Suboptimal Agreement Among Cytopathologists in Diagnosis of Malignancy Based on Endoscopic Ultrasound Needle Aspirates of Solid Pancreatic Lesions: A Validation Study

Carrie Marshall,[*,a] Rawad Mounzer,[‡,a] Matt Hall,[§] Violette Simon,[‖] Barbara Centeno,[¶] Katie Dennis,[#] Jasreman Dhillon,[¶] Fang Fan,[#] Laila Khazai,[¶] Jason Klapman,[**] Srinadh Komanduri,[‡‡] Xiaoqi Lin,[§§] David Lu,[‖‖] Sanjana Mehrotra,[*] V. Raman Muthusamy,[¶¶] Ritu Nayar,[§§] Ajit Paintal,[§§] Jianyu Rao,[‖‖] Sharon Sams,[*] Janak Shah,[##] Rabindra Watson,[¶¶] Amit Rastogi,[***] and Sachin Wani[‖]

*Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, Colorado; ‡Division of Gastroenterology, Digestive Institute, Banner University Medical Center, Phoenix, Arizona; §Children's Hospital Association, Overland Park, Kansas; ‖Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, Colorado; ¶Department of Pathology, Moffitt Cancer Center, Tampa, Florida; #Department of Pathology, University of Kansas School of Medicine, Kansas City, Kansas; **Gastrointestinal Tumor Program, Moffitt Cancer Center, Tampa, Florida; ‡‡Division of Gastroenterology and Hepatology, Northwestern University, Chicago, Illinois; §§Department of Pathology, Northwestern University, Chicago, Illinois; ‖‖Department of Pathology, University of California Los Angeles, Los Angeles, California; ¶¶Vatche and Tamar Manoukian Division of Digestive Diseases, University of California Los Angeles, Los Angeles, California; ##Division of Gastroenterology and Hepatology, Ochsner Medical Center, New Orleans, Louisiana; and ***Division of Gastroenterology and Hepatology, University of Kansas School of Medicine, Kansas City, Kansas

BACKGROUND & AIMS: **Despite the widespread use of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) to sample pancreatic lesions and the standardization of pancreaticobiliary cytopathologic nomenclature, there are few data on inter-observer agreement among cytopathologists evaluating pancreatic cytologic specimens obtained by EUS-FNA. We developed a scoring system to assess agreement among cytopathologists in overall diagnosis and quantitative and qualitative parameters, and evaluated factors associated with agreement.**

METHODS: **We performed a prospective study to validate results from our pilot study that demonstrated moderate to substantial inter-observer agreement among cytopathologists for the final cytologic diagnosis. In the first phase, 3 cytopathologists refined criteria for assessment of quantity and quality measures. During phase 2, EUS-FNA specimens of solid pancreatic lesions from 46 patients were evaluated by 11 cytopathologists at 5 tertiary care centers using a standardized scoring tool. Individual quantitative and qualitative measures were scored and an overall cytologic diagnosis was determined. Clinical and EUS parameters were assessed as predictors of unanimous agreement. Inter-observer agreement (IOA) was calculated using multi-rater kappa (κ) statistics and a logistic regression model was created to identify factors associated with unanimous agreement.**

RESULTS: **The IOA in final diagnoses, based on cytologic analysis, was moderate (κ = 0.56; 95% CI, 0.43–0.70). Kappa values did not increase when categories of suspicious for malignancy, malignant, and neoplasm were combined. IOA was slight to moderate for individual quantitative (κ = .007; 95% CI, –0.03 to –0.04) and qualitative parameters (κ = 0.5; 95% CI, 0.47–0.53). Jaundice was the only factor associated with agreement among all cytopathologists on multivariate analysis (odds ratio for unanimous agreement, 5.3; 95% CI, 1.1–26.89).**

CONCLUSIONS: **There is a suboptimal level of agreement among cytopathologists in diagnosis of malignancy based on analysis of EUS-FNA specimens obtained from solid pancreatic masses. Strategies are needed to refine the cytologic criteria for diagnosis of malignancy and improve tissue acquisition techniques to improve diagnostic reproducibility among cytopathologists.**

[a]Authors share joint authorship and contributed equally to this manuscript.

Abbreviations used in this paper: CI, confidence interval; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; IHC, immunohistochemical.

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Pancreatic cancer continues to be the fourth leading cause of cancer-related deaths in the United States with a persistent rise in incidence noted based on the most recent American Cancer Society estimates.[1–3] In 2017, an estimated 53,670 people will be diagnosed and more than 43,000 are expected to die of pancreatic cancer.[1] By 2030 the incidence of pancreatic cancer is projected to increase by 55%.[3] Despite extensive multidisciplinary efforts in diagnostic and therapeutic modalities to improve disease survival, mortality rates from pancreatic cancer remain high with 5-year survival rates of 7%.[4–6]

Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) have become the standard modality for the diagnosis and staging of pancreatic cancer.[7,8] EUS is the most sensitive imaging modality for the detection of pancreatic masses and is particularly useful when results of other cross-sectional imaging modalities are inconclusive.[9,10] Several studies have demonstrated a high sensitivity and specificity of EUS-FNA for diagnosing this disease and the technique is associated with an outstanding safety profile.[11] In a recent meta-analysis EUS-FNA was shown to have a pooled sensitivity of 85% (95% confidence interval [CI], 84%–86%) and pooled specificity of 98% (95% CI, 97%–99%) for diagnosing solid pancreatic neoplasms.[12] The overall morbidity associated with EUS is <1% with the risk of adverse events being comparable with that of diagnostic endoscopy.[13,14]

Despite the widespread use of EUS-FNA in diagnosing solid pancreatic neoplasms and the standardized nomenclature for pancreaticobiliary cytology established by the Papanicolaou Society of Cytopathology[15] (Supplementary Table 1), the interobserver agreement among cytopathologists evaluating the acquired tissue specimen remains to be thoroughly assessed.[16,17] In a pilot study, we showed that the interobserver agreement among cytopathologists for solid pancreatic EUS-FNA specimens was moderate ($\kappa = 0.45$; 95% CI, 0.4–0.49) for the final cytologic diagnosis with minimal improvement when suspicious and malignant diagnoses were combined ($\kappa = 0.54$; 95% CI, 0.49–0.6).[15,18] Interobserver agreement was evaluated through the use of a novel standardized scoring tool to assess individual EUS-FNA slides and final cytologic diagnosis based on predefined quantity and quality measures. In this study, the final clinical diagnosis of malignancy was found to be the strongest predictor of agreement (odds ratio, 3.99; 95% CI, 1.52–10.49).[18]

Interobserver agreement among pathologists, however, has been more rigorously assessed in other areas of gastroenterology including inflammatory bowel disease, colorectal polyps, and Barrett's esophagus.[19–22] In Barrett's esophagus, multiple studies have demonstrated the significant variability among pathologists in diagnosing dysplasia.[23–25] Based on these results, guidelines and recent quality indicator documents recommend that the diagnosis of Barrett's esophagus with dysplasia of any grade should be confirmed by an expert pathologist.[22,26,27]

Similarly, an accurate and reproducible diagnosis is critical for the appropriate and timely management of patients with solid pancreatic lesions. With this background, the primary aim of this multicenter validation study was to assess interobserver variability among cytopathologists in evaluating EUS-FNA specimens of solid pancreatic lesions for both overall cytologic diagnosis and individual quantitative and qualitative specimen-associated parameters using a novel standardized scoring system. The secondary aim was to evaluate clinical and EUS parameters as predictors of agreement among cytopathologists.

Methods

Study Design

This study included cytopathologists at 5 tertiary care referral centers in the United States. Approval for the study was obtained from the Institutional Review Board and Human Research Protection office at the University of Colorado Anschutz Medical Center.

Standardized Cytology Scoring Tool

This study was conducted in 2 phases. During phase 1 of the study, a consensus meeting was held with 3 experienced pathologists (with subspecialty board certification in cytopathology) at the University of Colorado. During this meeting, the criteria for assessment of quantity and quality measures were refined using a previously described and validated scoring tool (Table 1).[18] This tool was used to assess each pass for the quantity of nucleated and diagnostic cells present and for quality measures that could limit the cytologic diagnosis, such as obscuring blood, gastrointestinal contaminant, and preparation and staining artifacts (Supplementary Figure 1).[18,28–30] Diagnostic categories were assigned for each pass and for the overall case and included the following categories: insufficient for diagnosis, benign, atypical, suspicious for malignancy/neoplasm, neoplasm, and malignant (Figure 1). Cells of pancreatic origin (acinar, ductal, islet cells) were defined as diagnostic cells, and included both benign and malignant cells. Cells from peripheral blood or gastrointestinal contaminant were not considered as diagnostic cells. The quality measure for obscuring blood referred to the presence or absence of blood clot from within the FNA needle that entrapped and obscured diagnostic cells.