Research Article

A Comprehensive Study of Telecytology Using Robotic Digital Microscope and Single Z-Stack Digital Scan for Fine-Needle Aspiration-Rapid On-Site Evaluation

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Abstract

Background: The current technology for remote assessment of fine-needle aspiration-rapid on-site evaluation (FNA-ROSE) is limited. Recent advances may provide solutions. This study compared the performance of VisionTek digital microscope (VDM) (Sakura, Japan) and Hamamatsu NanoZoomer C9600-12 single Z-stack digital scan (SZDS) to conventional light microscopy (CLM) for FNA-ROSE. **Methods:** We assembled sixty FNA cases from the thyroid (n = 16), lymph node (n = 16), pancreas (n = 9), head and neck (n = 9), salivary gland (n = 5), lung (n = 4), and rectum (n = 1) based on a single institution's routine workflow. One Diff-Quik-stained slide was selected for each case. Two board-certified cytopathologists independently evaluated the cases using VDM, SZDS, and CLM. A "washout" period of at least 14 days was placed between the reviews. The results were categorized into satisfactory versus unsatisfactory for adequacy assessment (AA) and unsatisfactory, benign, atypical, suspicious, and malignant for preliminary diagnosis (PD). **Results:** For AA, the Cohen's kappa statistics (CKS) scores of intermodality agreement (IMA) were 0.74–0.94 (CLM vs. VDM) and 0.86–1 (CLM vs. SZDS). The discordant rates of IMA were 3.3% (4/120) for VDM versus CLM, and 1.7% (2/120) for SZDS versus CLM. For PD, the CKS scores of IMA ranged 0.7–0.93. The overall discordant rates of IMA were 15% (18/120) for CLM versus VDM and 10.8% (13/120) for CLM versus SZDS. The discordant rates of IMA with 2 or higher degrees were 5.8% (7/120) for CLM versus VDM and 1.7% (2/120) for CLM versus SZDS. The average time spent per slide was 270 s for VDM, significantly longer than that for CLM (113 s) or for SZDS (122 s). **Conclusions:** Our data demonstrate that both VDM and SZDS are suitable to provide AA and reasonable PD evaluation. VDM, however, has a significantly longer turnaround time and worse diagnostic performance. The study demonstrates both the potentials and challenges of using VDM and SZDS for FNA-ROSE.

Keywords: Adequacy assessment, Cohen's kappa statistics, conventional light microscopy, fine-needle aspiration-rapid on-site evaluation, intermodality agreement, NanoZoomer, preliminary diagnosis, single Z-stack digital scan, Telecytology, VisionTek digital microscope

Introduction

Given the increasing utilization of cytopathology as a way of obtaining a biopsy, fine-needle aspiration-rapid onsite evaluation (FNA-ROSE) has become a rate-limiting step in the whole process. A well-executed FNA-ROSE is an important quality control step and can significantly impact the diagnostic quality of the obtained biopsy material.[1] Given the dispersed nature of FNA service, many institutions employ some form of telecytology to facilitate FNA-ROSE. One of the most frequently used platforms is a webcam-based solution such as the NetCam (Olympus, Japan). However, most solutions have poor image quality and do not allow the cytopathologist to control the examination process through "driving." Robotic digital microscopes and whole-slide images overcome these limitations by offering direct region of interest manipulation through mechanical or electronic means. The image qualities are also higher through digital image process and more robust sensors.[2] Here, we explore the performance of using a robotic

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digital microscope (VisionTek digital microscope [VDM] M6) and single Z-stack digital scan (SZDS) as a possible substitute for FNA-ROSE.

Methods

Specimen collection

Based on the daily workflow of a single institution and College of American Pathologist guideline, we created a panel of sixty cases from the thyroid (n = 16), lymph node (n = 16), pancreas (n = 9), head and neck (n = 9), salivary gland (n = 5), lung (n = 4), and rectum (n = 1). For the purpose of the study, each case was consisted of a single representative slide prepared with Diff-Quik and the entire panel was composed of diverse set of sites, organs, and original diagnoses. Each case contained a brief clinical history, specimen source, and preparation method. The cases were randomized and distributed in batches of four. All cases had been blindly and independently assessed for preliminary diagnosis (PD) and turnaround time by two board-certified cytopathologists (arbitrarily designated as A and B). The adequacy assessments (AAs) were obtained by categorizing the results into satisfactory versus unsatisfactory. The preliminary diagnoses were categorized into unsatisfactory, benign, atypical, suspicious, and malignant. For example, a result of pleomorphic adenoma would be categorized as satisfactory for AA and benign for PD. Cases with lymphocytes and cannot exclude lymphoma without ancillary studies were categorized as satisfactory for adequacy assessment and atypical for diagnostic evaluation. All statistical data were processed by Microsoft Excel 2016 and analyzed using Python scikit-learn 0.19.2.

Instruments and image acquisition

We used three different types of assessment methods: conventional light microscopy (CLM) with glass slides, VDM M6 with glass slides, and SZDS of glass slides produced by Hamamatsu NanoZoomer C9600-12. For CLM, the cytopathologists used their accustomed microscopes (Olympus BX series). For VDM, we used the manufacturer's software and adjusted the gamma setting of the VDM software to "2" to optimize image quality for Diff-Quik stain per the instrument manufacturer [Figure 1]. Still poorly understood, gamma adjustment of digital images brings out more information by enhancing "contrast."[3] For the SZDS, we used the NDP.view2 (Hamamatsu Photonics, Japan) software and viewed the digital slides on a standard "office-grade" LCD monitor with 1080p resolution and 24-bit color. A washout period of 2 weeks or more was placed between each method for each cytopathologist.

Results

Table 1 contains all the detailed results from AA and PD between CLM, VDM, and SZDS from the two cytopathologists.

Adequacy evaluation

For each case, the adequacy was evaluated into either satisfactory or unsatisfactory category, and the Cohen's kappa statistics (CKS) scores were calculated [Tables 2 and 3].

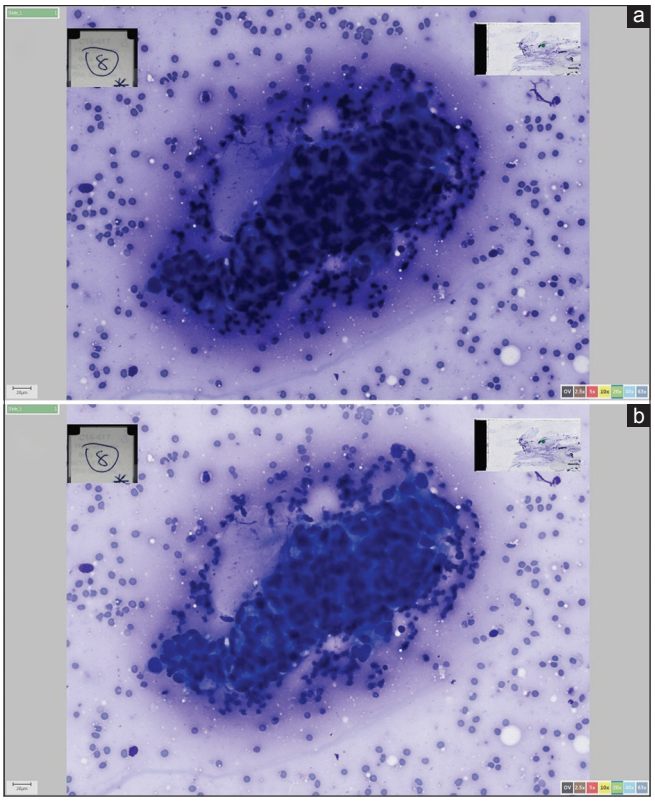

Figure 1: Pancreatic adenocarcinoma displayed on VisionTek software under default image quality settings (a). The same region after adjusting gamma to "2" (b)

For interobserver agreement (IOA), CKS score for CLM was 0.74 with 4 instances of disagreements (lymph node ×3 and pancreas ×1). CKS score for VDM was 0.58 with 6 instances of disagreements (thyroid ×2, lymph node ×3, and pancreas ×1). CKS score for SZDS was 0.74 with 4 instances of disagreements (thyroid ×1, lymph node ×2, and pancreas ×1).

For intermodality agreement (IMA), cytopathologist A achieved higher CKS scores (0.94 and 1) than cytopathologist B (0.74 and 0.86) for both CLM versus VDM and CLM versus SZDS, respectively. For cytopathologist A, only one instance of disagreement occurred on a lymph node specimen for CLM versus VDM and no disagreement occurred for CLM versus SZDS. Cytopathologist B had three instances of disagreement (thyroid ×2 and lymph node ×1) on CLM versus VDM and two instances of disagreement (thyroid ×1 and lymph node ×1) on CLM versus SZDS.

Preliminary diagnostic evaluation

Preliminary diagnoses were categorized into five categories including unsatisfactory, benign, atypical, suspicious, and malignant. The CKS scores were calculated [Tables 2 and 3].

For IOA, CKS score for CLM was 0.67 with 13 disagreements including 2 head and neck specimens (2 malignant vs. atypical), 4 lymph node specimens (1 suspicious vs. malignant and 3 unsatisfactory vs. benign), 2 pancreas specimens (1

Table 1: All results from cytopathologists, adequacy assessment, preliminary diagnosis, conventional light microscopy VisionTek digital microscope, and single Z-stack digital scan

Case	Location	Cytopathologist A						Cytopathologist B					
		Adequacy assessment			Preliminary diagnosis			Adequacy assessment			Preliminary diagnosis		
		CLM	VDM	SZDS	CLM	VDM	SZDS	CLM	VDM	SZDS	CLM	VDM	SZDS
1	Head and neck	sat	sat	sat	malig	malig	susp	sat	sat	sat	malig	malig	malig
2	Head and neck	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
3	Head and neck	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat
4	Head and neck	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	atypical	benign
5	Head and neck	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	malig	benign
6	Head and neck	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
7	Head and neck	sat	sat	sat	atypical	atypical	atypical	sat	sat	sat	malig	malig	susp
8	Head and neck	sat	sat	sat	atypical	atypical	atypical	sat	sat	sat	malig	malig	malig
9	Head and neck	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
10	Lung	sat	sat	sat	malig	susp	malig	sat	sat	sat	malig	malig	malig
11	Lung	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
12	Lung	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
13	Lung	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
14	Lymph node	sat	sat	sat	malig	benign	malig	sat	sat	sat	malig	malig	malig
15	Lymph node	sat	sat	sat	malig	susp	malig	sat	sat	sat	malig	malig	malig
16	Lymph node	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
17	Lymph node	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
18	Lymph node	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
19	Lymph node	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
20	Lymph node	sat	sat	sat	malig	susp	malig	sat	sat	sat	malig	malig	malig
21	Lymph node	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat
22	Lymph node	sat	sat	sat	malig	malig	malig	sat	sat	sat	susp	benign	malig
23	Lymph node	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat
24	Lymph node	sat	unsat	sat	benign	unsat	benign	unsat	sat	sat	unsat	atypical	benign
25	Lymph node	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
26	Lymph node	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
27	Lymph node	unsat	unsat	unsat	unsat	unsat	unsat	sat	sat	sat	benign	benign	benign
28	Lymph node	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
29	Lymph node	unsat	unsat	unsat	unsat	unsat	unsat	sat	sat	sat	benign	benign	benign
30	Other	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
31	Pancreas	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	atypical	malig
32	Pancreas	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
33	Pancreas	sat	sat	sat	susp	susp	susp	sat	sat	sat	malig	malig	susp
34	Pancreas	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
35	Pancreas	sat	sat	sat	malig	susp	susp	sat	sat	sat	malig	benign	malig
36	Pancreas	unsat	unsat	unsat	unsat	unsat	unsat	sat	sat	sat	benign	benign	susp
37	Pancreas	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
38	Pancreas	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
39	Pancreas	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
40	Salivary gland	sat	sat	sat	benign	benign	benign	sat	sat	sat	atypical	benign	benign
41	Salivary gland	sat	sat	sat	benign	benign	benign	sat	sat	sat	atypical	susp	susp
42	Salivary gland	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
43	Salivary gland	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	susp	malig
44	Salivary gland	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
45	Thyroid	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
46	Thyroid	sat	sat	sat	benign	benign	susp	sat	sat	sat	susp	benign	atypical
47	Thyroid	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
48	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	sat	susp	susp	susp
49	Thyroid	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig
50	Thyroid	sat	sat	sat	malig	malig	malig	sat	sat	sat	malig	malig	malig

Contd...

Table 1: Contd....

Case	Location	Cytopathologist A						Cytopathologist B					
		Adequacy assessment			Preliminary diagnosis			Adequacy assessment			Preliminary diagnosis		
		CLM	VDM	SZDS	CLM	VDM	SZDS	CLM	VDM	SZDS	CLM	VDM	SZDS
51	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
52	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
53	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	unsat	benign	benign	unsat
54	Thyroid	unsat	unsat	unsat	unsat	unsat	unsat	unsat	sat	unsat	unsat	benign	unsat
55	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	sat	atypical	atypical	susp
56	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign
57	Thyroid	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat
58	Thyroid	unsat	unsat	unsat	unsat	unsat	unsat	unsat	sat	unsat	unsat	benign	unsat
59	Thyroid	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat	unsat
60	Thyroid	sat	sat	sat	benign	benign	benign	sat	sat	sat	benign	benign	benign

Sat: Satisfactory, unsat: Unsatisfactory, susp: Suspicious, malig: Malignant, red: Interobserver disagreement, gray: Intermodality disagreement, CLM: Conventional light microscopy, SZDS: Single Z-stack digital scan, VDM: VisionTek digital microscope

Table 2: Concordance rates and Cohen's kappa statistics scores for interobserver agreement

	Adequacy assessment*	Preliminary diagnosis**
CLM	4/0.74***	2/13/0.67****
VDM	6/0.58	9/22/0.47
SZDS	4/0.74	5/12/0.70

*Limited to satisfactory versus unsatisfactory, **Categories includes unsatisfactory, benign, atypical, suspicious, and malignant, ***Instances of disagreement/CKS score, ****Instances of disagreement with two or higher degrees of discordance/total instances of disagreements/CKS scores. CKS: Cohen's kappa statistics, CLM: Conventional light microscopy, SZDS: Single Z-stack digital scan, VDM: VisionTek digital microscope

malignant vs. suspicious and 1 unsatisfactory vs. benign), 2 salivary gland specimens (2 atypical vs. benign), and 3 thyroid specimens (2 suspicious vs. benign and 1 atypical vs. benign). Two disagreements (2/13) had two or more degrees of discordance. The CKS score for VDM was 0.47 with 22 disagreements including 4 head and neck specimens (1 malignant vs. benign, 2 malignant vs. atypical, and 1 atypical vs. benign), 1 lung specimen (malignant vs. suspicious), 7 lymph node specimens (2 malignant vs. benign, 2 suspicious vs. malignant, 1 atypical vs. unsatisfactory, and 2 benign vs. unsatisfactory), 4 pancreas specimens (1 suspicious vs. benign, 1 malignant vs. atypical, 1 malignant vs. suspicious, and 1 benign vs. unsatisfactory), 2 salivary gland specimens (1 suspicious vs. benign and 1 malignant vs. suspicious), and 4 thyroid specimens (1 suspicious vs. benign, 2 benign vs. unsatisfactory, and 1 atypical vs. benign). Nine disagreements (9/22) had two or more degrees of discordance. The CKS score for SZDS was 0.70 with 12 disagreements including 3 head and neck specimens (1 malignant vs. atypical, 1 malignant vs. suspicious, and 1 suspicious vs. atypical), 2 lymph node specimens (both benign vs. unsatisfactory), 2 pancreas specimens (1 suspicious vs. unsatisfactory and 1 malignant vs. suspicious), 1 salivary gland specimen (suspicious vs. benign), and 4 thyroid specimens (2 suspicious vs. benign, 1 suspicious vs. atypical, and 1 benign vs. unsatisfactory). Five disagreements (5/12) had two or more degrees of discordance.

For intermodal agreement, CKS scores ranged from 0.7 to 0.93. Cytopathologist A had 6 instances (CKS score 0.85) of disagreements for CLM versus VDM including 1 lung specimen (malignant vs. suspicious), 4 lymph node specimens (1 malignant vs. benign, 2 malignant vs. suspicious, and 1 benign vs. unsatisfactory), and 1 pancreas specimen (malignant vs. suspicious). One disagreement had two degrees of discordance. There were 3 instances (CKS score 0.93) of disagreements for CLM versus SZDS including 1 head and neck specimen (malignant vs. suspicious), 1 pancreas case (malignant vs. suspicious), and 1 thyroid specimen (suspicious vs. benign). One disagreement (1/3) had two degrees of discordance. For cytopathologist B, there were 12 instances (CKS score 0.70) of disagreements for CLM versus VDM including 2 head and neck specimens (1 malignant vs. benign and 1 atypical vs. benign), 2 lymph node specimens (1 suspicious vs. benign and 1 atypical vs. unsatisfactory), 2 pancreas specimens (1 malignant vs. benign and 1 malignant vs. atypical), 3 salivary gland specimens (1 malignant vs. suspicious, 1 suspicious vs. atypical, and 1 atypical vs. benign), and 3 thyroid specimens (1 suspicious vs. benign and 2 benign vs. unsatisfactory). Six disagreements (6/12) had two or greater degrees of discordance. There were 10 disagreements (CKS score 0.75) for CLM versus SZDS including 1 head and neck specimen (malignant vs. suspicious), 2 lymph node specimens (1 malignant vs. suspicious and 1 benign vs. unsatisfactory), 2 pancreas specimens (1 suspicious vs. benign and 1 malignant vs. suspicious), 2 salivary gland specimens (1 suspicious vs. atypical and 1 atypical vs. benign), and 3 thyroid specimens (2 suspicious vs. atypical and 1 benign vs. unsatisfactory). Only 1 disagreement (1/10) had two degrees of discordance.

Turnaround time analysis

The average time spent per slide was 270 s for VDM (range: 60–1200 s), 113 s for CLM (range: 60–600 s), and 122 s for

Table 3: Concordance rate and Cohen's kappa statistics scores for intermodality agreement

	Adequacy assessment*		Preliminary diagnosis**	
	Cytopathologist A	Cytopathologist B	Cytopathologist A	Cytopathologist B
CLM versus VDM	1/0.94***	3/0.74***	1/6/0.85****	6/12/0.7****
CLM versus SZDS	0/1	2/0.86	1/3/0.93	1/10/0.75

*Limited to satisfactory versus unsatisfactory, **Categories includes unsatisfactory, benign, atypical, suspicious, and malignant, ***Instances of disagreement/CKS score, ****Instances of disagreement with two or higher degrees of discordance/total instances of disagreements/CKS scores. CKS: Cohen's kappa statistics, CLM: Conventional light microscopy, SZDS: Single Z-stack digital scan, VDM: VisionTek digital microscope

SZDS (range: 60–300 s). Statistical analysis demonstrated significant statistical difference ($P < 0.05$) between the turnaround time from VDM and the time from CLM or SZDS.

Conclusions

The gold standard for FNA-ROSE involves direct assessment of the cytologic preparation on glass slides by cytopathologists using a microscope. However, due to the increased utilization and dispersion of clinical services, many cytology departments face the pressure of meeting the demand for multiple concurrent FNA-ROSEs at different locations. While solutions such as NetCam or its variant of "webcam-" based system are easy to implement and maintain, in practice, they are unsatisfactory due to the inability to "drive" the slide and poor image quality. Based on our experience, most cytopathologists will only depend on the NetCam solution for procedures such as thyroid AA where a PD is not absolutely essential. In most instances, on-site assessment using a traditional microscope is preferred to render a reliable PD.

Although typically expensive, systems such as the VDM or rapidly scanned digital slides can alleviate the shortcomings of "webcam-" type solutions. Our data show that both solutions under ideal conditions have the potential to be just as accurate as the direct examination of the glass slides under CLM. The solutions achieve this feat by increasing image quality through digital image process, better sensors, and the ability to "drive" the slide. VDM has the advantage of being accepted as a solution for the remotely controlled frozen section at many institutions.[4] Rapid digital slide is also being evaluated as a possible alternative.[5]

Based on our data, it appears that VDM and SZDS each offers unique advantages and disadvantages. Because VDM is fundamentally a remotely controlled microscope looking at glass slides, theoretically it should offer superior image quality and flexibility comparable to CLM. Indeed, even the image quality issue presented by the Diff-Quik stain can be alleviated with the correct gamma setting per manufacturer's recommendation [Figure 1]. In addition, the "Z-stack" option is also present since the ability to adjust focal plane is a part of the control offered by the software interface. However, using the system remotely can be a slightly frustrating experience due to the subjective "lag" feeling caused by the delay between the time the cytopathologist executes a command and the time when it is carried out by the instrument. This "lag" can be appreciated by the vastly different turnaround time between VDM and SZDS.

SZDS suffers less from the "lag" because the images have already been captured/stored on the computer/network. However, a significant downside is that unlike VDM or CLM, the images are not immediately available.[6] Moreover, while the Z-stack option is available through some scanners, it may be impractical to implement in the FNA-ROSE setting as the slides take longer to scan and the storage requirements are higher.[7] SZDS, however, can be rapidly scanned and takes up significantly less storage space than Z-stack scanning. However, without Z-stack, there are concerns for the proper visualization of three-dimensional features prevalent in many cytology specimens.[6] It appears that our data suggest that the lack of Z-stack does not significantly impact diagnostic performance, and this finding has been collaborated in the literature previously.[7] Moreover, the advances in slide scanning technology have improved known issues such as uniformity of plane of focus, data storage requirement, and image quality.[8] The sufficiency of improvement is supported by the fact that a small number of institutions have started to pioneer on-site slide scanning for the frozen section as an alternative for the remotely controlled robotic microscope.[4]

It appears that both VDM and SZDS can potentially produce less reliable preliminary diagnosis. Cytopathology inherently suffers from it due to the use of subjective morphologic features and sampling errors.[9,10] The problems appear to exacerbate on the VDM when used for diagnostic evaluation compared to CLM and SZDS, even with help from "Z-stack." The potential culprit includes limitation of the field of view and the persistence of image quality problems despite enhancement by software [Figure 1]. In addition, cytopathologist B is known to have less exposure to digital pathology technologies, which can partially explain the noticeable decrease in his/her IMA when compared to cytopathologist A. Furthermore, the increase of interobserver disagreements with two or higher degrees of discordance with VDM and SZDS compared to CLM suggests that experience in microscopic workflow does not always translate into the same interpretative performance with newer digital modality, a finding that has been previously reported.[11]

Our study, to the best of our knowledge, is the first attempt to have a side-by-side performance comparison between glass slide, robotic microscope, and single Z-stack digital slide format for FNA-ROSE. Even though we carefully controlled the variables by blinding the cytopathologists to the diagnoses

and applied adequate "washout" period between the different assessment methods, some "carry-over" memory of the cases was inevitable and could have a confounding impact on the data. In addition, while the one slide per case format fits the need of the study, it does not simulate many FNA-ROSE scenarios where evaluating multiple smear slides is necessary, and therefore, performing telecytology using either technology may be time-consuming and difficult. Nonetheless, our data can serve as a guide for possible improvement in the technology for FNA-ROSE.

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Conflicts of interest

There are no conflicts of interest.

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