The Papanicolaou Society of Cytopathology has developed a set of guidelines for pancreatobiliary cytology including indications for endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) biopsy, techniques of EUS-FNA, terminology and nomenclature of pancreatobiliary disease, ancillary testing, and post-biopsy treatment and management. All documents are based on the expertise of the authors, a review of the literature, discussions of the draft document at several national and international meetings over an 18-month period and synthesis of online comments of the draft document on the Papanicolaou Society of Cytopathology web site (www.papsociety.org). This document selectively presents the results of these discussions and focuses on a proposed standardized terminology scheme for pancreatobiliary specimens that correlate cytological diagnosis with biological behavior and increasingly conservative patient management of surveillance only.

The proposed terminology scheme recommends a six-tiered system: Nondiagnostic, Negative, Atypical, Neoplastic (benign or other), Suspicious and Positive. Unique to this scheme is the “Neoplastic” category separated into “benign” (serous cystadenoma), or “Other” (premalignant mucinous cysts, neuroendocrine tumors, and solid-pseudopapillary neoplasms). The positive or malignant category is reserved for high-grade, aggressive malignancies including ductal adenocarcinoma, acinar cell carcinoma, poorly differentiated neuroendocrine carcinomas, pancreatoblastoma, lymphoma, and metastases. Interpretation categories do not have to be used. Some pathology laboratory information systems require an interpretation category, which places the cytological diagnosis into a general category. This proposed scheme provides terminology that standardizes the category of the various diseases of the pancreas, some of which are difficult to diagnose specifically by cytology. In addition, this terminology scheme attempts to provide maximum flexibility for patient management, which has become increasingly conservative for some neoplasms. Diagn. Cytopathol. 2014;42:338–350.

Key Words: PSC; terminology; nomenclature; pancreas; guidelines

Early detection of cancer whether it is malignancy of the ductal, acinar, or neuroendocrine system is the key to patient survival. With the increased use of endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) for the evaluation of pancreatobiliary lesions, coupled with our improved understanding of premalignant lesions and the evolving management algorithm for patients with
Pancreatic cysts,\textsuperscript{1,2} it is clear that cytopathologists play a very important role in the diagnosis and management of patients with pancreatic solid or cystic lesions and pancreatobiliary strictures. Hampering patient management is the lack of standardized nomenclature for pancreatobiliary disease, especially for the premalignant cysts. A standardized terminology and nomenclature system that provides intra- and interdepartmental guidance for diagnosis and which correlates with biological behavior and management recommendations is imperative for both FNA of pancreatic masses and cysts and brushing cytology of pancreatobiliary strictures. Interpretation categories do not have to be used. Some pathology laboratory information systems, however, require an interpretation category, which has been standard practice in cytology for decades. Such categories do aide in clinical and translational research, which is imperative for progress in the field. Below is a proposed terminology scheme with six categories including a category "Neoplastic" that is divided into clearly "benign" neoplasms and "other" neoplasms with less definitive biologic behavior predictable by cytological features.

These proposed guidelines on standardized terminology for pancreatobiliary cytology specimens stems from the expertise of the authors, review of the literature, discussions with pathologists at several national and international meetings over an 18-month period and synthesis of online comments of the draft document on the Papanicolaou Society of Cytopathology web site (www.papsociety.org).

\textbf{Proposed Pancreatobiliary Terminology Classification Scheme}

I. Nondiagnostic
II. Negative (for malignancy)
III. Atypical
IV. Neoplastic: benign and other
V. Suspicious (for malignancy)
VI. Positive/malignant

\textbf{Category I. Nondiagnostic}

\textit{Background.} Nondiagnostic specimens may be due to technical or sampling issues that preclude the pathologist from providing any useful information from the FNA biopsy relative to the lesion sampled. The clinical and imaging context should be taken into consideration. The absence of "epithelial cells" in the sample does not necessarily make a specimen nondiagnostic. For example, a pseudocyst by definition lacks an epithelial cyst lining, and mucinous cysts may only have thick colloid-like mucin, or a fluid with elevated carcinoembryonic antigen (CEA), findings sufficient to support an interpretation of a neoplastic mucinous cyst even when an epithelial component is lacking.\textsuperscript{3-5}

\textit{Definition.} A nondiagnostic cytology specimen is one that provides no diagnostic or useful information about the solid or cystic lesion sampled; for example, an acellular aspirate of a cyst without evidence of a mucinous etiology such as thick colloid-like mucus, elevated CEA or KRAS/\textit{GNAS} mutation (see category IV). Any cellular atypia precludes a nondiagnostic report.

\textit{Example cytological interpretations}

Evaluation limited by preparation artifact
Nondiagnostic
Tissue entrapped in blood clot and fibrin precluding cytological evaluation.
Satisfactory for evaluation
Nondiagnostic
Gastrointestinal (GI) contamination only.
Satisfactory for evaluation
Nondiagnostic
Normal acinar and ductal epithelium. The biopsy does not explain the well-defined pancreatic mass seen on imaging.
Evaluation limited by scant cellularity
Nondiagnostic
Nonspecific cyst contents with insufficient cyst fluid volume for ancillary testing.

\textbf{Category II. Negative (for Malignancy)}

\textit{Background.} A negative cytology sample is synonymous with the absence of malignancy and any cellular atypia in the cytology sample. A negative cytology interpretation that is descriptive without a diagnosis of a specific condition such as chronic pancreatitis or pseudocyst is not synonymous with a benign lesion. A descriptive negative interpretation implies that the sample is adequately cellular and that no cytological atypia is identified in the evaluated cytology sample. This includes the presence of normal pancreatic tissue in the appropriate clinical setting such a vague fullness on imaging and no distinct mass lesion. The false negative rate of an FNA of a solid mass lesion averages 15%, and in the setting of a clinically and radiologically suspicious mass with a presumed diagnosis of ductal adenocarcinoma, such an aspirate is presumed to be a false negative sample.\textsuperscript{6,7} The false negative rate for aspirates of cystic lesions is as high as 60% due to acellular or scantily cellular samples, in addition to the lack of defined nomenclature, criteria and experience in interpreting these lesions outside of
major academic hospital settings. That being said, the absence of high-grade epithelial atypia in a pancreatic cyst aspirate has a very high negative predictive value for malignancy. Since not all centers provide biochemical or molecular analysis of cyst fluid and/or the results of such testing may not be available at the time of cytological interpretation, it is reasonable to report as “negative” cyst fluids with mucinous debris of uncertain origin (lesional versus GI contamination) as such findings likely correlate with the clinical and imaging features of a low-grade branch-duct (BD) intraductal papillary mucinous neoplasm (IPMN). The clinician will find such a “negative” report much more helpful for patient management than a “nondiagnostic” report. See example cytological interpretations.

The false negative rate for the interpretation of pancreatobiliary brushing samples is also high due to the difficulty in obtaining diagnostic tissue that is often subepithelial, entrapped in desmoplastic stroma and/or markedly degenerated, coupled with the high threshold for a malignant interpretation due to the typical clinical setting of underlying inflammatory diseases such as primary sclerosing cholangitis and/or biliary stenting that can inherently cause marked reactive atypia.

Definition. A negative cytology sample is one that contains adequate cellular and/or extracellular tissue to evaluate or define a lesion that is identified on imaging. When using the negative category one should give a specific diagnosis when practical including:

- Benign pancreatobiliary tissue in the setting of vague fullness and no discrete mass
- Acute pancreatitis
- Chronic pancreatitis
- Autoimmune pancreatitis
- Pseudocyst
- Lymphoepithelial cyst
- Splenule/accessory spleen

Example cytological interpretations.

- Satisfactory for evaluation
  - Negative for malignancy
    Benign, reactive ductal epithelium and acinar tissue, acute and chronic inflammation and a background of necrotic, calcific debris consistent with chronic pancreatitis.
    - Evaluation limited by scant cellularity
      - Negative for malignancy
      - Cellular stromal fragments with lymphocytes and plasma cells suggestive of autoimmune pancreatitis.
      - Satisfactory for evaluation
      - Negative for malignancy

Cyst fluid with inflammation and histiocytes, yellow amorphous pigment and no cyst lining epithelial cells consistent with pseudocyst fluid.

[if available, add results of cyst fluid analysis; for example “low cyst fluid CEA (10 ng/mL) and markedly elevated amylase level (50,000 U/L) supports the diagnosis”].

- Satisfactory for evaluation
  - Negative for malignancy
    Mucinous cyst debris of uncertain etiology. No high-grade epithelial atypia identified. Correlation with imaging and ancillary studies required.
  - Satisfactory for evaluation
  - Negative for malignancy
    Nonmucinous cyst fluid with hemosiderin-laden macrophages and no epithelial cells, suggestive of serous cystadenoma. Correlation with clinical and imaging required.

    (if available, add results of cyst fluid analysis; for example “low CEA and amylase supports the interpretation”)

Category III. Atypical

Background. The interpretation category “Atypical” is heterogeneous and includes cases with reactive changes, low cellularity, premalignant changes (dysplasia), and cases assigned to this category due to observer caution in diagnosis. In one study, the risk of malignancy in this category for pancreatic and bile duct brushings was approximately 44%, and in another the risk of malignancy for atypical FNAs of pancreatic solid masses was approximately 82%.

This interpretation is used when a cytological specimen contains cellular or extracellular tissue that displays morphologic features beyond recognizable normal tissue components or reactive changes that can comfortably be interpreted as such and therefore classified as benign or “negative.” An atypical interpretation does raise the possibility of a neoplasm, and, in fact, may be suggestive of a low-grade neoplasm, but the cytological findings are insufficient to be suspicious for a high-grade malignancy, and tissue is insufficient for confirmation of a specific diagnosis. Conservative interpretation of diagnostic samples is not uncommon due to the significance of the surgical intervention, often a pancreaticoduodenectomy.

The negative and atypical categories have historically been the categories containing premalignant mucinous cysts, with benign appearing low-grade dysplastic cysts (adenomas) being placed in the negative category and the higher grade dysplastic cysts being placed in the suspicious category. The lack of well-established criteria for
the various grades of dysplasia in mucinous cysts has hampered a more standardized approach to classification. However, given the management algorithm for mucinous cysts which recommends a conservative approach for cysts at low risk of malignancy,\textsuperscript{1,2} it is imperative that the pathologist relate on the cytology report that a neoplastic mucinous cyst has been detected by FNA (e.g., neoplastic: other) and to relate the presence or absence of cytologically high-grade appearing epithelium (e.g., high-grade epithelial atypia that represents at least high-grade dysplasia and possibly invasive carcinoma\textsuperscript{12,13} (see category IV).

Abundant cytoplasmic mucin in pancreatic ducts is an abnormal finding and indicates a neoplastic change. The differential diagnosis for glandular epithelium with mucinous cytoplasm includes pancreatic intraepithelial neoplasia (PanIN), biliary intraepithelial neoplasia (BilIN), IPMN, mucinous cystic neoplasm (MCN), and adenocarcinoma. PanIN is not an entity recognized by imaging but it may be a source of atypia in aspirates of solid masses.\textsuperscript{14} Gastric epithelial contaminant is another source of mucin containing epithelium that may be confused with ductal epithelium with mucinous dysplasia.\textsuperscript{15} Of note, gastric epithelium may demonstrate some of the changes of pancreatic neoplasia, such as nuclear grooves and inclusions, and subtle crowding. Duodenal enterocytes are nonmucinous with a brush border, and, in addition to this feature, can be recognized by the presence of scattered goblet cells and intraepithelial lymphocytes.

Premalignant lesions of the bile ducts have historically been called biliary dysplasia or atypical biliary epithelium. A new consensus classification of biliary intraepithelial neoplasia (BilIN) was published in 2007,\textsuperscript{16} Using biliary brushing cytology derived from patient’s suffering from primary sclerosing cholangitis, choledochal cyst, or hepatolithiasis, this proposal classified BilIN into a three-grade classification scheme, similar to that used in other organs such as the pancreas and prostate. The histopathological criteria are similar to those for intraductal lesions of the pancreas; however, the cytopathological criteria of these lesions have not been defined. It can be assumed that their cytological features will be similar to what has been described as dysplasia in the biliary tract\textsuperscript{17} with grade 1 and 2 lesions causing atypia of bile duct epithelium on brushings, previously referred to as low grade dysplasia.

**Definition.** The category of atypical should only be applied when there are cells present with cytoplasmic, nuclear, or architectural features that are not consistent with normal or reactive cellular changes of the pancreas or bile ducts, and are insufficient to classify them as a neoplasm or suspicious for a high-grade malignancy. The findings are insufficient to establish an abnormality explaining the lesion seen on imaging. Follow-up evaluation is warranted.

**Examples of cytological interpretations.**

| Evaluation limited by preparation artifact | Atypical |
| Evaluation limited by scant cellularity | Atypical |
| Scant population of small monomorphic polygonal cells of uncertain origin: normal acinar cells versus endocrine proliferation. Additional tissue is warranted for diagnosis of this 2 cm round mass lesion in the pancreatic tail. | Atypical |
| Atypical bile duct epithelium with nuclear features suggestive of repair in a background of acute inflammation. | Atypical |
| Atypical bile duct epithelium with mucinous metaplasia and mild nuclear atypia. |

**Category IV. Neoplastic**

**IVA. Neoplastic: benign.**

**Background.** A common benign neoplasm of the pancreas is serous cystadenoma. Histologically, serous neoplasms consist of fine fibrous septae lined by cuboidal, glycogen-rich cells without atypia except for the occasional degenerative, reactive atypia. Fibrous septa include numerous small capillary structures. This dense vascularization explains the often hemorrhagic aspect of the cyst fluid as well as the presence of numerous hemosiderin-laden macrophages on cytological preparations. Such macrophages can be observed in up to 63% of cases, whereas they are almost always absent in cystic mucinous neoplasms.\textsuperscript{18} Macrophages can, however, only be considered as a surrogate marker of serous cystic neoplasms and cannot be used as a definitive cytological criterion. When coupled with cytological analysis, and with appropriate clinical and imaging features, biochemical analysis of CEA level, typically less than 5 ng/mL, and amylase levels, typically also very low relative to other pancreatic cysts (but can reach into the hundreds and rarely low thousands) support this diagnosis. Caution must be used because some mucinous cysts have very low CEA levels, and conversely, serous neoplasms can, albeit rarely, present with elevated CEA levels, which can reach into the hundreds and rarely low thousands.\textsuperscript{3–5} Other benign neoplasms in the pancreas such as cystic teratoma and...
schwannoma are extremely rare and are also placed in this category.

**Definition: neoplastic: benign.** This interpretation category connotes the presence of a cytological specimen sufficiently cellular and representative, with or without the context of clinical, imaging, and ancillary studies, to be diagnostic of a benign neoplasm.

**Example cytological interpretation.**

Evaluation limited by scant cellularity
Neoplastic: benign
Scant nonmucinous cuboidal epithelium and scant hemosiderin-laden macrophages in a nonmucinous cyst fluid consistent with the clinical impression of a serous cystadenoma

[if available, add results of cyst fluid analysis; for example “low CEA (0.5 ng/mL) and amylase (150 U/L) levels support the diagnosis”].

**IVB. Neoplastic: other.** Background. Aside from the clearly malignant neoplasms like conventional pancreatic ductal adenocarcinoma and the definitively benign neoplasms like serous cystadenoma, there are neoplasms (other) that are either preinvasive, premalignant neoplasms (IPMN and MCN with low, intermediate or high grade dysplasia) or of low-grade malignant behavior [pancreatic neuroendocrine tumor (PanNET) and solid-pseudopapillary neoplasm (SPN)] that warrant distinction from aggressive, high-grade malignancies (most notably pancreatic ductal adenocarcinoma (PDAC)). The rationale for this distinction and classification is explained in more detail below for each neoplasm, but, in general, the rational relates the desire to standardize the cytological nomenclature and terminology which correlates with the 2010 WHO classification and terminology. In addition, there was the need to remove the “malignant” classification from neoplasms diagnosed cytologically with uncertain or low-grade malignant potential, a move which provides a reasonable classification that correlates with the increasingly conservative approach to these neoplasms. The standard cytological categories of “atypical” and “suspicious for malignancy” (SFM) are categories that connote an indeterminate interpretation that does not provide for a definitive cytological interpretation of a neoplasm, which could lead to inappropriate patient management and possibly an unnecessary repeat diagnostic procedure.

All of these pancreatic tumors are clearly neoplastic, and some low-grade malignant. As such, the heading “neoplastic: other” is a reasonable generic term that accurately reflects the preoperative, cytological terminology. The terminology “neoplastic: other” does not define the neoplasm as benign or malignant nor does it correlate with a specific management algorithm.

**Definition: neoplastic: other.** This interpretation category defines a neoplasm that is either premalignant such as intraductal papillary neoplasm of the bile duct (IPNB), IPMN, or MCN with low-, intermediate-, or high-grade dysplasia by cytological criteria, or a low-grade malignant neoplasm such as well-differentiated PanNET or SPN. While mucinous epithelium in biliary brushing specimens may indeed represent a neoplastic change, given the lack of evidence-based literature on the cytological interpretation, histology and management of these lesions, low-grade mucinous change of biliary epithelium will remain in the “atypical” rather than “neoplastic” category.

**Pancreatic neuroendocrine tumor.** The current preferred nomenclature for this neoplasm is PanNET. Synonyms include pancreatic endocrine tumor, and pancreatic endocrine neoplasm. The term “neuroendocrine tumor” is inferred to mean a well-differentiated neoplasm, and is a term that should be used whether in the primary site or in a metastatic site (e.g., liver FNA with metastatic well-differentiated neuroendocrine tumor). In the WHO 2010 classification system, the term neuroendocrine carcinoma infers either high-grade large cell neuroendocrine carcinoma or small cell carcinoma. The cytological interpretation of PanNET infers a well-differentiated proliferation of the pancreatic endocrine cells creating a mass lesion greater than 0.5 cm that may or may not be functional by producing inappropriate levels of various hormones, and that may or may not demonstrate aggressive features on histological examination. Although it is now widely accepted that well-differentiated PanNETs all have malignant potential, albeit very slow growing, and even curable, if caught at an early stage, these neoplasms are placed in this more generic neoplastic category to distinguish them from highly aggressive malignant neoplasms and to offer management flexibility in elderly patients with small tumors where the risk to benefit ratio of surgery is high compared to conservative management.

**Solid-pseudopapillary neoplasm.** SPN is a solid, secondarily cystic low-grade epithelial neoplasm with established clonal mutations in cancer-associated genes and an ability to metastasize. They typically occur in young females and demonstrate a variably solid and cystic appearance on imaging. It is a parenchymal-rich, stromal-poor proliferation of monotonous cells that defy prediction of biological behavior based on cytological features. Although this neoplasm is one that will almost always be resected due to the typical young age of the patient, like PanNET, it is considered a low-grade malignancy, and, as such, it is included in this category.

**Neoplastic mucinous cysts of the pancreas IPMN and MCN.** The two primary neoplastic mucinous cysts of the pancreas consist of IPMN and MCN. Understanding the clinical, imaging and cyst fluid analysis characteristics of IPMN and MCN is vital to the interpretation of the cytological specimen. The pathologist should correlate the
clinical, imaging and cyst fluid analysis characteristics to make the most likely specific diagnosis.

Management guidelines have evolved over time and have become much more conservative given the prevalence of incidental, asymptomatic cysts identified in the general population and especially in the elderly. MCN, although mostly low grade,\textsuperscript{25,26} are usually identified in young to middle-aged women in the body or tail of the pancreas that can be relatively easily removed with a distal pancreatectomy alleviating the need for expensive, life-long surveillance. Main-duct and combined type IPMNs are all removed due to the inherent high risk of malignancy.\textsuperscript{27} BD-IPMNs are more often than not low-grade neoplasms identified in the pancreatic head of the elderly with co-morbid conditions making pancreaticoduodenectomy a high-risk procedure greater than the risk of the cyst progressing to malignancy.\textsuperscript{27} If a cyst is mucinous and there is no evidence of high-grade dysplasia or carcinoma, then conservative management is reasonable.\textsuperscript{1,2} The difficult position for the pathologist then becomes grading the epithelium of the cyst. It is quite difficult in other organ systems even on histology to stratify grades into four tiers: low, moderate, and severe dysplasia and carcinoma. This difficulty is exponential when interpreting just a few cells that have undergone partial degeneration in cyst fluid and that may be associated with GI contamination. A high threshold for malignancy is in order. That being said, recognition of atypical epithelial cells and their distinction from low-grade dysplasia is vitally important to the recognition of a cyst with high-grade atypia that likely corresponds to at least moderate dysplasia and in a high proportion of cases, high-grade dysplasia or worse.\textsuperscript{28–30} Resection prior to invasion provides the patient with the best prognosis, and high risk imaging features such as a markedly dilated main pancreatic duct or a mural nodule in a cyst that lead to resection are very often signs of an invasive neoplasm. As such, aspiration of cysts without these features provides the best opportunity for early detection of carcinoma.

\textit{Mucinous cystic neoplasm.} MCN of the pancreas is typically a multiloculated, mucin-producing epithelial neoplasm with subepithelial ovarian-type stroma that in almost all cases does not communicate with the pancreatic ductal system and in almost all cases occurs in women. Like IPMN, these neoplasms are stratified by the degree of cytological and architectural atypia into low-grade, intermediate-grade, and high-grade dysplastic, premalignant (noninvasive neoplasms) and invasive carcinomas (invasive mucinous cystadenocarcinoma). The invasive carcinomas are usually of tubular type, but rare carcinomas such as undifferentiated carcinoma with osteoclast-type giant cells may also be seen.\textsuperscript{25,26} A similar neoplasm occurs in the biliary tract. The cytological features will be similar to its pancreatic counterpart.

\textit{Intraductal papillary mucinous neoplasm.} IPMNs are primarily intraductal proliferations of ductal epithelium creating a macroscopic lesion resulting in ductal dilatation, cyst formation and/or a mass lesion. Intraductal tubulopapillary neoplasms are included with IPMN as this neoplasm is not only rare, but would be cytologically indistinguishable from some IPMNs. Invasion of the duct or cyst wall occurs in about one third of resected IPMN, and is most common in IPMN of main-duct type. There are three main types of IPMN\textsuperscript{27,31–34}:

1. \textit{Main-duct IPMN:} Generally associated with diffuse dilatation of any portion of the main pancreatic duct or the entire pancreas. The definition of “dilatation” is variable in the literature. The 2006 Sendai guidelines define it as >6 mm, but the new 2012 guidelines define it as 10 mm or greater with >5 mm being “worrisome.”\textsuperscript{2} Visualization of mucin extruding from the ampulla on EUS or ERCP is pathognomonic. The epithelial cell type most often associated with main-duct IPMN is intestinal type epithelium (MUC 5AC, MUC 2, and CDX2+) which, by definition, is at least of intermediate (moderate) grade dysplasia. Invasive carcinomas most often arising from intestinal-type IPMN are colloid carcinomas.\textsuperscript{33,35}

2. \textit{BD-IPMN:} Cysts adjacent to a nondilated main pancreatic duct, most often in the uncinate process, but occurring throughout the pancreas in one or more locations. Imaging features generally depict a thin-walled unilocular cyst that may or may not demonstrate a connection to the pancreatic ductal system. Small "raspberry-like" multiloculated cysts are also typical of BD-IPMN. The cyst lining is most often of gastric-foveolar type, and, although most are low grade, this epithelial cell type can display intermediate and high-grade dysplasia. Invasive carcinomas arising from these cysts tend to be of the tubular type and have a prognosis similar to conventional pancreatic adenocarcinoma.\textsuperscript{36}

3. \textit{Combined-type IPMN:} Neoplasia involving both the main and BDs of the pancreas typically represented on imaging by a dilated main pancreatic duct with one or more BD cysts.

Two other epithelial cell types may be seen in IPMN. Pancreatobiliary epithelium is relatively uncommon and, by definition, is equivalent to high-grade dysplasia. Oncocytic epithelium is the least common epithelial cell type, and is also considered high-grade. Oncocytic type epithelium is distinguished by the moderate amounts of dense, granular, and oncocytic cytoplasm. While low-grade gastric-foveolar type epithelium is recognizable, it may not be distinguishable from gastric epithelial contamination in
transgastric biopsies. It is generally not possible nor is it important to distinguish the epithelial cell types with intermediate to high-grade dysplasia.

**Cyst fluid analysis.** Analysis of the cyst fluid from pancreatic cysts is invaluable in accurate classification of the cyst as mucinous or nonmucinous. It is well established that although each lab should establish their own cutoff value, that, CEA levels of ~200 ng/mL is strongly supportive of a neoplastic mucinous cyst.\(^3\)\(^,\)\(^4\) A low CEA level does not exclude a mucinous etiology. In addition, CEA levels do not distinguish between benign and malignant cysts.\(^3\)\(^,\)\(^4\) Amylase levels of cyst fluid are helpful in supporting the interpretation of a pseudocyst as such fluids typically have amylase levels in the thousands,\(^5\) but amylase levels do not distinguish between IPMN and MCN.\(^3\)\(^,\)\(^7\)\(^,\)\(^8\) Serous cystadenomas tend to have both low CEA and amylase levels as do cystic PanNETs.\(^3\)\(^,\)\(^9\)\(^,\)\(^10\)

**Molecular analysis.** KRAS testing may supplement CEA as the detection of KRAS supports a mucinous etiology.\(^11\) Although the combination of KRAS, LOH and quality and quantity of DNA correlates with malignancy,\(^12\) a KRAS mutation in and of itself is not specific for malignancy. A recent study of pancreatic cyst fluid has shown that detection of GNAS supports a specific interpretation of IPMN, but does not distinguish premalignant from malignant (invasive) IPMN.\(^13\) See the report of Committee IV for a more detailed discussion of ancillary testing.

**Approach to the cytological analysis of pancreatic cysts.** The cytopathologist’s approach to the interpretation of a pancreatic cyst should be to address two basic questions. (1) Is the cyst mucinous or nonmucinous and (2) is the cyst high-grade or not? Malignant is defined as unequivocal features of adenocarcinoma (see section on positive for malignancy). Atypia less than overtly malignant is included in this category of neoplastic: other.

To answer the first question of a mucinous etiology, the first clue may come from the gastroenterologist who describes “thick, viscous or white, sticky” fluid upon aspiration. This type of fluid is generally thick enough to make a direct smear. Thinner fluids are best processed as a cytospin preparation in order to capture all of the cells and to preserve the characteristics of the cyst fluid. Placing the cyst fluid in a preservative attenuates the viscosity of the fluid and may make thin mucin difficult or impossible to appreciate. Contamination of the specimen with mucin from the GI tract is also a consideration. Thick, colloid-like mucin is neoplastic (with rare exception such as in a GI duplication cyst), and mucin with evidence of cellular cyst debris also supports origin from the cyst and not the GI tract.\(^14\) Conversely, thin mucous with naked grooved nuclei evoke GI contamination. Special stains for mucin may be helpful but should be interpreted with caution. A mucicarmine or Alcian blue positive thin film on a cytospin or thick wavy wisps of mucoid fluid that stains positively without significant GI epithelial contamination are stain outcomes that support a mucinous etiology. Negative mucin stains do not exclude a mucinous cyst. CEA elevation or detection of a KRAS mutation may be necessary to support a mucinous etiology, but, a nonelevated CEA or absent KRAS mutation does not exclude a mucinous cyst.

To answer the second question of high-grade or not, an evaluation of the epithelial component is required. Less than overt malignancy is best interpreted as either low-grade or high-grade atypia as the accuracy in distinguishing intermediate (moderate) from high-grade dysplasia is difficult if not impossible.\(^2\) GI contaminating epithelium needs to be recognized as such (see criteria under category I). Cytological criteria distinguishing high-grade atypia from low-grade atypia has recently been described.\(^12\) Cells smaller than a 12-µm duodenal enterocyte showing an increased nuclear to cytoplasmic ratio, an abnormal chromatin pattern, and background necrosis represent high-grade epithelial atypia placing the cyst at high-risk of malignancy.\(^1,\)\(^2\)\(^,\)\(^13\)\(^,\)\(^4\)\(^6\)\(^,\)\(^4\)\(^8\)

Both mucin production and epithelial cells are not required for the diagnosis of a mucinous cyst. The aspirates of some mucinous cysts are acellular but are clearly mucinous from the visible thick, colloid-like extracellular mucin, elevated CEA or KRAS/ GNAS mutation. Similarly, a cyst fluid with high-grade mucinous epithelial dysplasia or carcinoma may not demonstrate extracellular mucin or an elevated CEA.\(^2\)\(^,\)\(^2\)\(^8\)\(^,\)\(^4\)\(^9\)

**Approach to the cytological evaluation of biliary tract cysts.** The approach to evaluating cysts arising in the biliary tract has not been as formally studied as those of the pancreas. However, it can be surmised that IPN-B and MCN-B will have similar cytological features on aspiration. The role of ancillary studies in these cysts, such as measurement of CEA, is not established.

**Intraductal papillary neoplasm of the bile ducts.** Intraductal papillary neoplasm of the bile ducts shares many clinical and pathological features with IPMN of the pancreas. It is a neoplastic proliferation growing within the bile ducts composed of a papillary proliferation of mucin containing neoplastic cells that may occur anywhere in the ductal system. It progresses from low, to high-grade and eventually invasive carcinoma, just as IPMN of the pancreas does. Gastric, pancreatobiliary, intestinal, and oncocytic subtypes have been described, but show a different distribution than observed in IPMN-P.\(^5\)\(^0\)\(^,\)\(^5\)\(^1\) These are more likely to be sampled by brushing cytology than by FNA. When they present as cystic masses, they may be aspirated, and the cytological features of aspiration cytology will be similar to those of IPMN of the pancreas. The cytological features of brushing cytology for IPN-B are not described here. While there are no prospective or retrospective
reports, these features are extrapolated from the histopathological features and are similar to what is encountered in brushing cytology of IPMN of the pancreas.

**Gastrointestinal stromal tumor.** Gastrointestinal stromal tumors (GISTs) are very rare as a primary pancreatic neoplasm (extragastrointestinal stroma tumor); however, they commonly occur in a peripancreatic location such as the omentum, mesentery, duodenum and stomach, thus mimicking a primary pancreatic neoplasm at times. GIST are spindle cell and/or epithelioid mesenchymal neoplasms with differentiation along the lines of the interstitial cell of Cajal that usually expression c-kit protein (CD117), DOG1, and CD34 by immunohistochemistry.\(^5\)\(^-\)\(^7\) There is variable expression of alpha-smooth muscle actin and essentially no reactivity for desmin. As with all spindle cell lesions, procuring cellblocks on such specimens will facilitate a definitive diagnosis.

**Examples of cytological interpretations.**

- **Satisfactory for evaluation**
  - Neoplastic: other
  - Mucinous cyst fluid with low-grade dysplasia (see note).
  - Note: Benign-appearing mucinous epithelium is present from this transduodenal FNA in a background of abundant extracellular mucin. (If available, add CEA is elevated at 357 ng/mL supporting the diagnosis).
  - Satisfactory for evaluation
  - Neoplastic: other
  - Cyst fluid with thick colloid-like extracellular mucin containing cyst debris consistent with a neoplastic mucinous cyst, favor mucinous cystic neoplasm given the clinical and imaging findings of a 45-year-old female with a multiloculated cyst in the pancreatic tail. Scant benign appearing mucinous epithelium is present of uncertain origin, favor gastric contamination. No high-grade epithelial atypia present.
  - Evaluation limited by scant cellularity
  - Neoplastic: other
  - Mucinous cyst fluid with high-grade epithelial atypia (See note).
  - Note: No thick extracellular mucin is present but cyst fluid CEA is 1,267 ng/mL supporting the diagnosis. In addition, molecular analysis demonstrates a KRAS point mutation, which supports a mucinous etiology. The epithelial cells are most consistent with high-grade dysplasia, however, invasive carcinoma cannot be excluded. Correlation with imaging findings required.
  - Satisfactory for evaluation
  - Neoplastic: other
  - Well-differentiated neuroendocrine tumor.
  - Note: Tissue is not available for ancillary studies, however, the morphological features of endocrine differentiated are well-defined.

**OR**

- Immunohistochemical stains on the corresponding cellblock confirm endocrine differentiation (synaptophysin and chromogranin are positive). Proliferation marker Ki-67 shows less than 2% nuclear staining suggestive of a grade 1 tumor.
  - Satisfactory for evaluation
  - Neoplastic: other
  - Solid-pseudopapillary neoplasm

**V. Suspicious (for malignancy).**

Background. The cytological interpretation category of suspicious for malignancy (SFM) generally refers to pancreatic adenocarcinoma, but may be used with any malignant neoplasm, and this terminology scheme recommends using it for high-grade, aggressive malignancies. “Suspicious for” is NOT “diagnostic of,” and clinical and radiological information must be correlated with the suspicious cytological findings to justify surgical intervention. Like the “atypical” interpretation category, the “suspicious” category suffers from significant interobserver variability often stemming from varying experience of the pathologist in interpreting pancreatic cytology. Due to the high threshold of a malignant interpretation, and thus the low false positive rate of pancreatic cytology, many samples are conservatively interpreted and may benefit from a second opinion by an experienced pancreatic cytopathologist to save the patient the potential of a repeat diagnostic procedure.

Aspirates insufficient to make a definitive diagnosis of at least a neoplasm such as PanNET or SPN should be placed in the Atypical category with specification of the indeterminate interpretation in the diagnosis line. However, for aspirates that produce a “solid-cellular” clearly neoplastic epithelial proliferation which includes PanNET, acinar cell carcinoma, pancreatoblastoma and SPN in the differential diagnosis, but which has insufficient tissue for confirmatory ancillary studies to make a specific diagnosis, the SFM category is an appropriate classification.

SFM is an indeterminate category resulting from three major challenges with interpretation of FNA specimens of the pancreas. The first challenge is the very high level of differentiation of certain pancreatic adenocarcinomas that may harbor very subtle cytologic abnormalities.\(^5\)\(^5\) The second challenge is scant cellularity. Pancreatic adenocarcinoma induces a tumor-associated sclerotic response that may contribute to this sparse cellularity.\(^5\)\(^6\) The third problem that cytopathologists must address is GI contamination that, when substantial, may mask some scattered tumor cells, and when injured and reactive, may mimic carcinoma. When these challenges are faced in a single case, a definitive diagnosis of malignancy may be impossible, but malignancy is probable. In these cases, where the degree
of suspicion for malignancy is high enough to require therapeutic intervention, one may classify the lesion as SFM. This category has a very high positive predictive value for malignancy.\textsuperscript{56–58} The SFM diagnosis must be correlated with clinical symptoms and imaging characteristics. When a patient has a high clinical suspicion of pancreatic cancer and a pancreatic mass on imaging studies, the diagnosis of suspicious most likely indicates the presence of cancer.\textsuperscript{56–58} Autoimmune pancreatitis should be a clinical consideration as it is a well-known pitfall mimicker of PDAC clinically, radiologically, and cytologically. The distinction between a positive diagnosis and an SFM diagnosis is based on both quantitative and qualitative criteria. Suspicions cases represent 5–12\% of published cases,\textsuperscript{59} but most studies focus on pancreatic adenocarcinoma, so the number of cases that are considered as suspicious for Pan-NETs, acinar cell carcinomas, or lymphomas is very difficult to establish.

As a category, the risk of malignancy for brushing specimens designated SFM is approximately 80\% and 96\% for the EUS-FNA specimens identified as SFM.\textsuperscript{60}

\textbf{Definition.} A specimen is SFM when some but an insufficient number of the typical features of a specific malignant neoplasm are present, mainly pancreatic adenocarcinoma. The cytological features raise a strong suspicion for malignancy, but the findings are qualitatively and/or quantitatively insufficient for a conclusive diagnosis, or tissue is not present for ancillary studies to define a specific neoplasm. The morphologic features must be sufficiently atypical that malignancy is considered more probable than not.

\textit{Examples of cytological interpretations.}

\begin{itemize}
  \item Satisfactory for evaluation
  \item Suspicious (for malignancy)
  \item Rare markedly atypical epithelial cells suspicious for adenocarcinoma.
  \item Satisfactory for evaluation
  \item Suspicious (for malignancy)
  \item Mucinous cyst with high-grade epithelial atypia and abundant coagulative necrosis suspicious for invasive carcinoma.
  \item Satisfactory for evaluation
  \item Suspicious (for malignancy)
  \item Solid cellular neoplasm with features suspicious for acinar cell carcinoma. Tissue for confirmatory ancillary studies is not available.
\end{itemize}

\textbf{Category VI. Positive or Malignant}

\textbf{Background.} Since 9 of 10 malignancies in the pancreas are conventional PDAC, the "positive" or "malignant" category is often related to this category. Low-grade malignancies such as well-differentiated PanNET and SPN are included in the neoplastic: other category. Other high-grade malignancies are also included here such as acinar cell carcinoma, panreatoblastoma, lymphoma and metastases. The specificity of a positive or malignant interpretation for both pancreatic FNA and biliary brushing is very high, >90–95\% in most studies.\textsuperscript{6,7,10,57,61–65} Relying on strict criteria contributes to this high specificity at the expense of sensitivity. Rapid on site evaluation of solid mass lesion FNAs contributes to diagnostic yield.\textsuperscript{66–68}

\textbf{Definition.} A group of neoplasms that unequivocally display malignant cytologic characteristics and include PDAC and its variants, cholangiocarcinoma, acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), pancreatoblastoma, lymphomas, sarcomas and metastases to the pancreas.

\textbf{Pancreatic ductal adenocarcinoma.} PDAC is a malignant invasive gland (duct) forming epithelial neoplasm typically composed of classic tubular glands, but, in variants, with other morphologically diverse epithelial morphologies. Pancreatic ductal adenocarcinoma, or infiltrating ductal adenocarcinoma, is the most common primary cancer of the pancreas which accounts for 85–90\% of all pancreatic malignancies.\textsuperscript{27,34} Moderately to poorly differentiated tumors generally demonstrate overt features of malignancy that makes cytological diagnosis straightforward. Well-differentiated tumors can be extremely challenging due to minimal deviation from normal ductal morphology making definitive diagnosis of malignancy challenging.

\textbf{Cholangiocarcinoma.} The diagnostic criteria for invasive cholangiocarcinoma are the same as for ductal adenocarcinoma of the pancreas on FNA samples. Published diagnostic criteria for adenocarcinoma in a bile duct brushing specimen\textsuperscript{69,70} demonstrate variable predictive values.\textsuperscript{71} The presence of indwelling stents and the underlying inflammatory conditions that lead to bile duct sticture and the increased risk of malignancy are factors in and of themselves that contribute to the need for a high threshold for malignancy in these specimens. As such, the sensitivity of detecting malignancy in these specimens is low.\textsuperscript{10,61,62,65} An overall assessment for the presence of malignancy may be best in these samples. The addition of ancillary testing using FISH and other molecular methods may also improve sensitivity.\textsuperscript{55,72} (See report from Committee IV on Ancillary Testing in Pancreatobiliary Specimens).

Major diagnostic pitfalls in the evaluation of bile duct brushings include obscuring of malignant epithelium by overlying benign epithelium, insufficient sampling, degeneration due to bile or duodenal contents, primary sclerosing cholangitis\textsuperscript{73} and atypical squamous metaplasia due to bile duct stones and stents. Correlation of the cytological findings with the clinical findings may help, as a biliary stricture is more likely to be malignant in older male patients who are symptomatic and do not have a history of stones.\textsuperscript{10}
Colloid carcinoma (mucinous, noncystic). A carcinoma of ductal differentiation showing abundant extracellular mucin production, with at least 80% of the tumor on histology demonstrating large pools of extracellular mucin and cuboidal epithelial cells “floating” in the mucin. This uncommon variant accounts for 1–3% of PDAC and the vast majority arise in association with IPMN of intestinal type. Gender and age distribution is similar to PDAC; however, the prognosis appears to be significantly better.35

Medullary carcinoma. A carcinoma characterized by poor histologic differentiation, syncytial growth pattern, pushing borders, and an intense lymphoplasmacytic response. Medullary carcinoma is characterized by a special genetic profile with 69% of these tumors displaying wild-type KRAS genes and 22% of these tumors have microsatellite instability.

Adenosquamous carcinoma. A rare subtype with relative frequency of 3–4% and relatively poorer prognosis compared to the conventional ductal adenocarcinoma, this variant shows malignant glandular and squamous components ranging from extensive glandular differentiation with focal squamous differentiation to predominantly squamous differentiation.74

Undifferentiated carcinoma with osteoclast-like giant cells. Often admixed with ordinary PDAC, this tumor is a distinctive type of sarcomatoid carcinoma with the striking and unique cytologic features characterized by a prominent component of reactive osteoclast-like giant cells in a background of spindle cells. Often seen in association with MCN, these tumors may also arise with in situ (PanIN III and invasive ductal carcinoma.25

Undifferentiated carcinoma. Also known as anaplastic carcinoma this rare variant of pancreatic ductal adenocarcinoma has a relative frequency of 2–7%. It is a high-grade carcinoma composed of large, undifferentiated, markedly pleomorphic cells.76 Tumors with this morphology should prompt the pathologist to consider metastatic disease and to evaluate available tissue with ancillary studies to investigate the possibility.

Acinar cell carcinoma. A rare malignant epithelial neoplasm with exocrine acinar differentiation. Lipase hypersecretion syndrome is present in only 16% of the patients, but serves as a clinical clue to the diagnosis. A significant proportion of the cases have small neuroendocrine component or scattered neuroendocrine cells within the tumor. Approximately 50% of the patients have metastatic disease at presentation, often restricted to the regional lymph nodes and liver.77–83

Poorly differentiated neuroendocrine carcinoma (small cell carcinoma or large cell neuroendocrine carcinoma). Both small cell and large cell high-grade neuroendocrine carcinomas exhibit cytoarchitectural and clinicopathological features indistinguishable from their pulmonary (and extrapulmonary) counterparts. These carcinomas account for less than 1% of all primary pancreatic cancers and 2–3% of PanNETs. These carcinomas are extremely rare in the pancreas and the possibility of metastatic lung carcinoma or extension from the more common primary site of the ampulla (for large cell type) should always be excluded first.22,84

Pancreatoblastoma. A rare neoplasm, primarily of childhood, characterized by acinar differentiation, endocrine differentiation and distinctive squamoid nests. Also known as infantile pancreatic carcinoma, this is an extremely rare pancreatic tumor in childhood, comprising 0.5% of pancreatic nonendocrine tumors with rare occurrence in adults. Pancreatoblastoma tends to be less aggressive in infants and children compared to adults. The cancer has been associated with alterations in the Wnt signaling pathway and chromosome 11p loss of heterozygosity, Beckwith–Wiedemann syndrome and familial adenomatous polyposis. Alpha-fetoprotein may be elevated in up to 68% of patients with pancreatoblastoma and can be used to follow patients for recurrence postoperatively.85

Non-Hodgkin lymphoma. Hematopoietic malignancies in the pancreas are rare and usually involve the pancreas secondarily.86 Pancreatic lymphomas are most commonly non-Hodgkin lymphoma that can clinically mimic pancreatic adenocarcinoma. One of the advantages to FNA evaluation is that preoperative diagnosis of lymphoma can preclude unnecessary surgery. Primary pancreatic lymphomas are most commonly large B-cell lymphomas.86 While the cytomorphological features may suggest lymphoid differentiation, there may be overlapping features with other neoplasms that produce a solid cellular smear pattern. Ancillary tests such as flow cytometry and immunohistochemistry are typically necessary for diagnosis and especially for subclassification.

Metastatic tumors. Secondary neoplasms involving the pancreas are rare, and pancreatic involvement as the sole site of metastasis is even more uncommon. The common neoplasms that metastasize to the pancreas include melanoma, renal cell carcinoma and carcinomas from the lung, colorectum and breast.27 Direct extension from cancer of the stomach, duodenum, gallbladder, liver, and retroperitoneum may also occur.

Renal cell carcinoma is notorious for giving rise to a late solitary metastasis, even decades following nephrectomy. Renal cell carcinoma is also the most likely malignancy to metastasize to the pancreas and mimic a primary neoplasm.87 The cytological findings of metastatic renal cell carcinoma are similar to those seen in the kidney with bland polygonal cells, round slightly eccentric nuclei, prominent nucleoli and vacuolated cytoplasm. Distinction from clear cell or lipid rich neuroendocrine tumor is warranted as the morphology of these two neoplasms may be indistinguishable.
Examples of cytological interpretations.

Satisfactory for evaluation
Positive (for malignancy)
Adenocarcinoma.

Satisfactory for evaluation
Positive (for malignancy)
Malignant glandular and squamous cells consistent with adenosquamous carcinoma.

Satisfactory for evaluation
Positive (for malignancy)
Adenocarcinoma with morphological features consistent with renal primary.

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