Acta Cytologica

Techniques

Acta Cytologica
DOI: 10.1159/000527912

Received: October 3, 2022
Accepted: October 31, 2022
Published online: December 14, 2022

The World Health Organization Reporting System for Pancreaticobiliary Cytopathology

Martha B. Pitman[a] Barbara A. Centeno[b] Michelle D. Reid[c] Momin T. Siddiqui[d] Lester J. Layfield[e] Miguel Perez-Machado[f] Birgit Weynand[g] Edward B. Stelow[h] Maria D. Lozano[i] Noriyoshi Fukushima[j] Ian A. Cree[k] Ravi Mehrotra[l] Fernando C. Schmitt[m] Andrew S. Field[n]

[a]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [b]Department of Pathology, Moffitt Cancer Center, Tampa, FL, USA; [c]Department of Pathology, Emory University Hospital, Atlanta, GA, USA; [d]Department of Pathology, Weill Cornell Medicine, New York, New York, NY, USA; [e]Pathology and Anatomic Science Department, University of Missouri, Columbia, MO, USA; [f]Department of Cellular Pathology, Royal Free Hampstead NHS Trust, London, UK; [g]Department of Pathology, University Hospitals Leuven, Leuven, Belgium; [h]Department of Pathology, University of Virginia Hospital, Charlottesville, Charlottesville, VA, USA; [i]Department of Pathology Clinica University of Navarra, Pamplona, Pamplona, Spain; [j]Department of Diagnostic Pathology, Jichi Medical University Hospital, Shimotsuke, Japan; [k]International Agency for Research on Cancer [IARC], World Health Organization, Lyon, France; [l]Indian Cancer Genomic Atlas, Centre for Health, Innovation and Policy Foundation, Noida, India; [m]Department of Pathology, Faculty of Medicine of University of Porto, Porto, Portugal; [n]Department of Anatomical Pathology, St Vincent's Hospital, Sydney, University of New South Wales and University of Notre Dame, Sydney, NSW, Australia

Keywords
Pancreas · Cytology · WHO · Reporting · Terminology · Standardized

Abstract
The World Health Organization (WHO), the International Academy of Cytology, and the International Agency for Research on Cancer, with expert contributors from around the world, present an international approach to standardized reporting of pancreaticobiliary cytopathology. This reporting system is one of the first in a series from various body sites that mirror the WHO Classification of Tumours series and provides an evidence-based terminology system with associated risk of malignancy and diagnostic management recommendation per diagnostic category. The WHO Reporting System for Pancreaticobiliary Cytopathology (WHO system) revises the Papanicolaou Society of Cytopathology (PSC) system for Reporting Pancreaticobiliary Cytology published in 2015 and replaces the six-tiered system with a seven-tiered system: "insufficient/inadequate/nondiagnostic"; "benign (negative for malignancy)," "atypical," "pancreaticobiliary neoplasm of low risk/low grade," "pancreatic neoplasm of high risk/high grade," "suspicious for malignancy," and "malignant." The principal differences between the WHO and the PSC systems revolve around the classification of neoplasia. In the PSC system, there was a single category for "neoplastic" lesions that includes two groups, one for "benign neoplasms" [primarily serous cystadenoma] and one named "other," dominated by premalignant intraductal

Karger@karger.com
www.karger.com/acy

Correspondence to:
Martha B. Pitman, mpitman@mgh.harvard.edu

neoplasms (primarily intraductal papillary mucinous neoplasms) and low-grade malignant neoplasms [pancreatic neuroendocrine tumors (PanNETs) and solid pseudopapillary neoplasms (SPNs)]. In the WHO system, benign neoplasms with virtually no risk of malignancy are included in the "benign" category and low-grade malignancies (PanNET and SPN) are included in the "malignant" category, as per the WHO Classification of Digestive System Tumours, thus leaving in the "neoplasm" category primarily those noninvasive premalignant lesions of the ductal system. These neoplasms are divided by the cytomorphological grade of the epithelium into low risk/low-grade and high risk/high-grade, with distinctly different risks of malignancy. As with the PSC system, the WHO system advocates close correlation with imaging and encourages incorporation of ancillary testing into the final diagnosis, such as biochemical (CEA and amylase) and molecular testing of cyst fluid and bile duct brushings. Key diagnostic cytopathological features of specific lesions or neoplasms, ancillary studies for diagnostic and prognostic evaluation, and implications of diagnosis for patient care and management are discussed. In addition, the WHO system includes reporting and diagnostic management options that recognize the variations in the availability of diagnostic and prognostic ancillary testing modalities in low- and middle-income countries, where cytopathology is particularly useful and is increasingly available in the absence of histopathological services.

Introduction

The World Health Organization (WHO), the International Academy of Cytology (IAC), and the International Agency for Research on Cancer (IARC) have joined forces to publish a series of cytopathology reporting systems, which present an international approach to reporting cytopathology of various body sites and mirror the WHO Classification of Tumours series with links between the two series on the website and in the text. Like the WHO Classification of Tumours, the WHO reporting systems provide an evidence-based terminology system with associated risks of malignancy (ROMs) and diagnostic management recommendations for each diagnostic category aimed to facilitate diagnosis and patient management. Each standardized terminology system provides key diagnostic cytopathological features of specific lesions or neoplasms, discusses ancillary studies for diagnostic and prognostic evaluation, and touches on the implications of diagnosis for patient care and management, all of which aim to improve the quality of diagnosis and reporting of cytopathology. Importantly, however, the reporting systems include reporting options that will recognize the variations in the availability of diagnostic and prognostic ancillary testing modalities in low- and middle-income countries, where cytopathology is particularly useful and is increasingly available in the absence of histopathological services. In addition to the printed versions, the cytopathology volumes will be available through the WHO Classification of Tumours online website, which includes all figures in each book as well as additional whole slide images [https://tumourclassification.iarc.who.int/welcome/].

A Standing Committee or "series editors" for these books include co-chairs Ian Cree and Andrew Field, Fernando Schmitt, Martha Pitman, and Ravi Mehrotra. This Standing Committee oversees the organization, development, writing, and editing of the WHO systems. The first four books in the series include reporting systems for pancreaticobiliary, lung, lymph node and spleen, and soft tissue cytopathology. Each specific terminology system has an Expert Editorial Board (EEB), who are also the authors of this pancreaticobiliary system review. The EEB members were chosen based on their expertise in the field and/or diversity of geographical representation using the same methodology used for the 5th Editions of the WHO Tumour Classification books. The content of the books was distributed among the EEB as responsible authors and/or editors, and co-authors were then added throughout the sections. The assignment of writing and editing responsibilities used the same model used for the WHO Classification of Tumours (https://whobluebooks.iarc.fr/about/faq/) [1–3].

The WHO Reporting System for Pancreaticobiliary Cytopathology (WHO system) [4] revises and updates the Papanicolaou Society of Cytopathology (PSC) System for Reporting Pancreaticobiliary Cytology published in 2015 [5, 6]. The PSC system utilizes a six-tiered system and advocates close correlation with imaging and incorporation of ancillary testing into the final diagnosis, such as biochemical (CEA and amylase) and molecular testing of pancreatic cyst fluid [5]. The use of molecular tests on solid pancreatic neoplasms, biliary brushings, and neuroendocrine tumors is also addressed. The clear benefits of incorporating imaging information and ancillary testing are the decrease in the number of atypical and nondiagnostic reports and an increase in both sensitivity and specificity for the detection of neoplasia, which has helped refine the ROM in the diagnostic categories [5, 7–15].

Table 1. The World Health Organization System for Reporting Pancreaticobiliary Cytopathology: implied ROM and clinical management options by diagnostic category

Diagnostic category	Estimated ROM (%)[a]	Clinical management options[b]
1. Insufficient/inadequate/nondiagnostic	5–25	Repeat FNAB
2. Benign/negative for malignancy	0–15	Correlate clinically
3. Atypical	30–40	Repeat FNAB
4. PaN-low	5–20	Correlate clinically
5. PaN-high	60–95	Surgical resection in surgically fit patients Conservative management optional
6. Suspicious (for malignancy)	80–100	If patient to be surgically managed, treat as positive If patient requires pre-operative therapy, repeat FNAB
7. Positive (for malignancy)	99–100	Per clinical stage

Reproduced with permission from International Academy of Cytology – International Agency for Research on Cancer – World Health Organization Joint Editorial Board. WHO Reporting System for Pancreaticobiliary Cytopathology. Lyon (France): International Agency for Research on Cancer; forthcoming (IAC-IARC-WHO cytopathology reporting systems series, 1st ed.; vol. 2). https://publications.iarc.fr/). FNAB, fine-needle aspiration biopsy. [a] Estimated ROMs are based on retrospective and prospective studies with risk analysis based on pancreatic neoplasia with low-grade and high-grade cytologic atypia [10, 13, 17]. [b] Management options for patients with pancreatic lesions may depend on a variety of factors, including clinical and radiologic characteristics and overall functional status of the patient. Some clinical management suggestions are outlined as above.

This approach is maintained in the WHO system. The principal differences between the WHO system and the PSC system revolve around the classification of neoplasia. In the PSC system, there was a single category for "neoplastic" lesions not diagnostic of adenocarcinoma or other aggressive malignancies that included two groups, one for benign neoplasms (primarily serous cystadenoma [SCA]) and one named "neoplastic: other," dominated by premalignant intraductal neoplasms [primarily intraductal papillary mucinous neoplasms (IPMNs)] and low-grade malignant neoplasms [pancreatic neuroendocrine tumors (PanNET) and solid pseudopapillary neoplasms (SPN)]. The inclusion of both premalignant and low-grade malignant neoplasms in the "neoplastic: other" category made it difficult to determine a meaningful ROM for the neoplastic category as a whole and especially for the "other" group. In the WHO system, benign neoplasms with virtually no ROM are included in the "benign" category and low-grade malignancies (PanNET and SPN) are included in the malignant category, as per the WHO Classification of Digestive System Tumours [16], thus leaving in the "neoplasm" category primarily those non-invasive premalignant lesions of the ductal system. Because these lesions can be divided by the cytomorphological grade of the epithelium into low and high-grade with distinctly different ROMs [17], there are two distinct categories for these lesions in the WHO system: "pancreatic neoplasm of low risk/low-grade" (PaN-low) and "pancreatic neoplasm of high risk/high-grade" (PaN-high).

There are very few studies that provide data on the associated ROM that translate well into this new categorization system [10, 13, 17–19]. With the redistribution of certain tumors within the categories from the PSC system to this new WHO system, particularly given that both PanNET and SPN are now categorized as malignant, the associated ROM for the "PaN-low" and "PaN-high" categories likely lies within their estimated ranges. The ROM for bile duct brushings is higher per diagnostic category than for fine-needle aspiration biopsies (FNAB) of pancreatic masses. Because criteria are lacking for the diagnosis of specific premalignant intraductal bile duct neoplasms, most cytopathological interpretations fall in the "benign (negative for malignancy)," "malignant," or conventional indeterminate categories of "atypical" and "suspicious for malignancy" and not into the "PaN-low" or "PaN-high" categories.

The WHO system also discusses sampling techniques and tissue triage as well as rapid on-site evaluation (ROSE) and ancillary techniques, but the focus of this commentary is on the actual diagnostic categories, their ROM, and the recommended management per category, with an emphasis on the differences with the PSC Reporting System for Pancreaticobiliary Cytology. The categories of the WHO system along with the associated ROM and diagnostic management recommendations are detailed in Ta-

Table 2. The World Health Organization System for Reporting Biliary Cytopathology: implied ROM and clinical management options by diagnostic category

Diagnostic category	Estimated ROM (%)[a]	Clinical management options[b]
Insufficient/inadequate/nondiagnostic	28–69	Repeat ERCP with cholangioscopy, brushing, and biopsies
Benign/negative for malignancy	26–55	Correlate clinically
Atypical	25–77	Repeat ERCP with cholangioscopy, brushings, and biopsies; consider ancillary testing with FISH and/or NGS
PaN-low	NA[c]	NA
PaN-high	NA[c]	NA
Suspicious (for malignancy)	74–100	Repeat sampling with ancillary testing (FISH and/or NGS) or, if other factors support malignancy, surgical intervention; for neoadjuvant therapy, repeat ERCP with cholangioscopy and brushings/biopsies/ancillary testing
Malignant	96–100	Per clinical stage

Reproduced with permission from International Academy of Cytology – International Agency for Research on Cancer – World Health Organization Joint Editorial Board. WHO Reporting System for Pancreaticobiliary Cytopathology. Lyon (France): International Agency for Research on Cancer; forthcoming (IAC-IARC-WHO cytopathology reporting systems series, 1st ed.; vol. 2). https://publications.iarc.fr/). ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in situ hybridization; NA, not available/applicable; NGS, next-generation sequencing. [a] Estimated ROMs are based on retrospective studies [28–34]. [b] Management options for patients with bile duct strictures may depend on a variety of factors, including clinical and radiologic characteristics and overall functional status of the patient. Some clinical management suggestions are outlined as above. [c] Cytological criteria for premalignant neoplasms of the bile duct are lacking, and thus, there are no data on bile duct categorization in the PaN-low and PaN-high categories.

ble 1 for pancreas and Table 2 for bile duct brushings and are briefly described in the sections below along with selective illustrations.

Category: Insufficient/Inadequate/Nondiagnostic

Definition

A specimen categorized as "inadequate/insufficient/nondiagnostic" is one that for qualitative and/or quantitative reasons does not permit a diagnosis of the targeted lesion.

Discussion

Since precise terminology for this category varies among institutions, three terms are listed as options in the current terminology and any institution or cytopathology service should select one term and use it consistently to optimize communication with clinicians [6]. "Nondiagnostic" rates from published series with endoscopic ultrasound-directed FNABs of the pancreas show an average of 12% [20]. Diagnostic yield largely depends on the operator's experience, technique employed, and use of ROSE, which has proven to reduce the number of "insufficient/inadequate/nondiagnostic" samples [21–23]. Use of larger "core-like" needles has also been associated with fewer needle passes and shorter procedure times [24, 25]. The reason for an "insufficient/inadequate/nondiagnostic" sample may also be due to the nature of the lesion, since chronic and autoimmune pancreatitis shows extensive fibrosis and usually produces scant material. Brush cytopathology may also be paucicellular and often obscured by mechanical or preparation artifact, and an FNAB might be recommended when there is a significant thickening of the wall.

In pancreaticobiliary cytopathology, there is no established number of cells or epithelial tissue fragments defining a minimum for adequate cellularity, mainly due to its multidisciplinary approach, taking into consideration not only cytomorphological analysis of the slides but also imaging findings and chemical analysis of cyst fluids. While solid lesions or duct strictures with acellular to very paucicellular samples should be placed in this category, this is not true for cystic lesions, for which the presence of background mucin or high CEA levels may be enough to classify the cyst fluid as mucinous, even in the absence of an epithelial component [26, 27]. In this context, the main reasons for "insufficient/inadequate/nondiagnostic" samples include acellular or very paucicellular samples of a solid mass or duct brushing, technical issues, which obscure the cellular component, or the presence of only normal pancreatic tissue in the context

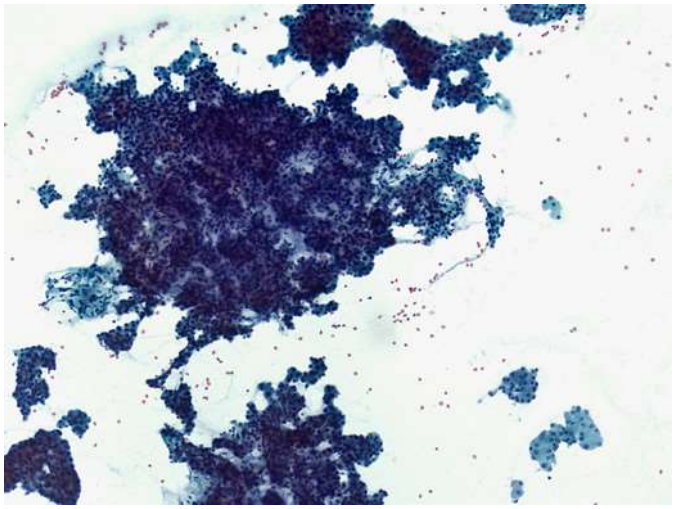

Fig. 1. Benign pancreatic tissue. Aspirates of normal pancreas are dominated by acinar tissue and when aspirated from a well-defined mass on imaging can be classified as inadequate/insufficient/nondiagnostic because, despite being a cellular sample, the biopsy does not explain or correlate with the targeted lesion [Papanicolaou. ×200].

of a well-formed solid or cystic lesion on imaging. Specimens containing only benign pancreatic acinar and/or ductal epithelial cells in the setting of a distinct solid or cystic lesion on imaging are classified as "nondiagnostic" by some cytopathologists, since the FNAB is regarded as most likely representing a sampling error as it does not explain the mass seen on imaging (Fig. 1). But it is recognized within the WHO system that some laboratories choose to classify such cases as "benign," describing what is present on the slides, and then adding a caveat in the report conclusion, "that the biopsy most likely is not representative of the targeted lesion." These different uses of the categories "nondiagnostic" and "benign" with a caveat may impact the ROM of these categories and require further study. It is important to note that the presence of any cellular atypia precludes categorization as "insufficient/inadequate/nondiagnostic" and the specimen should be placed in the "atypical" category for further follow-up.

ROM for the "insufficient/inadequate/nondiagnostic" category is based on retrospective and prospective studies and ranges from 5 to 25% [10, 13, 17, 20]. In biliary brushing specimens, the ROM in bile duct brushing specimens in the "insufficient/inadequate/nondiagnostic" category is high at 28–69% due to the sampling bias of targeting duct strictures with an inherently high ROM [28–34].

Management

Diagnostic management recommendations depend on the cause of an "insufficient/inadequate/nondiagnostic" sample. Operator experience, needle type and technique, lack of available organ-specific cytopathology expertise, and ROSE may all contribute to an insufficient biopsy [21–23]. A repeat biopsy is recommended in most cases, possibly with different gauges and type of needles, and an added focus on obtaining tissue in formalin since sclerosis from pancreatitis and cancer often contributes to scant specimens. Patients clinically suspected of autoimmune pancreatitis may have a trial of steroids [35]. Brush cytopathology specimens evaluated with direct smears can be repeated using liquid-based cytopathology to improve cellular preservation. For some patients, further clinical management decisions may be based on the clinical scenario and imaging alone, but neoadjuvant therapy requires a definitive malignant diagnosis.

Category: Benign/Negative for Malignancy

Definition

A specimen categorized as "benign (negative for malignancy)" demonstrates unequivocal benign cytopathological features, which may or may not be diagnostic of a specific process or benign neoplasm.

Discussion

A "benign" categorization is rendered when the prepared slides do not show evidence of malignancy or cellular atypia. In those cases where a specific benign condition is recognized, this should be clearly stated in the diagnostic summary field of the report. When a specific lesion is identified, a microscopic description may not be necessary. The interpretation of a cytopathology sample as "benign" implies that the cellularity of the sample is adequate and that there is no evidence of cytopathological atypia. A benign diagnosis may be made on the basis of diagnosing a specific lesion such as splenule or pseudocyst, but may also include cases where there are only exocrine and endocrine pancreatic elements on the slides. A sample composed of normal pancreatic tissue in the appropriate clinical setting and in the absence of a distinct mass lesion is appropriately placed in the "benign" category. However, if there is a distinctive mass detected on imaging and the cytopathology preparations only show normal pancreatic tissue, some cytopathologists will categorize such a case as "nondiagnostic," while others will categorize the case as "benign," with a caveat

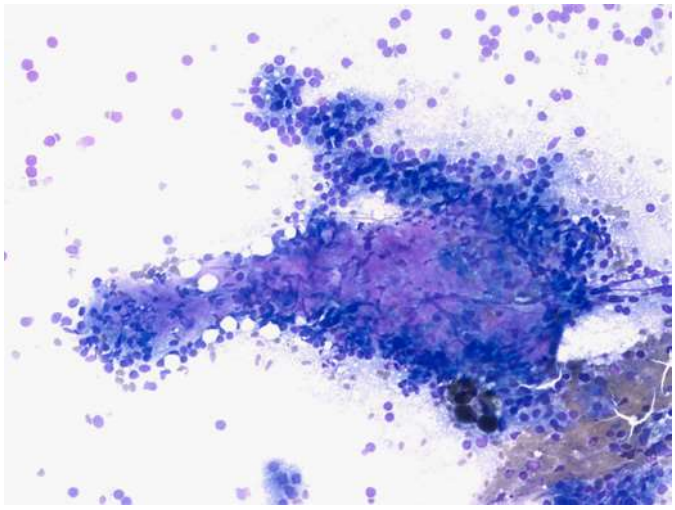

Fig. 2. Serous cystadenoma. This benign neoplasm is now placed in the "benign/negative for malignancy" category instead of the "neoplastic:benign" category because it has virtually zero risk of malignancy. Bland, uniform, cuboidal cells with clear but nonmucinous cytoplasm surround a fibrous septum with hemosiderin-laden macrophages [at 5 o'clock] [DiffQuik, ×200].

in the report conclusion that the sample may not be representative. These different uses of the categories are recognized by the WHO system, and such disparate use may impact the category ROM, and needs further research. If only gastrointestinal tract contaminants are present, the categorization is "insufficient/inadequate/nondiagnostic" [8, 20].

The benign category includes both non-neoplastic and neoplastic entities. This is in contrast to the PSC system that places benign neoplasms, mainly SCAs, in the "neoplastic:benign" category. The benign entities include acute pancreatitis, chronic pancreatitis, autoimmune pancreatitis, cholangitis, pseudocyst, lymphoepithelial cyst, accessory spleen (splenule), SCA (Fig. 2), and other rare benign neoplasms, such as lymphangioma and schwannoma.

The ROM for a benign pancreatic FNAB ranges from 0 to 15% [10, 13, 17, 19]. However, the ROM for benign lesions may be overestimated since it is usually calculated using histopathological confirmation, and most cases with high clinical and imaging suspicion are surgically excised after a "benign" diagnosis [20]. The ROM for a "benign" bile duct brushing is as high as 55% based on retrospective studies [28–34], and this high ROM should not be surprising given the high threshold for a malignant diagnosis in bile duct brushing cytopathology.

Management

Surgical resection is not required for benign lesions. However, surgery may be selected to alleviate symptoms. Pseudocysts may be drained, while treating the underlying etiology of acute pancreatitis is the focus of the patient management. Management of the causes of chronic pancreatitis and improvement of nutrition are essential in improving patient health. Corticosteroids are used in the treatment of autoimmune pancreatitis, which is why it is essential for cytopathologists to consider the possibility of the disease based on the FNAB. After a diagnosis of lymphoepithelial cyst and splenule, the patient can be discharged.

Category: Atypical

Definition

A specimen categorized as "atypical" demonstrates features predominantly seen in benign lesions and minimal features that may raise the possibility of a malignant lesion, but with insufficient features either in number or quality to diagnose a benign, PaN-low, PaN-high, or malignant process or lesion.

Discussion

As in the PSC system, the WHO system retains the two indeterminate categories, "atypical" and "suspicious for malignancy." The major benefit of implementing the PSC system in 2015 with the integration of imaging findings and ancillary tests into the final diagnosis was the decreased number of "atypical" diagnoses and the increase in definitive diagnoses of a "neoplasm," particularly for FNAB of cystic lesions [6]. The reasons for using the "atypical" category are multiple. The inherent characteristics of pancreaticobiliary lesion, low tumor cellularity, and anatomically challenging tumor sites may all preclude the rendering of a definitive diagnosis. Technical factors, such as the endosonographer's skill in procuring adequately cellular and representative samples, specimen preparation artifact, and the availability of ROSE will all also influence the quality of the specimen [36, 37]. In addition, different levels of experience and expertise, training and institutional case volume can result in significant inter- and intra-observer variability in the use of the "atypical" category [38]. The histopathological outcome of this category ranges from benign to premalignant and malignant entities [10–12, 17, 39–41]. FNAB with no supportive evidence of a specific neoplasm remains in the "atypical" category.

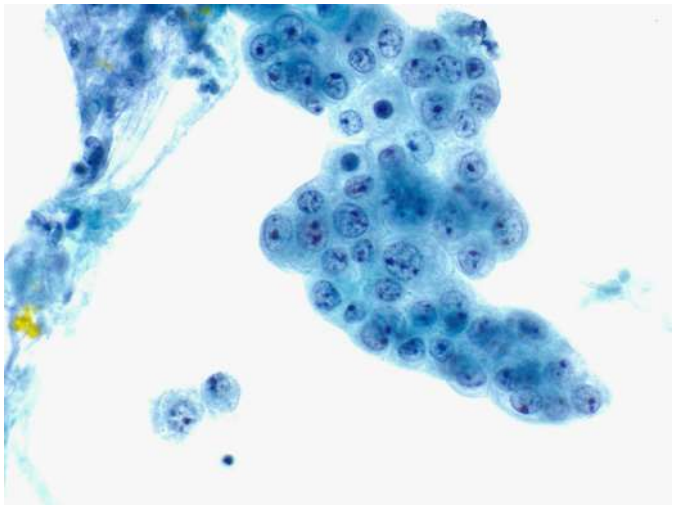

Fig. 3. Atypical bile duct epithelium. This epithelium from a brushing of a strictured and stented duct shows mildly atypical cells in a relatively uniform sheet with enlarged nuclei, and prominent nucleoli, but with smooth nuclear membranes and open vesicular chromatin [Papanicolaou, ×400].

The reported frequency of the "atypical" category for FNAB of pancreas ranges from 0 to 14% with an average of 5.5% [20, 42]. The frequency in bile duct brushings is higher, ranging from 11 to 39.8%, which may be partially due to the challenge in recognizing reactive atypia inherent to primary sclerosing cholangitis, stents, and biliary stones [29, 43–45].

In the PSC system, indeterminate FNAB not diagnostic of a well-differentiated PanNET or SPN, which are tumors that were in the "neoplastic: other" rather than "malignant" category, were classified as "atypical" rather than "suspicious for malignancy." Now that these tumors are classified as "malignant," if an FNAB of either of these tumors is not diagnostic, but is suspected, then the interpretation should be "suspicious for malignancy" and not "atypical." The "atypical" category is appropriate when the differential diagnosis of finding a few endocrine cells includes islet cell hyperplasia in the clinical setting of chronic pancreatitis [46, 47]. It is important to understand that "atypical" should be used judiciously and as seldom as possible, because an "atypical" report may lead to unnecessary additional investigations and procedures.

For bile duct brushings, the "atypical" category is applied to cases in which the atypia observed is beyond that seen for reactive and inflammatory changes while quantitatively and qualitatively insufficient for categorization as "suspicious for malignancy" (Fig. 3). Although low-grade biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct (IPN-B) are entities included in the "PaN-low" category in this WHO system, the most appropriate category is "atypical" because these entities lack well-defined criteria and the degree of atypia is mild [48, 49]. The known overlap in cytomorphology between reactive and reparative changes in bile duct epithelium from stents, stones, and inflammation, and well-differentiated adenocarcinoma leads to a high use of indeterminate interpretations [50].

The ROM associated with the diagnostic categories of the PSC system has been refined [11, 40, 43, 51]. ROM of the "atypical" category is different for bile duct brushings and EUS-FNAB of pancreatic lesions. There is a remarkable range in the ROM for bile duct brushings and pancreas FNAB depending on the type of study, date of the study (e.g., pre-PSC system), and experience of the institution reporting the study. Using studies following the establishment of the PSC system where the category "neoplastic: other" provided a home for nonmalignant neoplasia that otherwise would have been classified as "atypical" or "suspicious for malignancy," the ROM of the "atypical" category for pancreas FNAB is 30–40% and for bile duct brushings 25–77% [10, 13, 17, 28–31].

Management

The management of an "atypical" cytopathological diagnosis should include multidisciplinary discussion, consensus review, expert consultation, the use of ancillary tests, and repeat sampling with ROSE. In recent years, evolving technologies such as multiprobe fluorescence in situ hybridization (FISH) [52–55] and molecular tests with genetic sequencing have been reported to improve the classification of pancreatic cysts [56, 57] and the sensitivity of detection of malignancy in bile duct brushings [30, 58–61]. Molecular testing using either otherwise discarded supernatant fluid of cytocentrifuged bile duct brushing specimens [58] or an aliquot of a brushing rinsed in preservative has significantly increased the sensitivity of detecting malignancy to 93%, while maintaining a specificity of 100% and also identifying markers potentially predictive of a response to targeted therapy [59]. Therefore, molecular tests increase the information available for clinical decision-making. Precisely defining the correct categorization and specific diagnosis of pancreaticobiliary cytopathology is challenging, and thus, consensus review or second opinion from experienced pancreaticobiliary cytopathologists may be cost-effective and is recommended [62]. If ancil-

Fig. 4. Low-grade neoplastic mucinous epithelium from an intraductal papillary mucinous neoplasm [IPMN], branch-duct type. Mucinous epithelium with low- to intermediate-grade morphological atypia is classified as low-grade neoplasia and placed in the pancreatic neoplasm of low risk/low-grade category. Specificity of the diagnosis of IPMN generally requires clinical correlation or genetic mutations supporting the diagnosis. This strip of mucinous epithelium retains its columnar shape making the cells about the size of a 12-micron duodenal enterocyte, but the nuclear membranes are atypical with elongation, slight hyperchromasia, and stratification [Papanicolaou. ×600].

lary testing is not available and multidisciplinary discussion is inconclusive, further workup may include repeat sampling with ROSE.

Category: Pancreatic Neoplasm: Low Risk/Low-Grade (PaN-Low)

Definition

A specimen categorized as "PaN-low " has features of an intraductal and/or cystic neoplasm with low-grade epithelial atypia.

Discussion

The grading of intraductal neoplasia is now two-tiered as low and high-grade, with low-grade epithelial atypia representing low- to intermediate-grade dysplasia [63, 64]. The cytopathological ROM of PaN-low lesions is directly related to the epithelial atypia in the cyst fluid or brushing cytopathology. In one study on cases categorized in the PSC system as "neoplastic: other," which included all the lesions placed in that category, low-grade atypia had a ROM of 4.3% compared to 90% for high-grade atypia [65]. IPN-B is classified into two types, one of which is similar to pancreatic IPMN and occurs mostly in the intrahepatic ducts, and the other which is unlike pancreatic IPMN and occurs in the extrahepatic ducts [66–68]. IPMN and mucinous cystic neoplasm (MCN) are well-known cystic lesions for which cytopathological distinction between low and high-grades is essential for patient care. Cyst fluid CEA analysis is a valuable adjunct to the cytopathological diagnosis of these mucinous lesions. When its level is greater than 192 ng/mL, it is approximately 80% accurate for a mucin-producing neoplasm [69, 70]. Accurate grading of the epithelial atypia as low risk/low-grade, which includes intermediate-grade dysplasia, and distinguishing it from high-risk/high-grade atypia, is challenging requiring well-preserved epithelium and diagnostic experience. Undoubtedly, there will be interobserver variability that will need close cytohistologic correlation and quality assurance review in a prospective manner.

Low-grade IPMN (Fig. 4) is a mucin-producing epithelial neoplasm of the main and/or branch ducts of the pancreas characterized by an intraductal proliferation of columnar mucinous epithelium with mild to moderate cytoarchitectural atypia, lining cystically dilated ducts with or without intraductal papillae. Low-grade neoplasms typically show gastric and/or intestinal type epithelium [71]. The primary differential diagnosis for low-grade IPMN is gastrointestinal contamination [72]. Low-grade MCN is a cyst-forming and mucin-producing epithelial neoplasm with distinctive ovarian-like subepithelial stroma and low-grade dysplasia. Low-grade IPMN is not readily distinguished from low-grade MCN on cytopathology because subepithelial ovarian-type stroma is usually not sampled with aspiration of cyst fluid. The use of micro-forceps biopsy, which obtains a bite of the cyst wall, can help make a specific diagnosis of MCN by obtaining a tissue sample demonstrating the ovarian-type stroma [73]. Identification of a *GNAS* mutation supports the diagnosis of IPMN [56, 74, 75]. IPMN harbors *KRAS* mutations, but *KRAS* mutations are identified only in a small subset of low-grade MCN [76, 77]. Other gene alterations such as *TP53* and *SMAD4* mutations are absent in low-grade cysts [56, 75].

Management

Stratifying epithelial atypia into high-grade or low-grade leads to better patient management, as pancreatic cyst fluid FNAB is rarely interpreted as suspicious for or diagnostic of malignancy due to their scant cellularity. In

the absence of cytopathological high-grade atypia, and in the presence of low-grade atypia, the patient has the option of surveillance depending on the clinical and imaging features [78–80]. Patients with MCN and low-grade atypia on cytopathology can be referred for surveillance in the absence of other high-risk factors [81, 82].

Category: Pancreatic Neoplasm: High Risk/High-Grade (PaN-High)

Definition

A specimen categorized as "PaN-low" has features of an intraductal and/or cystic neoplasm with high-grade epithelial atypia.

Discussion

With the removal of PanNET and SPN from the PSC "neoplastic" category and the inclusion of SCA in the WHO system "benign" category, the "pancreatic neoplasm" category is left almost exclusively containing cystic mucinous and intraductal neoplasms. Given the marked difference in the ROM between low-grade and high-grade epithelial atypia [17], the neoplastic category was renamed "pancreatic neoplasm" and subdivided into low-grade (PaN-low) and high-grade (PaN-high) categories. PaN-high lesions include all intraductal and cystic pancreaticobiliary lesions with high-grade epithelial atypia [HGA]. In cytopathology of the pancreas, HGA encompasses lesions with high-grade dysplasia and invasive carcinoma since these usually cannot be distinguished in aspirates of cyst fluid. PaN-high is predictive of an increased risk for high-grade dysplasia or carcinoma and carries an estimated ROM of 60–95% [10, 13, 17, 19]. The PaN-high category provides a more flexible and less anxious patient management paradigm than the "suspicious for malignancy" category, particularly when conservative patient management is recommended. HGA has an 89% sensitivity and 98% specificity for detecting a high-risk cyst [65].

HGA is defined as a cell smaller than a 12-μ duodenal enterocyte with high nuclear-to-cytoplasmic ratio and abnormal chromatin, which can be hypochromatic or hyperchromatic and with or without background necrosis. When these criteria are used, there is overall good interobserver agreement in distinguishing low-risk/grade from high-risk/grade cysts [63, 80, 83–85]. However, if an intermediate-grade dysplasia is included in the grading scheme, it is virtually impossible to accurately stratify cysts with intermediate-grade dysplasia into low- and high-risk groups, making the addition of genetic testing very important in accurately identifying high-risk cysts [56, 84].

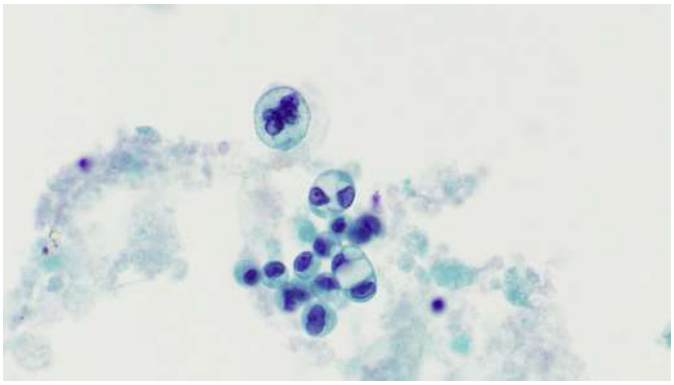

Fig. 5. High-grade neoplastic mucinous epithelium from an intraductal papillary mucinous neoplasm [IPMN], branch-duct type. Mucinous epithelium with high-grade morphological atypia is classified as high-grade neoplasia of at least high-grade dysplasia and placed in the pancreatic neoplasm of high-risk/high-grade category. These cells show a small cell size [less than a 12-micron duodenal enterocyte], high nuclear-to-cytoplasmic ratio with some residual mucinous cytoplasm, abnormal chromatin – some hypochromatic and some hyperchromatic – occasional irregular nuclear membranes and background necrosis [Papanicolaou, ×600].

Lesions included in the PaN-high category include flat high-grade pancreatic/biliary intraepithelial neoplasia, intraductal mucinous and nonmucinous lesions with HGA (IPMN, IPN-B, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm) and MCN with HGA. The PaN-high category is dominated by IPMN-high-grade, which is a grossly visible cystic lesion involving the main and/or branch pancreatic ducts. Histopathologically IPMN-high-grade forms macro- and micropapillae lined by cells with severe cytopathological atypia. Key cytopathological features include hypercellularity relative to low-grade IPMN, small cell size that is smaller than a 12-μm duodenal enterocyte, increased nuclear-to-cytoplasmic ratio, nuclear irregularity, abnormal chromatin, which can be hypochromasia or hyperchromasia, prominent nucleoli, variable cytoplasmic mucin, background necrosis, and inflammation (Fig. 5). The primary differential diagnosis is with MCN with HGA, which is a cystic mucin-producing epithelial neoplasm with distinctive subepithelial ovarian-type stroma, high-grade dysplasia with or without associated invasive carcinoma (15%), and no connection to the pancreatic ducts [86–89]. Almost all MCN with HGA occurs

in middle-aged women, and more than 90% arise in the pancreatic body/tail. On FNAB, MCN with HGA shows variable cellularity with thick, colloid-like mucin, necrosis and crowded sheets, papillae, and singly dispersed pleomorphic cells with high nuclear-to-cytoplasmic ratio, nuclear irregularities, hypo- or hyperchromasia, mitotic figures, and scant mucin. The entity-defining ovarian-type stroma is often not sampled on FNAB [82].

IPMN and MCN with HGA may show mutations known to be associated with adenocarcinoma and high-grade dysplasia. Late mutations in the adenoma-carcinoma progression include *TP53* [56, 57, 90, 91], *SMAD4* [56, 90, 91], *CDKN2A* (p16) [56, 91], *PTEN* [57, 92], *PIK3CA* [57], and aneuploidy/LoH in certain regions [93]. Mutant allelic frequency mutations in *PIK3CA, PTEN,* and *TP53* genes equivalent to *KRAS* or *GNAS* are sensitive and specific for IPMN with either high-grade dysplasia or invasive carcinoma [57]. Low-level mutations of *PTEN, PIK-3CA,* and *TP53* in low-grade IPMN suggest risk for transformation to high-grade [57]. Mutational allelic frequencies for *GNAS* greater than 55% correlate with high-grade IPMN [57]. Immunohistochemical stains on cell blocks include p53 mutant expression demonstrated by strong nuclear staining or no expression [null pattern] [94, 95], and loss of nuclear *SMAD4* [96, 97] or p16 [98]. These stains should be interpreted with caution on scant specimens.

Management

Surgically fit patients with PaN-high should be considered for surgical resection. However, conservative observation is a reasonable option where the risk of surgery is high and especially if the imaging features do not appear high risk and the patient is a poor surgical candidate.

Category: Suspicious for Malignancy

Definition

A specimen characterized as "suspicious for malignancy" demonstrates some cytopathologic features suggestive of malignancy but with insufficient features in either number or quality to make an unequivocal diagnosis of malignancy.

Discussion

The cytomorphological features of specimens obtained by FNAB or bile duct brushings show a spectrum of features ranging from those clearly representative of benign epithelium to those definitively diagnostic of malignancy. This spectrum is nearly continuous without obvious cut points for subcategorization. The two indeterminate categories of "atypical" and "suspicious for malignancy" help optimize the accuracy and predictive values of the categories "benign/negative for malignancy" and "malignant." Assignment of specimens to the "suspicious for malignancy" category varies among cytopathologists, and this variance is reflected in the published range for ROM [10, 11, 17, 19, 99] and reported interobserver agreement statistics [100, 101]. The reported ranges in ROM and interobserver reproducibility are associated with the overlapping clinical and imaging features of benign and malignant entities, difficulty in sampling and varying experience levels of both endoscopists and cytopathologists [17, 102–105]. All of these factors result in the need for intermediate categories which group the range of cytomorphological features into clinically useful and reproducible categories.

The use of these indeterminate categories should be limited to retain the diagnostic utility of the categorization system. The "suspicious for malignancy" category accounts for approximately 4.7–16% of all cytopathological diagnoses reported in the literature for the pancreaticobiliary tract [29, 51, 106]. The use of the "suspicious for malignancy" category indicates that the cytopathological findings are highly concerning for but not diagnostic of a malignancy. Factors contributing to the "suspicious for malignancy" category include scant cellularity, technical limitations of specimen staining or preparation, cytomorphological characteristics of the specimen along the spectrum of features, and caution on the part of the cytopathologist. These limiting factors may be especially constraining when insufficient tissue is present for ancillary testing. Additional factors resulting in a "suspicious for malignancy" rather than a "malignant" diagnosis include concurrent pancreatitis, stent placement, stones, inflammatory conditions such as sclerosing cholangitis, and sampling of subclinical premalignant lesions of the pancreas (high-grade pancreatic intraepithelial neoplasia/high-grade dysplasia/carcinoma in situ) [17, 107–109].

Specimens assigned to the "suspicious for malignancy" category demonstrate significant alterations in both architecture and the cytomorphology of single cells. Assignment to the "atypical," "suspicious for malignancy," or "malignant" categories depends on the combination of features and the degree to which they are expressed [110–112]. When the architectural and cytopathological features of malignancy are not there in quality or quantity to make a diagnosis of malignancy but are present to a sig-

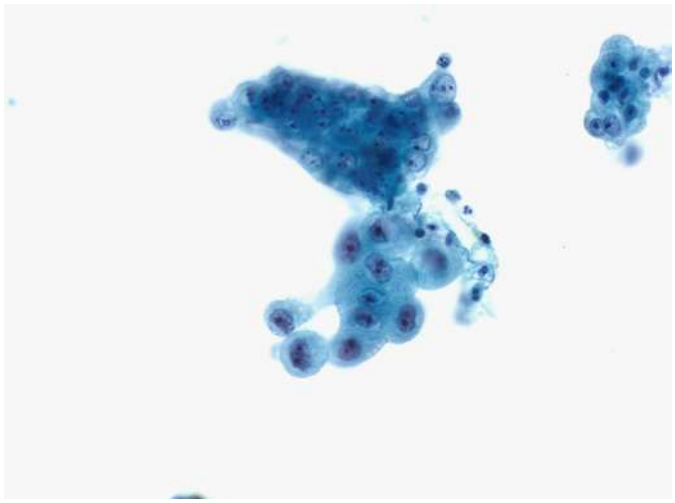

Fig. 6. Markedly abnormal bile duct epithelium suspicious for adenocarcinoma. These bile duct cells from a brushing of an unstented distal common bile duct stricture associated with a mass show a group of cells [center] with foamy, lacey cytoplasm, irregular, hyperchromatic nuclei and prominent nucleoli reminiscent of pancreatic carcinoma, but are few in number and associated with atypical and more reactive ductal cells [top of image] making the interpretation suspicious rather than malignant [Papanicolaou. ×600].

nificant enough degree to suspect that a malignancy is present, then the "suspicious for malignancy" category is used (Fig. 6). The cytopathologist should include details of the features that are suspicious and that have led to the categorization of a specimen as "suspicious for malignancy," to minimize the tendency to use this category as a waste basket. A discussion of any features limiting or compromising the evaluation should be noted, and the need for correlation with clinical and imaging findings should be emphasized. Finally, the use and results of any ancillary testing performed including immunohistochemical and molecular analysis should be included and evaluated.

The ROM varies depending on the solid or cystic nature of the lesion. Reported ROM for the "suspicious for malignancy" category for pancreatic FNAB has varied from 80 to 100% [10, 11, 17, 19, 99]. Malignancy risks for bile duct brushing specimens range from 74 to 100% [28–31, 33, 44, 113, 114]. These ranges in ROM are relatively wide and reflect the degrees of interobserver reproducibility [100, 101].

Management

Categorization of a specimen as "suspicious for malignancy" is not equivalent to a "malignant" diagnosis and should not by itself result in neoadjuvant therapy or radical surgery. In all cases, further patient management and clinical decisions require correlation of the "suspicious for malignancy" cytopathological categorization with clinical and imaging findings which are best correlated in a treatment planning multidisciplinary conference. When clinical and imaging findings strongly support the diagnosis of malignancy, a categorization of a specimen as "suspicious for malignancy" may in some restrictive settings allow for definitive therapy without further histopathological or cytopathological procedures. Ancillary testing also may contribute significantly to the clinical decision-making process.

Category: Malignant

Definition

A specimen categorized as "malignant" demonstrates unequivocal cytopathological features of malignancy.

Discussion

Tumors in this category include both primary and secondary malignancies with pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma accounting for most primary malignancies [115]. As in the PSC system [5], pancreatic acinar cell carcinoma, neuroendocrine carcinomas, pancreatoblastoma, primary and secondary hematopoietic malignancies, and sarcomas are also included in this category. A change from the original PSC system is the inclusion of well-differentiated PanNET and SPN in this category to make this system consistent with the classification of pancreatic tumors in the WHO 5th edition [115]. In the PSC system, these were included in the "neoplastic other" category.

The ROM of a positive pancreatic FNAB ranges between 97 and 100% [10, 11, 17, 48, 116], and the ROM of a positive bile duct brushing ranges between 96 and 100% [10, 11, 17, 48, 116]. The cytopathological features of PDAC on FNAB smears include hypercellularity, loss of the normal honeycomb pattern in cell groups, nuclear enlargement, chromatin clearing, nuclear membrane irregularities, anisonucleosis greater than 4: 1 in tissue fragments, cytoplasmic mucin, atypical mitotic figures, and dispersed single malignant cells. Coagulative background necrosis is present in higher grade carcinomas, but well-differentiated PDAC may have a clean background (Fig. 7) [110, 117–120]. The less common cytomorphological subtypes of PDAC include adenosquamous carcinoma characterized by the presence of keratinized tumor

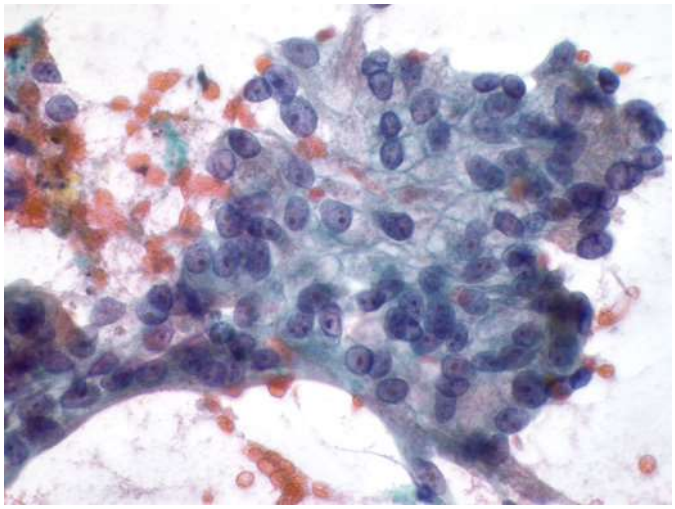

Fig. 7. Well-differentiated pancreatic adenocarcinoma. These ductal cells, which are presentative of many such groups on the slide, show variation in nuclear size [4:1 in a single sheet], mucinous cytoplasm [which is pathologic in the pancreas], uneven spacing due to the variable mucinous cytoplasm [drunken honeycomb], enlarged nuclei with coarse chromatin and prominent nucleoli, and are from an aspirate targeting a 30-mm hypoechoic mass in the pancreatic head, a combination of clinical and morphological findings that lead to a confident diagnosis of ductal adenocarcinoma [Papanicolaou. ×600].

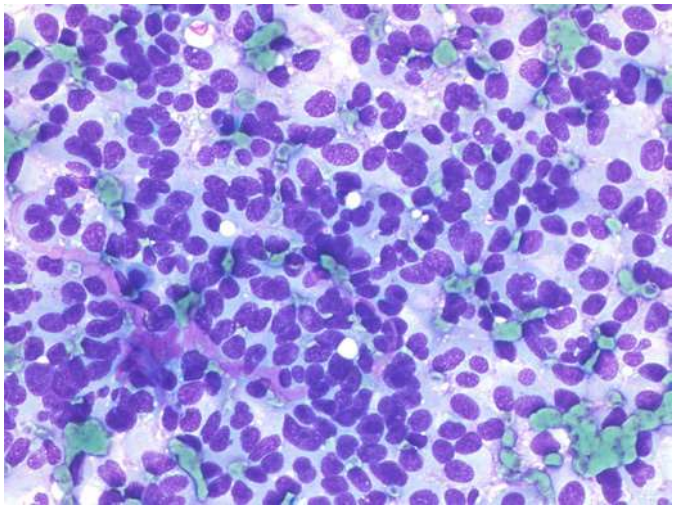

Fig. 8. Pancreatic neuroendocrine tumor. This aspirate from a 20-mm, round mass in the pancreatic tail of a 50-year-old man shows a cellular smear of uniform cells with round to oval nuclei and coarse chromatin associated with a blood vessel [7 o'clock]. While the clinical pathological findings support the diagnosis of a neuroendocrine tumor, confirmatory ancillary testing with immunohistochemistry is recommended due to overlapping morphology with other nonductal neoplasms [see Fig. 9]. The "malignant" category is used in the WHO system in contrast to the "neoplastic: other" category of the Papanicolaou Society of Cytopathology System [DiffQuik, ×400].

cells mixed with glandular elements, colloid adenocarcinoma with abundant background mucin, undifferentiated carcinoma which can be anaplastic or sarcomatoid, and undifferentiated carcinoma with osteoclast giant cells, which represent benign multinucleated histiocytes. Each of these subtypes has unique cytopathological features [121–123].

Nonductal neoplasms of the pancreas include PanNET (Fig. 8), SPN (Fig. 9), neuroendocrine carcinoma, acinar cell carcinoma (Fig. 10), and pancreatoblastoma. These share some common cytopathological features including hypercellular smears composed of loosely cohesive, monotonous appearing neoplastic cells, often with a vascular stroma, and stripped nuclei. However, they do have distinguishing cytopathological and immunophenotypical features (Table 3).

Management

Surgical management is usually the first-line treatment for malignancies of the pancreaticobiliary tract [124]. An exception is patients with a PanNET smaller than 2 cm and a Ki-67 less than 3%, who may be managed with surveillance [125]. Patients presenting with borderline or locally advanced PDAC may be treated with neoadjuvant therapies in an attempt to convert the PDAC to resectable disease [126]. Patients with unresectable disease are typically treated with a combination of chemotherapeutic agents and radiation therapy. The type of systemic therapy administered is dependent on the tumor type. Metastases may be treated with resection or systemic therapy, depending on the tumor type, e.g., metastatic renal cell carcinoma occurring many years after initial presentation may be resected.

Conclusion

As with all reporting systems involving categorization of cytopathology specimens, the new WHO Reporting System for Pancreaticobiliary Cytopathology is designed to improve communication between clinicians and cytopathologists about their patient's biopsy results. Each category has a calculated ROM that aims to assist the clinical care team in patient management. The authors recognize that the performance indicators for each category of the

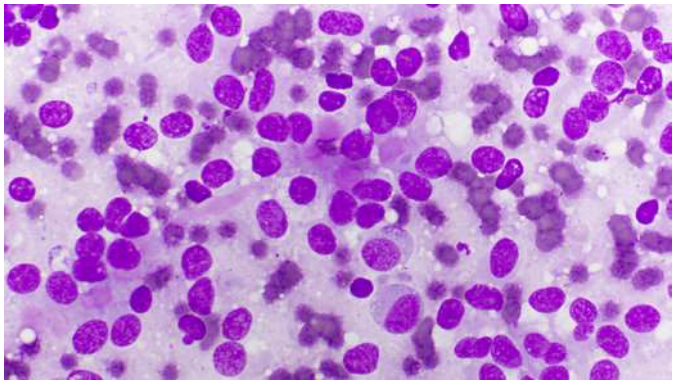

Fig. 9. Solid pseudopapillary neoplasm. A uniform population of polygonal cells with perinuclear vacuoles and hyaline globules in the cytoplasm support the diagnosis of solid pseudopapillary neoplasm over other nonductal tumors. The clinical history of a solid and cystic mass in the pancreas of a 28-year-old female also adds support to the diagnosis. Confirmation with ancillary testing is recommended nonetheless because neuroendocrine tumors can occur in young patients and can be cystic [DiffQuik, ×600].

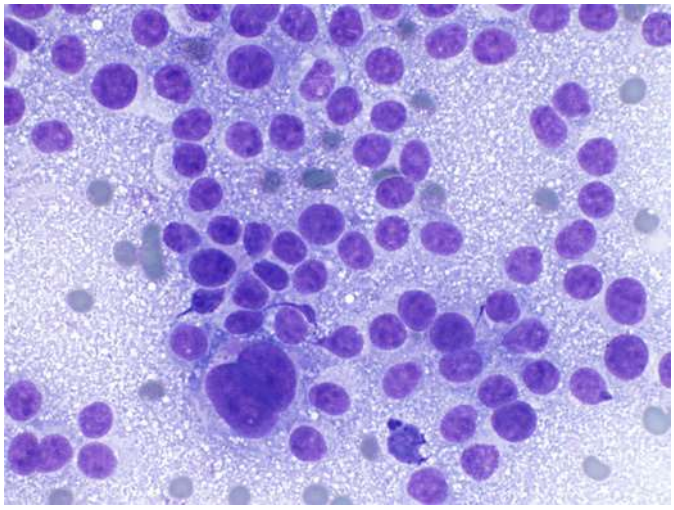

Fig. 10. Acinar cell carcinoma. The delicate cells of acinar cell carcinoma are often stripped of their granular cytoplasm resulting in a speckled background of negative images of granules on Romanowsky stain. The nuclei are round and relatively uniform and may or may not contain nucleoli [DiffQuik. ×600].

Table 3. Cytomorphological and immunohistochemical findings of nonductal neoplasms of the pancreas

Diagnosis	Key cytological features	Immunohistochemical profile
Neuroendocrine tumor	– Loosely cohesive groups and single cells, stripped nuclei – Variable cytoplasm, eccentric and plasmacytoid appearance – Vascular – Round, oval nuclei with salt and pepper chromatin	Cytokeratin INSM1, synaptophysin, chromogranin
Acinar cell carcinoma	– Grape-like clusters, single cells, stripped nuclei – Abundant granular cytoplasm – Negative cytoplasmic imprints representing zymogen granules on Romanowsky stained slides – Round nuclei with prominent nucleoli	BCL 10, trypsin, chymotrypsin
Solid pseudopapillary neoplasm	– Cellular smears with numerous fibrovascular fragments, single cells – Myxoid stroma surrounding capillaries is pathognomonic – Cells with vacuolated cytoplasm or cytoplasmic hyaline inclusions – Cells with cytoplasmic tails – Nuclei oval with grooves and occasional inclusions	CD 99 dot-like perinuclear pattern, nuclear beta-catenin
Pancreatoblastoma	– Cellular smears – Small, undifferentiated cells – Squamoid nests on cytology smears – Heterologous elements	– BCL 10, trypsin, chymotrypsin in fetal cells – Nuclear beta-catenin in squamoid morules

system are derived from reviews of relatively recent literature, so we hope that the WHO system will encourage research into the utility of the system and its management recommendations and provide an ever more precise ROM for each category.

The WHO system also defines through an international consensus the key diagnostic cytopathological criteria and differential diagnosis for each lesion or tumor, which is essential to improving the quality of diagnostic assessment and reporting of pancreaticobiliary cytopathology.

In addition, the WHO system provides the current best practice application of ancillary testing, including immunocytochemistry and molecular testing and, importantly, provides detailed descriptions of sampling and processing techniques to optimize the handling and preparation of the cytopathology sample. The authors of the WHO system recognize that local medical and pathology resources and infrastructure will vary, particularly in low- and middle-income countries. To make the WHO system applicable worldwide, the system is based on cytomorphology and provides options for further diagnostic workup of the specimen.

The WHO Reporting System for Pancreaticobiliary Cytopathology provides a direct and dynamic link to the WHO Classification for Gastrointestinal Tumours, 5th edition, and raises the profile and use of cytopathology by increasing awareness of its current role in diagnosis and management of patients with pancreaticobiliary disease.

Conflict of Interest Statement

The content of this article represents the personal views of the authors and does not represent the views of the authors' employers and associated institutions. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Funding Sources

There are no funding sources.

Author Contributions

Martha B. Pitman, Barbara A. Centeno, Michelle D. Reid, Momin T. Siddiqu, Lester J. Layfield, Miguel Perez-Machado, Birgit Weynand, Edward B. Stelow, Maria D. Lozano, Noriyoshi Fukushima, Ian A. Cree, Ravi Mehrotra, Fernando C. Schmitt, and Andrew S. Field: conceptualization. Martha B. Pitman, with collaboration of all authors: writing original draft. All authors read and approved the final manuscript: final review.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Cree IA, White VA, Indave BI, Lokuhetty D. Revising the WHO classification: female genital tract tumours. Histopathology. 2020 Jan;76(1):151–6.
2 Uttley L, Indave BI, Hyde C, White V, Lokuhetty D, Cree I. Invited commentary-WHO Classification of Tumours: how should tumors be classified? Expert consensus, systematic reviews or both? Int J Cancer. 2020 Jun 15;146(12):3516–21.
3 Yadav K, Cree I, Field A, Vielh P, Mehrotra R. Importance of cytopathologic diagnosis in early cancer diagnosis in resource-constrained countries. JCO Glob Oncol. 2022 Feb;8:e2100337.
4 WHO reporting system for pancreaticobiliary cytopathology; forthcoming. IAC-IARC-WHO cytopathology reporting systems series. 1ed. Lyon: International Agency for Research on Cancer.
5 Pitman MB, Centeno BA, Ali SZ, Genevay M, Stelow E, Mino-Kenudson M, et al. Standardized terminology and nomenclature for pancreatobiliary cytology: the Papanicolaou Society of Cytopathology guidelines. Diagn Cytopathol. 2014;42(4):338–50.
6 Pitman MB, Layfield L. The Papanicolaou society of cytopathology system for reporting pancreaticobiliary Cytology. 1 ed: Springer Cham; 2015. Vol. XV; p. 96.
7 McKinley M, Newman M. Observations on the application of the Papanicolaou Society of Cytopathology standardised terminology and nomenclature for pancreaticobiliary cytology. Pathology. 2016 Jun;48(4):353–6.
8 Perez-Machado MA. Pancreatic cytology: standardised terminology and nomenclature. Cytopathology. 2016 Jun;27(3):157–60.
9 Lopez-Ramirez AN, Villegas-Gonzalez LF, Serrano-Arevalo ML, Flores-Hernandez L, Lino-Silva LS, Gonzalez-Mena LE. Reclassification of lesions in biopsies by fine-needle aspiration of pancreas and biliary tree using Papanicolaou classification. J Gastrointest Oncol. 2018 Oct;9(5):847–52.
10 Sung S, Del Portillo A, Gonda TA, Kluger MD, Tiscornia-Wasserman PG. Update on risk stratification in the Papanicolaou society of cytopathology system for reporting pancreaticobiliary cytology categories: 3-year, prospective, single-institution experience. Cancer Cytopathol. 2020 Jan;128(1):29–35.
11 Wright PK, Shelton DA, Holbrook MR, Thiryayi SA, Narine N, Slater D, et al. Outcomes of endoscopic ultrasound-guided pancreatic FNAC diagnosis for solid and cystic lesions at Manchester Royal Infirmary based upon the Papanicolaou Society of Cytopathology pancreaticobiliary terminology classification scheme. Cytopathology. 2018 Feb;29(1):71–9.
12 Saieg MA, Munson V, Colletti S, Nassar A. The impact of the new proposed Papanicolaou Society of Cytopathology terminology for pancreaticobiliary cytology in endoscopic US-FNA: a single-institutional experience. Cancer Cytopathol. 2015 Aug;123(8):488–94.
13 Smith AL, Abdul-Karim FW, Goyal A. Cytologic categorization of pancreatic neoplastic mucinous cysts with an assessment of the risk of malignancy: a retrospective study based on the Papanicolaou Society of Cytopathology guidelines. Cancer Cytopathol. 2016 Apr;124(4):285–93.
14 Thornton GD, McPhail MJ, Nayagam S, Hewitt MJ, Vlavianos P, Monahan KJ. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: a meta-analysis. Pancreatology. 2013 Jan–Feb;13(1):48–57.
15 Saieg MA, Munson V, Colletti S, Nassar A. Impact of pancreatic cyst fluid CEA levels on the classification of pancreatic cysts using the Papanicolaou society of cytology terminology system for pancreaticobiliary cytology. Diagn Cytopathol. 2017 Feb;45(2):101–6.
16 Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010.

17 Hoda RS, Finer EB, Arpin RN3rd, Rosenbaum M, Pitman MB. Risk of malignancy in the categories of the Papanicolaou Society of Cytopathology system for reporting pancreaticobiliary cytology. J Am Soc Cytopathol. 2019 May–Jun; 8(3):120–7.
18 Gilani SM, Adeniran AJ, Cai G. Endoscopic ultrasound-guided fine needle aspiration cytologic evaluation of intraductal papillary mucinous neoplasm and mucinous cystic neoplasms of pancreas. Am J Clin Pathol. 2020 Sep 8;154(4): 559–70.
19 Hoda RS, Arpin RN3rd, Rosenbaum MW, Pitman MB. Risk of malignancy associated with diagnostic categories of the proposed world Health organization international system for reporting pancreaticobiliary cytopathology. Cancer Cytopathol. 2022 Mar;130(3):195–201.
20 Saieg M, Pitman MB. Experience and future perspectives on the use of the Papanicolaou Society of Cytopathology Terminology System for reporting pancreaticobiliary cytology. Diagn Cytopathol. 2020 May;48(5):494–8.
21 Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012 Feb;75(2): 319–31.
22 Mitchell RA, Stanger D, Shuster C, Telford J, Lam E, Enns R. Repeat endoscopic ultrasound-guided fine-needle aspiration in patients with suspected pancreatic cancer: diagnostic yield and associated change in access to appropriate care. Can J Gastroenterol Hepatol. 2016;2016: 1–7.
23 Conti CB, Cereatti F, Grassia R. Endoscopic ultrasound-guided sampling of solid pancreatic masses: the fine needle aspiration or fine needle biopsy dilemma. Is the best needle yet to come? World J Gastrointest Endosc. 2019 Aug 16;11(8): 454–71.
24 Bang JY, Kirtane S, Krall K, Navaneethan U, Hasan M, Hawes R, et al. In memoriam: fine-needle aspiration, birth: fine-needle biopsy: the changing trend in endoscopic ultrasound-guided tissue acquisition. Digestive Endoscopy. 2019 Mar;31(2):197–202.
25 Facciorusso A, Wani S, Triantafyllou K, Tziatzios G, Cannizzaro R, Muscatiello N, et al. Comparative accuracy of needle sizes and designs for EUS tissue sampling of solid pancreatic masses: a network meta-analysis. Gastrointest Endosc. 2019 Dec;90(6):893–903 e7.
26 Centeno BA, Pitman MB. Fine needle aspiration biopsy of the pancreas. Boston: Butterworth-Heinemann; 1999.
27 Centeno BA, Pitman MB. Fine needle aspiration biopsy of the pancreas: Hodder Education Publishers; 1998.
28 Vandervoort J, Soetikno RM, Montes H, Lichtenstein DR, Van Dam J, Ruymann FW, et al. Accuracy and complication rate of brush cytology from bile duct versus pancreatic duct. Gastrointest Endosc. 1999 Mar;49(3):322–7.
29 Chadwick BE, Layfield LJ, Witt BL, Schmidt RL, Cox RNK, Adler DG. Significance of atypia in pancreatic and bile duct brushings: follow-up analysis of the categories atypical and suspicious for malignancy. Diagn Cytopathol. 2014 Apr; 42(4):285–91.
30 Dudley JC, Zheng Z, McDonald T, Le LP, Dias-Santagata D, Borger D, et al. Next-generation sequencing and fluorescence in situ hybridization have comparable performance characteristics in the analysis of pancreaticobiliary brushings for malignancy. J Mol Diagn. 2016 Jan;18(1):124–30.
31 Yeo MK, Kim KH, Lee YM, Lee BS, Choi SY. The usefulness of adding p53 immunocytochemistry to bile drainage cytology for the diagnosis of malignant biliary strictures. Diagn Cytopathol. 2017 Jul;45(7):592–7.
32 Poller DN, Schmitt F. Should uncertainty concerning the risk of malignancy be included in diagnostic [nongynecologic] cytopathology reports? Cancer Cytopathol. 2021 Jan;129(1):16–21.
33 Layfield LJ, Zhang T, Esebua M. Diagnostic sensitivity and risk of malignancy for bile duct brushings categorized by the Papanicolaou Society of Cytopathology System for reporting pancreaticobiliary cytopathology. Diagn Cytopathol. 2022 Jan;50(1):24–7.
34 Nikas IP, Proctor T, Seide S, Chatziioannou SS, Reynolds JP, Ntourakis D. Diagnostic performance of pancreatic cytology with the Papanicolaou society of cytopathology system: a systematic review, before shifting into the upcoming WHO international system. Int J Mol Sci. 2022 Jan 31;23(3):1650.
35 Moon SH, Kim MH, Park DH, Hwang CY, Park SJ, Lee SS, et al. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. Gut. 2008 Dec;57(12):1704–12.
36 Eisen GM, Dominitz JA, Faigel DO, Goldstein JA, Petersen BT, Raddawi HM, et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc. 2001 Dec;54(6):811–4.
37 Koul A, Baxi AC, Shang R, Meng X, Li L, Keilin SA, et al. The efficacy of rapid on-site evaluation during endoscopic ultrasound-guided fine needle aspiration of pancreatic masses. Gastroenterol Rep (Oxf). 2018 Feb;6(1):45–8.
38 Layfield LJ, Schmidt RL, Chadwick BE, Esebua M, Witt BL. Interobserver reproducibility and agreement with original diagnosis in the categories "atypical" and "suspicious for malignancy" for bile and pancreatic duct brushings. Diagn Cytopathol. 2015 Oct;43(10):797–801.
39 Choi WT, Swanson PE, Grieco VS, Wang D, Westerhoff M. The outcomes of "atypical" and "suspicious" bile duct brushings in the identification of pancreaticobiliary tumors: follow-up analysis of surgical resection specimens. Diagn Cytopathol. 2015 Nov;43(11):885–91.
40 Ikemura K, Yan L, Park JW. Follow-up of indeterminate cytologic diagnoses of solid pancreatic lesions: atypia versus suspicious [one institution's experience]. J Am Soc Cytopathol. 2018 May–Jun;7(3):160–5.
41 Olofson AM, Biernacka A, Li Z, Boonipat T, Gutmann EJ, Smith KD, et al. Indeterminate diagnoses in EUS-guided FNA of the pancreas: analysis of cytologist and clinician perceptions, cytologic features, and clinical outcomes. J Am Soc Cytopathol. 2018 Sep–Oct;7(5):274–81.
42 Abdelgawwad MS, Alston E, Eltoum IA. The frequency and cancer risk associated with the atypical cytologic diagnostic category in endoscopic ultrasound-guided fine-needle aspiration specimens of solid pancreatic lesions: a meta-analysis and argument for a Bethesda System for Reporting Cytopathology of the Pancreas. Cancer Cytopathol. 2013 Nov;121(11):620–8.
43 Hacihasanoglu E, Memis B, Pehlivanoglu B, Avadhani V, Freedman AA, Goodman MM, et al. Factors impacting the performance characteristics of bile duct brushings: a clinico-cytopathologic analysis of 253 patients. Arch Pathol Lab Med. 2018 Jul;142(7):863–70.
44 Volmar KE, Vollmer RT, Routbort MJ, Creager AJ. Pancreatic and bile duct brushing cytology in 1000 cases: review of findings and comparison of preparation methods. Cancer. 2006 Aug 25; 108(4):231–8.
45 Aly FZ, Mostofizadeh S, Jawaid S, Knapik J, Mukhtar F, Klein R. Effect of single operator cholangioscopy on accuracy of bile duct cytology. Diagn Cytopathol. 2020 Dec;48(12):1230–6.
46 Chadwick BE. Beyond cytomorphology: expanding the diagnostic potential for biliary cytology. Diagn Cytopathol. 2012 Jun;40(6):536–41.
47 Pitman MB, Layfield LJ. Guidelines for pancreaticobiliary cytology from the Papanicolaou society of cytopathology: a review. Cancer Cytopathol. 2014 Jun;122(6):399–411.
48 Bergeron JP, Perry KD, Houser PM, Yang J. Endoscopic ultrasound-guided pancreatic fine-needle aspiration: potential pitfalls in one institution's experience of 1212 procedures. Cancer Cytopathol. 2015 Feb;123(2):98–107.
49 Jarboe EA, Layfield LJ. Cytologic features of pancreatic intraepithelial neoplasia and pancreatitis: potential pitfalls in the diagnosis of pancreatic ductal carcinoma. Diagn Cytopathol. 2011 Aug; 39(8):575–81.
50 Rosenbaum MW, Arpin R, Limbocker J, Casey B, Le L, Dudley J, et al. Cytomorphologic characteristics of next-generation sequencing-positive bile duct brushing specimens. J Am Soc Cytopathol. 2020 Nov–Dec;9(6):520–7.
51 Selvaggi SM. Bile duct brushing cytology: cytohistologic/fine-needle aspiration correlation and diagnostic pitfalls. J Am Soc Cytopathol. 2016 Sep–Oct;5(5):296–300.
52 Barr Fritcher EG, Voss JS, Brankley SM, Campion MB, Jenkins SM, Keeney ME, et al. An optimized set of fluorescence in situ hybridization probes for detection of pancreatobiliary tract cancer in cytology brush samples. Gastroenterology. 2015 Dec;149(7):1813–24.e1.
53 Chaiteerakij R, Barr Fritcher EG, Angsuwatcharakon P, Ridtitid W, Chaithongrat S, Leerapun A, et al. Fluorescence in situ hybridization compared with conventional cytology for the diagnosis of malignant biliary tract strictures in Asian patients. Gastrointest Endosc. 2016 Jun; 83(6):1228–35.

54 Kushnir VM, Mullady DK, Das K, Lang G, Hollander TG, Murad FM, et al. The diagnostic yield of malignancy comparing cytology, FISH, and molecular analysis of cell free cytology brush supernatant in patients with biliary strictures undergoing endoscopic retrograde cholangiography [erc]: a prospective study. J Clin Gastroenterol. 2019 Oct;53(9):686–92.
55 Nanda A, Brown JM, Berger SH, Lewis MM, Barr Fritcher EG, Gores GJ, et al. Triple modality testing by endoscopic retrograde cholangiopancreatography for the diagnosis of cholangiocarcinoma. Therap Adv Gastroenterol. 2015 Mar;8(2):56–65.
56 Rosenbaum MW, Jones M, Dudley JC, Le LP, Iafrate AJ, Pitman MB. Next-generation sequencing adds value to the preoperative diagnosis of pancreatic cysts. Cancer Cytopathol. 2017 Jan;125(1):41–7.
57 Singhi AD, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, et al. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. Gut. 2018 Dec;67(12):2131–41.
58 Harbhajanka A, Michael CW, Janaki N, Gokozan HN, Wasman J, Bomeisl P, et al. Tiny but mighty: use of next generation sequencing on discarded cytocentrifuged bile duct brushing specimens to increase sensitivity of cytological diagnosis. Mod Pathol. 2020 Oct;33(10):2019–25.
59 Singhi AD, Nikiforova MN, Chennat J, Papachristou GI, Khalid A, Rabinovitz M, et al. Integrating next-generation sequencing to endoscopic retrograde cholangiopancreatography [ERCP]-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures. Gut. 2020 Jan;69(1):52–61.
60 Trisolini E, Armellini E, Paganotti A, Veggiani C, Bozzola C, Frattini M, et al. KRAS mutation testing on all non-malignant diagnosis of pancreatic endoscopic ultrasound-guided fine-needle aspiration biopsies improves diagnostic accuracy. Pathology. 2017 Jun;49(4):379–86.
61 Vlajnic T, Somaini G, Savic S, Barascud A, Grilli B, Herzog M, et al. Targeted multiprobe fluorescence in situ hybridization analysis for elucidation of inconclusive pancreatobiliary cytology. Cancer Cytopathol. 2014 Aug;122(8):627–34
62 Virk RK, Gamez R, Mehrotra S, Atieh M, Barkan GA, Wojcik EM, et al. Variation of cytopathologists' use of the indeterminate diagnostic categories "atypical" and "suspicious for malignancy" in the cytologic diagnosis of solid pancreatic lesions on endoscopic ultrasound-guided fine-needle aspirates. Diagn Cytopathol. 2017 Jan;45(1):3–13.
63 Pitman MB, Centeno BA, Daglilar ES, Brugge WR, Mino-Kenudson M. Cytological criteria of high-grade epithelial atypia in the cyst fluid of pancreatic intraductal papillary mucinous neoplasms. Cancer Cytopathol. 2014 Jan;122(1):40–7.
64 The European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018 May;67(5):789–804.
65 Hoda RS, Lu R, Arpin RN3rd, Rosenbaum MW, Pitman MB. Risk of malignancy in pancreatic cysts with cytology of high-grade epithelial atypia. Cancer Cytopathol. 2018 Sep;126(9):773–81.
66 Nakanuma Y, Jang KT, Fukushima N, Furukawa T, Hong SM, Kim H, et al. A statement by the Japan-Korea expert pathologists for future clinicopathological and molecular analyses toward consensus building of intraductal papillary neoplasm of the bile duct through several opinions at the present stage. J Hepatobiliary Pancreat Sci. 2018 Mar;25(3):181–7.
67 Nakanuma Y, Uesaka K, Okamura Y, Terada T, Fukumura Y, Kakuda Y, et al. Reappraisal of pathological features of intraductal papillary neoplasm of bile duct with respect to the type 1 and 2 subclassifications. Hum Pathol. 2021 May;111:21–35.
68 Canepa M, Yao R, Nam GH, Patel NR, Pisharodi L. Cytomorphology of intraductal papillary neoplasm of the biliary tract. Diagn Cytopathol. 2019 Sep;47(9):922–6.
69 Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004 May;126(5):1330–6.
70 Cizginer S, Turner B, Bilge AR, Karaca C, Pitman MB, Brugge WR. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. Pancreas. 2011 Jul 14;40(7):1024–8.
71 Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, et al. A revised classification system and recommendations from the baltimore consensus meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol. 2015 Dec;39(12):1730–41.
72 Gonzalez Obeso E, Murphy E, Brugge W, Deshpande V. Pseudocyst of the pancreas: the role of cytology and special stains for mucin. Cancer Cytopathol. 2009 Feb 20;117(2):101–7.
73 Zhang ML, Arpin RN, Brugge WR, Forcione DG, Basar O, Pitman MB. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. Cancer Cytopathol. 2018 Jun;126(6):414–20.
74 Wu J, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011 Jul 20;3:92ra66.
75 Singhi AD, Nikiforova MN, Fasanella KE, McGrath KM, Pai RK, Ohori NP, et al. Preoperative GNAS and KRAS testing in the diagnosis of pancreatic mucinous cysts. Clin Cancer Res. 2014 Aug 15;20(16):4381–9.
76 Pittman ME, Rao R, Hruban RH. Classification, morphology, molecular pathogenesis, and outcome of premalignant lesions of the pancreas. Arch Pathol Lab Med. 2017 Dec;141(12):1606–14.
77 Wood LD, Hruban RH. Pathology and molecular genetics of pancreatic neoplasms. Cancer J. 2012 Nov–Dec;18(6):492–501.
78 Tanaka M, Fernandez-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017 Sep– Oct;17(5):738–53.
79 Pitman MB, Genevay M, Yaeger K, Chebib I, Turner BG, Mino-Kenudson M, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol. 2010 Oct 7;118(6):434–40.
80 Pitman MB, Yaeger KA, Brugge WR, Mino-Kenudson M. Prospective analysis of atypical epithelial cells as a high-risk cytologic feature for malignancy in pancreatic cysts. Cancer Cytopathol. 2013 Jan;121(1):29–36.
81 Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018 Apr;113(4):464–79.
82 Scourtas A, Dudley JC, Brugge WR, Kadayifci A, Mino-Kenudson M, Pitman MB. Preoperative characteristics and cytological features of 136 histologically confirmed pancreatic mucinous cystic neoplasms. Cancer Cytopathol. 2017 Mar;125(3):169–77.
83 Michaels PJ, Brachtel EF, Bounds BC, Brugge WR, Bishop Pitman M. Intraductal papillary mucinous neoplasm of the pancreas: cytologic features predict histologic grade. Cancer. 2006 Jun 25;108(3):163–73.
84 Goyal A, Abdul-Karim FW, Yang B, Patel JB, Brainard JA. Interobserver agreement in the cytologic grading of atypia in neoplastic pancreatic mucinous cysts with the 2-tiered approach. Cancer Cytopathol. 2016 Dec;124(12):909–16.
85 Pitman MB, Centeno BA, Genevay M, Fonseca R, Mino-Kenudson M. Grading epithelial atypia in endoscopic ultrasound-guided fine-needle aspiration of intraductal papillary mucinous neoplasms: an international interobserver concordance study. Cancer Cytopathol. 2013 Dec;121(12):729–36.
86 Kosmahl M, Pauser U, Peters K, Sipos B, Lüttges J, Kremer B, et al. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch. 2004 Aug;445(2):168–78.
87 Yamao K, Yanagisawa A, Takahashi K, Kimura W, Doi R, Fukushima N, et al. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma: a multi-institutional study of the Japan pancreas society. Pancreas. 2011 Sep 29;40(1):67–71.
88 Sarr MG, Carpenter HA, Prabhakar LP, Orchard TF, Hughes S, van Heerden JA, et al. Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant [or premalignant] neoplasms? Annals of Surgery. 2000 Feb;231(2):205–12.

89 Jang KT, Park SM, Basturk O, Bagci P, Bandyopadhyay S, Stelow EB, et al. Clinicopathologic characteristics of 29 invasive carcinomas arising in 178 pancreatic mucinous cystic neoplasms with ovarian-type stroma: implications for management and prognosis. Am J Surg Pathol. 2015 Feb;39(2):179–87.

90 Amato E, Molin MD, Mafficini A, Yu J, Malleo G, Rusev B, et al. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. J Pathol. 2014 Mar 6;233:217–27.

91 Jones M, Zheng Z, Wang J, Dudley J, Albanese E, Kadayifci A, et al. Impact of next-generation sequencing on the clinical diagnosis of pancreatic cysts. Gastrointest Endosc. 2016 Jan;83(1):140–8.

92 Garcia-Carracedo D, Turk AT, Fine SA, Akhavan N, Tweel BC, Parsons R, et al. Loss of PTEN expression is associated with poor prognosis in patients with intraductal papillary mucinous neoplasms of the pancreas. Clin Cancer Res. 2013 Dec 15;19[24]:6830–41,

93 Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, et al. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. Gastroenterology. 2015 Nov;149(6):1501–10.

94 Senoo J, Mikata R, Kishimoto T, Hayashi M, Kusakabe Y, Yasui S, et al. Immunohistochemical analysis of IMP3 and p53 expression in endoscopic ultrasound-guided fine needle aspiration and resected specimens of pancreatic diseases. Pancreatology. 2018 Mar;18(2):176–83.

95 Kim H, Park CY, Lee JH, Kim JC, Cho CK, Kim HJ. Ki-67 and p53 expression as a predictive marker for early postoperative recurrence in pancreatic head cancer. Ann Surg Treat Res. 2015 Apr;88(4):200–7.

96 Kuboki Y, Shimizu K, Hatori T, Yamamoto M, Shibata N, Shiratori K, et al. Molecular biomarkers for progression of intraductal papillary mucinous neoplasm of the pancreas. Pancreas. 2015 Mar;44(2):227–35.

97 Iacobuzio-Donahue CA, Klimstra DS, Adsay NV, Wilentz RE, Argani P, Sohn TA, et al. Dpc-4 protein is expressed in virtually all human intraductal papillary mucinous neoplasms of the pancreas: comparison with conventional ductal adenocarcinomas. Am J Pathol. 2000 Sep;157(3):755–61.

98 Abe K, Suda K, Arakawa A, Yamasaki S, Sonoue H, Mitani K, et al. Different patterns of p16INK4A and p53 protein expressions in intraductal papillary-mucinous neoplasms and pancreatic intraepithelial neoplasia. Pancreas. 2007 Jan;34(1):85–91.

99 Layfield LJ, Dodd L, Factor R, Schmidt RL. Malignancy risk associated with diagnostic categories defined by the Papanicolaou Society of Cytopathology pancreaticobiliary guidelines. Cancer Cytopathol. 2014 Jun;122(6):420–7.

100 Sigel CS, Edelweiss M, Tong LC, Magda J, Oen H, Sigel KM, et al. Low interobserver agreement in cytology grading of mucinous pancreatic neoplasms. Cancer Cytopathol. 2015 Jan;123(1):40–50.

101 Layfield LJ, Wang G, Yang ZJ, Gomez-Fernandez C, Esebua M, Schmidt RL. Interobserver agreement for the international Academy of cytology yokohama system for reporting breast fine-needle aspiration biopsy cytopathology. Acta Cytol. 2020;64(5):413–9.

102 Novikov A, Kowalski TE, Loren DE. Practical management of indeterminate biliary strictures. Gastrointest Endosc Clin N Am. 2019 Apr;29(2):205–14.

103 Navaneethan U, Njei B, Lourdusamy V, Konjeti R, Vargo JJ, Parsi MA. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. Gastrointest Endosc. 2015 Jan;81(1):168–76.

104 Robison LS, Canon CL, Varadarajulu S, Eloubeidi MA, Vickers S, Mel Wilcox C. Autoimmune pancreatitis mimicking pancreatic cancer. J Hepatobiliary Pancreat Sci. 2011 Mar;18(2):162–9.

105 Wani S, Muthusamy VR, McGrath CM, Sepulveda AR, Das A, Messersmith W, et al. AGA white paper: optimizing endoscopic ultrasound-guided tissue acquisition and future directions. Clin Gastroenterol Hepatol. 2018 Mar;16(3):318–27.

106 Youssef Y, Shen R, Tonkovich D, Li Z. Clinical features, onsite evaluation, and follow-up results in patients with suspicious for adenocarcinoma on EUS-guided FNA of pancreas. J Am Soc Cytopathol. 2018 Jul–Aug;7(4):212–8.

107 Siddiqui AA, Kowalski TE, Shahid H, O'Donnell S, Tolin J, Loren DE, et al. False-positive EUS-guided FNA cytology for solid pancreatic lesions. Gastrointest Endosc. 2011 Sep;74(3):535–40.

108 Furmanczyk PS, Grieco VS, Agoff SN. Biliary brush cytology and the detection of cholangiocarcinoma in primary sclerosing cholangitis: evaluation of specific cytomorphologic features and CA19-9 levels. Am J Clin Pathol. 2005 Sep;124(3):355–60.

109 Goyal A, Sharaiha RZ, Alperstein SA, Siddiqui MT. Cytologic diagnosis of adenocarcinoma on bile duct brushings in the presence of stent associated changes: a retrospective analysis. Diagn Cytopathol. 2018 Oct;46(10):826–32.

110 Cohen MB, Egerter DP, Holly EA, Ahn DK, Miller TR. Pancreatic adenocarcinoma: regression analysis to identify improved cytologic criteria. Diagn Cytopathol. 1991;7(4):341–5.

111 Nakajima T, Tajima Y, Sugano I, Nagao K, Sakuma A, Koyama Y, et al. Multivariate statistical analysis of bile cytology. Acta Cytol. 1994 Jan-Feb;38(1):51–5.

112 Mitchell ML, Carney CN. Cytologic criteria for the diagnosis of pancreatic carcinoma. Am J Clin Pathol. 1985 Feb;83(2):171–6.

113 Rabinovitz M, Zajko AB, Hassanein T, Shetty B, Bron KM, Schade RR, et al. Diagnostic value of brush cytology in the diagnosis of bile duct carcinoma: a study in 65 patients with bile duct strictures. Hepatology. 1990 Oct;12(4):747–52.

114 Eiholm S, Thielsen P, Kromann-Andersen H. Endoscopic brush cytology from the biliary duct system is still valuable. Dan Med J. 2013 Jul;60(7):A4656.

115 Makar AB, McMartin KE, Palese M, Tephly TR. Formate assay in body fluids: application in methanol poisoning. Biochem Med. 1975 Jun;13(2):117–26.

116 Chen B, Zhao Y, Gu J, Wu H, Liang Z, Meng Z. Papanicolaou Society of Cytopathology new guidelines have a greater ability of risk stratification for pancreatic endoscopic ultrasound-guided fine-needle aspiration specimens. Oncotarget. 2017 Jan 31;8(5):8154–61.

117 Al-Kaisi N, Siegler EE. Fine needle aspiration cytology of the pancreas. Acta Cytol. 1989 Mar–Apr;33(2):145–52.

118 Kocjan G, Rode J, Lees WR. Percutaneous fine needle aspiration cytology of the pancreas: advantages and pitfalls. J Clin Pathol. 1989 Apr;42(4):341–7.

119 Robins DB, Katz RL, Evans DB, Atkinson EN, Green L. Fine needle aspiration of the pancreas. In quest of accuracy. Acta Cytol. 1995 Jan–Feb;39(1):1–10.

120 Lin F, Staerkel G. Cytologic criteria for well differentiated adenocarcinoma of the pancreas in fine-needle aspiration biopsy specimens. Cancer. 2002;99(1):44–50.

121 Silverman JF, Finley JL, MacDonald KGJr. Fine-needle aspiration cytology of osteoclastic giant-cell tumor of the pancreas. Diagn Cytopathol. 1990;6(5):336–40.

122 Rahemtullah A, Misdraji J, Pitman MB. Adenosquamous carcinoma of the pancreas: cytologic features in 14 cases. Cancer. 2003 Dec 25;99(6):372–8.

123 Reid MD, Muraki T, HooKim K, Memis B, Graham RP, Allende D, et al. Cytologic features and clinical implications of undifferentiated carcinoma with osteoclastic giant cells of the pancreas: an analysis of 15 cases. Cancer Cytopathol. 2017 Jul;125(7):563–75.

124 McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018 Nov 21;24(43):4846–61.

125 Falconi M, Bartsch DK, Eriksson B, Kloppel G, Lopes JM, O'Connor JM, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology. 2012;95(2):120–34.

126 Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially curable pancreatic cancer: American society of clinical oncology clinical practice guideline. J Clin Oncol. 2016 Jul 20;34(21):2541–56.