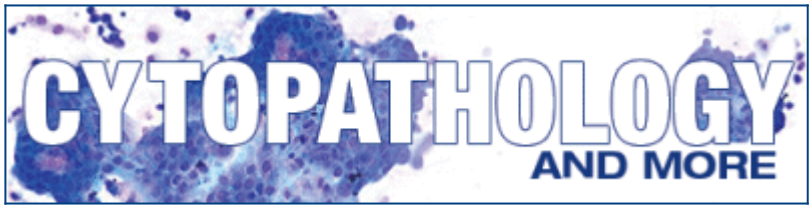
Cytopathology + More | Latest guidelines for pancreatobiliary cytology—a recap



Daniel F. I. Kurtycz, MD
Alice Laser, MD

May 2015—Pancreatobiliary malignancy currently accounts for about three percent of all cancer cases and six to seven percent of all cancer deaths, making it the fourth leading cause of death in the U.S. Between 2006 and 2010 the incidence rate of pancreatic cancer increased by 1.3 percent per year and the death rate increased by 0.4 percent per year.[1] The incidence of pancreatic cancer has tripled since the 1920s, likely secondary to an aging population, improved disease reporting, and possibly due to increased environmental mutagens[2] such as smoking.

In the majority of cases, these tumors are clinically asymptomatic in their early stages and only present once local involvement or metastatic disease is present. Once these lesions are discovered, the predominantly retroperitoneal location of the pancreas makes accessibility and sampling of lesions difficult. The pancreas is delicate and responds poorly to manipulation and biopsy. Cytological sampling by duct brushing and fine-needle aspiration are arguably the best methods available today to assess lesions in this region.[3-6] Of course, not every lesion represents a malignancy. There is a spectrum of pancreatobiliary neoplasia ranging from premalignant to aggressive malignancies. Recognizing and classifying these lesions is important because different entities have different biologic behaviors and treatment options.

Historically, the epidemiology of pancreatic neoplasia was centered on pancreatic ductal adenocarcinoma (PDAC). Over the past 30 years the story surrounding pancreatic neoplasia has gained breadth and been refined as the literature has described noninvasive lesions, precursor lesions, borderline lesions, and lesions arising from nonductal epithelium. Intraductal papillary mucinous neoplasms (IPMN) of the pancreas were described in the 1980s, and by the end of the century the concept of pancreatic intraepithelial neoplasia (PanIN) was fully evolved.[7] The World Health Organization and other professional groups have been involved in the evolution of these concepts, especially in efforts directed toward pancreatic neuroendocrine tumors (PanNET).

Nomenclature needs to reflect known biologic potential and consequent therapeutic reaction. In some lesions it has been difficult or impossible to decide on the morphologic and biochemical features that herald malignant behavior. The problems in diagnosis are amplified by the complex surgical therapies in this area up to and including pancreaticoduodenectomy (Whipple procedure). A major resection cannot be the response to every borderline lesion, but using the term malignant for these lesions cannot help but drive significant surgical intervention.

Martha Pitman, MD, of Massachusetts General Hospital, and Lester Layfield, MD, of the University of Missouri, spearheaded a nearly three-year effort to generate guidelines for cytologic diagnosis and recommendations under the auspices of the Papanicolaou Society of Cytopathology, a United States and Canadian Academy of Pathology companion society. Their group proposed a standardized terminology scheme that correlates cytopathologic diagnosis with biological behavior and stresses the increasingly conservative patient management of surveillance only for lesions of uncertain biologic potential. They were divided into five committees that developed a set of guidelines for pancreatobiliary cytology that includes indications for cytologic analysis, pancreatobiliary cytologic

methodology, terminology/nomenclature, ancillary techniques, and diagnostic management. Recent radiologic and laboratory-based diagnostic methods and methods of follow-up are also discussed. The committees were composed of an international assortment of expert pathologists, clinicians, and radiologists who brought their experience and knowledge to the project. The result of their efforts is published in the April 2014 issue of *Diagnostic Cytopathology*.[8]

The proposed terminology is the heart of the guidelines and recommends a multitiered system including: 1) non-diagnostic, 2) negative, 3) atypical, 4a) neoplastic benign, 4b) neoplastic other, 5) suspicious, and 6) positive. A brief discussion of the proposed terminology and reporting system follows.

Category I: Non-diagnostic. This category is provided for instances in which the specimen provides no diagnostic or useful information about the intended target. This may be the result of sampling, artifact, or hypo/acellularity in the presence of a solid mass. As is the case in most body sites, presence of any cellular atypia precludes the use of this category.

Category II: Negative(for malignancy). A negative cytology sample is one that contains adequate cellular and/or extracellular material to characterize a lesion seen on imaging studies. A negative report should also be rendered in the setting of various conditions and lesions considered benign. In these instances, the pathologist should give a specific diagnosis (for example, chronic pancreatitis, pseudocyst) whenever possible. These reports imply there is no evidence of malignancy or atypia and therefore have large clinical impact.

Category III: Atypical. This category should be applied only when the pancreatobiliary epithelium shows cytoplasmic, nuclear, or architectural features not consistent with normal or reactive changes and/or when these features are not sufficient to categorize the sample as neoplastic or suspicious for malignancy. In reality, some cases may be assigned to this category secondary to pathologist caution. Among the contributing factors that can lead to a diagnosis of atypical are limited cellularity, poor preservation, and obscuring background material.

A consensus classification of biliary intraepithelial neoplasia (BilIN) was published in 2007; however, it is still not as well defined in the literature as it is for PanIN, so the biologic potential is less clear. Bile duct samples that show mucinous features or atypia should be placed in this category unless they show clear morphologic evidence of malignancy. Cases in which it is not possible to distinguish normal acinar cells from an endocrine proliferation should be placed in this category also.

From a clinical standpoint, an interpretation of “suspicious for malignancy” will often invoke the same therapeutic reaction as a case that is called “malignant.” An interpretation of atypical will cause a more circumspect reaction, which may be much more appropriate in a diagnostically unclear situation. Cytologic findings that do not correlate with imaging studies and clinical history require total reconsideration of the clinical problem.

Category IV: Neoplastic: Benign or Other. This is the only category that is separated into two subcategories. This stratification strives to standardize the cytological nomenclature and terminology in accordance with the 2010 World Health Organization classification and terminology. This is the most innovative and controversial portion of the proposed guidelines and it attempts to provide a rational framework in which to deal with lesions that are clearly neoplastic but may or may not be capable of local invasion or metastatic behavior.

The use of Neoplastic: Benign (category IVA) is reserved for a small subset of specimens that are sufficiently cellular and representative of the lesion, with or without supporting imaging, laboratory, or ancillary studies, to be diagnostic of a benign neoplasm. The most classic example would be a serous cystadenoma, or much less commonly a neuroendocrine microadenoma, cystic teratoma, or schwannoma.

The second subcategory, Neoplastic: Other (category IVB) reflects an attempt to deal with a number of neoplasms with unclear malignant potential. Historically, many pathologists who use standard cytological interpretive categories have placed these neoplasms in the atypical or suspicious-for-malignancy categories, which may have led to unnecessary repeat procedures or under- or overtreatment. This new terminology does not attempt to classify the neoplasm as benign or malignant and thus does not necessitate specific clinical management.

Neoplasms that should be listed in this category include PanNET, solid pseudopapillary neoplasm, and neoplastic mucinous cysts of the pancreas (mucinous cystic neoplasm and intraductal papillary mucinous neoplasm).

Cytologic analysis of pancreatic cysts can be treacherous. The first branch in the decision tree is to determine if the cyst is mucinous or non-mucinous. The physical properties can often be gleaned during the time of the procedure and they are then correlated with the microscopic qualities of any extracellular material present. The next branch is to evaluate the atypia present in the epithelial component. Any epithelial atypia that does not meet the established criteria for malignancy should be classified as either low- or high-grade atypia. Several recent studies have shown that cells smaller than a 12 µ duodenal enterocyte with an increased nuclear-to-cytoplasmic ratio, an abnormal chromatin pattern, and background necrosis should be classified as high-grade epithelial atypia. Cyst fluid and molecular analysis of pancreatic cyst fluids are also described.

At our current level of expertise it is difficult to predict which mucinous lesions, GISTs, solid-pseudopapillary neoplasms, and PanNETs are going to remain harmless and which are going to become locally aggressive or metastasize. Similar to the Atypical category, the Neoplastic: Other category is clinically useful in that it does not tie the clinician's hands into an aggressive response as would suspicious or overtly malignant designations.

Tumor heterogeneity also makes the Neoplastic: Other category useful. The literature clearly shows that the morphology of any small sample may not be representative of all parts of the tumor. A sample that exhibits only defined monomorphic neuroendocrine cells may have been obtained only a few cells away from a region where the morphology is clearly high grade. In this instance, placing the specimen in the Neoplastic: Other category provides utility by reflecting an ambiguous level of risk. This category also looks toward the future and will be increasingly useful as research discovers the genetic faults that enable invasive behavior.

Category V: Suspicious for Malignancy. While this commonly is used to indicate there is suspicion for pancreatic ductal adenocarcinoma, the guidelines recommend that this category be used when there is suspicion for any aggressive or high-grade malignant neoplasm. This category is intended to be used when a cytology specimen has features that make the likelihood of malignancy greater than not, but when the features are qualitatively or quantitatively lacking to render a definitive diagnosis of malignancy. This category frequently shows significant interobserver variability, often corresponding to the pathologist's level of experience with pancreatobiliary cytology.

Despite having well-defined criteria for pancreatic malignancies, cytology samples present three major challenges. The first is the variable levels of differentiation that can be seen in pancreatic adenocarcinomas.9 Second, cellularity oftentimes is a problem. This may be a result of technical components or due to the sclerotic response of the tumor itself.[10] The third problem is the presence of gastrointestinal contamination. When these challenges are presented within a single case, a definitive diagnosis of malignancy may be difficult to reach. In these cases in particular, close correlation with clinical findings and ancillary testing is crucial.

Category VI: Positive or Malignant. This is defined as a group of lesions that are unequivocally malignant by cytologic criteria. The specificity of this category for pancreatic FNA and biliary brushing is greater than 90 to 95 percent in most studies. Roughly 85 to 90 percent of all pancreatic malignancies will be classified as pancreatic ductal adenocarcinoma. This category also includes entities such as cholangiocarcinoma, colloid carcinoma, medullary carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, acinar cell carcinoma, poorly differentiated neuroendocrine carcinomas (small cell carcinoma or large cell neuroendocrine carcinoma), pancreatoblastoma, lymphoma, sarcoma, as well as metastatic disease.

In addition to a revised nomenclature, the guidelines offer a useful state-of-the-art review of current indications for cytologic analysis, regional cytologic methodology, terminology, ancillary techniques, and post-biopsy treatment and management. The committees stressed that these guidelines, similar to practices in other areas of cytopathology, require shared information between clinicians, radiologists, and pathologists in the form of the "triple test," where management is determined by the congruence of findings between all parties.[11]

These guidelines present an evolutionary approach to cytologic diagnosis and classification based on the best knowledge available and the interpretation of the committee members. They form a body of information that indicates where the art exists as it looks toward the future for continued improvement.

Acknowledgment: We would like to thank Martha Pitman, MD, for her advice in the preparation of this article.

1. American Cancer Society. *Cancer Facts & Figures 2014.* Atlanta: American Cancer Society; 2014. www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf. Accessed March 2, 2014.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013;63(1):11–30.
3. Elek G, Gyökeres T, Schäfer E, et al. Early diagnosis of pancreatobiliary duct malignancies by brush cytology and biopsy. *Pathol Oncol Res.* 2005;11(3):145–155.
4. Glasbrenner B, Ardan M, Boeck W, et al. Prospective evaluation of brush cytology of biliary strictures during endoscopic retrograde cholangiopancreatography. *Endoscopy.* 1999;31(9):712–717.
5. Hruban RH, Pitman MB, Klimstra DS. Tumors of the Pancreas. Washington, DC: American Registry of Pathology; 2007. AFIP Atlas of Tumor Pathology, Series 4.
6. Kocjan G, Smith AN. Bile duct brushings cytology: potential pitfalls in diagnosis. *Diagn Cytopathol.* 1997;16(4):358–363.
7. Hruban RH, Maitra A, Goggins M. Update on pancreatic intraepithelial neoplasia. *Int J Clin Exp Pathol.* 2008;1(4):306–316.
8. Pitman MB, Centeno BA, Ali SZ, et al. Standardized terminology and nomenclature for pancreatobiliary cytology: The Papanicolaou Society of Cytopathology Guidelines. *Cytojournal.* 2014;11(suppl 1):3.
9. Lin F, Staerkel G. Cytologic criteria for well differentiated adenocarcinoma of the pancreas in fine-needle aspiration biopsy specimens. *Cancer.* 2003;99(1):44–50.
10. Eloubeidi MA, Jhala D, Chhieng DC, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. *Cancer.* 2003;99(5):285–292.
11. Layfield LJ, Pitman MB. The Papanicolaou Society of Cytopathology guidelines for pancreaticobiliary tract cytology: a new installment in the "Bethesda" style of guidelines from the Papanicolaou Society of Cytopathology. *Diagn Cytopathol.* 2014;42(4):283–284.

[hr]

Dr. Kurtycz is laboratory medical director, Wisconsin State Laboratory of Hygiene, and professor, Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health. Dr. Laser, of the Department of Pathology at Northshore-LIJ Health System in New Hyde Park, NY, is assistant professor and cytopathology fellowship program director, Hofstra NorthShore-LIJ School of Medicine. Both are members of the CAP Cytopathology Committee.