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EDITORIAL

Implementing the Papanicolaou Society of Cytopathology terminology system for reporting pancreaticobiliary cytology refines risk of malignancy in pancreatic specimens

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The Papanicolaou Society of Cytopathology (PSC) terminology system for reporting pancreaticobiliary cytology was first reported 5 years ago, with clear aims to better stratify the risk for the diagnostic categories used in pancreaticobiliary cytopathology, provide comparable reporting nomenclature in centers worldwide, and provide clinicians with flexible management options for patients with premalignant and low-grade neoplasms with malignant potential.[1,2] Subsequent studies have shown that most objectives have been achieved, in part owing to the unique characteristics of the PSC system.

Analogous to other standardized "Bethesda-like" systems, the PSC system presents a 6-tiered classification scheme with distinct presumed risks of malignancy (ROM) and follow-up clinical recommendations. Unique to the PSC system is the category "Neoplastic," which has been divided into "Neoplastic: benign" and "Neoplastic: other." This unique category offers a "nonmalignant" but still neoplastic interpretation category for entities such as neoplastic mucinous cysts, which have variable malignant potential that is not always possible to determine through cytological examination alone.[2] Although controversial and a matter of extensive debate, neuroendocrine tumors should also be included in this category, because the true nature of its malignant potential can usually only be clearly defined in the surgical excision specimen. Somewhat similar to this "borderline" category in the PSC system is the SUMP (salivary gland neoplasm of uncertain malignant potential) category in the new Milan system for reporting salivary gland neoplasms, encompassing neoplasms of undetermined potential of malignancy.[3] Also of particular importance to the PSC terminology system is the close correlation of cytology findings with radiological imaging and biochemical analysis (especially for cyst specimens), which has been shown to decrease the number of cases classified as nondiagnostic (ND) or negative using cytology alone.[4-7]

Reported studies have shown that most cases will be placed within the negative for malignancy and malignant categories[5-12] (Table 1). Such definitive stratification of biopsy findings strongly supports the use of the PSC system because dichotomization and proper treatment of patients is 1 of the main reasons for using standardized nomenclature. Nonspecific interpretations such as nondiagnostic and atypical, common reasons for increased anxiety in patients and physicians,[13] constitute a low percentage of cases owing to the clearly defined definitions proposed and the integrated multidisciplinary approach of the PSC system.[5-9] Incorporation of biochemical and genetic analysis information into the interpretation of cyst fluids, for example, will help to define many pancreatic cysts from ND cytology as neoplastic mucinous cysts and, thus, more accurately classifying these cysts and providing better risk stratification and more flexible treatment of these patients.[4,14,15] For indeterminate diagnoses, most cases will fall into the "Neoplastic: other category," mainly owing to the large number of entities included in this category. Despite the broad "gray-zone" group of diagnoses, follow-up strategies have been clearly defined for these neoplasms in this category.[2] Also, grading the atypia of the cells can distinguish most intraductal papillary mucinous neoplasms that would require surgical excision, with excellent correlation with the final histological diagnosis.[15]

The ROMs for each category have been reported in most of the studies since the implementation of the PSC system, with some variation from the original study by Layfield

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Table 1 Studies of implementation of the PSC terminology system for reporting pancreaticobiliary cytology and distribution of cases (percentage) in each category.

Investigator	ND (%)	Negative (%)	Atypical (%)	Neoplastic: benign (%)	Neoplastic: other (%)	Suspicious (%)	Positive (%)
Layfield, 2013	4.4	32.5	7.2	4.4[a]		6.9	44.5
Saieg, 2015	3.8	23.9	0	0	31.6	1.3	39.4
Smith, 2016	18.1	5.5	0	0	70.1	3.9	2.4
McKinley, 2016	11.2	47	11.2	5.6[a]		4.7	20.2
Chen, 2017	7.14	28.2	4.4	6.8[a]		10.9	42.5
Credidio, 2018	8.7	14.5	2.9	1.9	21.4	6.8	43.7
Sung, 2018	23.6	15.8	13.9	1.9	12.7	2.9	28.9
Wright, 2018	7.5	33.3	2.5	2.5	15	3.3	35.9
Average[b]	10.5	25.1	5.3	2.9	21	5.1	30

Abbreviations: NA, not applicable; ND, Non-diagnostic; PSC, Papanicolaou Society of Cytopathology.
[a]Studies classified cases as neoplastic, not otherwise specified.
[b]Average percentage of each category considering the cited studies.

et al.[8] Difficulties in defining the precise percentages, however, have included that most of the patients with a diagnosis of pancreatic adenocarcinoma or even suspicious lesions will often have an advanced stage of the disease and that no surgical specimen will be obtained, the usual reference standard sample for calculating overall performance and ROM. In addition, most low-grade branch duct intraductal papillary mucinous neoplasms will be followed up conservatively without resection, in part because of the clear classification of low-grade mucinous cysts using the PSC system.

In the study by Hoda et al they showed a 1-year prospective experience on the use of the PSC system, with analysis of 334 fine-needle aspirates of pancreatic lesions (approximately half solid, half cystic). They reported an overall distribution of categories and their respective ROM, increasing from negative to positive categories. Of great interest, when separating "Neoplastic: other" with low- and high-grade atypia by cytological examination, the ROM increases from 4.3% in the low-risk group to 90% in the high-risk group, confirming the distinct proposed clinical recommendations and accuracy of cytology in grading such lesions. Hoda et al also showed that when grouping "Neoplastic: other" with high-grade epithelial atypia with the "suspicious" and "positive" categories, the specificity and positive predictive value increased to almost 100%. The main limitations of the study, as previously stated, were that only one half of the cases had corresponding surgical specimens and a part of the calculations were performed using the clinical follow-up data.

Other studies have also used follow-up clinical data and cytological or histological confirmation of metastatic disease as surrogate method to confirm an initial fine-needle aspiration diagnosis.[10,11] Thus, the ROM summarized in Table 2 might underestimate the actual ROM for each category, because unresected lesions will be assumed to be benign. The indeterminate categories have shown wider ROMs among the different studies, ranging from 40% to 100% for the atypical category. Positive and suspicious categories have shown a consistently high ROM, with few false-positive cases, which translates into a high specificity and positive predictive value. As such, the implementation of the PSC system has been shown to improve the specificity and sensitivity and better stratify cases that should be removed or followed up clinically compared with the conventional cytology nomenclature.[5-7,10,12] In the report by Hoda et al, the false-positive results were limited to 2 cases with discordant grades of atypia between the cytology findings and final histological diagnosis, both overestimated in the cytological analysis. The false-negative results represented ~8% of cases, most of which resulted from scant cellularity or sampling errors.

Other factors that might influence the overall performance of pancreaticobiliary cytology and the implementation of the PSC system is the use of rapid on-site assessment (ROSE), the type of needle used, and the professional's (cytotechnologist, pathologist, and endoscopist) technical experience. ROSE has been advocated as a method for improving the diagnostic yield and overall sensitivity and decreasing the number of nondiagnostic cases, complication rate, and duration of the procedure.[16-18] The absence of ROSE has also been associated with a greater ROM in cases classified as ND.[5] Next-generation "core-type" needles produce larger tissue fragments, which contributes to greater

Table 2 Risk of malignancies (percentage) for each category of PSC terminology system for reporting pancreaticobiliary cytology.

Investigator	ND (%)	Negative (%)	Atypical (%)	Neoplastic: benign (%)	Neoplastic: other (%)	Suspicious (%)	Positive (%)	Samples with histology/follow-up (n)
Layfield, 2013	21.4	12.6	73.9	14.2[a]	14.2[a]	81.8	97.2	317
Smith, 2016	17	0	NA	NA	64	80	100	127
Chen, 2017	57.1	18.1	69.2	2		87.5	100	294
Sung, 2018	41	30	41	0	34	91	98	322
Credidio, 2018	0	NA	100	NA	33	100	100	26
Wright, 2018	33.3	8.3	100	66.7	100	100	100	112
Weigted average[b]	35.6	13.7	66.1	17.1	34.7	87.6	98.7	

Abbreviations: NA, not applicable; ND, nondiagnostic; PSC, Papanicolaou Society of Cytopathology.
[a]Studies classified cases as neoplastic, not otherwise specified.
[b]Based on the number of studies per case.

diagnostic yield from solid lesions, potentially decreasing the number of suspicious and atypical cases.[19,20]

In conclusion, implementing the PSC system for reporting pancreaticobiliary cytology has been, to date, an overall successful experience worldwide, with multiple centers around the globe reporting better risk stratification, improved sensitivity and specificity, and easy implementation of the system compared with conventional cytology nomenclature. Further studies reporting their experience with the PSC system will help to make improvements in refining the system to further improve diagnosis and patient treatment.

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References

1. Perez-Machado MA. Pancreatic cytology: standardised terminology and nomenclature. *Cytopathology*. 2016;27:157−160.
2. Pitman MB, Centeno BA, Ali SZ, et al. Standardized terminology and nomenclature for pancreatobiliary cytology: the Papanicolaou Society of Cytopathology guidelines. *Diagn Cytopathol*. 2014;42:338−350.
3. Pusztaszeri M, Rossi ED, Baloch ZW, Faquin WC. Salivary gland fine needle aspiration and introduction of the Milan reporting system. *Adv Anat Pathol*. 2019;26:84−92.
4. Ajaj Saieg M, 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;45:101−106.
5. 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;8:8154−8161.
6. 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;123:488−494.
7. Wright PK, Shelton DA, Holbrook MR, 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;29:71−79.
8. 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;122:420−427.
9. 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;124:285−293.
10. Credidio C, Pastorello R, Destefani C, et al. Experience of the use of the Papanicolaou Society of Cytopathology system for reporting pancreaticobiliary cytology in a cancer center. *J Am Soc Cytopathol*. 2018;7:S36.
11. Sung S, Del Portillo A, Oberstein P, Kluger M, Tiscornia-Wasserman P. Update on the risk stratification of the Papanicolaou Society of Cytopathology pancreaticobiliary guidelines. *J Am Soc Cytopathol*. 2018;7:S36.
12. Simonovic A, Perez-Machado M, Weerasinghe K, Rathbone M. Impact of Papanicolaou Society of Cytopathology classification for pancreaticobiliary endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) cytology in predictability of high-grade malignancy a British experience. *J Am Soc Cytopathol*. 2018;7:S36.
13. Barkan GA, Wojcik EM, Pambuccian SE. A tale of atypia: what can we learn from this? *Cancer Cytopathol*. 2018;126:376−380.
14. Layfield LJ, Ehya H, Filie AC, et al. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolaou Society of Cytopathology guidelines. *Cytojournal*. 2014;11:4.
15. 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;122:40−47.
16. Hebert-Magee S, Bae S, Varadarajulu S, et al. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. *Cytopathology*. 2013;24:159−171.
17. Khan MA, Grimm IS, Ali B, et al. A meta-analysis of endoscopic ultrasound-fine-needle aspiration compared to endoscopic ultrasound-fine-needle biopsy: diagnostic yield and the value of onsite cytopathological assessment. *Endosc Int Open*. 2017;5:E363−E375.
18. Mohanty SK, Pradhan D, Sharma S, et al. Endoscopic ultrasound guided fine-needle aspiration: what variables influence diagnostic yield? *Diagn Cytopathol*. 2018;46:293−298.
19. Abdelfatah MM, Grimm IS, Gangarosa LM, Baron TH. Cohort study comparing the diagnostic yields of 2 different EUS fine-needle biopsy needles. *Gastrointest Endosc*. 2018;87:495−500.
20. Fitzpatrick M, Hernandez-Barco Y, Forcione D, Pitman M. Retrospective evaluation of the novel SharkCore EUS-guided fine needle biopsy. *J Am Soc Cytopathol*. 2018;7:S37.