ORIGINAL ARTICLE

A COMPARATIVE ANALYSIS OF DIGITAL CYTOPATHOLOGY AND CONVENTIONAL LIGHT MICROSCOPY EVALUATION OF THYROID FINE NEEDLE ASPIRATION CYTOLOGY: FOCUSING ON INDETERMINATE CATEGORIES

Tiroid İnce İğne Aspirasyon Sitolojisinin Dijital Sitopatoloji ve Konvansiyonel Işık Mikroskobu ile Değerlendirilmesinin Karşılaştırmalı Analizi: Belirsiz Kategorilere Odaklanarak

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ABSTRACT

Objective: Digital pathology has rapidly evolved with the advent of Whole Slide Imaging (WSI); however, its diagnostic use in cytopathology remains limited due to technical challenges. This study aimed to evaluate the diagnostic concordance between digital cytopathology and conventional light microscopy (LM) in thyroid fine needle aspiration (FNA) cytology, focusing on indeterminate categories according to the Bethesda System for Reporting Thyroid Cytopathology.

Material and Methods: Sixty thyroid FNA cases, excluding non-diagnostic ones, signed out by cytopathologist 1 (CP1) in 2023 at Hacettepe University Faculty of Medicine Department of Pathology were retrieved from the archives. After the cases were reviewed by an independent cytopathologist 2 (CP2), six cases were excluded due to poor slide quality. For the remaining 54 cases, the most representative 2 to 3 slides were selected and scanned using Philips IntelliSite Pathology Solution Systems® in 1 focal Z-plane, at x20 magnification. CP1 re-evaluated the selected slides via WSI, and diagnostic agreement between digital cytopathology and LM was assessed by Cohen's kappa statistics.

Results: Of the 54 cases, the initial LM diagnoses were: 15 benign, 18 atypia of undetermined significance (AUS), 3 follicular neoplasia, 8 suspicious for malignancy (SM), and 10 malignant. After WSI review, 17 cases (31.4%) showed diagnostic changes, mostly in the AUS and SM categories. The overall diagnostic concordance showed a moderate level of agreement (kappa=0.584). Among the discrepant cases, 10 were attributed to intraobserver variability, while 7 were due to digital imaging limitations, such as thick cell clusters, obscuring material, and unfamiliar virtual slide navigation.

Conclusion: Digital cytopathology demonstrates acceptable concordance with LM. In digital cytopathology, the main challenges are the greater scanning area of the glass slides, obscuring material, and variable smear thickness with 3-dimensional cell groups. Continued improvements in WSI technology and pathologist familiarity with digital tools are essential for broader adoption.

Keywords: *Whole Slide Imaging; Digital; Cytopathology; Thyroid*

ÖZET

Amaç: Dijital patoloji, Tüm Slayt Görüntüleme (Whole Slide Imaging - WSI) teknolojisinin gelişmesiyle hızla ilerlemiştir; ancak sitopatolojide tanısal amaçlı kullanımı, teknik zorluklar nedeniyle sınırlı kalmaktadır. Bu çalışmada, tiroid ince iğne aspirasyon (İİA) sitolojisinde dijital sitopatoloji ile ışık mikroskobu (LM) arasında tanısal uyumun, özellikle belirsiz kategorilere odaklanılarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Hacettepe Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı'nda 2023 yılında sitopatolog 1 (CP1) tarafından raporlanmış 60 tiroid İİA vakası (non-diagnostik olanlar hariç) arşivden çıkarıldı. Bağımsız bir sitopatolog (CP2) tarafından olgular tekrar değerlendirildikten sonra, preparat kalitesi düşük olan 6 vaka dışlandı. Elli dört vakaya ait 2 ila 3 adet temsili nitelikte preparat seçildi. Seçilen slaytlar Philips IntelliSite® cihazında tek düzlemde, x20 büyütmede tarandı. CP1, seçilen preparatları WSI üzerinden yeniden değerlendirdi ve LM ile WSI tanıları arasındaki uyum Cohen's kappa istatistiği ile analiz edildi.

Bulgular: Elli dört vakanın LM ile konulan ilk tanıları şöyleydi: 15 benign, 18 önemi belirsiz atipi (AUS), 3 folliküler neoplazi, 8 malignite şüphesi (SM) ve 10 malign. WSI ile tekrar değerlendirildikten sonra 17 vakada (%31,4) tanı değişikliği gözlendi. En fazla uyumsuzluk AUS ve SM kategorilerinde görüldü. Genel tanısal uyum orta düzeyde olup kappa değeri 0,584 olarak bulundu. Uyumsuz 17 vakanın 10'u gözlemci içi yorum farklılığına, 7'si ise dijital görüntüleme ile ilgili sınırlamalara (örneğin kalın hücre grupları, örtücü materyal, dijital slayt kullanımına aşina olmama) bağlı olarak değerlendirildi.

Sonuç: Tiroid sitopatolojisinde WSI ve LM ile konulan tanılar kabul edilebilir düzeyde bir uyum göstermektedir. WSI teknolojisinin gelişmesi ve patologların dijital araçlara daha fazla aşinalık kazanması, bu yöntemin daha yaygın olarak kullanılmasını destekleyecektir.

Anahtar Kelimeler: *Tüm Slayt Görüntüleme; Dijital; Sitopatoloji; Tiroid*

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INTRODUCTION

Pathology has significantly advanced through the integration of innovative digital technologies, transforming traditional diagnostic methods into more efficient and precise processes. Whole Slide Imaging (WSI), a key component of digital pathology, enables the conversion of entire glass slides into high-resolution digital images, also known as virtual slides or e-slides (1). WSI was first developed in 1999, and since that time, its use for surgical pathology has increased rapidly. Whole slide images acquired with a 20x scan typically have a resolution of 0.25 µm/pixel, which is comparable to examining a glass slide with light microscopy (LM). This technology eliminates the need for a physical microscope when allowing the user to access all regions of the slide, focus at different magnifications, and annotate areas of the image that are of particular interest (2). Its increasing adoption prompted the College of American Pathologists Pathology and Laboratory Quality Center to publish the first set of clinical diagnosis validation guidelines for WSI systems (3). These standards ensure that digital pathology workflows are reliable, reproducible, and safe for patient care.

However, its adoption for routine diagnostic cytopathology has been limited for several reasons. High volume of cytopathology specimens, the greater scanning area of the glass slides, obscuring material, and variable smear thickness with 3-dimensional cell groups, particularly for conventional smear preparations, offer unique challenges (3,4).

Current WSI technology enables depth of focus by scanning a slide at multiple focal planes, which are then merged to create a composite z-stack image. However, Z-stack has different challenges, including enormous image file size, which leads to increased slide scanning time, slower slide review, and difficulties with archiving (5). These technical constraints have hindered the widespread use of WSI in primary cytological diagnosis. Nonetheless, WSI has been increasingly used in education, second opinion consultation, research activity, and proficiency testing, because of its advantages of easy portability and sharing of digital slides (6,7).

The cytology literature on using WSI in diagnostic cytological applications is scarce. However, with the increasing potential of WSI for replacing conventional LM, many studies have been published exploring the concordance between these two modalities.

Our study aimed to determine the diagnostic concordance of thyroid fine needle aspiration cytology between digital cytopathology and conventional LM. For thyroid fine-needle aspiration (FNA) cytology, “The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)” has been in use since 2010 (8). This system presents six diagnostic categories, which include three indeterminate categories: "Atypia of Undetermined Significance" (AUS), "Follicular Neoplasm" (FN), and "Suspicious for Malignancy" (SM), in addition to the non-diagnostic, benign, and malignant categories. We aimed to focus particularly on indeterminate categories according to TBSRTC.

MATERIAL AND METHODS

The study was approved by the Hacettepe University Ethics Committee for Health Sciences Research with the approval number SBA 25/540, date: 24.06.2025.

Thyroid fine needle aspiration (FNA) cytology cases, which were signed out on standard LM by cytopathologist 1 (CP1) in 2023, were retrieved from the Hacettepe University Faculty of Medicine Department of Pathology electronic medical record system. The “non-diagnostic” cases were excluded. A total of sixty cases, representing all diagnostic categories but predominantly belonging to the indeterminate category, were identified and retrieved from the cytopathology archives. Each case had 4 to 10 conventional smear slides stained with May-Grünwald Giemsa (MGG) and Papanicolau (PAP). All thyroid FNA slides of these 60 cases were reviewed by an independent cytopathologist 2 (CP2). After reviewing, 6 cases were excluded because of poor quality preparations, due to contributing factors like hypocellularity, the presence of air bubbles, uncovered glass slides, and broken slides. For the remaining 54 cases, the most cellular and representative 2 or 3 FNA slides (PAP and/or MGG stained) were selected for each case, ensuring a comprehensive representation. The selected representative slides of 54 cases were scanned using the Philips IntelliSite Pathology Solution Systems®, in 1 focal Z-plane at x20 magnification. CP1, who had originally signed out the cases, had a

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washout period of at least 6 months between the initial sign-out and the viewing of whole slide images (WSI) on a digital platform. CP1 had no prior experience in digital cytopathology. The WSI were assessed blinded to the initial diagnoses and clinical/imaging findings, and one of the following diagnoses was assigned according to 'The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), 3rd edition': Benign, AUS (Atypia of undetermined significance), FN (follicular neoplasm), SM (suspicious for malignancy), M (malignant).

The initial diagnoses given by standard LM were compared with the WSI diagnoses. Diagnostic agreement was determined across each category and three risk groups: benign, intermediate, and high risk. The benign group included benign cytologic cases, the intermediate risk group included AUS and FN cases, and the high-risk group included the SM and malignant cases. The concordance was calculated using Cohen's kappa statistics. Agreement was categorized as follows: 0 to 0.2, slight; 0.21 to 0.4, fair; 0.41 to 0.6, moderate; 0.61 to 0.8, substantial; and 0.81 to 1, almost perfect.

RESULTS

According to TBSRTC, the initial sign-out diagnoses for the 54 selected cases were as follows: Benign, 15 (27.7%); Atypia of Undetermined Significance (AUS), 18 (33.3%); Follicular Neoplasia (FN), 3 (5.5%); Suspicious for Malignancy (SM), 8 (14.8%); and Malignant, 10 (18.5%) (shown in Table 1).

After reviewing the cases on WSI, the diagnoses of 17 (31.4%) cases changed, and 37 (68.5%) remained the same. The initial standard LM diagnoses and WSI diagnoses after re-evaluation of the selected slides are shown in Table 2.

The highest number of discrepancies occurred in the AUS and SM categories. Of the 18 AUS cases, eight were reclassified. Based on revised interpretations, four cases were downgraded to benign. In two of these, nuclear atypia was attributed to underlying lymphocytic thyroiditis, one to reparative changes, and in the final case, minor nuclear alterations were considered non-significant. The diagnostic category was upgraded in the other four cases, 1 to FN and 3 to SM, due to the difference in the interpretation of microfollicular pattern and/or nuclear atypia. On WSI, the ability to zoom in at magnifications exceeding 400x led to the overinterpretation of nuclear features, as the pathologist was unaccustomed to digital evaluation. Additionally, the absence of a routine clinical diagnostic setting may have contributed to a tendency to assign higher diagnostic categories more readily.

Table 1. Initial diagnoses of thyroid FNA cases according to TBSRTC

The diagnostic category	Number of cases (%)
Benign	15 (27.7%)
AUS	18 (33.3%)
FN	3 (5.5%)
SM	8 (14.8%)
Malignant	10 (18.5%)
Total	54

FNA: Fine needle aspiration, TBSRTC: The Bethesda system for reporting thyroid cytopathology, AUS: Atypia of undetermined significance, FN: Follicular neoplasm, SM: Suspicious for malignancy

Table 2. The comparison of LM and WSI diagnoses of thyroid FNA cases

LM diagnoses	WSI diagnoses				
	Benign	AUS	FN	SM	Malignant
Benign	13	2			
AUS	4	10	1	3	
FN			3		
SM		3		2	3
Malignant				1	9

Abbreviations: LM: Light microscopy, WSI: Whole slide image, FNA: Fine needle aspiration, AUS: Atypia of undetermined significance, FN: Follicular neoplasm, SM: Suspicious for malignancy

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Among the 8 SM cases, 3 were downgraded to AUS and 3 upgraded to the malignant category. In two cases, a few intranuclear pseudoinclusions were missed when reviewing on the WSI and re-categorized as AUS. These two cases were diagnosed as papillary thyroid carcinoma in the follow-up surgical resection. In the other case, blood obscuring the cell groups caused focusing problems, leading to a downgrade in the diagnosis. Three cases were interpreted as malignant. During follow-up, papillary thyroid carcinoma was confirmed in the thyroidectomy specimens of two of these cases. Notably, the clinical management recommendations are the same as lobectomy or near-total thyroidectomy for both categories.

Among the 15 benign cases, 2 were reclassified as AUS, and the others remained the same. One of the discrepant cases had lymphocytic thyroiditis, which can cause nuclear changes and be diagnosed as AUS. And the other one was obscured by blood, which makes it difficult to focus on the cells in WSI.

Among the 10 malignant cases, only 1 was reclassified as SM, and the rest remained the same. For that one case, the cytomorphological features were looking malignant but not specific for primary papillary thyroid carcinoma; a metastatic tumor was considered in the differential diagnosis, and an SM diagnosis was prefered in the review.

Three FN cases were again diagnosed as FN. On follow-up surgical resection, one case was diagnosed as oncocytic adenoma, and one as well-differentiated thyroid carcinoma.

The diagnostic concordance between LM and WSI diagnoses was 0.584 (Cohen's kappa value), indicating a moderate agreement between the two diagnostic methods. After grouping into three diagnostic categories as benign, intermediate risk (AUS and FN), and high risk (SM and malignant), the kappa value was found as 0.684, indicating a substantial agreement.

DISCUSSION

Fine-needle aspiration (FNA) cytology is an essential diagnostic tool for evaluating thyroid nodules, identifying malignancies, and guiding appropriate management. To standardize the reporting of thyroid FNAs, "The Bethesda System for Reporting Thyroid Cytopathology" (TBSRTC) was introduced in 2010, then revised in 2017 and 2023 (8-10). The most recent edition presents six diagnostic categories as follows: non-diagnostic, benign, atypia of undetermined significance (AUS), follicular neoplasm (FN), suspicious for malignancy (SM), and malignant. AUS, FN, and SM are the indeterminate categories in TBSRTC.

Our study investigated diagnostic concordance of thyroid FNA cases across digital cytopathology and routine LM diagnoses, focusing on indeterminate categories.

In digital pathology, Whole Slide Imaging (WSI) is the primary step that enables the conversion of entire glass slides into high-resolution digital images (1). However, in cytopathology, some technical issues, including variable smear thickness with 3-dimensional cell groups or material obscuring the cells, limit its adoption for routine diagnostic purposes (3,4). Current WSI technology aims to overcome this limitation through Z-stacking, which completes multiple scans of a slide at slightly different focal planes and then combined them to form the z-stack final image. However, Z-stacking significantly increases scan time, and comes with larger digital file size that slows down the slide review, and poses difficulties for archiving (5). Literature on the use of WSI in routine diagnostic cytology practice, especially for primary diagnosis, is limited. However, with the increasing potential of WSI for replacing LM, many studies have been published exploring the concordance between these two modalities.

In our study the diagnostic concordance between routine LM and WSI diagnoses indicated a moderate agreement (Cohen's kappa value=0.584). Gerhard et al. reported a moderate agreement between LM and WSI similar to our study (11). And also, several studies and systematic reviews have shown a good overall diagnostic concordance between LM and WSI (12-16).

When we analyzed the discrepancies case by case, the WSI interpretation wasn't the main reason for most of the indeterminate cases, since only minor diagnostic changes had occurred in more unequivocal categories. Among the 17 discrepant cases, 10 of them were mainly due to the intraobserver interpretation variability, rather than digital imaging factors. Intra-interobserver

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variability in assessing indeterminate categories, particularly in AUS category, has been well-known in the literature. Padmanabhan et al. identified the AUS category as the most variable among observers, with only one-third of AUS cases being reclassified into the same category upon reevaluation (17). In contrast, benign and malignant diagnoses demonstrated greater consistency. Sripodok et al. and Słowińska-Klencka et al. both reported fair to poor interobserver agreement for indeterminate categories, emphasizing the significant variability and diagnostic challenges within this category (18,19).

Seven of the 17 discrepant cases were mainly due to factors affected by digital imaging. In two cases, the thick cell groups and obscuring material caused focusing problems; therefore, one benign and one SM case turned out AUS on WSI interpretation. In our study, slides were prepared in the conventional smearing method, which contains thick cell groups and preparation artifacts, and they were scanned in just one plane.

To avoid this problem, liquid-based cytology (LBC) slides, which provide a thin uniform layer of cells on the glass slide could be examined. LBC preparations are more capable for digital cytopathology, as a significant number of studies in this field have been conducted on gynecological cytology specimens prepared using LBC methods (13). On the other hand, the limited focusing capability can be solved with Z-stacking. However, it has its own challenges (20).

The most important challenge with WSI was the longer time during the image download and clarifying the image with the slide movement and zooming in and out. Similar issues with “freezing” or “lock out” of the software were reported in the literature (11,21). These technical issues led to increased evaluation time and screening the entire slide unmethodically, skipping from one cellular area to another. This unmethodical screening of the entire scanned slide caused a few intranuclear pseudoinclusions to be missed in two cases, which were later downgraded from SM to AUS.

In the literature it was also reported that the time to render a diagnosis was longer with WSI than LM. Several studies found statistically significant differences in time spent, increasing with digital cytopathology. The longer time needed for WSI evaluation may be attributed to the speed of the network and computer, as well as the file size. These issues may be alleviated by improving the viewing software, upgraded network and computer capabilities, or new advances in file storage that decrease file size. While some studies, such as Hanna et al., have demonstrated that Z-stacking of representative “Regions of Interest” (ROIs) can overcome focusing problems without the storage burden of entire slide Z-stacks, this approach is highly operator-dependent (13,21-23). Multi-Camera Array Scanner (MCAS), a high-throughput imaging system designed to overcome the limitations of traditional single-objective scanners in digitizing thick (>50 µm) cytopathology specimens. By employing a parallelized architecture consisting of 48 individual image sensors in a 6x8 grid, the system is capable of digitizing the entire volume of three slides in 3D across depths up to 150 µm at cellular resolutions (0.6 µm and 1.2 µm) within minutes (24). Future advancements in digital “fine-focus” (micro-screw) functionalities may provide more efficient solutions for navigating 3D cell groups while maintaining manageable data volumes.

In LM screening, magnification has been changed between 40x, 100x, 200x, and 400x in routine practice. However, in digital pathology, the virtual magnification could be changed to a lower and higher power for screening, such as 320x, 450x, etc. Getting higher magnification than 400x can lead to overinterpreting the minor nuclear changes for unaccustomed eyes. Moreover, users need to become familiar with identifying cellular features in WSIs compared to the LM, which can be linked to color or resolution differences between the two methods. In our study, 3 cases were upgraded from AUS to SM, considering these reasons. It can be hypothesized that with training and exposure to WSI over time, familiarity and confidence will increase. The growing adoption of WSI in pathology and cytology practice underscores the necessity of incorporating digital pathology into residency training programs to ensure competency in this field (25).

The study has several limitations. First, our study was a simulation, and the absence of a real clinical diagnostic setting may have contributed to a tendency to assign higher diagnostic categories more readily. Moreover, the evaluating cytopathologist (CP1) was blinded to

clinical and imaging findings, results of the previous fine-needle aspirations (if present), and any other medical information. And also, CP1 reviewed only the selected slides that CP2 picked.

The absence of Z-stack scanning is an acknowledged limitation of this study. Although digital cytopathology has not yet been firmly integrated into routine diagnostic practice, it is increasingly utilized in education, second opinion consultation, proficiency testing, research activity, and archiving. The main advantages of digital images are easy access to slides "anytime, anywhere", sharing of digital slides, the use of image analysis, and easier archiving (7). With the improvement of the access speed and quality of virtual slides, the diagnostic accuracy and speed will also improve. Negative aspects can be overcome with appropriate scanning parameters, stable computer network connections, user-friendly virtual microscopy software programs, and suitable image archiving systems, as well as developing up-to-date training programs and getting familiar with this technology.

CONCLUSION

This study showed moderate agreement between digital cytopathology using WSI and conventional LM in diagnosing thyroid FNA specimens, especially in indeterminate categories like AUS and SM. Most discrepancies were due to intraobserver variability rather than limitations of digital imaging. However, technical issues such as lack of focal depth, thick smears, and slower navigation did contribute to some diagnostic differences.

While WSI is not yet standard for primary diagnosis, it holds promise—particularly with improvements in slide preparation, Z-stacking, software performance, and user training. Familiarity with digital tools and incorporating WSI into pathology education are key to successful adoption. As technology evolves, digital cytopathology is likely to play an increasingly important role in clinical practice.

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