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Low interobserver agreement in cytology grading of mucinous pancreatic neoplasms

Carlie Sigel, MD¹, Marcia Edelweiss, MD¹, Leung Chu Tong, MD, FRCPC², Joanna Magda, CT ASCP, MPH¹, Handy Oen, CT ASCP¹, Keith Sigel, MD, MPH³, and Maureen Zakowski, MD¹

¹Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

²Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada

³ Division of General Internal Medicine, Mount Sinai School of Medicine, New York, NY

Abstract

Background—Identifying high grade features in pancreatic mucinous neoplasms (MN) is important for patient management. It is not clear if MNs can be graded with reproducibility in routine practice. We evaluated interobserver variability in grading MNs and identification of neoplastic mucin in endoscopic ultrasound guided fine needle aspirations (EUS-FNA).

Methods—We created a 54 case grading set from histologically confirmed MNs (N=44) and nonmucinous lesions (NML) with abundant gastrointestinal contamination (N=10). Six observers received a tutorial, reviewed pre-screened slides, and recorded: 1) a diagnosis according to a 6-tiered system (TS) (nondiagnostic (NDX), atypical (ATP), mucinous cyst low grade (LG), mucinous cyst high grade (HG), suspicious for adenocarcinoma (SSPA), positive for adenocarcinoma (PA)); 2) a diagnosis with cyst fluid CEA (CEADX); and 3) the presence of neoplastic mucin. Interobserver agreement (IOA) was evaluated by calculation of Kappa coefficients. Diagnostic accuracy was not evaluated.

Results—IOA was lowest for 6-TS (K=0.13, P<.001). CEADX was available for 18 (33%) cases, including 6/24 (25%) of LG. CEADX modestly improved IOA for combined tiers of the 6-TS with ATP and LG as separate categories. The highest IOA was with a 3-TS (NDX, ATP/LG, HG/SSPA/PA; K=0.28, P<.001) and various 4-TS (K=0.22-0.23). IOA was low for neoplastic mucin (K=0.15, P<.001).

Conclusions—In a study using simulated cytology practice, observers showed fair IOA for grading MNs and low IOA for identifying neoplastic mucin. Knowledge of cyst fluid CEA level modestly improved IOA for low grade lesions.

Corresponding Author Carlie Sigel. 1275 York Ave, New York, NY 10065. Phone: 212-639-5900 Fax: 212-639-6318 sigelc@mskcc.org.

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Introduction

The frequency of incidentally detected pancreatic cysts in adults by magnetic resonance imaging (MRI) is estimated at up to 20%.¹ The differential diagnosis of pancreatic cysts is broad because virtually all pancreatic neoplasms can have a cystic presentation but the majority of small cysts (<3 cm) are mucinous and pre-malignant representing either intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN). Most of these patients are followed conservatively with periodic radiologic evaluation.² Nevertheless, all cystic mucinous neoplasms have a risk of associated malignancy or malignant progression and identifying this subset of patients pre-operatively is challenging.³

There is no single biochemical or molecular study to date that can reliably predict malignancy in cystic mucinous lesions of the pancreas. CEA cyst fluid analysis has established utility in differentiating mucinous versus non-mucinous pancreatic cysts.⁴ Elevated cyst fluid CEA is not definitive for a mucinous neoplasm but combined with cytology findings it may provide additional support for the interpretation of a mucinous neoplasm. Cytology or biopsy remain the only options for pre-operative confirmation of malignancy.⁴⁻⁷ Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) diagnosis of pancreatic cysts has been shown to have moderate specificity and low sensitivity for diagnosing mucinous neoplasms because cystic specimens can be paucicellular and frequently contain contaminating gastrointestinal epithelium and mucin.⁷ The cytologic presentation is diverse due to various epithelial subtypes (gastric, intestinal, pancreatobiliary, oncocytic), epithelial grade, and intralesional heterogeneity. EUS-FNA cytology is known to have low sensitivity and specificity for diagnosing mucinous differentiation in cystic lesions.^{4, 7} Studies describing criteria for cytologic grading of mucinous lesions are limited.⁸⁻¹⁰ Cytology has been shown to undergrade mucinous lesions and overcall abundant gastrointestinal contamination as mucinous neoplasm in EUS-FNA.^{8, 11, 12} Despite these limitations, finding high grade atypia has been shown to correlate with significant histologic findings ranging from moderate dysplasia to invasive carcinoma.^{8, 12}

The Papanicolaou Society of Cytopathology (PSC) has published diagnostic categories for the reporting of pancreatic cyst cytology which includes six major diagnostic categories: “nondiagnostic,” “benign,” “atypical,” “suspicious,” “neoplasm,” and “malignant” and these categories have shown an increasing risk of associated malignancy.^{13, 14} The nomenclature scheme also indicates that mucinous neoplasms may be further subclassified by high and low grade but whether reporting these subcategories is predictive for histology in routine practice is not known. The reproducibility of grading these lesions has recently been evaluated specifically for intraductal papillary mucinous lesions (IPMN).¹⁵ The objective of this study was to evaluate interobserver agreement (IOA) in the diagnosis and grading of various histologically confirmed mucinous pancreatic neoplasms using a method simulating cytology practice.

Methods

Case selection

We collected 54 EUS-FNA specimens containing mucinous epithelium associated with mucin from patients with 1) a histologically confirmed mucinous/ductal neoplasm (N=44) or 2) a histologically confirmed non-mucinous lesion (NML) (N=10) in which the specimen contained abundant gastrointestinal contaminants. Histology slides were reviewed for available cases. A summary of histologic diagnoses and original cytology diagnoses for the grading set is listed in Table 1. Cytology slides were screened by an experienced cytotechnologist (CT). Then, 5-15 representative areas (RA) identified by screening were marked by a cytopathologist (CS) on 1-6 slides (average=2.6). The preparations for each case comprised one or more of the following: air dried Diff Quik stained smear, alcohol-fixed hematoxylin and eosin or Papanicolaou stained smear, ThinPrep, and cell block. A minority of cases consisted one slide and in those cases a single ThinPrep was available. The RAs included areas of highest atypia and representative foci of extracellular mucin or mucin-like material. The EUS-FNA cases corresponding to histologic NMLs were selected based on the presence of abundant glandular epithelium and mucin. The histology of the cases containing invasive adenocarcinomas included in the grading set were either colloid carcinoma (defined by >80% extracellular mucin) or conventional ductal adenocarcinomas with an extracellular mucin component not meeting criteria for colloid carcinoma.

Slide evaluation

The observers consisted of 3 general cytopathologists (including 1 cytopathologist also practicing gastrointestinal histopathology as a subspecialty), 2 cytotechnologists, and 1 cytology fellow (MD); all practice in a single tertiary care specializing in oncologic pathology. Observers received an illustrated tutorial powerpoint presentation on mucinous cyst cytologic diagnosis and grading with cyto-histological correlation (Figure 1). Grading criteria were established based on literature review and the proposed Bethesda nomenclature system by the Papanicolaou Society (Table 2).¹⁴ Neoplastic mucin was defined by abundant mucin admixed with degenerating non-epithelial cellular debris (blood, degenerating cells, inflammation, foamy histiocytes) or necrotic material.^{11, 18-23} The slides were de-identified and observers were blinded to the original cytology and final histologic diagnosis. Each case in the grading set was accompanied by a brief clinical history describing patient age, anatomic site, lesion size, and lesion character (cyst, cystic mass, dilated duct, or mass). Lesion character was obtained from the clinical EUS record. Observers independently reviewed RAs and recorded a diagnosis according to a 6-tiered system (TS): nondiagnostic (NDX), atypical (ATP), mucinous cyst low grade (MCLG), mucinous cyst high grade (MCHG), suspicious for adenocarcinoma (SSPA), positive for adenocarcinoma (PA) (Table 2). The observers recorded a new diagnosis if the observers opinion changed after being provided the cyst fluid CEA (CEADX) using the guidelines that a cyst fluid level of ~200 ng/ml is supportive of a mucinous cyst.^{4, 16} Observers were instructed to categorize the mucin as neoplastic, non-neoplastic or of uncertain origin using the above definition. Aspirates with mucin and mucinous epithelium of uncertain origin or with low/unknown CEA were to be given the diagnosis ATP. Aspirates containing neoplastic mucin could be

by cytomorphologic interpretation and/or an elevated cyst fluid CEA and were given a diagnosis of mucinous cyst of high or low grade.

Statistical analysis

Various combinations of tiers from the original 6-TS were evaluated for IOA by calculating unweighted multirater Cohen's kappa coefficients with corresponding significance testing.¹⁷ Results were interpreted according to the following guidelines: <0 = no agreement, $0-0.2$ = low, $0.21-0.40$ = fair, $0.41-0.60$ = moderate, $0.61-0.80$ = substantial, and $0.81-1$ = near perfect.¹⁸ All analyses were performed using Stata 10.0 (Stata Corporation, College Station, TX).

This study was performed with the approval of the Memorial Sloan Kettering Cancer Center Institutional Review Board.

Results

Overall, IOA was low for the diagnosis and grading of mucinous neoplasms using a 6-TS. In less than half of cases (21/54, 39%) 4 of 6 observers showed agreement. The lowest IOA was for 6-TS ($K=0.13$, $P<.001$) when no CEA cyst fluid level was obtained. CEA was available for 18 (33%) cases, which included 6/24 (25%) of MCLG and none of the 10 NMLs. No lesion had a CEA within 100 ng/mL of the provided cut-off (200 ng/mL). Combining the morphologic interpretation with cyst fluid CEA modestly improved IOA for any variation of the grading system with separate categories for ATP and MCLG (Table 3). Knowledge of CEA did not affect IOA for MCHG, SSPA or PA.

In order to determine the grading scheme with the best IOA, various combinations of related categories in the grading system were assessed and the results (using the CEADX) are shown in Table 4. The highest overall IOAs were attained in a 3-TS with CEADX (NDX, ATP/MCLG, MCHG/SSPA/PA) ($K=0.28$, $P<.001$). Variations on a 4-TS had similar IOA, including a scheme grouping roughly clinically equivalent findings: absence of high grade atypia (ATP/MCLG), high grade atypia (MCHG/SSPA), and malignancy (PA). Representative images from the grading set that illustrate the range in observer responses are presented in Figure 2.

IOA was low for the identification of neoplastic mucin ($K=0.15$, $P<.001$) overall, but in 4/5 colloid carcinomas neoplastic mucin was diagnosed by 5/6 observers. For 78/324 (24%) of case encounters, the observer was uncertain of whether the mucin was from contamination or a neoplasm. Representative images from the grading set that illustrate the range in observer categorization of mucin are presented in Figure 3.

Table 5 shows the distribution of observer diagnoses divided by histologic lesion type including the original cytology diagnosis, clinical presentation, and CEA. Due to the limited number of each histologic lesion type, statistical analysis was underpowered for whether the type of lesion or clinical presentation influenced IOA. The only histologic type of lesion showing significant IOA in this underpowered analysis was invasive conventional ductal adenocarcinoma ($K=0.32$ (fair), $P<.001$).

IOA was not influenced by separately analyzing the results by the degree of training (MD versus CT). IOA was not significantly altered when analysis excluded the least experienced reviewer.

Discussion

In the present study we found that IOA for mucinous lesions was low but improved after simplifying the diagnostic scheme by combining categories such as MCHG/SSPA/PA or MCHG/SSPA. Algorithmic approaches for the differential diagnosis of pancreatic lesions make a branch point between radiologic cysts versus solid masses. Cysts suggest a premalignant mucinous cyst while solid masses raise concern for invasion. In practice however, mucinous lesions may not show this clear cut dichotomy in clinical presentation. Our results suggest that when high grade atypia is present, making a diagnosis of MCHG for a cyst versus SSPA/PA for a mass may not be straightforward. For example, 7 of the 31 (23%) IPMNs, including 5/10 (50%) of high grade IPMNs, included in this study were described radiologically as a mass. This finding explains why cytologists may consider the diagnosis of neoplastic mucinous cyst for an aspirate from a mass containing abundant atypical glandular epithelium and atypical mucin (figure 1A,B). We observed only fair agreement for the usually straightforward diagnosis of PA and factors leading to this include variable clinical presentation (mass, dilated duct) and that the grading set cases had mucin of a quantity and quality leading some observers to consider that the lesion had a cystic component as illustrated by figure 1-G,H. Ultimately, clinical management of pancreatic lesions involves consideration of the combined pathologic and radiologic findings. Diagnosing high grade atypia by cytology in a cystic or solid lesion by fine needle aspiration should prompt surgical intervention in a clinically appropriate patient regardless of the high risk category (MCHG, SSPA, or PA.)

Aspirates containing either low grade mucinous epithelium or abundant gastrointestinal contamination showed minimal IOA particularly in the absence of CEA results (Table 3). IOA improved when cyst fluid CEA was available and when ATP/MCLG were combined. Contributing factors for the low IOA included the small subset of cases with concurrent cyst fluid CEA, difficulty in diagnosing neoplastic mucin, the presence of intermediate grade atypia, and lesion heterogeneity. If more cases had CEA cyst fluid analysis IOA would have likely improved. CEA is not uniformly obtained in our institution because it depends on the fluid yielded from the aspirated lesion and the discretion of the EUS operator. The low IOA for “neoplastic mucin” also contributed to low IOA for ATP and MCLG. Contaminants from the duodenum may not have presented a problem. In contrast, low grade gastric epithelial contamination is identical to gastric type IPMN epithelium and mucin produced by non-intestinal-type neoplastic epithelium may be thin and watery, poorly preserved on ThinPrep, and may not be readily discernable on smears or cell blocks even with special stains.¹⁹ The presence of intermediate grade atypia may also have contributed to inconsistent grading. This phenomenon has been previously described.^{15, 20} Histologic intermediate grade lesions may be upgraded to high grade if the areas of atypia are well sampled, but they may be interpreted as low grade if the intermediate grade atypia is only focally present. Table 5 shows the distribution of observer diagnoses for intermediate grade IPMNs which shows 17 diagnoses of HG or worse for 84 possible responses. Because

histologic lesions are graded on the epithelium of highest grade which may be only focal, aspirates from intermediate and high grade cysts may contain abundant lower grade epithelium. Figure 1-C,D illustrates a case of histologic high grade IPMN diagnosed as low grade by the majority of observers. This case showed abundant epithelium with low nuclear: cytoplasmic ratio and moderate atypia suggestive of intermediate grade atypia with focal, scattered areas of clearly high grade atypia. There is inherent difficulty in assigning grade in these heterogeneous lesions. Although representative groups were designated, the worst areas of atypia may have been limited. The threshold for the quantitative assessment of atypia among different observers also likely varied. For example, some authors have assigned high grade atypia to as few as two well-preserved cells with markedly abnormal cytomorphology.¹² Figure 1E, F shows areas from a high grade IPMN with focal marked atypia and apoptotic debris yet it was categorized as low grade by two observers. This suggests that the quantity of atypia was below their threshold for high grade atypia. These factors have also been recognized as challenges in the qualitative and quantitative assessments used in histologic grading of mucinous neoplasms.²¹

When the present study was conducted, there were no established criteria for grading mucinous lesions of the pancreas. The study challenged the participants to classify mucinous cysts as low grade versus high grade and this differed from their usual practice which focused mainly on segregation of possible mucinous cysts from possible malignancy with rare comments on cystic lesion grade. The observers were given criteria for grading that were compiled from small case series describing cytologic features associated with histologic grade.^{8, 10, 11, 19, 22-26} Recently, Pitman et al used a small number of aspirates from IPMNs to establish criteria for high and low grade atypia and reported the following criteria support high grade atypia: cell size smaller than an enterocyte, increased nuclear: cytoplasmic ratio, marked nuclear membrane abnormalities, abnormal chromatin pattern, and background cellular necrosis.⁹ Using these criteria, Pitman et al also reported fair IOA for grading cytologic atypia in aspirated IPMNs.¹⁵ Their results improved by limiting analysis to two experienced observers and a 2-TS (low grade/high grade).¹⁵ In the present study, using fewer and validated criteria and improved training including review at a multi-headed microscope may have improved IOA.

The system used for grading in this study differs slightly from the PSC classification which had been proposed but not published at the time of the study, but the main diagnostic tiers are the same.¹⁴ Other weaknesses of the study include that we did not re-evaluate the study slides to investigate reasons for low observer agreement such as slide quality, preparation method, quantity of atypical cells, and mucin characteristics but this is an area of possible future analysis. We also did not include results of *KRAS* mutational analysis in our study. *KRAS* mutational analysis shows high specificity and low sensitivity for mucinous differentiation in contrast to CEA which has lower sensitivity but higher specificity.^{7, 27} *KRAS* analysis is not routinely performed in our institution and too few cases in the study group had this information. We did not include the original cytology diagnosis in the analysis because the tiered system used in this study did not correlate with the original diagnostic scheme used by the institution. For example, “suspicious for mucinous neoplasm” was commonly the original diagnosis (Tables 1, 5) and it corresponded to a range of

histologic diagnoses including high grade and nonmucinous lesions (e.g. high grade IPMNs, colloid carcinoma, and all of the false positive non-mucinous lesions selected for the study). It was also unknown whether the original reviewing cytologist was aware of CEA results and what clinical information used to make the diagnosis. Based on these reasons, the original diagnosis did not reflect a standard for comparison. Furthermore, it was subject to the same interobserver agreement as demonstrated by the study participants. Some observer diagnoses suggest areas of potential misunderstanding in applying diagnostic criteria. For example, observers used the diagnostic category ATP for some aspirates with highly elevated CEA. It is known that CEA can show false positives such as in a pancreatic lymphoepithelial cyst, however the majority of observers for these few cases were able to make a diagnosis of neoplastic cyst so this disagreement may suggest individual misunderstanding.

In the pre-operative clinical management of cystic pancreatic lesions there is great value in identifying potentially high risk mucinous lesions by recognizing marked cytologic atypia because cytology/small biopsy remains the sole diagnostic method for assessing lesion grade and risk of malignancy. In summary, observers showed fair interobserver agreement for grading EUS-FNAs of pancreatic lesions where a mucinous lesion is in the differential diagnosis and low interobserver agreement for identifying neoplastic mucin. Agreement was improved by combining low risk (ATP/MCLG) and high risk categories (MCHG, SSPA, PA) which was facilitated by using a standard terminology scheme based on the PSC classification system. Knowledge of cyst fluid CEA level modestly improved interobserver agreement for low grade neoplasms and supports inclusion of this value in the PSC classification. As increasing numbers of these cysts are identified in older patients with comorbid conditions, the need persists for ancillary studies to enhance the pre-operative assessment of lesion grade so that patients with high risk cytology can be managed timely and appropriately.

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Condensed abstract

Observers showed fair interobserver agreement for grading mucinous pancreatic neoplasms and low interobserver agreement for identifying neoplastic mucin. Knowledge of cyst fluid CEA level modestly improved interobserver agreement for low grade neoplasms.

Figure 1. Representative images from the training module

A) Sheets of foveolar epithelium with some dispersed bland nuclei characterize the typical appearance of gastric epithelium. (Air-dried, Diff Quik stained smear, 40x) B) An organized honeycomb sheet of glandular cells with bland nuclei and abundant apical cytoplasm from a low grade IPMN. (Alcohol-fixed, hematoxylin and eosin stained smear, 40x) C) A drunken honeycomb sheet and marked nuclear irregularities are seen in an aspirate of a mass-forming high grade IPMN. (Alcohol-fixed, papanicolaou stained smear, 40x) D) Similar high grade features from an aspirate targeting a dilated duct. The corresponding resection showed a well differentiated invasive adenocarcinoma. (Alcohol-fixed, papanicolaou stained smear, 40x)

Figure 2. Four case examples from the grading set with observer diagnoses

A-B. This EUS-FNA from a mass (no cyst fluid CEA level) contained two cell populations. There were foci of typical gastrointestinal contamination (1A, clusters at right) and glandular epithelium with mild-moderate atypia (1A clusters on left, and 1B). Histologic correlation showed autoimmune pancreatitis and the atypical glandular epithelium corresponded to ductal atypia. Scant intraepithelial lymphoid cells were identified (1B), but stromal fragments which have been described in autoimmune pancreatitis were absent. Abundant mucin (not shown) in combination with atypical glandular epithelium may have contributed to observer interpretation of a mucinous neoplasm. Observer diagnoses: ATP (1), MCLG (3), MCHG (2); histologic diagnosis: autoimmune pancreatitis. (A: Alcohol-fixed, hematoxylin and eosin stained smear, 20x; B: Air dried, Diff Quik stained smear, 40x)

C-D. This EUS-FNA from a cyst (no cyst fluid CEA level) had crowded sheets of glandular epithelium with small nuclei and abundant apical cytoplasm. Other areas showed high nuclear: cytoplasmic ratio (1C). In some areas nucleus crowding and overlapping was more apparent, but the cells lacked significant nuclear membrane abnormalities (1D). This aspirate was from a high grade lesion but the majority of observers undergraded it because of the predominant population showing mild (low grade) to moderate (intermediate grade) atypia. Observer diagnoses: MCLG (5), MCHG (1); histologic diagnosis: IPMN with high grade dysplasia. (C: Alcohol-fixed, hematoxylin and eosin stained smear, 40x; D: Alcohol-fixed, papanicolaou stained smear, 40x)

E-F. An EUS-FNA from a cystic mass exhibited rare clusters of crowded cohesive clusters of columnar cells. There was elevated N:C ratio, nuclear hyperchromasia, moderate nuclear size variation and some nuclear contour angulation. Scattered apoptotic debris and degenerating cellular material was focally present. These findings were focal leading some

observers to undergrade. Observer diagnoses: MCLG (2), MCHG (1), PA (2), and SSPA (1); histologic diagnosis: IPMN with high grade dysplasia. (E-F: ThinPrep, 40-60x).

G-H. An EUS-FNA from a clinically dilated duct shows predominantly disorganized sheets and single cells with markedly abnormal contours (G), moderate nuclear size variation, and a background of thin mucin with degenerating and necrotic debris (H). Observer diagnoses: MCHG (4), PA (1), SSPA (1); histologic diagnosis: invasive conventional ductal adenocarcinoma with no intraductal papillary mucinous neoplasm identified. (G: ThinPrep, 40x, H: Air-dried, Diff Quik stained smear, 40x).

Figure 3. Examples of mucin from the grading set with observer responses. CEA levels are cited when available

- A) Thick, viscous colloid-like mucin with degenerating cellular debris and dystrophic calcification were seen in this aspirate from a colloid carcinoma. Observer diagnoses: Neoplastic (5), non-neoplastic (1). (Air-dried, Diff Quik stained smear, 20x)
- B) Thin watery mucin with a ferning pattern from a low grade IPMN. Observer mucin diagnosis: Neoplastic (5), non-neoplastic (1). (Air-dried, Diff Quik stained smear, 20x)
- C) Abundant thin strands of blue mucin was clear of cellular debris and was admixed with bland glandular epithelium were seen in a low grade IPMN. The CEA level was 4.1 ng/ml leading the majority of observers to be uncertain of the origin of the mucin. Observer mucin diagnoses: Neoplastic (1), nonneoplastic (2), uncertain (3). (ThinPrep, 20x)
- D) In this intermediate grade IPMN the mucin was sheet-like with a granular texture. Embedded degenerating inflammatory cells and debris were seen. Observer mucin diagnoses: Neoplastic(2), nonneoplastic (3), uncertain (1). (ThinPrep, 20x)
- E) Thick strands of mucin admixed with well preserved nuclei were seen in this aspirate containing gastrointestinal contamination. The targeted lesion was a serous cystadenoma. Observer mucin diagnoses: Neoplastic (2), non-neoplastic (2), uncertain (2). (Alcohol-fixed, hematoxylin and eosin stained smear, 20x)
- F) Gastrointestinal mucin with watery and thin character was abundant in this aspirate targeting a serous cystadenoma. Observer mucin diagnoses: Neoplastic (2), non-neoplastic (1), uncertain (3). (Air-dried, Diff Quik stained smear, 20x)

Table 1

Summary of pancreatic lesion characteristics and histology diagnoses (N=54)

Lesion characteristics	N (%)
Cyst	28 (52)
Cystic mass	6 (11)
Dilated duct	4 (7)
Mass	16 (30)
Original cytologic diagnosis	
Negative/Nondiagnostic	12 (22)
Atypical	9 (17)
Suspicious for mucinous neoplasm	17 (31)
Neoplasm (mucinous or papillary)	5 (9)
Suspicious for adenocarcinoma	7 (13)
Positive for Adenocarcinoma	4 (8)
Histology	
MCN, low grade	5 (9)
IPMN, low grade	4 (8)
IPMN, intermediate grade	14 (26)
IPMN, high grade	10 (19)
IPMN, with focal invasion	3 (5)
Colloid carcinoma	5 (9)
Pancreatic ductal adenocarcinoma	3 (5)
Non-mucinous lesion	10 (19)
Serous cystadenoma	6 (60)
Chronic pancreatitis	2 (20)
Autoimmune pancreatitis	2 (20)

Abbreviations: IPMN=intraductal papillary mucinous neoplasm; MCN=mucinous cystic neoplasm

Table 2Six-tiered diagnostic scheme¹

Nondiagnostic
Atypical
Mucinous neoplasm, low grade
Mucinous neoplasm, high grade
Suspicious for adenocarcinoma
Adenocarcinoma

¹ Adapted from the proposed Bethesda nomenclature system by the Papanicolaou Society.¹⁴

Table 3

Knowledge of cyst fluid CEA shows a modest improvement in interobserver agreement.

6-tier scheme	<u>kappa coefficient (P value)</u>	
	No CEA	CEA
Overall	0.13 (<.001)	0.17 (<.001)
NDX	0.05 (.10)	0.07 (.02)
ATP	0.15 (<.001)	0.2 (<.001)
MCLG	0.09 (.01)	0.18 (<.001)

Table 4

Variations on a tiered system for reporting the grade of mucinous cysts by cytology¹

Tiers	Diagnostic category	Kappa	P value
6-tiers	overall	0.17	<.001
	NDX	0.07	.02
	ATP	0.20	<.001
	MCLG	0.18	<.001
	MCHG	0.13	<.001
	SSPA	0.10	.003
	PA	0.34	<.001
4-tiers (1)	overall	0.23	<.001
	NDX	0.07	.10
	ATP	0.20	<.001
	MCLG/MCHG	0.27	<.001
	SSPA/PA	0.28	<.001
4-tiers (2)	overall	0.23	<.001
	NDX	0.07	.10
	ATP	0.20	<.001
	MCLG/	0.18	<.001
	MCHG/SSPA/PA	0.35	<.001
4-tiers (3)	overall	0.22	<.001
	NDX	0.07	.02
	ATP/MCLG	0.23	<.001
	MCHG/SSPA	0.23	<.001
	PA	0.34	<.001
3-tiers	overall	0.28	<.001
	NDX	0.07	.10
	ATP/MCLG	0.23	<.001
	MCHG/SSPA/PA	0.35	<.001

Abbreviations: ATP= atypical, MCLG= mucinous cyst low grade, MCHG= mucinous cyst high grade, NDX= nondiagnostic, SSPA= suspicious for adenocarcinoma, PA= positive for adenocarcinoma.

¹ Diagnoses include 18 cases where cyst fluid CEA level was available.

Table 5

Distribution of observer diagnoses for the 54 case grading set.

Histologic diagnosis	Original cytology diagnosis	Clinical finding	CEA (ng/ml)	Benign/low grade			High grade/malignant		
				NDX	ATP	LG	HG	SSPA	PA
MCN, low grade	NEG	C	4877.3	0	1	3	1	1	0
	ATP	M	-	2	3	0	0	1	0
	ATP	C	1.6	1	5	0	0	0	0
	NEO	M	-	1	2	2	1	0	0
	SSPA	C	-	0	3	1	1	1	0
IPMN, low grade	NDX	C	-	1	4	1	0	0	0
	NEG	C	448	0	2	4	0	0	0
	NEG	C	21030	0	1	1	3	0	0
	SMN	C	4	0	4	2	0	0	0
IPMN, focal intermediate grade	NDX	C	41	1	4	0	0	1	0
	NDX	DD	-	0	3	0	0	3	0
	NEG	C	46	0	4	1	1	0	0
	ATP	C	338	0	0	6	0	0	0
	ATP	C	-	0	1	4	1	0	0
IPMN, intermediate grade	ATP	C	5	0	2	2	1	1	0
	SMN	C	-	0	2	2	1	1	0
	MN	C	1149	0	0	4	1	0	0
	NDX	C	-	0	4	2	0	0	0
	NEG	C	72	1	3	2	0	0	0
	NEG	C	1765	0	1	5	0	0	0
	SMN	C	-	2	2	2	0	0	0
	MN	C	-	1	0	3	2	0	0
	SMN-HG	M	-	0	0	1	2	2	0
	ATP	M	-	0	2	0	0	3	1
IPMN, focal high grade	SMN	M	1888	0	0	1	5	0	0
	SMN-IG	M	-	0	1	4	1	0	0
	ATP	C	-	1	2	3	0	0	0
IPMN, high grade	SMN	CM	-	0	0	2	1	1	2
	SMN	DD	-	0	0	5	1	1	0
	SSPA	C	26351	1	1	1	1	2	0
	SSPA	C	-	0	0	1	1	3	1
	SSPA	M	-	0	2	2	0	1	1
	PA	M	-	0	0	1	3	1	1
	NEG	DD	-	0	5	1	0	0	0
	NEG	DD	-	0	5	1	0	0	0
IPMN, NOS with focal invasion	NDX	M	-	0	0	3	3	0	0
	ATP	C	-	0	2	2	1	0	0
Colloid carcinoma	ATP	C	-	2	3	1	0	0	0

Histologic diagnosis	Original cytology diagnosis	Clinical finding	CEA (ng/ml)	Benign/low grade			High grade/malignant		
				NDX	ATP	LG	HG	SSPA	PA
Ductal adenocarcinoma	SMN	CM	-	0	2	0	2	1	1
	SMN	CM	-	0	0	2	3	1	0
	SMN	M	-	0	3	1	1	0	1
	PA	C	1100	0	0	0	2	2	2
	MN	DD	-	0	0	0	4	1	1
	PA	CM	92	1	0	0	1	3	1
Chronic pancreatitis	PA	M	-	0	0	0	0	0	6
	SMN	M	-	1	2	1	1	0	0
	SSPA	CM	26	0	1	1	2	2	0
Autoimmune pancreatitis	SMN	M	-	0	1	3	2	0	0
	SSPA	M	-	0	2	2	2	0	0
Serous cystadenoma	SMN	C	-	1	5	0	0	0	0
	SMN	CM	-	1	5	0	0	0	0
	SMN	M	-	1	4	1	0	0	0
	SMN	C	-	1	4	1	0	0	0
	SMN	C	-	1	1	0	2	2	0
	SSPA	M	<5	4	1	1	0	0	0

Abbreviations: ATP=atypical, C=cyst, CM=cystic mass, DD=dilated duct, HG=high grade, IG=intermediate grade, M=mass, MCN=mucinous neoplasm, MN=mucinous neoplasm, NDX=nondiagnostic, NEO=neoplasm, NEG=negative, NOS=not otherwise specified, SMN=suspect mucinous neoplasm, SSPA=suspicious for adenocarcinoma, PA=positive for adenocarcinoma