always clear radiologically and/or grossly. A highly illustrative representation of IOPN is provided in Figure 1, which shows its typical radiological and macroscopic features.

The modality of involvement of the pancreatic ductal tree was reported in 191 cases. Main duct vs branch duct involvement was equally distributed (73/191 each; 38.2%), with the remaining cases classified as mixed-type IOPN, with the involvement of both the main and branch ducts (45/191; 23.6%).

The "watchful waiting" approach per the Sendai/Fukuoka criteria[86] did not seem to be considered, presumably because all IOPNs (almost by definition) had florid papillary nodules.

Pathologic Features

The most typical histologic features of pancreatic IOPN are summarized in Figure 2A-G. Data regarding the whole tumor size were available for 289 cases, with a mean size of 45.5 mm (range, 2-240 mm). Large tumor extension was also common (49/237; 20.6%), with synchronous involvement of the body and tail (40/237; 16.8%), head and body (6/237; 2.5%), and even the entire gland (3/237; 1.3%).

The grade of the lesion was mentioned in 290 cases and was scored as high grade (high-grade dysplasia [HGD]) in 280 (96.6%) cases, and as low or moderate grade in the remaining 10 (3%-4%) cases. In studies focusing specifically on this entity, all cases were by default regarded as high grade (in situ carcinoma [CIS]) because they all showed substantial cytoarchitectural complexity by definition.

The presence or absence of an invasive carcinoma component was specified in 336 cases; an invasive carcinoma was present in 168 (50.0%) cases. However, in the studies that specifically focused on this entity, the frequency of invasion was far less.[1,87] These studies discussed this issue and attributed the high frequency in other reports to the fact that IOPNs are highly complex lesions (the commonness of the extensive pagetoid spread to atrophic lobules leads to highly deceptive pseudoinfiltrative patterns). Along with this impression, the specific size of the invasive component was reported in only 6 cases, and its mean value was 14 mm (range, 0.5-30 mm).

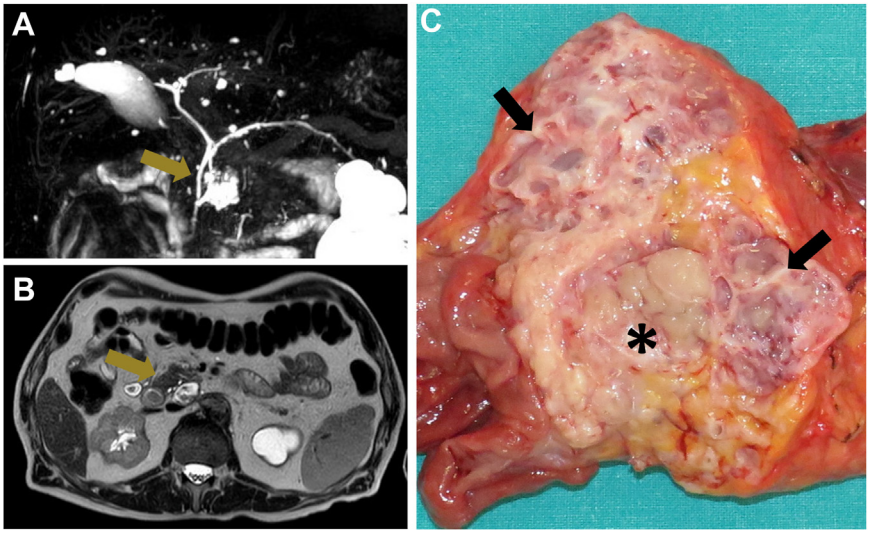


Figure 1.
Typical radiologic and macroscopic presentation of an intraductal oncocytic papillary neoplasm of the pancreas. (A) Cholangiopancreatography magnetic resonance imaging and (B) T2 magnetic resonance imaging of a pancreatic intraductal oncocytic papillary neoplasm, showing a solid or cystic lesion (yellow arrow) in the pancreatic head, involving the uncinate process. (C) A macroscopic photograph of the solid or cystic lesion in the pancreatic head (asterisk: solid component; arrows: cystic components).

In 40 cases, pT staging was provided (pT1: 27/40 [67.5%]; pT2: 6/40 [15.0%]; pT3: 7/40 [17.5%]; and pT4: 0/40 [0%]). However, in most studies, this seemed to have been based on the overall size of the tumor (including the preinvasive component), and many of the reports used the 7th edition of the American Joint Committee on Cancer/Union for International Cancer Control. Considering that the size of invasive carcinoma was reported in only 6 cases (and the mean size was 14 mm), the pT-stage distribution may vastly differ from the current size-based 8th edition of the American Joint Committee on Cancer or Union for International Cancer Control.

In lesions with a reported invasive component, vascular invasion was evaluated in 29 cases and present in 6 (6/29; 20.6%) cases; perineural infiltration was also assessed in 29 cases and present in 2 (2/29; 6.9%) cases. The surgical margin status was reported in 63 cases, with R0 representing the most common situation (50/63; 79.4%). However, in most cases, whether the margin status referred to the preinvasive or invasive component of the tumor was not specified. Metastasis status was not documented in most cases, likely because many were negative and were not considered true "cancers." The lymph node status reported in 44 cases was as follows: pN0: 36 (81.8%) of 44; pN1: 6 (13.6%) of 44; and pN2: 2 (4.5%) of 44; and distant metastases reported in 29 cases were as follows: M0: 25 (86.2%) of 29 and M1: 4 (13.8%) of 29.

Specific data on survival, along with its duration, were reported for 42 patients, of which 29 were with an associated invasive carcinoma. Excluding 6 patients who died because of surgery-related problems (n = 3) or other causes (n = 3), the majority were alive and free of disease after surgical resection (23/36; 63.9%). Ten patients were alive with disease (10/36; 27.8%), and only 3 died of disease (3/36; 8.3%). It must be noted that many patients (n = 138) reported in the literature have been generally described as alive—not otherwise specified, or alive and free of disease, but without reporting the duration of follow-up. Thus, only a very small percentage of mortality was attributed to this tumor type, with more than 90% of patients recorded to be alive—not otherwise specified or alive and free of disease after surgical resection. However, specific data on the duration of the follow-up are mainly lacking.

Immunohistochemical Features

The IHC data are summarized in Supplementary Table S3. Among the IHC expression of MUCs commonly used in the differential diagnoses of pancreatic lesions, the most expressed were MUC5AC (110/112; 98.2%) and MUC6 (78/84; 92.8%), followed by MUC1 (80/132; 60.6%) and MUC2 (73/133; 54.8%). Of note, MUC1 expression was almost always (89.2%) referred to as "focal," and MUC2 expression, when specified, was restricted to the goblet cell component. Along those lines, in the studies explicitly focusing on the IHC profile of IOPNs, most examples tested for MUC6 were positive, and only <30% were labeled with MUC2, which was very focal. Classical staining patterns of the 3 positive MUCs in IOPN, such as MUC1, MUC2, and MUC6, are represented in Figure 2H-J.

Molecular Profile

Molecular alterations have been analyzed in 95 pancreatic IOPN cases and summarized in Supplementary Table S4. Regarding the most common PDAC or IPMN driver genes, *KRAS* was the only one with a relevant variation prevalence, mutated in 20 out of 95 (21.1%) cases. The other genes were either not mutated or rarely (<5% of all cases) altered (*TP53*: mutated in 2 cases; *SMAD4*: no alteration; *CDKN2A*: loss of heterozygosity in 1 case; and *GNAS*: mutated in 4 cases). Of note, 68 cases were also investigated for fusion gene detection. All the 68 cases tested harbored a gene fusion, which always involved the *PRKACA* or *PRKACB* gene. The most common fusion was *PRKACB::ATP1B1* (27/68 cases; 39.7%) (Fig. 3), followed by *PRKACA*::*ATP1B1* (21/68; 30.9%) and *PRKACA*::*DNAJB1* (20/68; 29.4%).

The evaluation of the specificity of the molecular changes in IOPN, in juxtaposition with the typical molecular profile of conventional PDAC/IPMN using data from The Cancer Genome Atlas cohort, showed statistically significant differences regarding the prevalence of alterations of classic PDAC or IPMN drivers. Indeed, IOPN showed a reduced prevalence of alterations involving *KRAS*, *TP53*, *SMAD4*, *CDKN2A*, and *GNAS* ($P < .01$). At the same time,

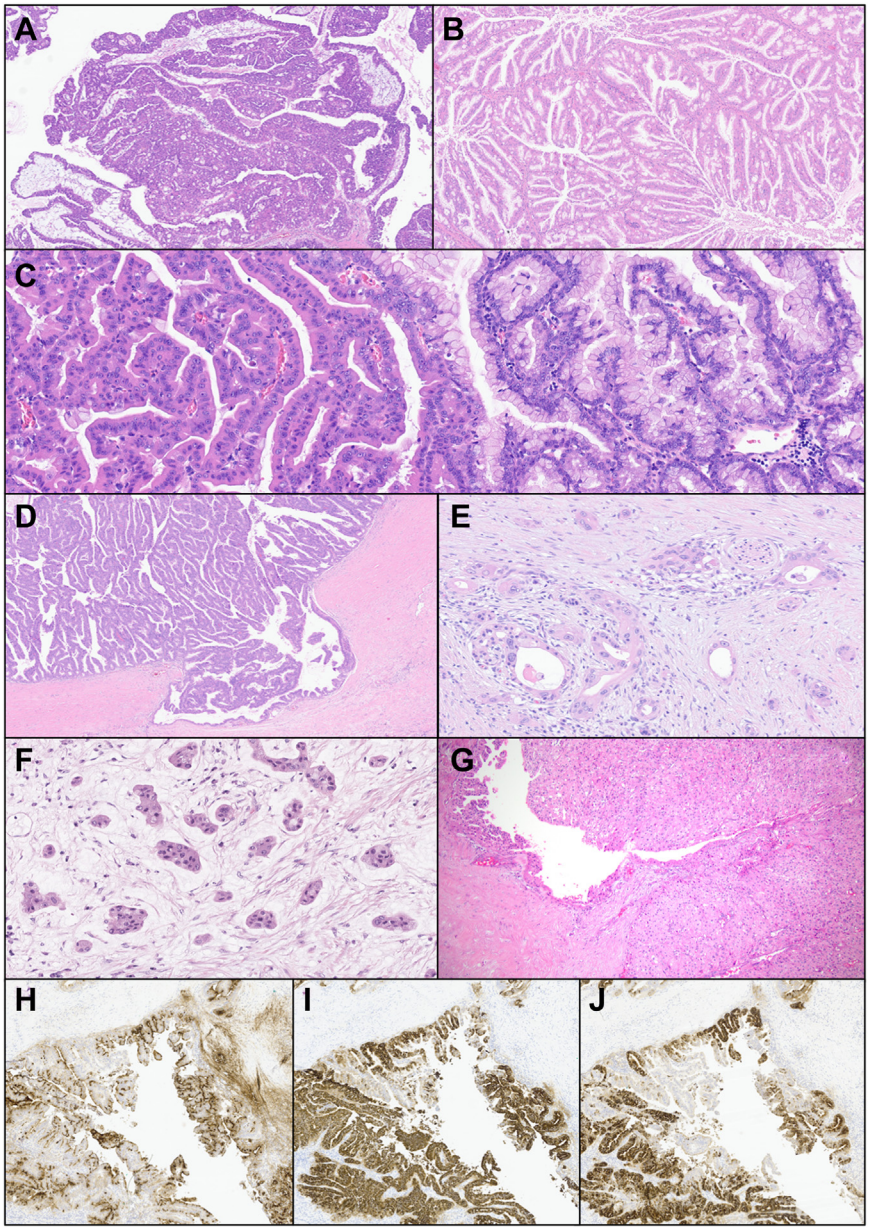


Figure 2.
A highly representative image of the most typical histologic and immunohistochemical features of pancreatic intraductal oncocytic papillary neoplasm (IOPN). (A, B) Architectural complexity and mass-forming capacity (hematoxylin and eosin stain; original magnification: A, ×4 and B, ×10). (C) Pancreatic IOPN can show intratumor heterogeneity, with the coexistence of oncocytic epithelium (left) with another epithelium (right, in this case, gastric epithelium) within the same lesion, and even in the same papilla, as in this case (hematoxylin and eosin stain; original magnification, ×40). (D) A classic example of pseudoinvasion. This histologic feature is frequently seen in pancreatic IOPN and represents a diagnostic challenge (hematoxylin and eosin stain; original magnification, ×10). (E-G) Infiltrating carcinoma originating from pancreatic IOPN can be represented by tubular adenocarcinoma (E; hematoxylin and eosin stain; original magnification, ×20), colloid carcinoma (F; original magnification, ×20), or carcinoma with solid nests (G; original magnification, ×4). (H-J) The expression patterns of the most commonly expressed mucins by pancreatic IOPN: MUC1 (H; original magnification, ×10), MUC5AC (I; original magnification, ×10), and MUC6 (J; original magnification, ×10).

fusions involving *PRKACA* or *PRKACB* were consistently associated with IOPN, emerging as an entity-defining genomic alteration of this type of neoplasm ($P < .01$). Furthermore, 1 study presenting data based on RNA sequencing revealed whole transcriptomic signatures for IOPN that were characterized by differentially expressed genes involved within the protein kinase A/epidermal growth factor receptor/extracellular signal-regulated kinase signaling pathways.[10] They were unique to IOPN as compared with IPMN.[10,15]

Discussion

In this study, we present a systematic review of the clinicopathologic, IHC, and molecular features of pancreatic IOPN. We also provided statistical analysis to highlight the specific molecular alteration of this entity. The core findings of this study underscore the unique features of IOPN among the intraductal neoplasms of the pancreas. The key areas are represented based on the following criteria: (1) definition and identity, (2)

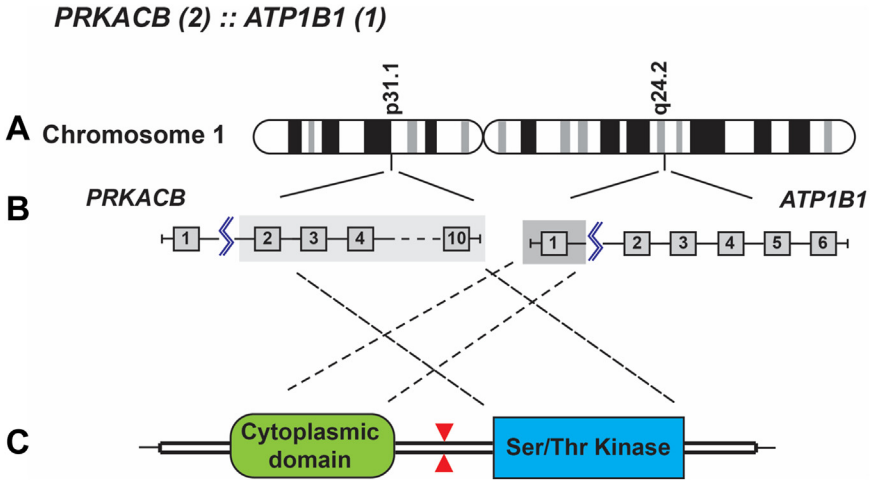


Figure 3.
Schematic representation of the *PRKACB* (2)::*ATP1B1* (1) gene fusion on chromosome 1. This is the most common fusion gene in pancreatic intraductal oncocytic papillary neoplasms. (A) *PRKACB* and *ATP1B1* genes are located on chromosome 1 at 1p31.1 and 1q24.2, respectively. (B) The *PRKACB* gene contains 10 exons with the kinase domain mapping from 2 to 10 exons. The *ATP1B1* gene contains 6 exons, of which exon 1 encodes for the cytoplasmic domain. Exons 2 to 10 of the *PRKACB* gene are fused with exon 1 of the *ATP1B1* gene to create the *PRKACB* (2)::*ATP1B1* (1) gene fusion. (C) The fusion protein consists of the cytoplasmic domain of the *ATP1B1* gene and the serine or threonine kinase domain of the *PRKACB* gene. p, short arm of the chromosome; q, long arm of the chromosome.

clinicopathologic features, and (3) IHC features and molecular profile, which are as follows.

Identity of Intraductal Oncocytic Papillary Neoplasm and Historic Evolution of the Entity

IOPN was first described and defined in 1996,[1] and its salient characteristics were put forth in the same study in an analysis of 11 cases. Until the observations in this original study were confirmed in other works that focused explicitly on this tumor type,[4-12,87] these cases were classified as a subtype of IPMN by the WHO.[3]

Conceptually and phylogenetically, IOPN belongs to the family of "tumoral intraepithelial neoplasms"[14,15,88] along with IPMNs (pancreas),[2,3,14,15] intraductal papillary neoplasms (bile ducts),[89] ITPNs (pancreas and bile ducts),[17,90-94] intraampullary papillary-tubular neoplasms (ampulla),[95] intracholecystic papillary-tubular neoplasms (gallbladder),[96] and intracholecystic tubular nonmucinous neoplasms (gallbladder).[97] These are fundamentally mass-forming, preinvasive dysplastic lesions that present clinically and can develop into invasive carcinoma. Later, the distinct clinical, pathologic, and behavioral characteristics of this tumor type discussed below were appreciated, and this entity began to be regarded as a separate entity, as advocated in the original study. Finally, with the discovery of molecular alteration, which is not otherwise seen in any other pancreatic tumor type (fusion involving *PRKACA* or *PRKACB*), IOPN was recently placed into a separate category based on the current (2019) WHO and other guideline texts and reports.[2,15] The main features distinguishing this tumor from other related entities are discussed below.

Clinicopathologic Characteristics

Clinical Features

IOPNs are slightly more common in male patients (with a male-to-female ratio of about 1.5), almost as common in the body or tail as in the head (unlike ordinary PDACs), and with a mean age at diagnosis of 58 years. This is comparable with other intraductal neoplasms. However, excessive MUC production, which often exudes from the ampulla and creates a characteristic endoscopic finding in IPMN patients, is not a feature of IOPN. Also, in pancreatic IOPNs, patterns of larger tumor extension, that is, tumors involving more than one portion of the pancreas, were observed more commonly (20.6% of cases). Additionally, it appears that IOPNs often present as complex cystic lesions and receive the diagnosis of "cystadenocarcinoma." It was even questioned whether some cases might be De Novo cystic lesions, such as mucinous cystic neoplasms, without overt communication with the native ductal system. This contrasts with IPMNs, most of which are noncomplex cystic tumors and are amenable to "watchful waiting" by Sendai or Fukuoka criteria.[86] In other words, owing to the complexity and florid papillary nodules (which typically translate to "mural nodules"), by default, IOPNs have "worrisome features" per Sendai or Fukuoka criteria and thus warrant resection. Of note, it was evident in the literature (and this is also our experience) that the complexity of IOPNs, combined with the associated fibrosing inflammatory changes, often leads to an erroneous impression of an unresectable tumor, only to show a noninvasive neoplasm once the tumor is removed. This is also important, considering most IOPNs (even those with invasion) appear curable if resected (see the section below). Therefore, with the current knowledge in hand, even if an IOPN looks seemingly unresectable, the possibility of resection should be carefully evaluated, if necessary, with vascular resection.

Pathologic Features

Studies documenting these tumors in detail emphasize 4 main features that distinguish them from other similar neoplasia: (1) a multilocular cystic pattern with many cysts containing tan friable papillary nodules; (2) the complex branching (arborizing) nature of the papillae, in contrast with the more villous architecture of IPMNs; (3) intraepithelial lumina formation (the punched-out spaces occurring in the epithelium that focally create a cribriform-like pattern), some containing MUCs; and (4) oncocytic cytology with monotonous cells that have round nuclei, single, prominent, and eccentrically located nucleoli, and abundant

acidophilic granular cytoplasm. Although IOPNs have been viewed as a "variant" of IPMNs, they are not mucinous neoplasms per se. They only have very limited MUCs, confined mainly to the goblet cells and intraepithelial luminal areas. Some examples have edematous cores in the papilla, and some have a band of edematous/myxoid stroma around the ducts.

Additional findings commonly observed include scattered goblet cells and rarely neuroendocrine cells. Convincing examples of IOPN are often pure, displaying this characteristic morphology in all the papillary/polypoid nodules. However, background cysts are usually lined by gastric-like mucinous epithelium; some have pancreatic intraepithelial neoplasia—type changes in the normal background pancreas. On occasion, it can be challenging to distinguish IOPNs from pancreatobiliary-type IPMNs because the latter also has more complex papillae and cuboidal cells with nucleoli. However, the striking oncocytic cytology and "neat-and-clean appearance" (in contrast with pancreatobiliary-type IPMNs, which often have neutrophils, necrotic changes, and marked disorganization of the proliferation) often allow the recognition of IOPN.

Grading and Reporting

In many studies published, the grade of the lesion was not provided, although the guidelines recommend this. This is most likely because, by default (owing to the cytoarchitectural complexity), virtually all IOPNs qualify as high grade. This was also reflected in the studies focused explicitly on this entity and provided grade information. It should be noted that this is very different from IPMNs, in which a substantial proportion of the resected cases are of low grade. Additionally, as most IOPNs look alike, this entity has no recognizable subgrades. More importantly, however, as this analysis illustrated amply, the connotation of the term "high grade" is markedly different in IOPNs than in other intraductal neoplasms. As also detailed below, IOPNs are curable even when they are invasive, with very few mortalities attributed to this tumor type. Whereas, in IPMNs (and in other tumoral intraepithelial neoplasms of ampullary, biliary, and gallbladder origin), HGD is very commonly associated with invasion, and these high-grade neoplasms behave aggressively even if invasion cannot be documented. This has far-reaching implications, especially on biopsy specimens, because if the biopsy with HGD/CIS is IOPN, there is an indication for surgery with hope for a total cure. Thus, although all IOPNs harbor HGD by definition, it is crucial to define the grading in the final pathology report, not to define the lesion itself but for the implications derived from the presence of HGD. In contrast, other entities with HGD/CIS typically have a high risk of mortality.

In addition, because the invasion associated with IOPNs is often not well documented in most studies (presumably because convincing invasion, if present, is often small), it has been challenging to document the relative frequency of different types of invasive carcinoma arising in IOPNs. It is, however, clear that invasion can occur in 3 different patterns in these unusual tumors: (1) small infiltrative tubules, (2) mucinous or colloid patterns (often mixed with the other 2), and (3) solid nests of oncocytic cells.[87] The distinction of true invasion may be challenging for pathologists. The biological significance of these different types is difficult to determine now.

It should be noted here that in a significant proportion of the studies on IOPNs analyzed in this study, several of the oncologic reporting principles and parameters established in seminal or guideline reports[14,15,88,98-100] were lacking, which can potentially lead to mismanagement of the patients and hamper better characterization of these tumors. Additionally, it was clear that in a significant proportion of the reported cases, the pT category was based on the overall tumor size, and the size and type of the invasive component, constituting the essence of current reporting recommendations,[14,15,88] were not even recorded.

Immunohistochemical and Molecular Profile

IOPN morphology is unique enough that IHC is generally not needed for diagnosis, especially in surgically resected specimens. However, the profile helps highlight the cell lineage and relationship of IOPN. For example, IOPNs share with IPMNs the MUC5AC (110/112; 98.2%) expression, but they do not show the diffuse intestinal differentiation (MUC2/CDX2 expression) of the intestinal subset of IPMNs. IOPNs also share the MUC1 expression common in pancreatobiliary-type IPMNs and the papillary components of mucinous cystic neoplasms. However, typically, the MUC1 expression is less in IOPNs than in pancreatobiliary-type IPMNs. Diffuse strong expression of MUC6, a common feature of ITPNs, can also be seen in the majority of IOPNs (78/84; 92.8%), but often, they are less diffuse and less intense. This suggests a pyloric differentiation in this tumor. MUC6 is not a common feature in papillary components of IPMNs; if present, it is typically confined to the pyloric-like glands that can be seen in the base of the cystic zones of IPMNs.

Of note, the potential differential diagnoses of IOPN include not only lesions with a typical intraductal growth but also other neoplasms that can show only rarely this pattern, such as acinar cell carcinoma (especially the intraductal/papillary examples)[101] and well-differentiated neuroendocrine tumors. Neuroendocrine tumors can enter this differential, producing an even more challenging scenario in cases with oncocytic and hepatoid features.[102,103] In addition, solid pseudopapillary neoplasms of the pancreas, in the case of hepatoid differentiation, can also enter such a differential.[104,105] Tumors with hepatoid differentiation typically express the hepatocyte paraffin 1 antibody (Hep Par 1), a classic hepatocytic marker, which is also positive in pancreatic IOPN.[2,78] Thus, if these tumor types are being entertained in the differential, it is advisable to perform not only some markers typically positive in IOPN such as Hep Par 1 and CD117,[18,78,82] but also BCL-10 for acinar cell carcinoma, chromogranin A and synaptophysin for neuroendocrine tumors, and beta-catenin for solid pseudopapillary neoplasms. This is particularly important in the biopsy setting, in which the morphologic hallmarks for the diagnosis can be very focal.[105,106]

IHC can also be used for studying the immune microenvironment of neoplasms. In the specific case of pancreatic IOPN, the protracted clinical course of patients with this rare entity can be partly explained by its peculiar tumor microenvironment, with an increased rate of CD8+ lymphocytes in the invasive component.[13,107] This finding could suggest the presence of active autoimmune surveillance in invasive IOPN, counteracting tumor growth and its potential for progression and distant metastasis. Together, all these features highlight the importance of considering IOPN in the differential diagnoses of intraductal pancreatic neoplasms and the central role played by pathologists in this challenging scenario.

The molecular profile of IOPNs is highly distinctive, even among tumoral intraepithelial neoplasms of the pancreatobiliary tract. The classic pancreatic drivers of PDAC/IPMN, such as *KRAS*, *TP53*, *CDKN2A*, *SMAD4*, and *GNAS*, were consistently reported as significantly less frequent in IOPN. In contrast, fusions involving

PRKACA or *PRKACB* emerged as an entity-defining genomic alteration of pancreatic IOPN ($P < .001$). The most common fusion gene was *PRKACB*::*ATP1B1*. By acting on pathways related to protein kinase A enzyme, these fusions may cause mitochondrial hyperplasia within the cells, resulting in the oncocytic appearance.[9] This hypothesis is reinforced by the fact that *DNAJB1*::*PRKACA* fusions are also observed in fibrolamellar hepatocellular carcinoma, another neoplasm composed of cells with oncocytic morphology.[9] A recent investigation generated other insights along those lines. Indeed, analyzing a cohort of IOPN (defined by the authors as typical IOPN) and a cohort of intraductal neoplasms of the pancreas with only focal oncocytic morphology ("atypical" oncocytic neoplasms), the authors demonstrated that fusions involving *PRKACA* and *PRKACB* represented a driver alteration toward the acquisition of oncocytic morphology.[12] Even at the transcriptomic level, there were specific alterations in IOPN, such as signatures involving genes of protein kinase A or epidermal growth factor receptor/extracellular signal-regulated kinase signaling pathways.[10]

The uniqueness of the genomic landscape of IOPN, also in comparison with that of PDAC/IPMN, confirms at the genomic level its clinicopathologic and IHC particularities, further highlighting that IOPN represents a specific and separate entity among intraductal pancreatic neoplasms.[108] Of note, such findings may also have potential implications for the application of next-generation sequencing into the diagnostic workflow of cystic lesions of the pancreas.[15,109-111] Given the importance of correctly diagnosing the different cystic neoplasms potentially arising in the pancreas, molecular-based tools may represent decisive support for improving diagnostic precision and accuracy. The specific association of IOPN with fusions involving *PRKACA* or *PRKACB* renders such genomic events an ideal diagnostic biomarker. Their cyst fluid detection represents an undebatable element for establishing the diagnosis of pancreatic IOPN or at least intraductal neoplasms with oncocytic features. Regarding the use of molecular diagnostics for addressing specific strategies of precision oncology, it should be acknowledged that IOPNs do not harbor specific potentially actionable alterations unlike, for example, their kindred ITPNs.[17,90,91] Thus, the application of molecular tools for pancreatic IOPN should be mainly intended for diagnostic purposes.

Differential Diagnosis With Other Tumoral Intraepithelial or Intraductal Neoplasms

Unlike in the gallbladder and ampulla, in which a significant proportion of the tumoral intraepithelial neoplasms have mixed morphologic features, in the pancreas, if the classification is based on the proliferative/papillary component of the lesion as it should be, the vast majority of cases have a more classifiable phenotype. It should be recognized that, in the pancreas, low-grade pancreatic intraepithelial neoplasia, which by definition has a "gastric phenotype," is very common in the general population.[112,113] Moreover, any cystic change in the ducts, either primary as in early IPMNs, or secondary, as a part of postobstructive dilatation, typically have mucinous alteration (also of gastric features).[114,115] For these reasons, in the original description of classification of IPMN papillae, gastric phenotype was also referred as the "null type."[116] It was emphasized that the gastric type of epithelium was also present in the background of even normal pancreata including other IPMNs and in the cystic components of most cases as well. Unfortunately, in some studies, it appears that this criterion (that the classification is based on the papillary component—ie, the main proliferative component—of the lesion) was not used and thus the mixture of epithelial elements was noted in a much higher frequency.[15]

When histotyping of intraductal neoplasia is based on the papillary components of the lesions as it should be, it is exceedingly uncommon to see a distinctively intestinal type papilla (with corresponding IHC profiles) to be admixed with a conventional IOPN pattern. Similarly, florid papillary nodules lined by gastric-foveolar–type epithelium are also uncommonly admixed with a classical IOPN, although background ducts or cystic components may naturally show gastric epithelium. Along those lines, the recent description of oncocytoid changes in IPMN is a phenomenon that warrants further attention and analysis, since it may provide interesting perspectives regarding the subclonal plasticity of intraductal neoplasms at the subcellular level.[12] Interestingly, the main challenge may be represented by the distinction of IOPNs from pancreatobiliary-type IPMN with HGD. For such cases, the criteria to identify or distinguish IOPNs, along with the oncocytic appearance of cells, are as follows: (1) the relative monotony (relative paucity of pleomorphism), (2) the "clean-and-neat appearance," (3) the lack of irregular cellular tufting in the epithelium, (4) the lack of intraepithelial tumor-infiltrating neutrophiles, (5) the lack of necrobiotic changes, and (6) the presence of the distinctive intraepithelial lumina.[1,2,14-16,117] Moreover, at the IHC level, expression of MUC6, Hep Par 1, and CD117 is much more common, diffuse, and strong in IOPNs compared with pancreatobiliary-type IPMNs. In this context, the presence of *PRKACA* or *PRKACB* fusions would also be very helpful.[118] In the rare instances in which this distinction cannot be made (or if one of those very uncommon mixtures of intestinal papillae with IOPN is encountered), such cases should be classified as "intraductal papillary neoplasm with mixed X and Y epithelium types" (where X is the most represented/dominant epithelium, ie, >50%, and Y is the other one).

Additional Considerations

As mentioned previously, this critical review of the literature performed in this study and our own experience highlight that IOPNs are quite different behaviorally than the other intraductal or intramucosal (tumoral intraepithelial) neoplasms of the pancreatobiliary tract. They are typically relatively large and complex when they come to clinical attention, presumably because they are relatively slow growing and nondestructive, enabling them to achieve larger sizes and complexity before causing symptoms. At the same time, they are seldom amenable to Sendai/Fukuoka "watchful-waiting" criteria by the time of diagnosis. Along the same lines, although they are relatively complex and with a degree of cytoarchitectural atypia that warrants the diagnosis of HGD/CIS at minimum, they are often curable by complete resection (unlike other intraductal neoplasia in which a diagnosis of HGD/CIS is often an ominous sign).

In the literature, the overall reported frequency of invasive carcinoma in IOPNs was 50%; however, several findings suggest this figure may be misleading.[87] First, this figure is much lower in studies focusing only on these tumors. In addition, the relatively benevolent behavior of IOPNs contradicts this frequency. An important factor contributing to the overreporting of "invasion" in IOPNs is the complexity of IOPN and its pagetoid spread to atrophic lobules, which it naturally elicits altogether, creating a pseudoinvasive appearance. The fact that the size of the invasive component was not reported in the vast majority of cases in the literature, and that in the few cases it was reported, it was pretty

small (mean, 1.4 cm), is also of note. The low frequency of metastasis (and vascular and perineural invasion) in these tumors also supports this impression. Most importantly, even cases interpreted as invasive often follow a benevolent course.[5,87] Therefore, despite their complexity and larger size, IOPNs appear to be curable tumors, with very few mortalities attributed to this tumor type. For these reasons, if a pancreatic tumor is diagnosed as IOPN, every attempt should be made to resect it. More controlled studies regarding adjuvant therapy after resection for invasive cases are needed.

Ultimately, all these observations underscore the importance of evaluation of IOPNs with total sampling and, if there are any foci suspicious of invasion, their careful assessment, perhaps with second opinions, and the documentation of such foci in detail, including their size and whether they show any oncologic risk factors pertinent to management as advocated in consensus reports.[14,15,88]

Our study does have some limitations. First, most data were extracted from single case reports or case series based on a small sample size, thus reducing their reliability in the comparative analysis. Furthermore, since the distinction of IOPN as a separate entity among intraductal neoplasms has been introduced only recently,[1] manuscripts published before this date may have included IOPNs without having identified them, thus making their inclusion in this systematic review impossible. Along this line, due to the different nomenclatures and histologic definitions of this entity, the search strategy may have failed to retrieve all reports containing IOPN data. However, it was designed following the highest quality standard for metaresearch.[119] Another potential limitation is with regard to IHC. What constitutes "positivity" for MUCs has been highly variable in the literature (in many studies, it was not even specified), and whether the interpretation refers to the papillary or the cystic component was also not specified. Additionally, most case reports did not specifically report using exclusionary ancillary stains (eg, neuroendocrine and acinar stains), representing a crucial step in the differential diagnosis. Finally, the molecular analyses in the different studies are based on very different methodologies and next generation sequencing–based panels. In this heterogeneous landscape, however, detecting fusions involving *PRKACA* or *PRKACB* appears to be a very reliable finding that can be used as an entity-defining genomic alteration in the heterogeneous landscape of pancreatic intraductal neoplasms.

Conclusions

In summary, this systematic review provides a general representation of the most critical and distinguishing characteristic features of pancreatic IOPN. These are often large and complex tumors at the time of diagnosis, presumably owing to their proliferative but slow growing and nondestructive nature. Pathologically, they are characterized by florid arborizing papillae that have intraepithelial lumina formation and oncocytic cells that lack any evidence of intestinal differentiation (MUC2/CDX2 negative) but appear to have pyloric lineage–like ITPNs. Molecularly, they lack the common characteristic findings of PDACs and IPMNs such as *KRAS*, *TP53*, *CDKN2A*, *SMAD4*, and *GNAS* genes but instead commonly show *PRKACA* or *PRKACB* fusions, which are otherwise not seen in any pancreatic tumors.[118] Although they are often reported to be invasive, this may be an overinterpretation of the pseudoinvasive nature of IOPNs, which is characteristic, and most cases in which invasion was documented in detail had small invasion. The prognosis of IOPNs seems to be very good, and even cases with convincing invasion are often curable by resection. For this reason, if a preoperative diagnosis of IOPN is achieved, every attempt to resect is warranted, highlighting the importance of a correct diagnosis. It should be established based on morphology, but in cases with scant and/or fragmented tissue samples or mixed epithelium (including contaminations), an IHC panel including MUCs and some more entity-specific markers (eg, Hep Par 1 and CD117) and, if available, molecular tests for detecting *PRKACA* or *PRKACB* fusions represent critical support. More studies are needed to investigate pancreatic IOPN further, considering all the most crucial aspects of this entity, and determine the role of adjuvant therapy for IOPNs with definitive invasion.

Author Contributions

G.P., O,B., A.S., V.A., and C.L. conceived and designed the study. G.P. and C.L. performed the systematic review. G.P. and C.L. conducted statistical analysis. All authors performed data elaboration, discussion, and interpretation. G.P., O.B., V.A., and C.L. edited the paper. All authors performed final editing and approved the present version of the manuscript.

Data Availability

All data generated in this article are available in the manuscript and related supplementary material.

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Declaration of Competing Interest

None declared.

Ethics Approval and Consent to Participate

Not applicable (systematic review of published data).

Supplementary Material

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