A REVISED CLASSIFICATION SYSTEM AND RECOMMENDATIONS FROM THE BALTIMORE CONSENSUS MEETING FOR NEOPLASTIC PRECURSOR LESIONS IN THE PANCREAS

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Abstract

International experts met to discuss recent advances and to revise the 2004 recommendations for assessing and reporting precursor lesions to invasive carcinomas of the pancreas, including pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm, and other lesions. Consensus recommendations include the following: 1) To improve concordance and to align with practical consequences, a two-tiered system (low vs. high-grade) is proposed for all precursor lesions, with the provision that the current PanIN-2 and neoplasms with intermediate-grade dysplasia now be categorized as low-grade. Thus, "high-grade

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dysplasia" is to be reserved for only the uppermost end of the spectrum ("carcinoma in situ" type lesions). 2) Current data indicate that PanIN of any grade at a margin of a resected pancreas with invasive carcinoma does not have prognostic implications; the clinical significance of dysplasia at a margin in a resected pancreas with IPMN lacking invasive carcinoma remains to be determined. 3) Intraductal lesions 0.5–1 cm can be either large PanINs or small IPMNs. The term "incipient IPMN" should be reserved for lesions in this size with intestinal- or oncocytic-papillae or *GNAS* mutations. 4) Measurement of the distance between an IPMN and invasive carcinoma and sampling of intervening tissue are recommended to assess concomitant versus associated status. Conceptually, concomitant invasive carcinoma (in contrast with the "associated" group) ought to be genetically distinct from an IPMN elsewhere in the gland. 5) *"Intraductal spread of invasive carcinoma"* (aka, "colonization") is recommended to describe lesions of invasive carcinoma invading back into and extending along the duct system, which may morphologically mimic high-grade PanIN or even IPMN. 6) *"Simple mucinous cyst"* is recommended to describe cysts > 1 cm having gastric-type flat mucinous lining at most minimal atypia without ovarian-type stroma to distinguish them from IPMN. 7) Human lesions resembling the acinar-to-ductal metaplasia and atypical flat lesions of genetically engineered mouse models exist and may reflect an alternate pathway of carcinogenesis; however, their biological significance requires further study. These revised recommendations are expected to improve our management and understanding of precursor lesions in the pancreas.

Keywords

Pancreatic intraepithelial neoplasia (PanIN); intraductal papillary mucinous neoplasm (IPMN); mucinous cystic neoplasm (MCN); precursor; adenocarcinoma; atypical flat lesions (AFL)

INTRODUCTION

International consensus meetings held in 1999, 2000, and 2003 formed the basis for the current definition and classification of the two major precursor lesions to invasive pancreatic carcinoma; pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) [1, 2]. PanIN is defined as *a microscopic, flat or papillary, noninvasive epithelial neoplasm characterized by varying amounts of mucin and degrees of cytologic and architectural atypia.* IPMN is defined as *a grossly visible, predominantly papillary or rarely flat, noninvasive mucin-producing epithelial neoplasm arising in the main pancreatic duct or branch ducts* [1, 2]. All grades of PanINs and IPMNs are regarded to be neoplastic, and these lesions are divided into three tiers based on the degree of dysplasia[1, 2]. The classification and grading system developed for PanIN, IPMN, and mucinous cystic neoplasm (MCN) has tremendously helped our understanding of these lesions and was subsequently incorporated in the classifications of the Armed Forces Institutes of Pathology/ American Registry of Pathology (AFIP/ARP) [3] and of the World Health Organization (WHO) [4]. The classification system has also helped researchers interpret genetically engineered mouse models (GEMM) that recapitulate human disease and formed the basis for studies of the genetics and gene expression patterns of these precursor lesions in the human pancreas [5–10].

However, when the original classification was introduced, pancreas surgery was mainly performed at a few large tertiary referral centers, mostly on patients with invasive pancreatic carcinoma. In spite of a rising academic awareness of pancreatic cancer precursor lesions at that time, meticulous pathologic studies in conjunction with molecular analyses were just in their infancy. The classification was therefore based on limited data on the natural history and clinical significance of the lesions, which were almost all studied in the setting of invasive carcinoma, and genetic analyses, while they supported the classification, were incomplete. With improvements in imaging to detect minute pancreatic lesions and increases in the number of centers now performing pancreatic surgery, although the situation that surgeries are performed mainly for PDA at a few large tertiary referral centers is still the case, more surgeries have been performed for indications other than invasive carcinoma. This has enormously added to our knowledge of the whole spectrum of pancreatic neoplasms including PanIN and IPMN [11–19]. In addition, our understanding of the genetics of precursors has greatly expanded with the introduction of routine molecular genetic analyses, including next generation sequencing [20–28].

Clinical advances have produced a management dichotomy, especially for IPMNs, such that lesions with low-grade or intermediate-grade dysplasia are mostly regarded as low-risk for progression and therefore amenable to clinical observation, whereas the precursor lesions with high-grade dysplasia (also called "carcinoma in situ" based on geographic practice preferences) are considered to have a significant potential for progression to invasive carcinoma and thus usually are surgically resected [29]. Similarly, we also recognize that while PanINs are biologically important for understanding the origins of invasive carcinoma, PanIN-1s and PanIN-2s are common incidental findings and probably not clinically relevant at this time [30].

To assess the impact of these advances and to discuss the possibility of devising a pathologic definition and classification system that more accurately reflects our new knowledge and new clinical needs, an international consensus meeting was organized by Drs. Ralph H. Hruban and David S. Klimstra. The group convened at The Johns Hopkins University School of Medicine from June 17 to 18, 2014, under the auspices of The Sol Goldman Pancreatic Cancer Research Center, and included an international group of experts from various disciplines.

DESIGN

An international consensus meeting as well as pre- and post-meeting analyses were organized and co-chaired by R.H.H. and D.S.K. Participants including pathologists, surgeons, and gastroenterologists from North America (Mexico, USA), Europe (France, Germany, Netherlands, United Kingdom), and Asia (Japan, Korea) were selected based on participation in the 2003 consensus meeting or significant contributions to the field after the 2003 meeting. Before the meeting, an elaborate list of discussion topics was created based on input from all meeting participants. These discussion topics were collated and recirculated for further input from all of the participants in the meeting, and selected meeting participants were tasked to give presentations at the meeting summarizing the current

published data and highlighting issues of controversy related to these topics during the meeting.

The discussion was focused on classification, reporting and histologic grading of PanINs, IPMNs, and MCNs, as well as on additional lesions with possible relevance to pancreatic carcinogenesis, such as acinar-ductal metaplasia and atypical flat lesion. After discussion, specific questions and action items were proposed and subjected to voting by the participants. Agreement among >80% of participants was regarded as consensus.

RESULTS

TWO-TIERED VS THREE-TIERED CLASSIFICATION SYSTEM FOR PanINs, IPMNs AND MCNs

Problematic Issues—The three-tiered grading systems for PanINs, IPMNs, and MCNs were originally created to encompass the full spectrum of lesions, and because it was felt that they would allow for detailed clinical and genetic studies of the entire range of lesions observed, which they did. However, the clinical significance of PanIN 1 and 2 lesions has been questioned [13, 31]. Moreover, with the growing use of abdominal imaging, more IPMNs are being diagnosed incidentally, and many of these are low- or intermediate-grade and of uncertain clinical significance [31–35]. Non-operative follow-up of these cysts has revealed a very low risk of progression to invasive cancer [36]. In the meantime, the distinction of these innocuous processes from more clinically-relevant advanced forms of intraepithelial neoplasia has become more than an academic exercise, with major clinical implications in daily clinical management of these patients. Therefore, it is not surprising that the current three-tiered classification scheme is not in line with the 2012 consensus guidelines of the International Association of Pancreatology for the management of IPMNs and MCNs. According to these guidelines, precursor lesions with either low-grade or intermediate-grade dysplasia are mostly regarded as amenable to clinical observation, whereas surgery is recommended for precursor lesions with high-grade dysplasia [29].

As the goal of clinical management is to observe low- and intermediate-grade precursor lesions and to resect high-grade precursor lesions in order to decrease the risk of invasive cancer, a two-tiered classification scheme was felt to be more in line with practical consequences: low-grade and intermediate-grade dysplasia likely has no immediate clinical consequences, whereas high-grade dysplasia usually requires clinical attention.

Revised Classification—A two-tiered classification, low-grade versus high-grade, was recommended to replace the former three-tiered classification for PanIN, IPMN and MCN (Table 1).

The former PanIN-2 and intermediate-grade dysplasia IPMN/MCN categories are now to be categorized as low-grade. Accordingly, the term high-grade is to be reserved ONLY for the uppermost end of the spectrum, i.e. most advanced dysplasia. In some geographic regions, high-grade dysplasia is parenthetically referred to as "carcinoma in situ". As in the former three-tiered classification, this revised two-tiered classification is also based ONLY on the

histology, and the lesions are graded on the basis of the highest degree of architectural and cytologic atypia identified anywhere within the lesion (Figures 1–3).

Reporting of Cases—The recommended terminology is:

- For PanIN:

    - Low-grade PanIN

    - *High-grade PanIN ("carcinoma in situ"*, according to local usage)

- For tumor-forming intraepithelial neoplasms (IPMN and MCN)

    - IPMN/MCN, low-grade

    - IPMN/MCN, high-grade

        ♦ *IPMN (and MCN), high-grade* may be further classified with the relevant local usage such as "carcinoma in situ" in parenthesis.

- For cases that also have an associated invasive carcinoma

    - IPMN/MCN, ___ grade, with an associated invasive carcinoma

        ♦ *Invasive carcinoma with an associated IPMN/MCN* may also be used.

In reporting IPMN and MCN, it is suggested that the order of reporting starts with the entity name (IPMN or MCN), followed by the grade, and then the morphologic type (gastric, intestinal, pancreatobiliary, or oncocytic) [37], an involved portion of ducts (the main or branch) (if relevant), and size. It is of utmost relevance to determine and document the presence or absence of an associated invasive carcinoma. If there is an associated invasive carcinoma, the pathology report should separately and clearly document the detailed characteristics of the precursor lesion (IPMN or MCN) and the invasive components (type, grade, size, and the stage) [38]. Although the recommended terminology is IPMN or MCN with an associated invasive carcinoma, in order to report the biologically more important lesion first, "Invasive carcinoma with an associated IPMN/MCN" may also be used. Following the WHO 2010's recommendation, the terms "invasive IPMN/MCN", "malignant IPMN/MCN", or "mucinous cystadenocarcinoma" (which have been used in the literature to describe a wide variety of neoplasms ranging from precursors with high-grade dysplasia to invasive carcinoma) should be avoided, as they are non-specific and may create confusion and prevent accurate comparison of data from different centers,[39–53].

During transition to the revised two-tiered classification and for research purposes, the diagnosis may be further supplemented with the former three-tiered classification for each precursor lesion [1, 2]. If the former three-tiered classification is used, it should be reported in parentheses after the main diagnosis. For example, a neoplasm previously reported as "MCN with intermediate-grade dysplasia" would now be reported as *MCN, low-grade (intermediate-grade dysplasia in WHO-2010).*

Because they are so common and of no proven clinical significance [13, 30, 31, 35, 54–57], it was agreed that *low-grade PanIN* lesions (PanIN-1 or PanIN-2 in WHO 2010) do not need to be reported in pathology reports, especially in patients with an invasive ductal adenocarcinoma.

Given the low rate of progression from low-grade PanIN to invasive carcinoma, the clinical significance of isolated foci of *low-grade PanIN* is regarded to be negligible [58]. If these lesions are to be included in reports, it is advisable to emphasize their clinical inconsequentiality in order to avoid overtreatment [30].

In contrast, if *high-grade PanINs* (PanIN-3 in WHO 2010) are encountered, these lesions may have clinical significance and should be reported, particularly in the absence of an invasive carcinoma elsewhere in the pancreas. In fact, *high-grade PanINs* are usually found in pancreata with an invasive carcinoma, and they may in fact serve as a surrogate marker for invasion elsewhere in the organ [31, 59].

ASSESSMENT OF PanIN AND IPMN LESIONS ON RESECTION MARGINS

Current data suggests that the presence of PanIN lesions at a surgical resection margin does not affect the survival of patients who undergo resection for invasive carcinoma; i.e., no significant difference in the median survival time was observed between patients with PanIN of any grade at a resection margin and those without PanIN at the margin [30]. In the absence of an established invasive carcinoma, if *high-grade PanIN* is present at a margin, additional surgery may be justifiable because of the rarity of *high-grade PanIN* lesions in the absence of an invasive carcinoma [60].

The clinical significance of IPMN at a resection margin in patients without an invasive carcinoma is less clear [61–65]. Some have reported that recurrences after surgical resection are associated with the presence of IPMN at a margin, while others have not found such an association [61–65]. Other data suggest that the risk for recurrence is more related to the overall grade of dysplasia within the IPMN than with the status of the margin [66]. Many studies of recurrence after resection of IPMNs are limited by relatively short follow-up, and emerging data suggest that patients with resected IPMNs are at increased risk of developing a metachronous IPMN or invasive carcinoma after prolonged follow-up [67–69]. In addition, IPMNs can be multifocal, and this multifocality can confound the interpretation of recurrences after the surgical resection of an IPMN [70]. Regardless of whether disease in the remnant pancreas is caused by recurrence of the patient's original IPMN or the growth of a separate lesion, careful clinical follow-up after the resection is warranted for patients with an IPMN of any grade dysplasia and any margin status.

Intraoperative frozen sections may be used to evaluate resection marginal status [71]. At research centers, frozen sections can also be used to guide the harvesting of tissues for research purposes. The value of frozen sections in evaluating the main lesion in IPMNs is less clear, unless an intraoperative decision would depend on the results of the frozen section diagnosis. Similarly, there are few data to guide the use of frozen sections in evaluating resection margins for IPMNs without an associated invasive carcinoma. Although the evidence is not strong, further resection is recommended if high-grade dysplasia is present at a resection margin at the time of frozen section [72]. Due to the low probability of a positive result, evaluation of margin status may be inconsequential for cases with branch duct IPMNs without main duct dilatation. If a margin is submitted for frozen section diagnosis, the grade of dysplasia at the margin may be reported without distinguishing IPMN from PanIN because such distinction can be difficult based purely on histology [2]. In this case, a

diagnosis of *intraductal mucinous epithelium with low- /high-grade dysplasia (PanIN or IPMN)* may be rendered.

DIFFERENTIAL DIAGNOSIS OF PRECURSOR LESIONS

Lesions Between PanIN and IPMN—Although PanINs and IPMNs are distinct intraductal neoplasms in their most classic manifestations[73], the distinction between PanINs and IPMNs is often a difficult task in daily practice. As discussed in the previous consensus report, PanINs and IPMNs share fundamental common features, i.e., they are composed of mucinous columnar cells with papillary configuration, they exhibit various grades of atypia, and they may involve both smaller and major ducts [2]. Size is the major feature used to distinguish these lesions: PanINs usually are < 0.5 cm, while IPMNs usually are 1.0 cm in diameter [2]. Although this classification is clinically useful (as clinical imaging can routinely detect lesions 1 cm), the classification does leave a "no man's land" of lesions between 0.5 and 1.0 cm. Such lesions can be large PanINs or small IPMNs.

One feature that can be useful in classifying lesions between 0.5 and 1 cm is the direction of differentiation of the neoplastic cells. The epithelial cells in almost all PanINs have gastric-foveolar differentiation. By contrast, IPMNs can have a variety of different directions of differentiation including gastric, intestinal, pancreatobiliary, and oncocytic [37]. Therefore, although small gastric-type IPMNs are difficult to distinguish from large PanINs, lesions with intestinal or oncocytic differentiation are most likely IPMNs. Unfortunately, the majority of intraductal lesions in the size range of 0.5–1.0 cm exhibit gastric differentiation, limiting the utility of this criterion.

GNAS mutations typically occur in IPMNs, mostly of intestinal or gastric subtype [22, 23, 74], whereas they are very rarely encountered in PanIN lesions [75]. Therefore, *GNAS* mutations could be used for the differential diagnosis of small cyst-forming lesions 1.0 cm, as has been recently shown [75, 76] (Figure 4). At the molecular level, it is clear that IPMNs start as smaller lesions, some of which overlap with PanIN lesions.

Based on these results, it is recognized that there is likely a continuum of progression in gastric-type lesions from some that would be initially classified as a PanIN and later be recognizable as IPMN because of larger size. The term *incipient IPMN* can be applied to lesions between 0.5 and 1.0 cm in diameter with long finger-like papillae, villous intestinal or oncocytic differentiation, or with a *GNAS* mutation. Small cystic gastric-type lesions without any features of the incipient IPMN should be documented descriptively (such as *intraductal neoplasm, 0.7 cm, lined by low-grade gastric type epithelium; differential diagnosis includes low-grade PanIN and IPMN, low-grade*). Finally, because such thin walled cysts may collapse during resection or pathological examination, the suggestion was made that radiographic findings may be integrated to determine the actual size of small cysts. When this is done, some lesions that microscopically fall in the 0.5 to 1 cm range may in fact be larger and reach diagnostic size criteria for an IPMN.

IPMN with Concomitant Invasive Carcinoma—It is now well-established that invasive carcinoma can arise from an IPMN [74]. However, invasive carcinoma can also arise independently in a pancreas that also contains an IPMN elsewhere. This has been previously

referred to as IPMN with "concomitant" invasive carcinoma to distinguish it from cases in which the relation of the IPMN and the invasive carcinoma is more clearly evident [77, 78]. These two situations in which IPMN and invasive carcinoma occur in the same pancreas are conceptually quite distinct: the IPMN is a direct precursor to the carcinoma in IPMN-associated carcinoma, while the IPMN and carcinoma are separate and likely independent in IPMN with a concomitant invasive carcinoma. These two situations may also be clinically distinct. For example, Yamaguchi, *et al.* found that IPMNs and their associated invasive carcinomas are enriched for main duct IPMNs and colloid carcinomas, whereas IPMNs with concomitant carcinoma are almost always branch duct type, and the invasive carcinomas are rarely colloid carcinomas [78]. Interestingly, the reported survival difference between the concomitant invasive carcinomas and invasive carcinomas without IPMN suggest that the presence of IPMN (even separate from the invasive carcinoma) is associated with improved patient outcome [78]. Some of this difference is lost after adjusting for tumor stage, suggesting that the survival difference is due to earlier diagnosis of IPMN with a concomitant invasive carcinoma [79]. Further clinicopathological and genetic studies are needed to definitively characterize the relationship of IPMNs with concomitant invasive carcinoma and to determine the clinical relevance of this entity.

Although conceptually concomitant invasive carcinoma ought to be genetically distinct from an IPMN elsewhere in the gland (in contrast with the "associated" group), there are no definite criteria to clearly distinguish between the two situations on a morphological basis besides a clear transition between in situ and invasive carcinoma supports a carcinoma associated with IPMN while intervening uninvolved pancreas supports that the carcinoma is concomitant rather than associated. In order to produce evidence to support this distinction, radiologic, gross, and microscopic findings should be incorporated. At the pathologic level, we therefore recommend careful gross measurement of the distance between the IPMN and the invasive carcinoma, as well as extensive or complete histologic sampling of intervening pancreatic tissue to determine the microscopic relationship of the IPMN to the invasive carcinoma. Although currently only performed in the research setting, genetic studies may indicate that concomitant invasive carcinomas are independent from the IPMN in contrast to IPMN-associated carcinomas, which should share most genetic alterations with the IPMN.

Intraductal Spread of Invasive Carcinoma—Invasive ductal adenocarcinoma can invade back into and extend along the duct system, morphologically mimicking intraductal neoplasia such as PanIN or even IPMN (Figure 5). Although few studies address this specific issue, this form of intraductal spread, also known as "cancerization of the ducts," is common and has been reported in as many as 70% of resections for invasive pancreatic cancer [80]. This difficulty has hampered research on PanIN lesions in pancreata with an invasive cancer, as the investigator can never be certain if the lesion being studied is a true precursor lesion or just invasive carcinoma growing along a duct.

The meeting participants reached the consensus that the term *intraductal spread of invasive carcinoma* should be used to describe these lesions. This consensus was reached with the understanding that intraductal spread of invasive carcinoma can sometimes be impossible to distinguish definitively from *high-grade PanIN*, as both consist of cytologically malignant

epithelium within a duct. We also recognize the difficulty in dealing with such lesions at resection margins, particularly on frozen section.

Macroscopic Cysts with Flat Mucinous Lining—Cysts with predominantly flat (i.e. non papillary) mucinous lining, usually with gastric phenotype (MUC1 and MUC2 negative, MUC5AC positive) and at most minimal atypia, are sometimes encountered in daily practice (Figure 6). These cysts lack ovarian-type stroma and are >1 cm. These lesions have been addressed with different terms in the literature, depending for instance on the features of the surrounding pancreatic tissue. In the presence of an obstruction of the pancreatic duct, they have been interpreted as retention cysts with partial PanIN1-lining [3]. Lesions with no visible obstructive process surrounded by paucicellular fibrous bands have been termed as "mucinous non-neoplastic cysts" [81] or "cystic mucinous duct lesion" (Figure 6) [82]. Although their pathogenesis remains elusive, the participants felt that these lesions are benign with no potential for progression and should be clearly distinguished from IPMN and MCN. The term *simple mucinous cyst* is recommended.

ACINAR-DUCTAL METAPLASIA AND ATYPICAL FLAT LESIONS

Acinar-Ductal Metaplasia—A growing body of evidence, mostly coming from recently developed GEMMs but also based on observations in the pancreas of individuals with a history of familial pancreatic cancer, supports the concept of a possible alternative pathway to the development of invasive carcinoma, originating through so-called acinar-ductal metaplasia (ADM). It is suggested that ADM could be related to ductal carcinogenesis along a metaplasia-dysplasia-cancer sequence [83].

ADM lesions are usually associated with fibrosis and inflammation, and the formation of tubular complexes is accompanied by loss of acinar markers and progressive increase of ductal markers (Figure 7) [84–86]. The role of ADM as a possible precursor lesion of infiltrating pancreatic cancer has been boosted in the last years by numerous mouse models, which have shown that *KRAS*-based genetic targeting of acinar cells leads to the development ADM, PanIN, and invasive carcinoma [87–89], while genetically targeting the mature ductal compartment produces little change [90, 91]. ADM lesions have been described in humans, but the biological significance of these lesions is unclear [92, 93]. ADM is quite common in pancreatic resection specimens for both inflammatory and neoplastic diseases and can harbour *KRAS* mutations [94, 95]. On the other hand, genetic analyses of human PanIN lesions and their associated ADM suggest that the two lesions are not always genetically linked, as in some instances a *KRAS* gene mutation can be found in a PanIN but not in its associated ADM [4, 94–96].

Atypical Flat Lesions—Atypical flat lesions (AFLs) have recently been described. They are mostly non-mucinous, intralobular aggregates of small ducts usually measuring less than 0.5 cm, lined by cuboidal cells with cytologic atypia and surrounded by cellular stroma, often with whorls of spindle cells in a myxomatous matrix (Figure 7) [97]. AFLs were first described in genetically engineered mouse models, where they seem related to the process of ADM. However, AFLs are distinguished from ADM by the presence of cytological atypia and their peculiar stromal reaction (Figure 7). Due to their immunophenotypical and

molecular resemblance to invasive carcinoma in mouse models, it has been hypothesized that AFLs are also alternative precursor lesions. Morphologically similar lesions have been identified in the pancreata of human patients with an inherited predisposition for pancreatic cancer. In humans, AFLs occur in areas of lobulocentric atrophy and often harbour *KRAS* mutations [97, 98]. Whether AFLs represent alternative precursors to invasive carcinoma or are merely reactive changes or retrograde growth of PanINs in humans remains to be determined. ADM and AFL may be included in histopathological descriptions for research purposes, but they need not be documented in routine clinical pathological reports until their true significance is known.

CONCLUSIVE REMARKS

Recent advances in genetics and molecular biology, as well as more sensitive imaging methods and new surgical techniques, have improved our understanding of the precursor lesions that give rise to invasive carcinoma in the pancreas. There is now overwhelming evidence in the literature for a variety of organs that the clinical management of precursor lesions is best served by two-tiered classification systems. In these systems, the uppermost end of the spectrum (those that represent the most advanced dysplasia) requires careful clinical attention and treatment [99–101], while lower grade lesions lack a significant risk for progression to invasive carcinoma, and as such, do not warrant therapy [102–107]. These advances represent the basis for the introduction of two-tiered classification systems for PanIN, IPMN and MCN described here. Furthermore, it has been shown that two-tiered systems improve concordance and uniformity over three-tiered systems [1, 108–113]. Even in pure morphology, the two-tiered system is suggested to classify the dysplasia grade of precursor lesions most appropriately[114]. The applicability of the proposed two-tiered classification system to cytopathology is, however, potentially problematic because cytologic (or any preoperative) diagnosis is not intended to establish the final grade of dysplasia but rather to provide an assessment of the risk of finding high-grade dysplasia or invasive carcinoma in the resected specimen, and it is therefore we conclude that most of the classification issues discussed above are not applicable to pancreatic fine needle aspiration specimens. While our recommendations concerning differential diagnosis of precursor lesions, frozen section diagnostic, terminology and reporting are supported by experimental and clinical data, strong evidence for some of the topics addressed in this manuscript (e.g. definition of incipient IPMN; distinction between carcinoma with concomitant IPMN and carcinoma originating from IPMN; significance of ADM) is still lacking.

Despite these limitations, we believe that a more clinically relevant classification of precursor lesions, together with the use of standardized nomenclature and advances in molecular testing, will help answer most of the open questions outlined in this paper, and in particular those that are prone to have major impact on diagnosis, treatment and prognosis of patients with pancreatic diseases.

Acknowledgments

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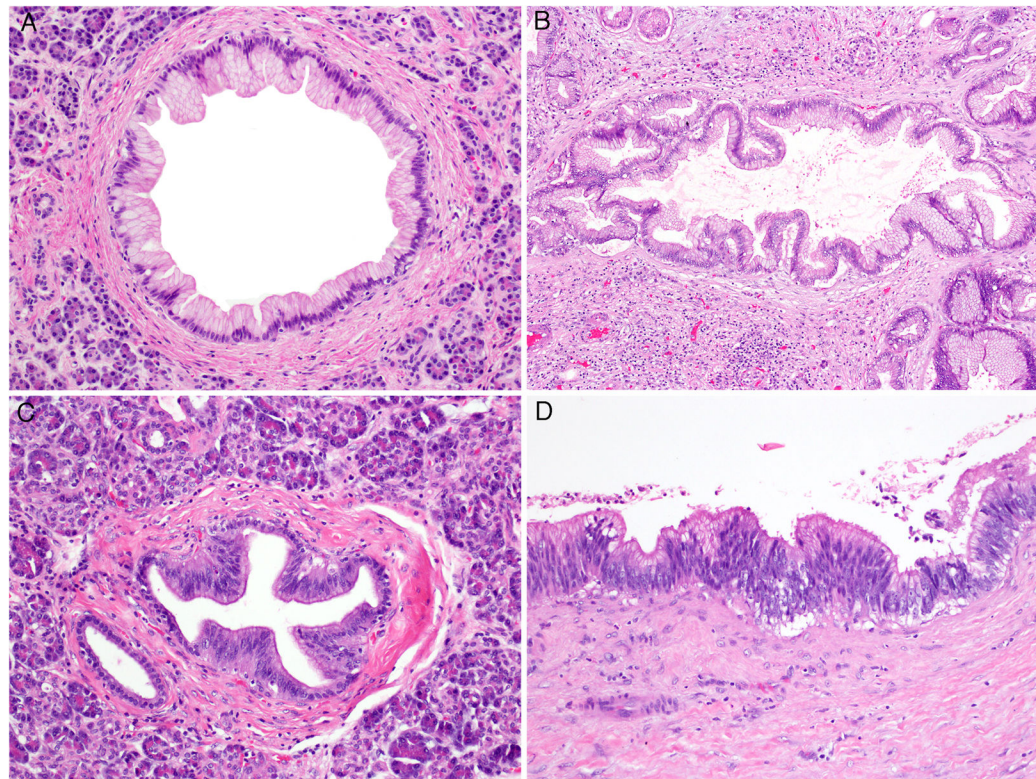
Figure 1.
Low-grade PanINs. **A.** Low-grade PanIN previously regarded as PanIN-1a in WHO 2010.
B. Low-grade PanIN previously regarded as PanIN-1b in WHO 2010. **C and D.** Low-grade
PanIN previously regarded as PanIN-2 in WHO 2010. All panels are hematoxylin and eosin
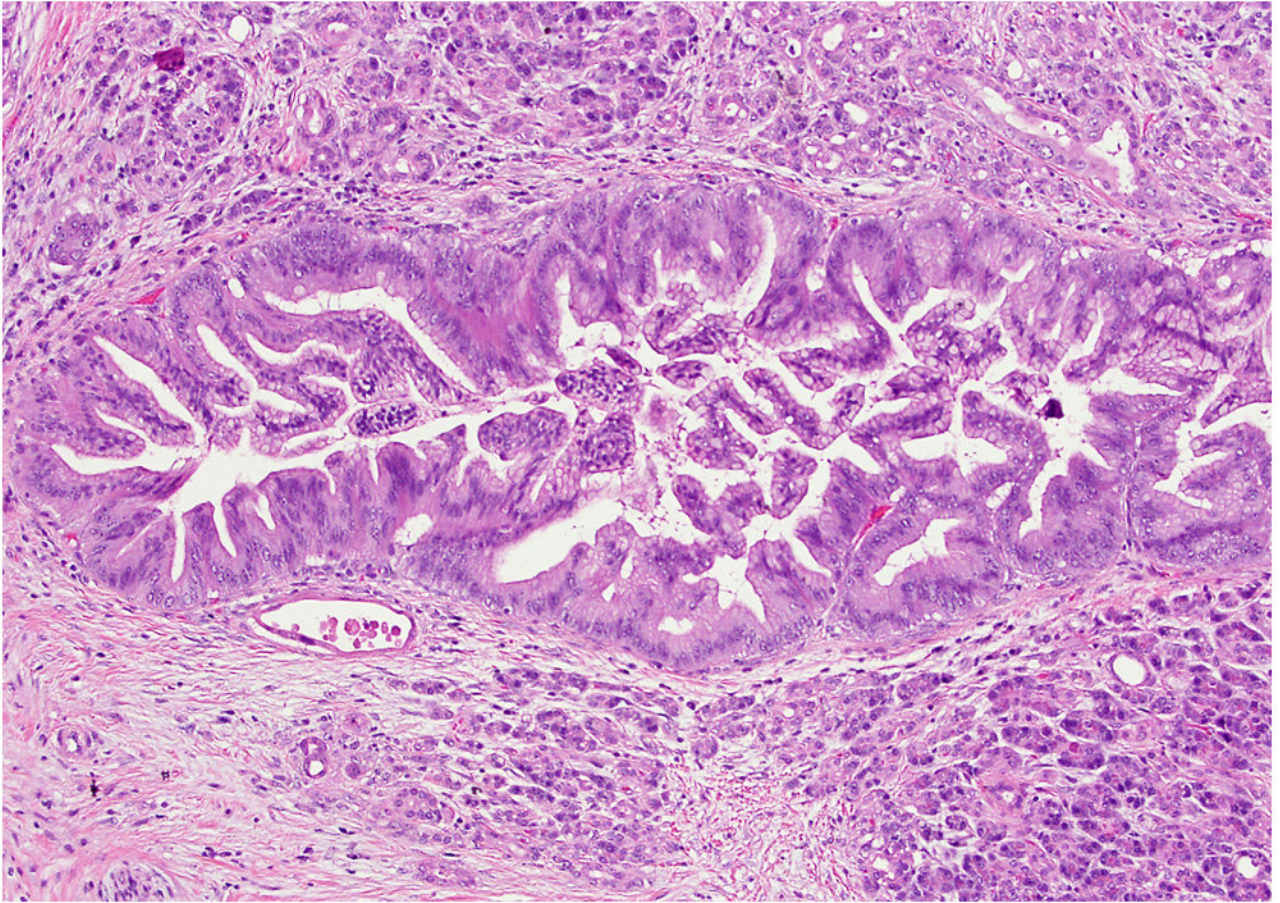staining. Original magnifications were A–C, 10×; D, 20×.

Figure 2.
High-grade PanIN previously regarded as PanIN-3 in WHO 2010. This lesion may be
termed as carcinoma in situ in some geographical regions. Hematoxylin and eosin staining.
An original magnification was 20×.
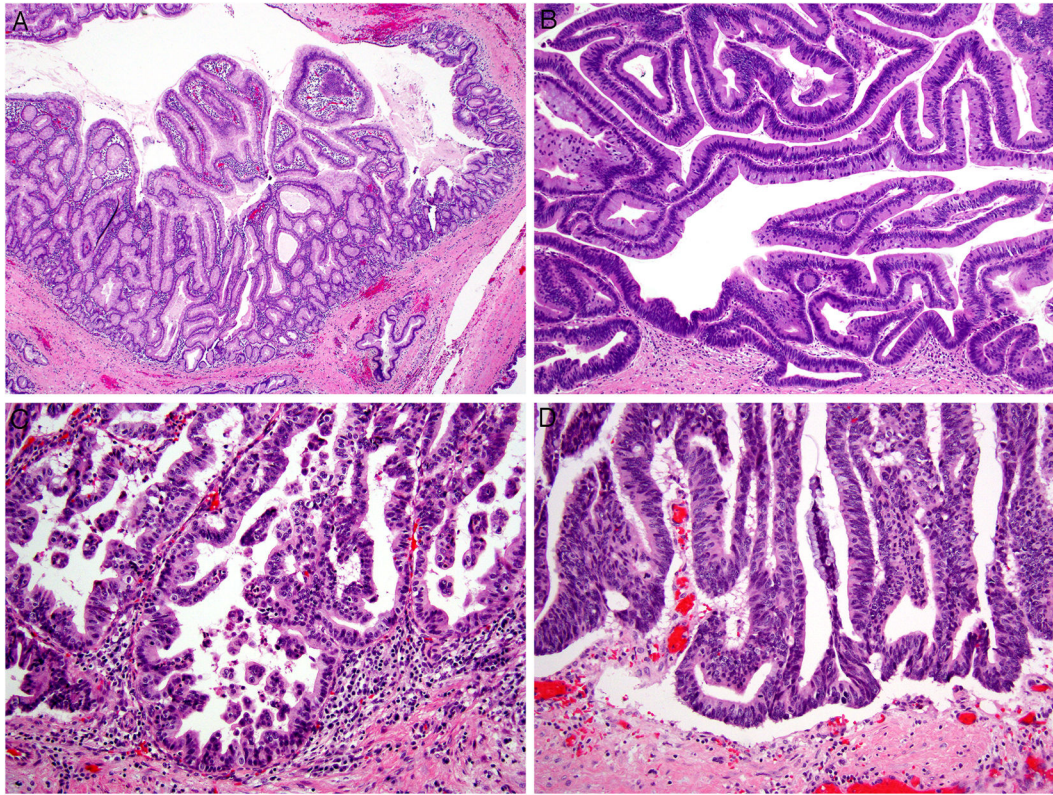
Figure 3.
IPMNs in various grades. **A.** IPMN, low-grade, previously regarded as IPMN with low-grade dysplasia in WHO 2010. **B.** IPMN, low-grade, previously regarded as IPMN with intermediate-grade dysplasia in WHO 2010. **C and D.** IPMN, high-grade, previously regarded as IPMN with high-grade dysplasia in WHO 2010. All panels are hematoxylin and eosin staining. Original magnifications were A, 4×; B–D, 20×.
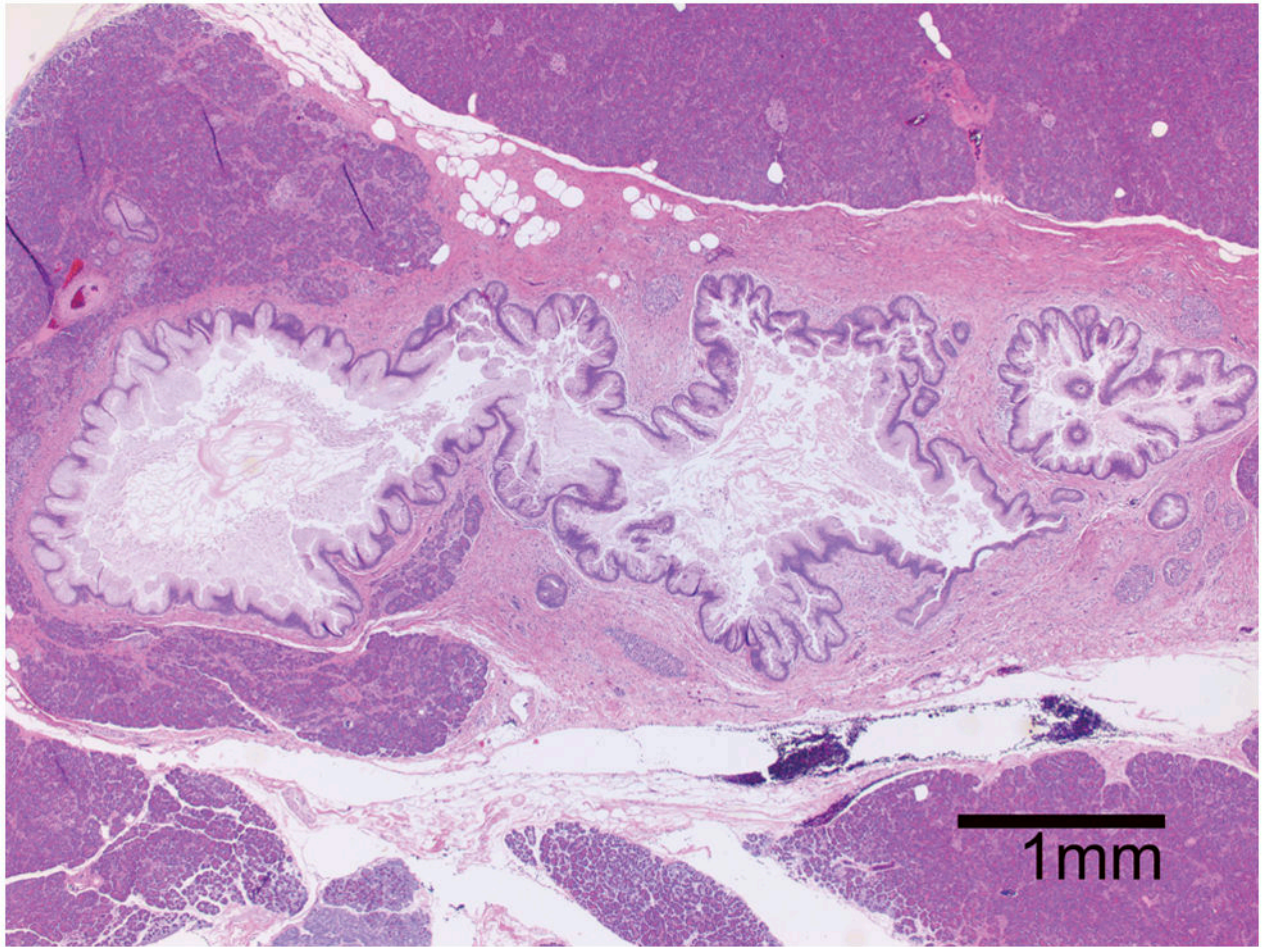
Figure 4.
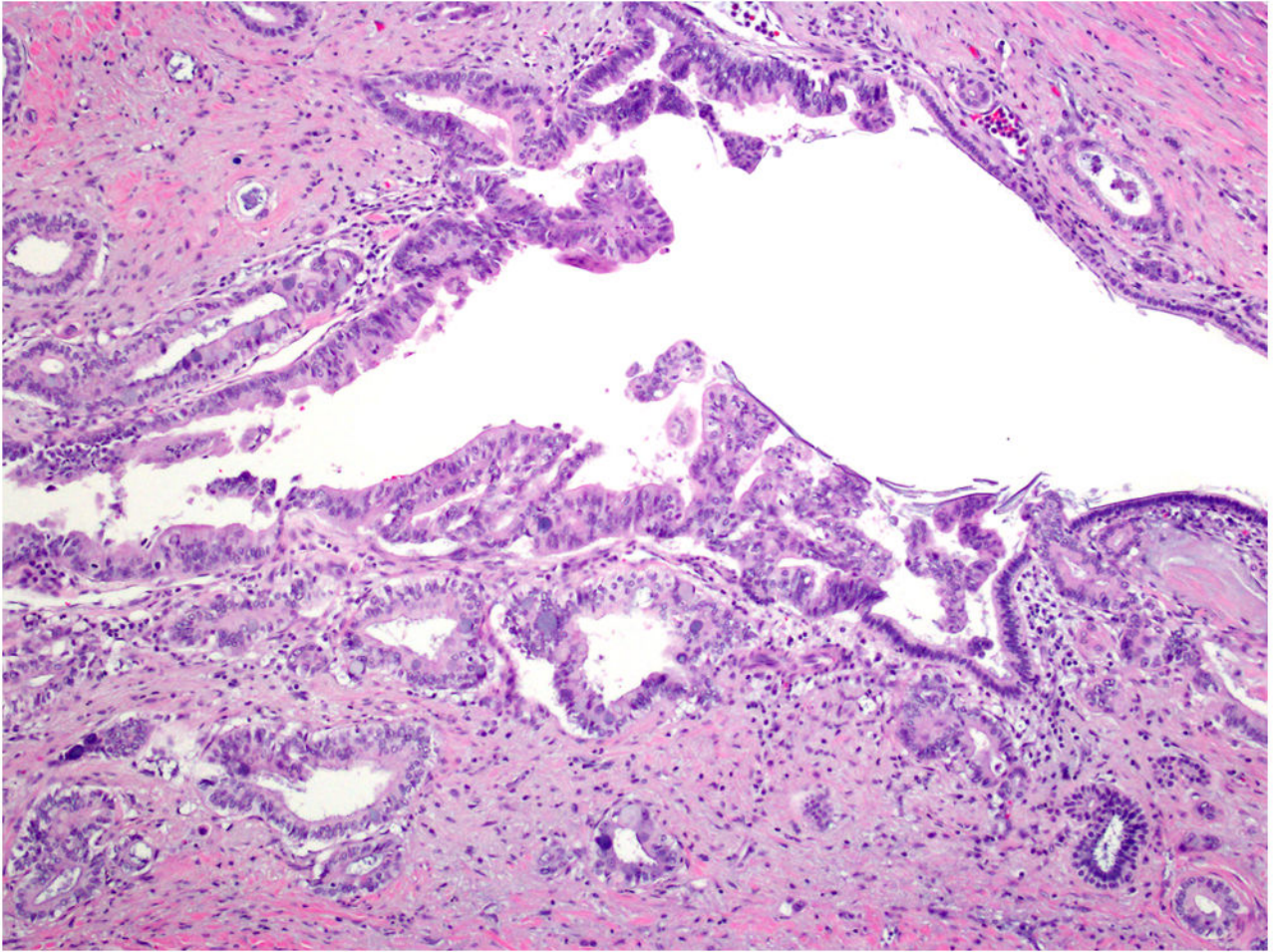Incipient IPMN lined with intestinal-type papillae.

Figure 5.
Intraductal spread of invasive carcinoma. Highly atypical epithelia undistinguishable from invasive carcinoma line a duct. Front-formation between normal cuboidal epithelia and the atypical epithelia can be recognized. Hematoxylin and eosin staining. An original magnification was 10×.
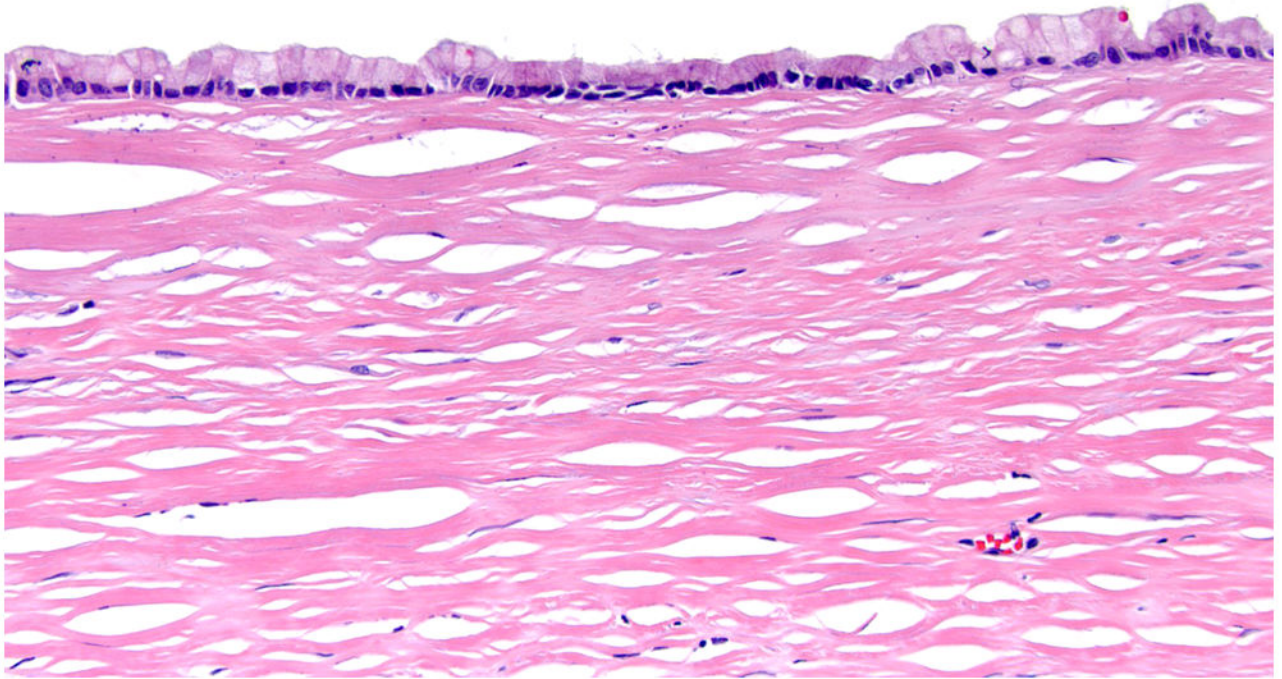
Figure 6.
Macroscopic cyst with flat mucinous lining. A cyst with predominantly flat mucinous lining with gastric phenotype is shown. Note no ovarian-like stroma. Hematoxylin and eosin staining. An original magnification was 20×.
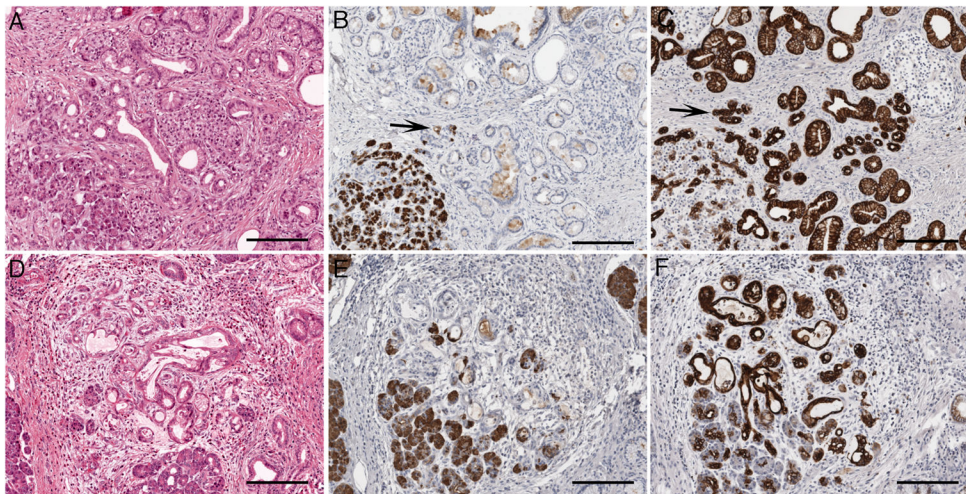
Figure 7.
Acinar-ductal metaplasia (ADM) and the atypical flat lesion (AFL) in the human pancreas.
AC: ADM presents as an **i**ntralobular change characterized by progressive replacement of
acini by ductular structures, which might display intracytoplasmic mucin, thereby
resembling low-grade PanIN. Arrows indicate hybrid ductuli with co-expression of trypsin
(**B**) and CK7 (**C**). Scale bars: 200μm. **D–F:** AFL are intralobular ductular proliferations with
cytological atypia surrounded by a loose matrix with inflammatory infiltrates. AFL are
located in ADM areas and may show focally retained tryspin expression (**E**), but mostly
display a ductal phenotype with strong and diffuse CK7 staining (**F**). Scale bars: 200μm.

Table 1

Proposed Revised Terminology of PanIN, IPMN and MCN

Former terminology (based on 2004 Classification[2] and 2010 WHO)	Revised terminology (2015)
PanIN-1a	Low-grade PanIN
PanIN-1b	Low-grade PanIN
PanIN-2	Low-grade PanIN
PanIN-3 (*carcinoma in-situ*)	High-grade PanIN
IPMN with low-grade dysplasia	IPMN, low-grade
IPMN with intermediate-grade dysplasia	IPMN, low-grade
IPMN with high-grade dysplasia (*carcinoma in-situ*)	IPMN, high-grade
IPMN with an associated invasive carcinoma	IPMN with an associated invasive carcinoma/invasive carcinoma with an associated IPMN (the latter may be used if the invasive component is substantial)
MCN with low-grade dysplasia	MCN, low-grade
MCN with intermediate-grade dysplasia	MCN, low-grade
MCN with high-grade dysplasia (*carcinoma in-situ*)	MCN, high-grade
MCN with an associated invasive carcinoma	MCN with an associated invasive carcinoma/invasive carcinoma with an associated MCN (the latter may be used if the invasive component is substantial)