Journal of the American Society of Cytopathology (2019) 8, 120–127

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/

ORIGINAL ARTICLE

Risk of malignancy in the categories of the Papanicolaou Society of Cytopathology system for reporting pancreaticobiliary cytology

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Received 7 December 2018; received in revised form 9 January 2019; accepted 9 January 2019

KEYWORDS
Endoscopic ultrasound;
Fine-needle aspiration biopsy;
Malignancy risk;
Pancreas;
Papanicolaou Society of Cytopathology

Background Management of pancreatic lesions depends on the risk of malignancy, which is primarily determined from the cytologic and radiologic evaluation findings. The Papanicolaou Society of Cytopathology (PSC) published a classification system for reporting pancreaticobiliary cytology. However, the "neoplastic: other" category can be further stratified by high-grade atypia (HGA). Studies on the risk of malignancy using the PSC system have been limited.

Materials and methods All patients who had undergone endoscopic ultrasound-guided fine-needle aspiration (FNA) for a pancreatic lesion at Massachusetts General Hospital from January 2016 to December 2016 were prospectively classified. The clinical, radiographic, and endoscopic findings, cytologic and histologic diagnoses, and follow-up data from 334 FNA biopsies from 322 patients were reviewed. The neoplastic: other category was subclassified as low-grade atypia or HGA. The absolute risk of malignancy was determined by the histologic outcome or follow-up of $\geq$6 months.

Results The absolute risk of malignancy was 7.7% for the nondiagnostic category; 1.0% for negative; 28.0% for atypical; 0.0% for neoplastic: benign; 30.3% for neoplastic: other; 90.0% for neoplastic: other with HGA; 100% for suspicious; and 100% for positive. When the neoplastic: other with HGA, suspicious, and positive cytologic diagnoses were considered positive, the sensitivity, specificity, positive predictive value, and negative predictive value for pancreatic FNA biopsy was 92.2%, 98.8%, 98.3%, and 94.3%, respectively.

This research was presented at the 108th Annual Meeting of the United States and Canadian Academy of Pathology, National Harbor, Maryland, March 2019.

E.B. Finer, who was a premedical student at University of Rochester, Rochester, New York, performed this study as an intern for Dr. Martha B. Pitman.

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https://doi.org/10.1016/j.jasc.2019.01.002

Conclusions Categories of the PSC system each carry an implied absolute risk of malignancy, increasing from the negative to positive categories. The presence of HGA identifies lesions at the greatest risk of malignancy in the neoplastic: other category, and its inclusion with suspicious and positive as positive diagnoses optimizes the diagnostic performance of identifying high-risk lesions that warrant surgical excision.

Introduction

Pancreatic lesions encompass a broad differential diagnosis of benign, premalignant, and malignant entities. An accurate preoperative diagnosis is crucial for appropriate clinical management. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) biopsy of the pancreas has demonstrated high sensitivity and specificity for the evaluation of pancreatic solid and cystic masses and has been proved to be a safe, accurate, and minimally invasive diagnostic test.[1-4] In a meta-analysis of 15 studies on the diagnostic performance of EUS-FNA for solid pancreatic lesions, Chen et al[1] reported a pooled sensitivity and specificity of 92% and 96%, respectively.

Clear communication among the multidisciplinary team of pathologists, endoscopists, radiologists, surgeons, and medical and radiation oncologists is essential for timely and accurate patient care. Uniform diagnostic criteria and terminology form the foundation of standardized reporting. To that end, the Papanicolaou Society of Cytopathology (PSC) has published recommendations to standardize the diagnostic categories for pancreaticobiliary cytology and to define the criteria. These standardized reporting categories were designed to allow for flexible patient care and to translate across a multidisciplinary team.[5,6] Using these guidelines, the cytologic diagnoses of pancreaticobiliary lesions can be classified into 6 interpretation categories: I, nondiagnostic; II, negative for malignancy; III, atypical; IV, neoplastic: benign or other; V, suspicious for malignancy; and VI, positive or malignant.[6] Examples of the diagnoses within each category of *The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology* (PSC system) have been provided in Table 1. Unique to this terminology scheme is the "neoplastic" category, which separates benign lesions, such as serous cystadenomas, from lesions with malignant potential, including intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms, well-differentiated neuroendocrine tumors, and solid pseudopapillary neoplasms. Our group has examined the clinical value in identifying high-grade epithelial atypia within the "neoplastic: other" category to further stratify patients in this category between those who can be observed (low-risk or low-grade lesions) and those who should undergo surgery (high-risk or high-grade lesions).[7,8] The introduction of this "neoplastic" category has provided a conservative interpretation category for lesions of uncertain malignant potential in contrast to the "suspicious" and "positive" categories and, thus, providing for flexibility in clinical management. Few have investigated the risk of malignancy associated with the categories set forth in the PSC system.[9-11] We have reviewed our experience at Massachusetts General Hospital in a prospective, one-year study to evaluate the associated risk of malignancy with each diagnostic category of the PSC system.

Materials and methods

The institutional review board approved the present study. All patients who had undergone EUS-FNA for a pancreatic lesion at Massachusetts General Hospital from January 1, 2016 to December 31, 2016 were included in the study cohort. The clinical data and radiologic impressions from computed tomography (CT), magnetic resonance imaging, and EUS scans were obtained from the electronic medical records. The location, size, and solid or cystic nature of the lesion were aggregated from the CT, magnetic resonance imaging, and EUS reports.

Cytologic preparations

The cytologic material was processed as direct smears, Cytospin preparations (Thermo-Shandon Instruments, Asheville, NC), and/or SurePath liquid-based preparations (Becton Dickinson Co, Franklin Lakes, NJ). Direct smears were fixed in ethanol and stained using hematoxylin and eosin or Papanicolaou stains. Liquid-based and cytospin preparations were both stained with Papanicolaou stains. All cytologic diagnoses were classified prospectively using the PSC system (Table 1). Pancreatic cysts within the "neoplastic: other" category were further stratified by the presence of epithelial high-grade atypia (HGA), as defined by Pitman et al.[8] The 5 cytologic features of HGA are an increased nuclear/cytoplasmic ratio, abnormal chromatin pattern, background cellular necrosis, small cell size compared with a 12-μm enterocyte, and nuclear membrane irregularities (Fig. 1).

Follow-up histologic findings and clinical data

Each cytologic diagnosis was correlated with the histologic or clinical follow-up findings. Concurrent or subsequent formalin-fixed paraffin-embedded tissue samples were treated as comparative histologic samples for statistical analysis. Malignant (true positive) histologic findings included lesions with high-grade dysplasia,

Table 1 Diagnostic categories of PSC system.

Diagnostic category	Examples of diagnostic entities
I. Nondiagnostic	Acellular aspirate with no evidence of a mucinous etiology
	Gastrointestinal contamination
	Benign pancreatic parenchyma, if a well-defined mass is identified on imaging
II. Negative for malignancy	Benign pancreatic parenchyma, if a well-defined mass is not identified on imaging
	Acute pancreatitis
	Chronic pancreatitis
	Autoimmune pancreatitis
	Pseudocyst
	Lymphoepithelial cyst
	Ectopic splenic tissue
III. Atypical	Atypical ductal cells, obscured by artifact
IV. Neoplastic: benign	Serous cystadenoma
	Lymphangioma
IV. Neoplastic: other	Neuroendocrine tumor, well-differentiated
	Intraductal papillary mucinous neoplasm (including all grades of dysplasia)
	Mucinous cystic neoplasm (including all grades of dysplasia)
	Solid pseudopapillary neoplasm
V. Suspicious for malignancy	Rare markedly atypical epithelial cells, insufficient in quality or quantity for positive or malignant diagnosis
VI. Positive or malignant	Pancreatic ductal adenocarcinoma
	Cholangiocarcinoma
	Acinar cell carcinoma
	Neuroendocrine carcinoma, poorly differentiated
	Pancreatoblastoma
	Lymphoma
	Metastatic malignancy

Abbreviation: PCS, Papanicolaou Society of Cytopathology.
Data from Pitman et al.[5]

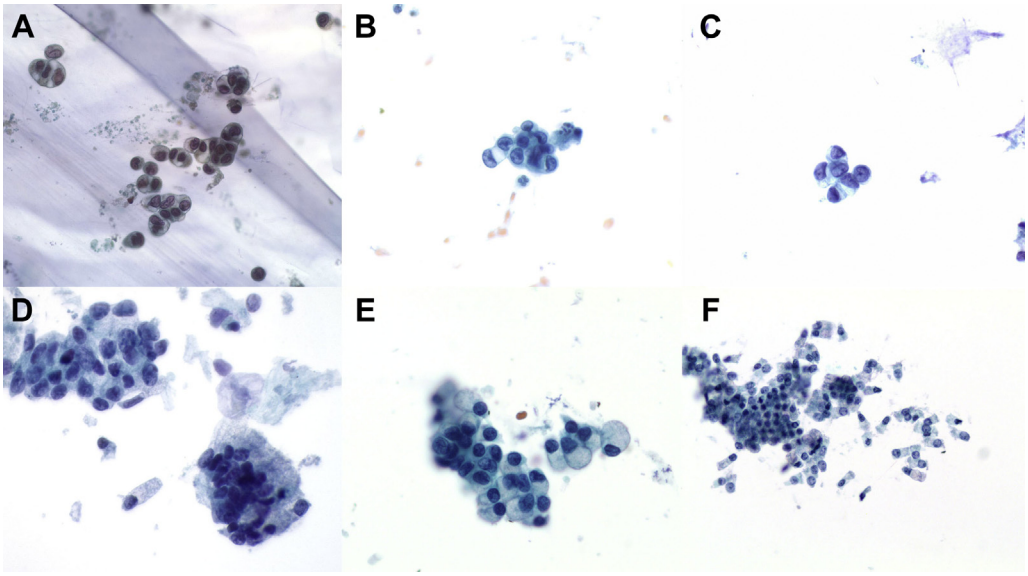

Figure 1 Spectrum of atypia seen in neoplastic mucinous cysts using different preparations. A-C, High-grade atypia is seen in these scattered and tight groups of small mucinous epithelial cells with a high nuclear/cytoplasmic ratio, abnormal chromatin, nuclear membrane irregularities and variable nucleoli (A, direct smear; B, Cytospin; C, ThinPrep; all preparations with Papanicolaou stain). D-F, Low-grade atypia shown in these small clusters and flat sheets of bland-appearing mucinous epithelial cells with a low nuclear/cytoplasmic ratio, visible mucin vacuoles, even chromatin, round nucleoli, and inconspicuous nucleoli (D, ThinPrep; E, Cytospin; F, ThinPrep; all preparations with Papanicolaou stain).

adenocarcinoma, or neuroendocrine tumor, because these lesions have been demonstrated to be either malignant, in the case of adenocarcinoma, or lesions at high risk of malignancy, according to our previous reported studies.[2,7,12,13] If no corresponding histologic findings were available, malignant cytologic diagnoses were classified as true-positive results if the clinical follow-up and/or imaging findings demonstrated overt malignant features or metastasis. Benign cytologic findings were considered as true negative cases if the corresponding histologic findings demonstrated a benign neoplasm (ie, serous cystadenoma), or, if no corresponding histologic findings were available, the clinical follow-up data showed no emergence of malignant features or evidence of metastasis.

Statistical analysis

Sensitivity was calculated as the number of malignant (high-grade or high-risk) cases correctly diagnosed by cytology divided by the total number of histologically or clinically proven malignant (high-risk or high-grade) cases. Specificity was determined by the number of benign cases correctly identified by cytology divided by the total number of histologically or clinically proven benign cases within the study cohort. The positive predictive value (PPV) was established as the number of malignant (high-risk and high-grade) cases correctly diagnosed by cytology divided by the total number of malignant (high-risk and high-grade) cytology results. The negative predictive value (NPV) was calculated as the number of benign cases correctly identified by cytology divided by the total number of benign cytology results. The sensitivity, specificity, PPV, and NPV were calculated for various groups of diagnostic categories considered positive: (1) atypical, neoplastic: other, suspicious, and positive; (2) atypical, neoplastic: other with HGA, suspicious, and positive; (3) neoplastic: other with HGA, suspicious, and positive; (4) suspicious and positive; and (5) positive. The false-positive rate was calculated as the number of benign cases incorrectly identified by cytology as malignant (high-grade and high-risk) divided by the total number of histologically or clinically proven benign cases. The false-negative rate was determined by the number of malignant (high-risk and high-grade) cases incorrectly identified by cytology as benign divided by the total number of histologically or clinically proven malignant (high-risk and high-grade) cases. The absolute risk of malignancy for each diagnostic category was determined by the number of malignant (high-risk and high-grade) cases according to the histologic and/or clinical follow-up data, divided by the total number of cases within each corresponding category. The relative risk was established as the ratio of the absolute risk of malignancy of each diagnostic category to the absolute risk of malignancy of the "negative for malignancy" category. Nondiagnostic specimens were excluded from the statistical calculations, except for the calculation of the nondiagnostic rate, which was defined as the number of nondiagnostic cytology samples divided by the total number of cytology specimens. P values for relative risk were assessed using Fisher's exact test. Statistical significance was established at $P = 0.05$.

Results

Clinical profile of study cohort

During the study period, 322 patients had undergone pancreatic FNA biopsy with 334 specimens. The study cohort included 168 men (52.2%) and 154 women (47.8%). The patients' ages ranged from 18 to 91 years (mean, 66.1 years; median, 68 years). Of the 334 pancreatic lesions, 171 (51.2%) were cystic and 163 (48.8%) were solid. Pancreatic masses were found more commonly within the head (n = 139; 41.6%), tail (n = 79; 23.7%), and body (n = 74; 22.2%). Less commonly, the lesions were found in the neck (n = 19; 5.7%), uncinate (n = 2.7%), peripancreatic area (n = 8; 2.4%) and main duct, not otherwise specified (n = 6; 1.8%). The median clinical follow-up time was 18 months (mean, 15 months). The histologic findings were available for 137 cases (41.0%), and clinical follow-up data were used for 197 cases (59.0%). The histologic specimens included 71 core needle biopsy samples, cell block preparations, and EUS next-generation needle biopsy samples (51.8%), 45 Whipple (pancreaticoduodenectomy) specimens (32.8%), and 21 distal pancreatectomy specimens (15.4%). Of the 66 surgical specimens, which encompassed only those from Whipple procedures and distal pancreatectomy, 46 cases were malignant on resection, for an overall surgical malignancy rate of 69.7%.

Absolute risk of malignancy for diagnostic categories

The overall distribution of cytologic diagnoses among the PSC system categories was as follows: 39 nondiagnostic specimens (11.7%); 100 negative (29.9%); 25 atypical (7.5%); 4 neoplastic: benign (1.2%); 66 neoplastic: other (19.8%); 6 suspicious (1.8%); and 94 positive (28.1%). Among these cytologic categories, cystic lesions accounted for 23 nondiagnostic specimens (59.0%); 67 negative (67.0%); 15 atypical (60.0%); 4 neoplastic: benign (100%); 51 neoplastic: other (77.3%); 4 suspicious (66.7%); and 7 positive (7.4%). The correlation of the cytologic diagnoses and follow-up data is presented in Table 2. The absolute risk of malignancy for each diagnostic category were as follows: nondiagnostic, 7.7%; negative for malignancy, 1.0%; atypical, 28.0%; neoplastic: benign, 0.0%; neoplastic: other, 30.3%; suspicious for malignancy, 100.0%; and positive or malignant, 100.0%. The absolute risk and relative risk of malignancy for the diagnostic categories in the PSC system and the categories with statistically significant differences in the risk of malignancy from that of the negative category are

Table 2 Cytologic correlation with clinicopathologic diagnoses in 334 pancreatic EUS-FNA biopsy specimens.

Diagnostic category	Histologic diagnosis and/or clinical follow-up finding		Total cases
	Benign	Malignant	
I. Nondiagnostic	36 (92.3)	3 (7.7)	39 (11.7)
II. Negative for malignancy	99 (99.0)	1 (1.0)	100 (29.9)
III. Atypical	18 (72.0)	7 (28.)	25 (7.5)
IV. Neoplastic: benign	4 (100)	0 (0)	4 (1.2)
IV. Neoplastic: other	46 (69.7)	20 (30.3)	66 (19.8)
With low-grade atypia	44 (95.7)	2 (4.3)	46 (69.7)
With high-grade atypia	2 (10.0)	18 (90.0)	20 (30.3)
V. Suspicious for malignancy	0 (0)	6 (100)	6 (1.8)
VI. Positive or malignant	0 (0)	94 (100)	94 (28.1)
Total cases	203 (60.8)	131 (39.2)	334 (100)

Data presented as n (%).
Abbreviation: EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

presented in Table 3. Within the "neoplastic: other" category, the identification of epithelial HGA yielded an absolute risk of malignancy of 90.0% (Table 3).

Diagnostic performance of pancreatic EUS-FNA biopsy

The sensitivity, specificity, PPV, and NPV for the pancreatic EUS-FNA biopsy, using various cutoff points for malignancy, are listed in Table 4. If the "atypical," "neoplastic: other," "suspicious," and "positive" categories were considered positive and the "negative" and "neoplastic: benign" categories were considered negative, the sensitivity, specificity, PPV, and NPV were 99.2%, 61.7%, 66.5%, and 99.0%, respectively. If the "atypical," "neoplastic: other," "suspicious," and "positive" categories were considered positive and the "negative" and "neoplastic: benign" categories were considered negative, the sensitivity, specificity, PPV, and NPV were 99.2%, 61.7%, 66.5%, and 99.0%, respectively. When the "atypical," "neoplastic: other with epithelial HGA," "suspicious," and "positive" were considered positive and the "negative," "neoplastic: benign," and "neoplastic: other without HGA" categories were considered negative, the sensitivity, specificity, PPV, and NPV were 97.7%, 88.0%, 86.2%, and 98.0%, respectively. If the neoplastic: other with HGA," "suspicious," and "positive" were considered positive and the "negative," "atypical," "neoplastic: benign," and "neoplastic: other without HGA" were considered negative, the sensitivity, specificity, PPV, and NPV were 92.2%, 98.8%, 98.3%, and 94.3%, respectively. When the "suspicious" and "positive" categories were considered positive and the "negative," "atypical," "neoplastic: benign," and "neoplastic: other" were considered negative, the sensitivity, specificity, PPV, and NPV were 78.1%, 100%, 100%, and 85.6%, respectively. When only the positive category was considered positive and all other categories were considered negative, the sensitivity, specificity, PPV, and NPV were 66.2%, 100%, 100%, and 77.7%, respectively.

False-positive cases

Considering the cases in the "neoplastic: other with HGA," "suspicious," and "positive" categories as positive (high-

Table 3 Absolute risk and relative risk of malignancy of the diagnostic categories in the PCS system.

Diagnostic category	Absolute risk of malignancy (%)	Relative risk	*P* value (relative to benign category)
I. Nondiagnostic	7.7	7.7	0.07
II. Negative for malignancy	1.0	1.0	NA
III. Atypical	28.0	28.0	0.001[a]
IV. Neoplastic: benign	0.0	0.0	1.00
IV. Neoplastic: other, all grades of atypia	30.3	30.3	<0.001[a]
With low-grade atypia	4.3	4.3	0.23
With high-grade atypia	90.0	90.0	<0.001[a]
V. Suspicious for malignancy	100.0	100.0	<0.001[a]
VI. Positive or malignant	100.0	100.0	<0.001[a]

Abbreviations: NA, not applicable; PCS, Papanicolaou Society of Cytopathology.
[a]Statistically significant ($P < 0.05$).

Table 4 Performance characteristics of pancreatic EUS-FNA biopsy, stratified by category for positive cutoff.

Diagnostic categories considered positive	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Atypical; neoplastic: other; suspicious; and positive	99.2	61.7	66.5	99.0
Atypical; neoplastic: other with HGA; suspicious; and positive	97.7	88.0	86.2	98.0
Neoplastic: other with HGA; suspicious; and positive	92.2	98.8	98.3	94.3
Suspicious; and positive	78.1	100	100	85.6
Positive	66.2	100	100	77.7

Abbreviations: EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; HGA, high-grade atypia; NPV, negative predictive value; PPV, positive predictive value.

risk) cytologic diagnoses, we found 2 false-positive cases within our study group, for a false-positive rate of 1.2%. The first patient was a 74-year-old man with a 3.3-cm cyst in the head of the pancreas.[7] In brief, the EUS-FNA biopsy specimen displayed mucinous cells with a high nuclear/cytoplasmic ratio and a small cell size, in keeping with intermediate-grade atypia to HGA. The subsequent Whipple procedure showed a 3.5-cm predominantly branch-duct IPMN with intermediate-grade dysplasia. The second false-positive case was of a 65-year-old woman, who had presented with a 2.8-cm cystic lesion in the body of the pancreas. The details of the second case have been previously reported by Chen et al.[14] In brief, the EUS-FNA biopsy demonstrated mucinous epithelial cells with a high nuclear/cytoplasmic ratio and some nuclear membrane irregularities, which led to a cytologic diagnosis of IPMN with HGA. However, the patient's distal pancreatectomy displayed acinar cell cystadenoma.

False-negative cases

Considering the cases in the negative, atypical, neoplastic: benign, and neoplastic: other without HGA categories as negative cytologic diagnoses, we found 10 false-negative cases within our study cohort, for a false-negative rate of 7.8%. In 7 of the false-negative cases, the EUS-FNA biopsy specimens displayed atypical glandular cells. However, the evaluation was limited by scant cellularity, and all had been included in the atypical category. The histologic findings for these cases ultimately showed pancreatic ductal adenocarcinoma in 4, metastatic renal cell carcinoma to the pancreas in 2, and poorly differentiated pancreatic neuroendocrine carcinoma in 1.

In 2 false-negative cases, the EUS-FNA biopsy specimens demonstrated mucinous neoplasms with epithelial cells with low- to intermediate-grade dysplasia, with no evidence of high-grade dysplasia. In 1 case, the mucinous etiology was established by the presence of thick, extracellular mucin. In the second case, a carcinoembryonic antigen level of 223.4 ng/mL supported the mucinous etiology. Both cases showed IPMNs with high-grade dysplasia associated with invasive adenocarcinoma.

The remaining false-negative case was in a 65-year-old woman, who was found to have a 3.7-cm, solid mass in the head of the pancreas. The EUS-FNA biopsy specimen showed benign ductal cells and was classified as negative for malignancy. This diagnosis was accompanied by a note in the cytopathology report that advised clinical correlation, because this sample was thought to not likely be representative of the targeted lesion. The concurrent histologic sample and subsequent resection using the Whipple procedure both displayed pancreatic ductal adenocarcinoma.

Nondiagnostic cases

Within our study group of 334 EUS-FNA biopsy specimens, 39 cases were in the nondiagnostic category, for a nondiagnostic rate of 11.7%. One patient underwent a follow-up FNA biopsy, for which the cytologic findings were consistent with autoimmune pancreatitis and further management was clinical. Of the remaining patients, 5 underwent subsequent surgical resection, which showed 3 malignant lesions, including 1 pancreatic ductal adenocarcinoma and 1 acute lymphoblastic leukemia, and 3 benign processes, including 1 IPMN with low-grade dysplasia, 1 low-grade pancreatic intraepithelial neoplasm, and 1 serous cystadenoma. For 5 nondiagnostic cases, the concurrent histologic samples demonstrated 1 malignancy, which was a pancreatic ductal adenocarcinoma, 3 benign samples of pancreatic parenchyma, and 1 nondiagnostic sample, which consisted of contaminating gastrointestinal epithelium. No further surgical intervention was pursued in these latter cases. Overall, the absolute risk of malignancy for the nondiagnostic category was 7.7%.

Discussion

In the present study, we have demonstrated the increasing risk of malignancy associated with the diagnostic categories of the PSC system. The absolute risk of malignancy for each category was as follows: nondiagnostic, 7.7%; negative, 1.0%; atypical, 28.0%; neoplastic: benign, 0.0%; neoplastic: other, 30.3%; suspicious, 100.0%; and positive, 100.0%. We also found that the presence of epithelial HGA in neoplastic: other lesions carries an absolute risk of malignancy of 90.0% and relative risk of 90.0 compared with a negative diagnosis ($P < 0.001$). The diagnostic performance of pancreatic EUS-FNA was ideal when the lesions

classified as "negative," "atypical," "neoplastic: benign," or "neoplastic: other with low-grade atypia" were considered negative results and "neoplastic: other with HGA," "suspicious," and "positive" were considered positive results (Table 4). Using this grouping of categories yielded a sensitivity, specificity, PPV, and NPV of 92.2%, 98.8%, 98.3%, and 94.3%, respectively.

Studies on the associated risk of malignancy with the diagnostic categories of the PSC system remain limited.[9-11] Wright et al[10] reported their prospective experience using the PSC system for EUS-FNA biopsy of both solid and cystic pancreatic lesions. Their risk of malignancy or neoplasia with malignant potential for the diagnostic categories was as follows: nondiagnostic, 33.3%; negative, 8.3%; atypical, 100%; neoplastic: benign, 66.7%; neoplastic: other, 100%; suspicious, 100%; and positive, 100%.[10] Layfield et al[9] likewise included solid and cystic lesions of the pancreas but combined their reporting of "neoplastic: benign" and "neoplastic: other" categories. The group found the risk of malignancy for the PSC system categories in their study was as follows: nondiagnostic, 21.4%; negative, 12.6%; atypical, 73.9%; neoplastic: benign or neoplastic: other, 14.2%; suspicious, 81.8%; and positive, 97.2%.[9] Smith et al[11] focused only on cystic mucinous neoplasms and stratified the "neoplastic: other" by the presence of HGA. They reported the risk of malignancy in their retrospective study as follows: nondiagnostic, 17.4%; negative, 0%; atypical, 63.6%; neoplastic: other without HGA, 13%; neoplastic: other with HGA, 64%; suspicious, 80%; and positive, 100%.[11] When considering the true associated risk of malignancy with the diagnostic categories of the PSC system, the sample size and study methods could contribute to the spectrum seen among the cited studies. Studies relying solely on the histologic findings from subsequent surgical resections, such as in the study by Smith et al,[11] will overestimate the true risk of malignancy, especially in the nondiagnostic, benign and atypical categories, because only a few cases will ultimately be resected. Studies depending on histologic and clinical follow-up data, such as in the studies by Layfield et al,[9] Wright et al,[10] and the present study, will underestimate the risk of malignancy, especially in the benign and atypical categories, because most of the unresected cases will be considered benign.

Meta-analyses of EUS-FNA biopsy using the PSC system have been few, given its relatively recent publication. In meta-analyses conducted before the report of the PSC system, the pooled sensitivities and specificities ranged from 51% to 92% and 93% to 96%, respectively.[1,3,15,16] In more recent studies that used the PSC system, the sensitivities and specificities were more comparable with our findings (range, 71.2%-95.4% and 93.8%-100%, respectively).[9,10]

The false-negative rate of 7.8% for EUS-FNA pancreatic biopsy found in our study is comparable to those reported by other groups, which ranged from 1% to 25% (n = 5; mean, 11.6%).[7,10,17-19] Most of the false-negative cases (70%) in our study resulted from atypical epithelial cells in scantily cellular specimens, which precluded a more definitive diagnosis. In accordance with management guidelines, a high degree of clinical suspicion and concerning imaging features in these cases led to referral for surgical evaluation, which confirmed malignancy in all 7 cases. Sampling accounted for 1 false-negative case (10%) in our study cohort. This false-negative case showed benign glandular cells in the setting of a well-defined mass on imaging. In retrospect, this case might have been more accurately classified as nondiagnostic rather than negative for malignancy. A concurrent histologic sample demonstrated pancreatic ductal adenocarcinoma, and the patient subsequently underwent Whipple resection. In the absence of this concurrent biopsy specimen, the recommendation for management of nondiagnostic cases in the PSC system is clinical and radiologic correlation. In our patient, the CT scan of the abdomen and pelvis revealed a 4.0-cm, solid, infiltrative pancreatic head mass that had encased multiple vessels and was associated with regional lymphadenopathy, strongly suggestive of invasive pancreatic ductal adenocarcinoma.

In 2014, Pitman et al[8] reported cytologic criteria for epithelial HGA in IPMNs, which correlate histologically with high-grade dysplasia or adenocarcinoma. In a subsequent prospective study, we demonstrated that epithelial HGA was the only statistically significant predictor of malignancy in pancreatic cysts.[7,11] In those studies, we showed that the identification of HGA had a sensitivity of 89%, specificity of 98%, and PPV of 80% for malignancy. In the present study, we found that the recognition of HGA portends a significant risk of malignancy. In the present cohort, the absolute risk of malignancy associated with the neoplastic: other with HGA category was 90% compared with an absolute risk of malignancy of 4.3% associated with the neoplastic: other with low-grade atypia.

Our study was limited by the number of cases with histologic follow-up data available. Of the 334 EUS-FNA biopsy specimens in our study cohort, 137 (41.0%) had histologic findings available. Nearly 30% of our study cohort had cytology findings classified as negative for malignancy. Only 17% of these negative samples had corresponding histologic findings available, as imaging surveillance is the recommended follow-up protocol for this category. In contrast, all 6 patients with suspicious cytologic diagnoses subsequently underwent surgery, and all were found to have malignant lesions.

Conclusions

The results of our prospective, one-year study of 334 pancreatic lesions have demonstrated an increasing risk of malignancy associated with the diagnostic categories of the PSC system. These results have confirmed the clinical utility of the 6-tiered diagnostic scheme. We have confirmed the value of the identification of HGA in the neoplastic: other category, which carries a high risk of malignancy.

Standardization of the reporting terminology of pancreaticobiliary cytology translates across institutions, allowing for easy auditing of diagnostic accuracy. We found that the diagnostic performance of the PSC system is optimal when neoplastic: other with HGA, suspicious for malignancy, and positive were considered as positive results for surgical triage.

Funding sources

No specific funding was disclosed.

Conflict of interest disclosures

The authors made no disclosures.

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