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PATHOLOGIC EVALUATION AND REPORTING OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMNs) OF THE PANCREAS AND OTHER TUMORAL INTRAEPITHELIAL NEOPLASMS OF PANCREATOBILIARY TRACT: RECOMMENDATIONS OF VERONA CONSENSUS MEETING

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Abstract

Background—There are no established guidelines for pathologic diagnosis/reporting of IPMNs.

Design—An international multidisciplinary group brought together by the Verona Pancreas Group in Italy-2013, was tasked to devise recommendations.

Results—1) Crucial to rule out invasive carcinoma with extensive (if not complete) sampling. 2) Invasive component is to be documented in a full synoptic report including its size, type, grade, stage. 3) The term “minimally invasive” should be avoided; instead, invasion size with stage and substaging of T1 (1a, b, c; 0.5, >0.5– 1, >1 cm), is to be documented. 4) Largest diameter of the invasion, not the distance from the nearest duct, is to be used. 5) A category of “indeterminate/ (suspicious) for invasion” is acceptable for rare cases. 6) The term “malignant” IPMN should be avoided. 7) The highest grade of dysplasia in the non-invasive component is to be documented separately. 8) Lesion size is to be correlated with imaging findings in cysts with rupture. 9) The main duct diameter, and if possible, its involvement is to be documented; however, it is not required to provide main vs branch duct classification in the resected tumor. 10) Subtyping as gastric/intestinal/pancreatobiliary/oncocytic/mixed is of value. 11) Frozen section is to be performed highly selectively, with appreciation of its shortcomings. 12) These principles also apply to other similar tumoral intraepithelial neoplasms (mucinous cystic neoplasms, intra-ampullary, intra-biliary/cholecystic).

Conclusion—These recommendations will ensure proper communication of salient tumor characteristics to the management teams, accurate comparison of data between analyses, and development of more effective management algorithms.

INTRODUCTION

The term IPMN was created in 1994 by Klöppel et al¹ to embrace entities previously reported in the literature under a plethora of designations including duct-ectatic mucinous cystic neoplasms,^{2, 3} mucin-producing tumors,^{4–6} intraductal papillary neoplasms,⁷ papillary adenocarcinomas,⁸ villous adenomas⁸ and others. Since then much has been learned about the nature and behavior of these distinctive neoplasms; however, many of the diagnostic criteria and management protocols remain challenging to apply and some are highly controversial.

The challenges also extend to, and often stem from, a lack of uniform criteria in the pathologic evaluation, terminology and parameters to be reported. In fact, the absence of a

uniform approach in pathology may be partly responsible for the obstacles to better characterization of these tumors. For example, the terms “malignant IPMN”^{9–28} and “minimally invasive IPMN”^{29–39} have been highly variably defined in the literature creating great confusion in understanding the behavior of different stages of this entity and leading to major contradictions in establishing uniform management protocols for patients with this tumor.

In April of 2013, an international meeting was convened in Verona, Italy, under the leadership and organization of Verona Pancreas Group. The Pathology team of this consensus meeting was tasked with assessing the current state and possible improvements in the pathologic evaluation of terminology and documentation of IPMNs, as well as determination of clinically relevant parameters for the management of these tumors. Accordingly, through literature analysis as well as interdisciplinary discussions with various experts both among the participants of the meeting and outside of the meeting, this group developed consensus on refined definitions and basic guidelines for the pathologic evaluation and reporting of IPMNs, which are discussed in detail in this manuscript.

METHODS

A pathology task group was created in 2012 in preparation for the consensus meeting to be held in Verona, Italy, in April 2013, under the leadership of Verona Pancreas Group. This task group consisted of an interdisciplinary team of participants with invested interest in the pathologic evaluation of branch duct IPMNs including pathologists, surgeons, radiologists, and gastroenterologist (VA, MMK, TF, GZ, CLW, HM, JO, MA, MJB). The team was tasked with analyzing the state of pathologic diagnosis of IPMNs.

Pre-meeting analysis of the literature was performed especially focusing on the pathologic assessment of IPMNs, and a list of discussion points was created by participation of all the team members. During this preparation, it was determined that wide disparities in pathologic evaluation, terminology and reporting of IPMNs existed. These disparities were presented to the participants of the Consensus Meeting in Verona in a general session, followed by active discussions conducted with the participation of the entire consensus meeting membership. Further discussions were held in break-out sessions. The results of these discussions were collated and presented to the participants at the last day of the meeting.

After the meeting, further analyses were performed as tasked during the consensus meeting. These included the analysis of institutional databases for the parameters in question and investigation of pathology reports on IPMN (performed in the community as well as in expert institutions). Evaluation of these pathology reports revealed that crucial pieces of information were missing from the vast majority of these reports, even in institutions where IPMN surgery is performed routinely.

In establishing the clinically relevant pathologic parameters, consultation with other experts from various disciplines who had not participated in the consensus meeting was also sought.

Separately, another international consensus meeting was held on the topic of pancreatic intraepithelial neoplasia (including IPMNs) at The Johns Hopkins University School of

Medicine, led by Drs. Ralph Hruban and David Klimstra, under the auspices of the Sol Goldman Pancreatic Cancer Research Center of The Johns Hopkins University in June 2014. Some of the parameters and salient issues were also discussed during this meeting. Although the proceedings of this meeting are the subject of another manuscript, the conclusions presented below are in accordance with the conclusions of that latter meeting.

RESULTS/DISCUSSION

Definition

Intraductal papillary mucinous neoplasms^{40–43} are pathologically defined as mass-forming pre-invasive neoplasms (tumoral intraepithelial neoplasms) that grow within the ducts of the pancreas (Table 1)^{40–43}. In the WHO-2010 classification,⁴⁴ in order to distinguish IPMNs from incidental microcysts and large pancreatic intraepithelial neoplasms (PanINs), IPMNs were required to be > 1 cm in diameter.⁴⁴

With the current definitions,^{40, 41, 43, 44} IPMNs encompass a spectrum of lesions ranging from those that are very innocuous-appearing (what used to be called “hyperplasia”) to those that are full-blown intramucosal carcinomatous lesions (those used to be designated as “papillary adenocarcinoma”).^{40, 41, 43, 44} This spectrum, previously classified⁴⁵ as “hyperplasia → adenoma → borderline → *in-situ* carcinoma → invasive carcinoma” was later re-categorized⁴² as “low-grade dysplasia → intermediate-grade dysplasia → and high-grade dysplasia → invasive carcinoma” (Table 2).⁴⁵ As such, IPMNs represent adenoma-carcinoma sequence (tumoral intraepithelial neoplasia). Invasive carcinoma arising in or concomitant with IPMN can be of various types (especially colloid or tubular), and can be very limited or extensive.

IPMNs have different cytologic types classified as gastric, intestinal, pancreatobiliary, and oncocytic and it has been shown that these cell types not only have different morphologic and immunohistochemical phenotypes, but also some have different genetic drivers^{46–55} (see below, the subtypes section).

IPMNs can progress to invasive carcinoma of different types (ductal/tubular^{44, 56–61} and colloid/muconodular^{51, 62–65}) and of variable extent. The invasive component of these tumors ought to be regarded and documented separately (see below invasive carcinoma section for details).

Branch vs Main duct IPMN: Documentation of main pancreatic duct findings pathologically

The classification of IPMNs as branch (Fig. 1) versus main duct (Fig. 2) type is of utmost importance in assessing the risk of carcinoma during the pre-operative management of patients with an IPMN,^{40, 41, 66–74} however, once the tumor is resected, naturally, this separation loses virtually all of its clinical value, and is superseded at that point by the absence or presence of an associated invasive carcinoma.^{40, 41, 75, 76} Furthermore, recent pathology studies have shown that the main duct not infrequently shows some degree of involvement even in the IPMNs that were classical branch duct type by imaging, and more importantly, those IPMNs with minimal involvement of the main duct, defined as “non-circumferential main duct involvement limited in a few histologic sections”, were very

similar to branch duct cases and were different from main duct IPMNs, both by clinicopathologic features and clinical outcome.⁷⁷ Consequently, for pathologic reporting, it is advised to make an attempt to document the widest diameter of the main duct, and also the extent of involvement of main duct by abnormal epithelium, if possible; however, it is not required for pathologists to make a specific distinction between the two groups.^{78–84}

Measuring overall tumor size

Size of an IPMN at the time of diagnosis and its growth over time is an important criterion in the pre-operative management of IPMNs^{12, 40, 41, 69, 85–88} although its significance becomes less in resected specimens. Regardless, every attempt should be made to accurately determine the size of the lesion in the pathology report. This may be important not only for assessment of future risk but also serves as a feedback for radiologists to hone their skills.

There are, however, challenges in measuring the size of cystic lesions. Some IPMNs have very thin walled cysts that can rupture between the time of specimen resection and measurement in the gross room due to manipulation, dissection or for tumor banking purposes, which leads to shrinkage of the lesion. Therefore, for such thin-walled cystic IPMNs the true size needs to be determined by close correlation with the imaging findings, and in fact, if the size measured in the gross room is smaller, then, the clinical measurement is to be included in the pathology report. For these reasons, it is recommended that the size of the lesion be documented along with the mode of measurement as, for example: “*Overall size of IPMN: 3 cm, as measured clinically (cyst ruptured during processing)*”.

Documenting the gross size of any solid component can be useful as invasive carcinomas are often solid and the size is prognostically significant for invasive cancers. These also often correspond to “mural nodules” detected by imaging pre-operatively. For cases with a solid component, florid papillary nodules or invasive areas, imaging studies may underestimate or mis-calculate the overall tumor size, and thus gross and microscopic evaluation is crucial for determining the size in such cases. If there is a discrepancy with the clinically measured size, an attempt can be made to explain this discrepancy in a comment.

In the physical measurement of the cysts in the gross room, certain issues ought to be kept in mind. For *unifocal but multilocular lesions*, it is preferable to document the overall size of the collection of locules along with the size of the largest locule. If a papillary lesion is present, it too can be measured. For *multifocal lesions*, the size of the largest focus should be documented, as can the sizes of the smaller lesions if it is clinically indicated.

Every attempt should be made to also measure the diameter of the main pancreatic duct. This requires proper identification of the main duct, which can be altered due to tumor, and may prove difficult to trace in a significant proportion of the cases. However, if the main duct is identifiable, then its diameter in the widest focus ought to be documented. Most importantly, the size of the invasive component, if present, should be carefully and separately documented. This will be discussed in detail in the invasive carcinoma section below.

Invasive carcinoma: Evaluation and reporting

Significance—The most important determinant of outcome in the management of patients with IPMN is whether an associated invasive carcinoma is present or not.^{42, 44, 59, 87, 89–92} Recent studies have uniformly shown that the vast majority of completely resected non-invasive IPMNs have a very positive outcome, with a 5-year survival of >90%,^{59, 87, 93} whereas half of those with an associated invasive carcinoma die from their disease.^{32, 33, 57, 76, 94–97}

Sampling—An invasive carcinoma arising in association with an IPMN can only be definitely excluded with thorough evaluation of not only the entire lesion but also the uninvolved pancreas as well, since the neighboring pancreas often shows peri-tumoral abnormalities and may harbor subtle invasive carcinomas. In fact, the aggressive behavior of tumor reported in some patients with a “non-invasive IPMN,” may be due to “missed” invasive carcinomas in under-sampled IPMNs.⁴² Some invasive carcinomas also arise away from the lesion, and that is why it is important to regard the entire specimen as suspect for invasive carcinoma, perform thorough gross examination, as well as liberal sampling of even seemingly normal pancreas.

Typing of associated invasive carcinoma—Different histologic types of invasive carcinoma can arise from IPMNs, and these histologic types are associated with markedly different prognostic and biologic properties.^{51, 62, 64, 65, 98–100} About half of the invasive carcinomas that arise in association with an IPMN are ordinary tubular (ductal) adenocarcinoma (Fig. 3A), characterized by infiltrating small to medium tubular units separated by abundant stroma.^{44, 60} This type often arises from either gastric or pancreatobiliary type IPMN, and appears to have an aggressive behavior, although its prognosis may not be as poor as for ordinary PDACs, either due to early stage detection, and/or different molecular/biologic characteristics (although it is often morphologically indistinguishable from ordinary PDACs).^{32, 33, 57, 94–97}

The other half of the invasive carcinomas that arise in association with IPMNs are colloid carcinomas (Fig. 3B), characterized by muconodular type invasion (nodules of stromal mucin that contain relatively scant clusters of carcinoma cells). Colloid carcinomas typically arise from the intestinal type IPMN, and are seldom, if ever, seen in association with other IPMN subtypes or with mucinous cystic neoplasms.^{65, 101, 102} Patients with colloid carcinomas have a significantly better prognosis than do patients with tubular invasive carcinomas.^{51, 62, 63, 65, 98, 100} Further, both colloid carcinoma and its common precursor, intestinal type IPMN, are characterized by intestinal type differentiation markers - diffuse and strong expression of the intestinal epithelial marker, MUC2, and, the intestinal differentiation marker, CDX2, - neither of which are expressed substantially in any other tumor type in the pancreas.^{50–52, 103–105} These render colloid carcinomas a potential candidate for a different management approach, and thus accentuate the importance of its recognition and proper documentation in the pathology reports.

Rarely, other invasive carcinoma types can arise in association with IPMNs, such as oncocytic,⁵⁵ sarcomatoid/undifferentiated (some with osteoclast-like giant cells), medullary,

or neuroendocrine carcinomas.^{106, 107} These also ought to be recognized and reported accordingly. Some carcinomas are of mixed type.^{108, 109}

Grading of invasive carcinoma—The histologic grade of invasive carcinoma ought to be given separately from the grading of the non-invasive component. For tubular/ductal carcinomas, the principles employed in grading of ordinary PDACs can be employed.¹¹⁰ There are different grading schemes with their corresponding challenges, which are beyond the scope of this manuscript. Readers are referred to appropriate literature.^{111–114}

For the grading of colloid type carcinoma, there are currently no guidelines. Most colloid carcinomas are by default well differentiated. However, some mucinous carcinomas in the pancreas exhibit significantly more prominent cellularity, cytologic atypia and cells clinging to the stroma. These tend to be more aggressive neoplasms. In such cases, the possibility of a non-colloid type mucinous carcinoma arising from the ampulla such as mucinous signet ring carcinoma or mixed mucinous-intestinal carcinoma, or a pancreatic ductal adenocarcinoma with excessive mucin production ought to be considered.^{108, 109, 115}

Size of invasive carcinoma—As in any other cancer types, the size (and stage) of the invasive carcinoma is one of the most important prognostic parameters in IPMNs.^{32, 37, 56, 97} Unfortunately, many studies have failed to analyze this as a separate parameter. In fact, our review of the literature highlighted the unfortunate fact that the size of overall tumor (with non-invasive and invasive components lumped together) is often used interchangeably with the size of the invasive carcinoma.

The consensus at the Verona meeting was that it is imperative to measure the size of invasive carcinoma as accurately as possible, and, if this cannot be achieved (due to fragmented sampling or multifocality), then, to at least give an estimation of the invasion size. The invasive component should be staged, independent of the non-invasive component, as in any other cancer (see discussion below on staging).

If the invasive carcinoma is *unifocal*, the recommendation is to measure the largest diameter of the invasive focus, as is done for any invasive carcinoma in this organ and in other solid organs. An alternate possibility of measuring the “depth” from the nearest duct was discussed but dismissed because it is often impossible to determine where the nearest duct is located in 2-dimensional histologic sections.

For *multifocal* tumors,¹¹⁶ it is recommended that both the diameter of the largest one as well as the overall estimated size of all foci in aggregate be provided in the comment of the report (Synoptic 1). As in other organs such as the breast, it is not yet clear as to which one of these better reflects the tumor burden and thus is to be taken as the main tumor size.^{114, 117, 118}

Indeterminate (suspicious) for invasion—Due to the complexity of the intraductal lesions and their common extension into the neighboring smaller ductules, non-invasive IPMNs often show remarkable architectural complexity with a pseudo-invasive appearance. This is especially striking in main duct lesions (of the intestinal type) where atrophy and fibrosis of the surrounding pancreatic parenchyma can be prominent, further accentuating

the pseudo-invasive pattern. Prior biopsy site changes and inflammation also contribute to and accentuate this challenge. Separately, rupture of the ducts can lead to extrusion of mucin into the stroma. This acellular mucin is not invasive carcinoma, but in some instances it can be very difficult to distinguish from true invasive colloid carcinoma (Fig. 4). As a result, in some cases, it may be extremely difficult to determine whether a focus is invasive or pseudo-invasive. For such cases, the diagnosis of “indeterminate for invasion” may have to be rendered. This would correspond to the “suspicious for invasion” category of the Vienna classification of reporting GI malignancies.¹¹⁹ It is not yet known the clinical implications and behavior of such cases of IPMNs; however, it is certain that some cases cannot be classified definitively as invasive versus non-invasive and thus this category is a necessary one. In such cases, the estimated size of a suspect focus should be provided in a comment.

Staging of invasive carcinoma; proposed refined definition of “minimally

invasive” as pT1 and T1a, b and c—As for any invasive cancer, it is required to stage invasive carcinomas arising from (or in association) with IPMNs.⁴⁴ A significant proportion of the invasive carcinomas discovered in IPMNs is small, and have been termed “minimally invasive”. However, this term is vague, non-specific and potentially misleading since it has been used highly variably in the literature: In some studies, also including “indeterminate” cases,^{29–39, 120–122} in others,^{32–37} the term minimally invasive was reserved for cases with minute invasive foci, while in others,^{120–122} the term was defined as a carcinoma having invaded slightly beyond the duct wall, and yet in still others, as T1 cancers, and in yet others, for invasion not appreciated grossly but discovered on microscopic examination. Thus it is recommended that the term “minimally invasive” be abandoned and replaced by proper documentation of the size of invasive carcinoma and its proper staging. It has been proposed to sub-stage these small carcinomas as pT1a, if ≤ 0.5 cm; pT1b, if >0.5 and ≤ 1.0 , and as pT1c, if > 1.0 and ≤ 2.0 cm, although this classification needs to be validated in large-scale (multiinstitutional) studies.⁴⁰

In staging of IPMNs with more overt invasive carcinomas, it is recommended that the UICC/AJCC staging protocol be employed.¹¹⁴ Unfortunately, numerous studies have disclosed that the current T-stage protocol lack linear prognostic correlation due to the irreproducibility and pathologic inapplicability of ill defined parameters like “peripancreatic soft tissue involvement,”^{123–125} or “common bile duct involvement” (as to which part of the common bile duct is to be taken into consideration).^{126, 127} For these reasons, a protocol that replaces these parameters with tumor size as the main defining parameter for also pT3 (in the current system, pT1 and T2 are already defined by size) is being considered to replace the current failed protocol.¹²⁸ Until this change is formally adopted, however, it is recommended that both the size of invasive carcinoma as well as the current AJCC/UICC stage be documented.¹¹⁴

Invasive carcinoma “derived from” or “concomitant with” IPMN—There is emerging evidence that there may be some biologic and prognostic differences between carcinomas “derived from” (arising in the area of) IPMN versus those that are “concomitant” (not contiguous with) IPMN.^{97, 129} Therefore, it is recommended that every attempt be made to document the relationship of invasive carcinoma to the IPMN. For this

purpose, it is recommended that sections be taken to verify the continuity (or discontinuity) of the invasive carcinoma with the IPMN. Considering that tumors and carcinomas can grow in a dumb-bell fashion or with skip areas, examination of the complete, full-thickness of the tissue and assurance of the discontinuity between the invasion and IPMN have to be documented unequivocally before a case can be classified as “concomitant” rather than primarily arising in IPMN. Many current grossing/sampling protocols used in the West may fall short in being convincing in this regard. Therefore, this distinction may not be achievable in every case.

Evaluation of invasive carcinomas for adjunct parameters—Invasive carcinomas in IPMN cases ought to be evaluated, in addition to staging, for adjunct parameters that are typically required in cancer synoptic reporting such as those recommended by the College of American Pathologists. These include grade, perineural invasion, vascular invasion, and optionally also for budding.¹³⁰ Invasion to neighboring organs ought to be documented as well.

N-stage—It is imperative that the lymph node status be documented properly in IPMNs, regardless of whether invasion is detected or not. There have been cases in which the identification of lymph node metastasis has led to a more careful investigation of the IPMN and ultimate detection of invasive carcinoma in an otherwise seemingly non-invasive IPMN.¹³¹ It is recommended that a minimum of 12 lymph nodes be identified in a pancreatoduodenectomy specimen as recommended by American College of Surgeons,^{132, 133} and if this is not achieved, additional sampling should be performed in an attempt to identify more lymph nodes, and this should be clarified in a comment. Certain grossing approaches such as the “orange-peeling” method may facilitate a more complete harvesting of lymph nodes.⁷⁸

For assessment and documentation of lymph nodes, routine protocols in the AJCC/UICC guidelines¹¹⁴ are to be followed. Accordingly, a direct invasion to a lymph node is regarded as lymph node metastasis, although the prognostic¹³⁴ and scientific merit of this is being debated. For pancreatic cancers, the number of lymph nodes involved also appears to be a significant prognosticator and for this reason sub-staging of node-positive cases as N1 and N2 has been proposed.¹³⁵ Similarly, lymph node ratio may also have prognostic significance but is currently not applicable in daily practice. For these reasons, it is recommended to document the number of lymph nodes involved, as in any other oncologic pathology report.

Definition of “malignant IPMN”

In the literature, the term “malignant” has been used highly variably, and this has led to major confusion in assessing the behavior and significance of IPMNs: In some studies, the term malignant IPMN was used in reference to clinical behavior with the term “malignant” used to refer only to those cases with metastasis and mortality. In other studies, both high-grade dysplasia (carcinoma *in-situ*) and invasive carcinomas were regarded as “malignant”,⁹⁻²⁰ whereas, in other studies, only the cases with an associated invasive carcinoma were classified as “malignant”.²¹⁻²⁸ Considering that only invasive cases have the ability to exhibit true malignant behavior (uncontrollable growth, destruction and

metastasis), the latter definition was determined at the Verona meeting to be the most accurate. Nevertheless, in order to avoid confusion, and in accordance with routine oncologic pathology practice in other organs, it was recommended that the term “malignant IPMN” should not be used, and instead, clarification is provided as to whether it is invasive versus non-invasive.

Grading of IPMN

The degree of cytoarchitectural atypia (dysplasia) in IPMNs is graded as low, intermediate and high.⁴⁴ The criteria for this is established in previous publications and are now widely in use.^{40, 41, 43, 50, 51, 136} In the WHO-2010, it was advocated to avoid the term carcinoma in-situ or intramucosal carcinoma, to be replaced by “high-grade dysplasia” for all duct-confined (non-invasive) neoplastic changes. The main reason for this was to avoid over-treatment. However, it should be noted here that, in many parts of the world the word “carcinoma” (in-situ) is still employed for the most advanced forms of high-grade dysplasia. If this is preferred, then it is also crucial that this is clarified explicitly as “*non-invasive carcinoma*”.

In a given case, the final grade of IPMN is based on the highest-grade focus, no matter how small. In cases with high-grade dysplasia (“carcinoma in-situ”), it is advisable to document the extent of this as focal (< 25% of the tumor), substantial (25–75%) or diffuse (> 75%) (Synoptic 2), although the clinical and behavioral relevance of this has not yet been established.

IPMN subtypes

The category of IPMN had been created as an umbrella entity to encompass all tumoral intraepithelial neoplasms (intraductal mass-forming neoplasms) with a predominantly papillary architecture involving the large ducts of the pancreas.^{43, 44, 51} It has now become clear that the four cell lineages (Fig. 5) that occur in the papillary components of IPMNs may represent different carcinogenetic pathways with significant differences in their clinicopathologic associations, cancer progression rates, immunophenotype and molecular characteristics.^{33, 36, 44, 46, 62, 87, 137–139}

Most branch duct IPMNs prove to be of *gastric type*,^{49, 50} characterized by papilla lining that is highly similar to gastric foveolar epithelium. Although invasive carcinoma is less commonly associated with gastric IPMNs than it is with the other IPMN types, once it occurs, it is typically of the tubular/ductal type with aggressive behavior akin to the ordinary PDAC.^{62, 140, 141, 136} Intestinal type IPMNs are similar to colonic adenomas, distinguished by villous architecture and pale basophilic mucin that is typically diffusely positive for MUC2, in addition to expression of CDX2 (transcription factor of intestinal programming)^{50, 51, 142} Intestinal type IPMNs are typically main duct type, and fairly extensive.^{50–52, 103–105, 143} and are more likely to harbor *GNAS* mutations than are the other types of IPMN.^{144–146} Invasive carcinoma is identified in a third of intestinal IPMNs resected, and these invasive foci often prove to be of colloid type^{51, 65} with surprisingly protracted clinical course.^{51, 62, 63, 65, 100}

Oncocytic IPMNs, previously called intraductal oncocytic papillary neoplasms,^{53, 55} typically present as complex, large multilocular cystic lesions rather than the typical IPMN presentation of ductal dilatation or mucin extrusion from the ampulla. They are characteristically complex, arborizing, with florid proliferation of oncocytic cells with a relatively monotonous appearance.^{53–55} Despite their large size and striking complexity, invasive carcinoma is surprisingly rare in these tumors, and if seen, is usually very limited in quantity. The prognosis seems to be relatively indolent as well. Mutations in *KRAS* and *GNAS*, which are otherwise common in IPMNs, are seldom detected in this group.^{147, 148}

IPMNs that have cuboidal cells with high-grade cytology and that do not have the characteristics of the intestinal or oncocytic types are designated as pancreatobiliary.⁵¹ Many of these may represent high-grade transformation of gastric type IPMN; however, some have a distinctive pattern and morphology that supports a separate lineage. It is also this pattern that has overlapping features with intraductal tubulopapillary neoplasms.^{149–155}

It is acknowledged that in some cases (about 15%), there are overlapping features, and it is not possible to place a given tumor into any one category, in which case the term “mixed” is to be employed, with an explanatory note in the comment section.

Definition and delineation of IPMN from its mimickers

Large PanINs—Gastric type IPMNs have significant morphologic and molecular overlaps with PanINs. IPMNs are defined by their “tumoral” nature (formation of clinically or grossly visible cystic and papillary nodules that are typically > 1 cm) and PanINs are incidental/microscopic (< 0.5 cm) forms of dysplasia (intraepithelial neoplasia), but otherwise they have very similar pathologic characteristics.^{43, 44} In order to provide a numerical value to this distinction, the size criterion of 1 cm is generally employed. For cysts < 1 cm and > 0.5 cm that are lined by gastric-like mucinous epithelium, the term “incipient IPMN” has been proposed as an option.^{156, 157} For intestinal and oncocytic lesions, this differential is largely a moot point, because these are classified as IPMN irrespective of size, although it is exceedingly uncommon for them to be discovered when less than 1 cm.¹⁵⁶

Simple mucinous cyst (cystic mucinous duct lesion)—Cysts larger than 1 cm lined by mucinous epithelium but without overt papillary configuration and without any ovarian type stroma create a challenging entity to classify. Previously, the term “mucinous non-neoplastic cyst” has been recommended for such lesions,^{158–160} but considering that mucinous change in the pancreas is now equated with the earliest form of neoplastic transformation, this name is no longer practical. Since many of these lesions do not show any signs of obstruction or any other abnormality in the remaining pancreas, they cannot be exactly regarded as retention cysts either. Of note, these appear to be mega-cystic versions of PanIN-1A (also known as “mucinous duct lesion”), and thus, the term *cystic mucinous duct lesion* was also proposed.¹⁶¹ However, the true identity and the best name to assign to this entity require further analysis and discussions.

Retention cysts; secondary dilatation of the ducts—Mass lesions (and other obstructive factors) can lead to secondary dilatation of the pancreatic ducts, and when these

acquire mucinous epithelium, they can be difficult to distinguish from IPMNs. Lack of florid papillary elements and their round open lumina as well as the location of the lesions (commonly located in the periphery of the main mass) may help differentiate these from true IPMNs. Additionally, they often have at least focal cuboidal lining.⁴²

Occasionally, the main pancreatic duct is also dilated significantly due to an obstructive process. Recently, minute neuroendocrine tumors arising on the duct wall (especially from serotonin cells) are coming to clinical attention, and may clinically mimic an IPMN as they can cause significant ductal dilatation.^{162, 163} More importantly, on rare occasions, small PDACs can lead to marked dilatation of the main duct, again clinically mimicking an IPMN. In these cases the obstructive carcinoma can be missed.

Similar tumoral intraepithelial neoplasms—Intraductal tubular/tubulopapillary neoplasms are very close kindreds of IPMNs, to an extent that some have proposed to regard them as a variant of IPMN. However, since they lack two of the characteristic features of IPMN that even have been incorporated into the name,¹⁵² i.e., significant mucin production and papilla formation, this entity was kept separate from IPMN in the WHO-2010 classification.⁴⁴ ITPNs are composed of non-mucinous (or minimally mucinous) cells, which grow in a predominantly tubular pattern with minimal papilla formation.^{44, 149, 154, 155}

In the areas lacking the ovarian type stroma, mucinous cystic neoplasms can appear identical to branch duct IPMNs, and in the areas with florid papilla formation, they are very similar to pancreatobiliary type IPMNs.^{101, 164, 165}

Adenomas and non-invasive papillary neoplasms growing within the ampulla, which have recently been proposed to be unified under the heading of intra-ampullary papillary tubular neoplasms can also be virtually identical to IPMNs, especially when they show extension into the pancreatic ducts.¹⁶⁶ If taken out of context, intraductal papillary neoplasms of the bile ducts are also indistinguishable from IPMNs.¹⁶⁷ Proper grossing, dissection and sampling (with identifiers of the location of each tissue sampled) are crucial in making the distinction between these entities, because without knowledge of the specific location of a given lesion, these can be indistinguishable at microscopic level. For the appropriate grossing protocols, the readers are referred to other detailed texts.⁷⁸ It should also be noted here that some intestinal type IPMN show fistulous extension into adjacent organs¹⁶⁸ which can mimic tumors of those secondary sites.

Large duct type invasive adenocarcinomas—Some invasive ductal adenocarcinomas of the pancreas are composed of larger dilated ducts, rather than the more classical small tubular pattern. These are often well-differentiated and may exhibit abortive papillary elements, such that, when taken in isolation, many of the invasive glandular units can closely mimic IPMNs. These large duct type invasive adenocarcinomas can be distinguished from IPMNs by the highly irregular contours of the ducts, relatively flat epithelial lining, open, round lumen formation (rather than the compressed ducts with undulating contours), and the presence of necrotic, granular debris in their lumen.^{169–171} The distinction of these invasive carcinomas from non-invasive IPMNs is of utmost significance since both the

outcome and pathogenesis are vastly different. In fact, some of the rapidly progressive IPMNs in some studies may belong to this category.

Congenital, duplication, enteric and paraduodenal wall cysts—A variety of cysts close to duodenal wall can clinically mimic IPMNs. In fact, when these cysts develop papillary carcinomatous changes, they can be indistinguishable from IPMNs.¹⁷² Some congenital, duplication or enteric cysts can be recognized by the presence of a muscular wall, which can be very helpful. Some also have focal ciliated epithelium that is not seen in IPMNs.

Para-ampullary duodenal wall cysts that occur as a consequence of paraduodenal (groove) pancreatitis often have partial mucinous lining, because they arise from preferential injury of pancreatic tissue that occurs on the wall of the duodenum (“cystic dystrophy of heterotopic pancreas”).^{173–176} These can be confused with IPMNs.

Co-incidental tumors and uninvolved pancreas

In a patient with IPMN, it is important to analyze the uninvolved parts of the specimen. As discussed previously, it is now well established that IPMNs can be multifocal,^{177,116} and furthermore, concomitant invasive carcinomas can be encountered far away from the main IPMN lesions.^{97, 178–181} Although neuroendocrine tumors can occur synchronously with IPMNs, it is much more common to see a non-neoplastic aggregation of the islets of Langerhans secondary to long-standing duct obstruction.^{182–185} This latter finding should not be over-diagnosed as “islet cell hyperplasia,” or as a neuroendocrine neoplasm.

It should also be kept in mind that many patients with IPMNs have metachronous and synchronous tumors in other organs particularly the colon, and some of these can be present in the resection specimen, including the ampulla and duodenum.^{186–191}

It is also advisable to document the changes in the uninvolved portions of the pancreas. Peritumoral pancreatitis is very commonly encountered in main duct IPMNs as a consequence of the local effects of the tumor, and it would be preferable to not designate these as chronic pancreatitis, since chronic pancreatitis is a specific disease entity, defined by a constellation of findings at the clinical level.^{192–194} It may be more appropriate to be descriptive about these chronic changes as atrophy, inflammation and others.

Sampling of seemingly uninvolved pancreas can also reveal subtle, grossly-unapparent obstructive lesions that lead to “pseudo-IPMN”¹⁶².

Frozen section evaluation

After discussions at both the Verona and Johns Hopkins consensus meetings, where different opinions were raised initially, it was finally widely agreed that if routine frozen section of the primary tumor is performed, it should be done with the understanding that: 1) Both high-grade dysplasia and invasive carcinoma, which are the main targets of a frozen section, are typically focal and often grossly not distinguishable from lower grade portions of the lesion, and therefore, cannot be confidently excluded in a frozen section setting. Thus, discrepancy is commonly observed between frozen section and permanent findings. 2) Even

if such a focus of high-grade dysplasia and/or carcinoma is present, histologic interpretation can be difficult due to the freezing artifact, the small size of the focus, and considering that the pathologic assessment of IPMNs is already difficult even in properly obtained sections. 3) Freezing of tissue often leads to adverse alterations in the specimen that may hamper the final diagnostic evaluation in permanent sections, especially considering that the focus of concern is often small and may disappear as well.^{195–198}

Evaluation of *margins* by frozen sections may be indicated in some cases of IPMNs.^{93, 199–202} When evaluating the margins, the concerns described above would have to be taken into consideration. The main task for the pathologist is to determine whether there is high-grade dysplasia or invasive carcinoma, because it is believed that these require more aggressive management with consideration of the performance of more extensive surgery, including total pancreatectomy. The current data indicate that the presence of low-grade dysplasia or intermediate-grade dysplasia do not require any further surgery provided that there are no other lesions clinically (and intra-operatively) in the remaining pancreas.²⁰³ This approach also pertains to incidental low-grade PanINs at a margin. Low-grade PanINs are often encountered in general population²⁰⁴ and thus also in pancreata with IPMNs (see below for mimickers of IPMN). While intestinal and oncocytic type IPMNs are easy to distinguish from PanINs, gastric IPMNs (and cystic components of intestinal and oncocytic IPMNs which also often have gastric type epithelium) are virtually indistinguishable from PanINs. For this reason, it is recommended that low-grade gastric like epithelium in pancreatic margins be reported as “No high-grade dysplasia or invasive carcinoma is identified; low-grade mucinous epithelium is present (low-grade PanIN or low-grade IPMN)”. Current data indicate that these findings by themselves do not justify further resection.^{205, 206}

One challenging finding in frozen sections for margins is the inflamed ducts with denuded epithelium, especially if the duct is dilated.²⁰⁷ These should be reported as “denuded epithelium, cannot assess for neoplastic process”. At this point, clinical and operative judgment may have to be used in determining the course of action, and the presence or absence of a lesion in the remaining pancreas may be an important factor in this decision.

In terms of indications to obtain frozen sections, it should also be kept in mind that a frozen section should only be performed if it might change the course of the operation. Since such criteria are mostly surgical, the specific situations that it might be needed are beyond the scope of this manuscript and require further discussions.

Reporting of cytology specimens

There are different opinions on the value of fine needle aspiration in the diagnosis of IPMNs. In Japan, this is mostly avoided because of concerns about tumor seeding or biopsy-related complications. In the United States, however, endoscopic-ultrasound-guided FNA biopsy is widely utilized in the diagnostic algorithm of IPMNs,^{208–210} especially those with undetermined risk, such as branch duct IPMNs with indeterminate features, or in patients in whom surgery is contraindicated

The findings of FNA biopsy ought to be interpreted in the context of the clinical findings, and with close communication between the radiologist, clinical management team and cytopathologists.^{211–216} Otherwise, results can be misleading. For example, in the right context, the presence of thick mucin alone may be sufficient for a diagnosis of IPMN, even if it is relatively acellular.

Most branch duct IPMNs (and the cystic component of other IPMN types) have a lining that is indistinguishable from that of normal gastric epithelium.⁴⁴ For this reason, the presence of gastric type epithelium on FNA smears from a pancreatic cyst should be reported as “gastric type epithelium, cannot exclude gastric contamination or a low-grade gastric type IPMN”. If present, parietal cells may help make this distinction.

It is important to note that foci of invasive carcinoma are often small and the “invasive/ carcinomatous” cells are less likely to be shed into the cyst fluid. Therefore, unless the solid areas containing these invasive elements are sampled separately, invasive carcinoma can easily be missed by FNA. The same is also true for microfocal high-grade dysplasia. Conversely, reactive ductal epithelium can be mistaken as “carcinomatous” changes. For these reasons, the results of FNA should be evaluated with the clinical findings in mind.

It is also often impossible to distinguish the cells of high-grade dysplasia from those of invasive carcinoma. For these cases, the diagnosis of “high-grade atypia, possible carcinomatous change in IPMN” is recommended, with the understanding that “high-grade atypia” is an all-encompassing term that incorporates features of both “high-grade dysplasia” as well as “invasive carcinoma,” which are cytologically inseparable and both require resection. It should be noted here that, the diagnosis of “high-grade atypia” is to be used only in FNA specimens (not in surgical biopsies or resections), and even in FNAs, it must be followed by a comment indicating that this diagnosis conveys a suspicion of carcinomatous transformation, but cannot distinguish between in-situ or invasive carcinoma, since this distinction is typically not possible in cytologic specimens.

IPMNs and MCNs are indistinguishable on FNA.²¹⁵ This is because the subepithelial ovarian stroma of MCN is often not sampled or recognizable on smears or cell block. For this reason, in cytologic specimens deemed to represent one of these entities, the term “mucinous neoplastic cyst” is preferred, with a qualifying comment indicating that both these two differentials are included. Once a cyst is determined to be a neoplastic mucinous cyst it is important to determine the presence, and grade of cytologic atypia (low- versus high-grade atypia) in all cases, so as to better stratify risk of invasion.

Reporting principles for IPMN are also applicable for other tumoral intraepithelial neoplasms of the pancreatobiliary tract

Although the main task of the consensus group was to focus on pancreatic IPMNs, further detailed elaborations have led to the conclusion that IPMNs are indeed the prototype of a group of closely related lesions that occur in various aspects of the pancreatobiliary tract, and that many of the principles discussed above regarding pathologic evaluation and reporting would be highly applicable to these similar tumors, namely tumoral intraepithelial neoplasms, as well.

Mucinous cystic neoplasms (of the pancreas and hepatobiliary tract),^{40, 41, 217, 218} intraductal tubular/tubulopapillary neoplasms (of the pancreas and bile ducts),^{149–155} “adenomas” and “papillary neoplasms” growing within the ampulla (recently proposed to be collected under the heading of intra-ampullary papillary tubular neoplasm with an approach similar to IPMNs),¹⁶⁶ and “adenomas” and “intracystic papillary neoplasms” of the gallbladder (recently proposed to be unified under one title of intracholecystic papillary tubular neoplasms),²¹⁹ all share various important characteristics with IPMN. All are mass-forming non-invasive neoplasms that show a spectrum of neoplastic transformation; i.e., adenoma-carcinoma sequence, with the intramucosal/intraepithelial spectrum ranging from hyperplastic-like gastric epithelium to full-blown intramucosal/intraepithelial carcinomatous changes that used to be referred as “papillary adenocarcinomas”. All of these entities also exhibit cell lineages identified in IPMNs (gastric, intestinal, pancreatobiliary, oncocytic and mixed). The grading scheme and terminology for these tumors are mostly adopted from those used for IPMNs. Furthermore, they can be associated with invasive carcinoma of various types. All the reporting principles discussed above (grading, staging, typing, separate reporting of invasive carcinoma, and staging of invasive carcinoma) are also applicable to these tumors.

CONCLUSION

Proper, consistent evaluation and thorough documentation of pathologic characteristics of the neoplasms and application of uniform terminology are crucial for both the management of patients with IPMNs and further unraveling of many puzzles of this entity as well as other similar tumoral intraepithelial neoplasms of the pancreatobiliary tract.

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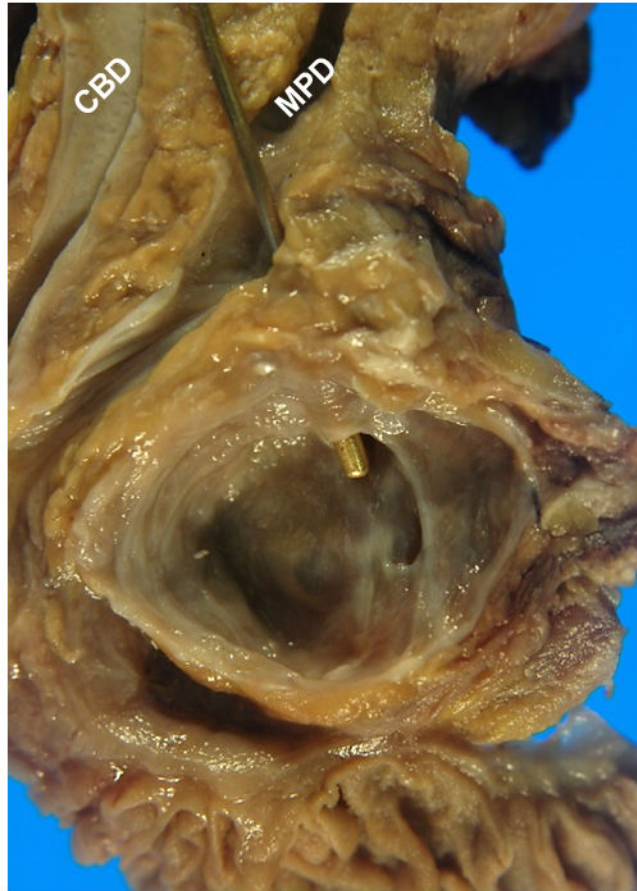


Figure 1. A branch duct IPMN manifesting as a cyst without any significant dilation of the main pancreatic duct. Papilla formation is not evident grossly.

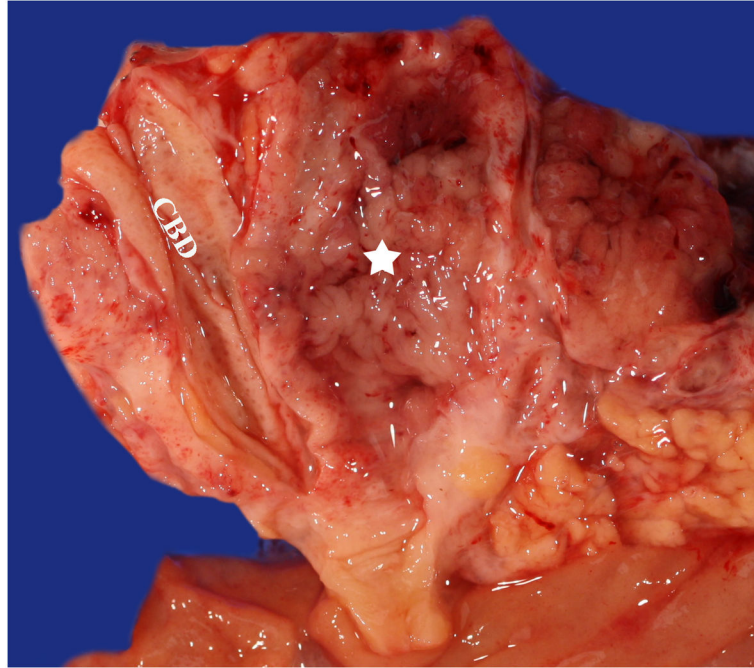


Figure 2. Main duct IPMN involving the entire pancreatic duct (star), filled with friable papillary projections and sticky mucin. Note the adjacent normal common bile duct (CBD).

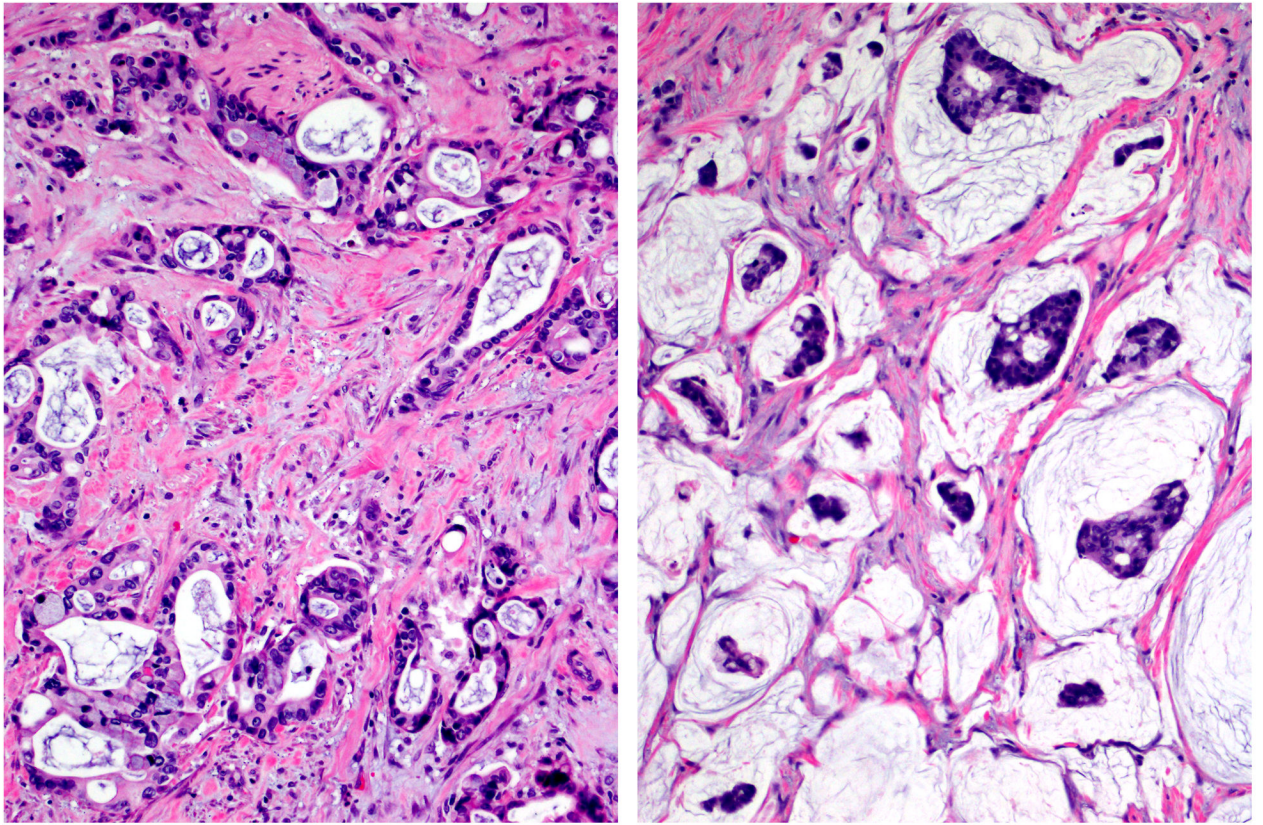


Figure 3. Ductal (tubular)-type invasive carcinoma arising in IPMN (left) is virtually indistinguishable from ordinary pancreatic ductal adenocarcinomas, characterized by atypical cells forming irregular, often complex, tubular or glandular structures, usually accompanied by dense stroma. In contrast, colloid carcinoma (right) is characterized by the mucinodular pattern composed of distinct pools of mucin that contain scanty clusters of carcinoma cells, floating within the mucin (hematoxylin and eosin stain).

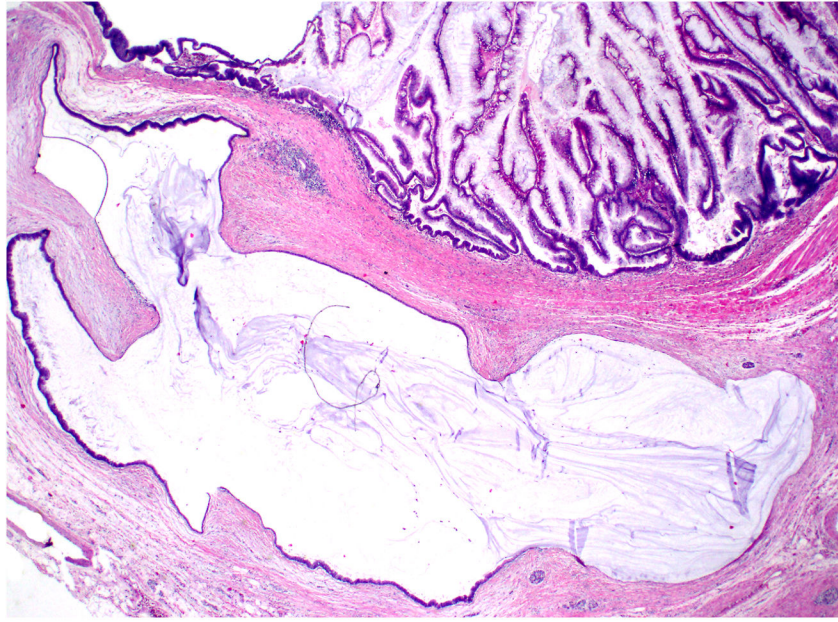


Figure 4.
In IPMNs, rupture of the ducts can lead to extrusion of mucin into the stroma, which can be difficult to distinguish from true invasive colloid carcinoma (hematoxylin and eosin stain).

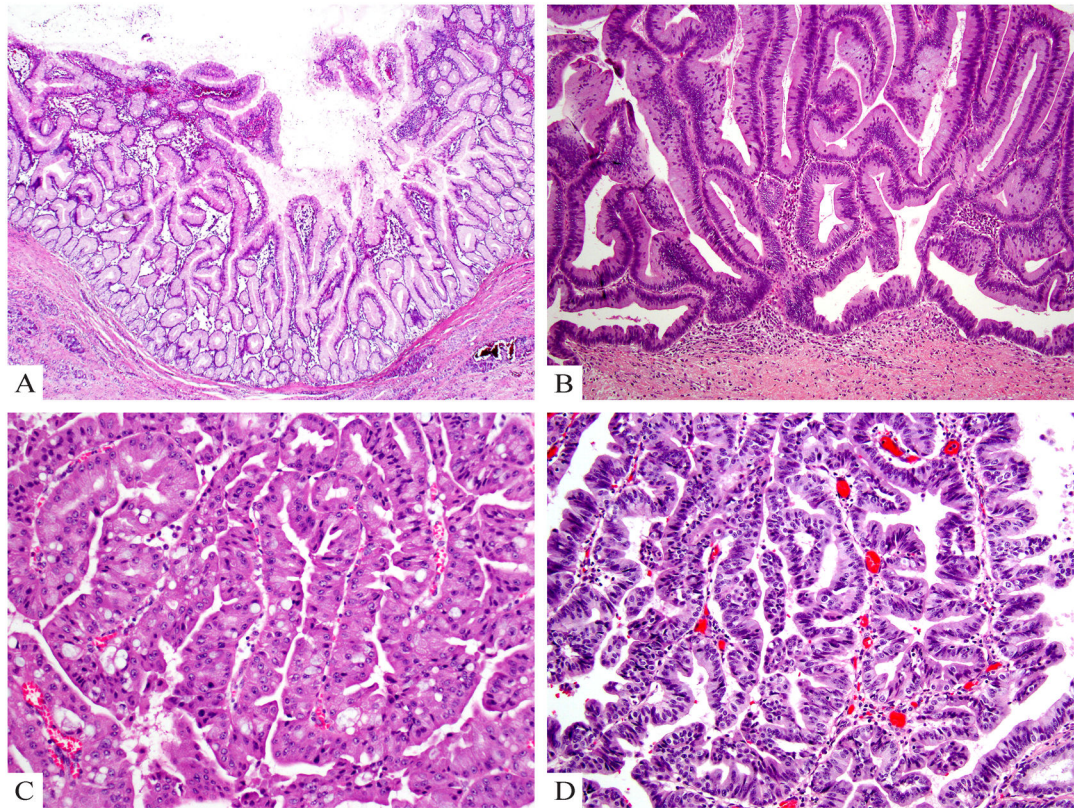


Figure 5.

A) Gastric type IPMN shows relatively simple and typically short papillae and often have pyloric-like glandular elements at their base in the cyst wall. The epithelial lining is highly similar to gastric foveolar epithelium. **B)** Intestinal type IPMN typically has a villous growth pattern and reveals pseudostratified columnar cells with a basophilic appearance and apical mucin. **C)** Oncocytic type IPMN reveals arborizing papillae lined by 2–5 layers of cuboidal cells with oncocytic cytoplasm and prominent, eccentric nucleoli as well as intraepithelial lumina. **D)** Pancreatobiliary type IPMN has complex arborizing and interconnecting papillary configurations with delicate fibrovascular cores and is composed of cuboidal cells with enlarged nuclei and little mucin production (hematoxylin and eosin stain).

Table 1

PANCREATIC RESECTION FOR INVASIVE CARCINOMAS ARISING IN ASSOCIATION WITH INTRADUCTAL NEOPLASMS

Tumor type

- Invasive carcinoma arising in association with an intraductal papillary mucinous neoplasm (IPMN)
- Invasive carcinoma arising in association with an intraductal tubulopapillary neoplasm (ITPN)
- Invasive carcinoma arising in association with mucinous cystic neoplasm (MCN)
- _____

Invasive carcinoma type

- Tubular
- Colloid
- _____

Grade of invasive carcinoma

- Well differentiated
- Moderately differentiated
- Poorly differentiated
- _____

Location of invasive carcinoma

- Head of the pancreas
- Body of the pancreas
- Tail of the pancreas
- Unknown
- _____

Size of invasive carcinoma

- Unifocal, --cm in greatest dimension
- Multifocal
 - Estimated size of all foci in aggregate: -- cm
 - Size of the largest focus: --cm

Extrapancreatic invasion

- Not identified
- Peripancreatic soft tissue
- Common bile duct
- Duodenal wall (including the mucosa)
- Ampulla of Vater
- Spleen
- Major vessel: _____
- Other organs: _____
- _____

Vascular invasion

- Not identified
- Suspected
- Identified
- _____

Perineural invasion

- Not identified
- Identified
- _____

Connectivity of preinvasive and invasive components (if documentable)

- Invasive carcinoma is connected to the preinvasive component (“invasive carcinoma derived from IPMN”)
- Invasive carcinoma is -- cm away from the IPMN (“invasive carcinoma concomitant with IPMN”)
- _____

Size of intraductal/preinvasive neoplasm

- -- cm, as measured grossly/microscopically
- -- cm, measured clinically (thin-walled cyst, partial rupture before pathologic measurement)
- _____

Maximum diameter of the main duct (if identified)

- -- cm
- Could not be determined
- _____

Gross papillary nodules (in the preinvasive component)

- Not seen
- Present, largest nodule -- cm, estimated - - % of the tumor surface
- _____

Intraductal/preinvasive neoplasm cell type

- Gastric
- Intestinal
- Oncocytic
- Pancreatobiliary
- Mixed
- Other
- _____

Grade of intraductal/preinvasive neoplasm

- Low grade
- Intermediate grade
- High grade
- _____

Adjacent pancreas

- Unremarkable

- Atrophy- mild, moderate, severe
- Fibrosis- mild, moderate, severe
- Inflammation- mild, moderate, severe
- _____

Neck (pancreatic duct) margin

- Negative
- Indeterminate for dysplasia
- Positive for dysplasia, of -- grade
- Positive for suspect invasion
- Positive for invasive carcinoma
- _____

Retroperitoneal (SMA/uncinate) margin

- Negative
- Indeterminate for dysplasia
- Positive for dysplasia, of -- grade
- Positive for suspect invasion
- Positive for invasive carcinoma
- _____

CBD margin

- Negative
- Indeterminate for dysplasia
- Positive for dysplasia, of -- grade
- Positive for suspect invasion
- Positive for invasive carcinoma
- _____

Other organs

- Stomach is unremarkable
- Stomach exhibits _____
- Duodenum is unremarkable
- Duodenum exhibits _____
- Spleen is unremarkable _____
- Spleen exhibits
- _____

Lymph nodes

- Number of lymph nodes examined: ____
- Number of lymph nodes with metastasis: _____
- Perinodal extension
 - Present
 - Absent
- _____

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Staging (AJCC 2010)

pT1 Invasive carcinoma is limited to the pancreas and ≤ 2 cm in greatest dimension

T1a: ≤ 0.5 cm

T1b: > 0.5 cm; ≤ 1 cm

T1c: > 1 cm; ≤ 2 cm

pT2 > 2 Invasive carcinoma is limited to the pancreas and cm in greatest dimension

pT3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

pT4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

pN0 No regional lymph node metastasis

pN1 Regional lymph node metastasis

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Table 2

PANCREATIC RESECTION FOR PREINVASIVE NEOPLASMS

Intraductal/preinvasive neoplasm type

- Intraductal papillary mucinous neoplasm (IPMN)
- Intraductal tubulopapillary neoplasm (ITPN)
- Mucinous cystic neoplasm (MCN)
- _____

Grade of intraductal/preinvasive neoplasm

- Low grade
- Intermediate grade
- High grade (Tis)
- _____

Extent of high grade dysplasia (Tis)

- Focal (<25% of neoplasm)
- Substantial (25–75%)
- Diffuse (>75%)
- _____

Invasion

- No invasion is identified
- Indeterminate (suspicious) for invasion
 - Suspect focus -- centimeter
 - Suspect focus composed of -- (mucin, tubules, other).
- (If there is definite invasion, please see synoptic form for invasive carcinomas arising in association with IPMN).
- _____

Predominant cell type

- Gastric
- Intestinal
- Oncocytic
- Pancreatobiliary
- Mixed
- Other
- _____

Location

- Head of the pancreas
- Body of the pancreas
- Tail of the pancreas
- Undetermined
- _____

Size of preinvasive neoplasm

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- -- cm, as measured grossly/microscopically
- -- cm, measured clinically (thin-walled cyst, partial rupture before pathologic measurement)
- _____

Gross papillary nodules

- Not seen
- Present, largest nodule -- cm, estimated -- % of the tumor surface
- _____

Multifocality

- Unifocal, multilocular
Overall size:
Size of the largest loculi:
- Multifocal
Numbers of the foci:
Size of the largest focus:
- _____

Maximum diameter of the main duct (if identified)

- -- cm
- Could not be determined
- _____

Adjacent pancreas

- Unremarkable
- Atrophy- mild, moderate, severe
- Fibrosis- mild, moderate, severe
- Inflammation- mild, moderate, severe
- _____

Neck (pancreatic duct) margin

- Negative
- Indeterminate for dysplasia
- Positive for dysplasia, of -- grade
- Positive for suspect invasion
- _____

Retroperitoneal (SMA/uncinate) margin

- Negative
- Indeterminate for dysplasia
- Positive for dysplasia, of -- grade
- Positive for suspect invasion
- _____

CBD margin

- Negative
- Indeterminate for dysplasia

- Positive for dysplasia, of -- grade
- Positive for suspect invasion
- _____

Other organs/findings

- Stomach is unremarkable.
- Stomach exhibits _____
- Duodenum is unremarkable
- Duodenum exhibits _____
- Spleen is unremarkable
- Spleen exhibits _____
- _____

Lymph nodes

- All -- lymph nodes are negative for tumor (If there is tumor in lymph nodes, please see form for invasive carcinomas arising in association with IPMN).
- _____

Tumor sampling:

- The tumor was submitted entirely for microscopic examination in -- blocks.
- _____

Overall sampling:

- The uninvolved pancreas was submitted entirely for microscopic examination in -- blocks.
- The uninvolved pancreas was submitted representatively for microscopic examination in -- blocks.

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