



VALIDATION OF REMOTE DIGITAL PATHOLOGY FOR PRIMARY DIAGNOSTIC SIGN-OUT USING WHOLE SLIDE IMAGING DURING A PUBLIC HEALTH EMERGENCY.


Dr. Veeravalli Sudheer Kumar*

Assistant Professor, Department of Pathology, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Puducherry - 605502.

ABSTRACT

Remote digital pathology supports the continuation of routine pathology workflows when places are on lockdown. Based on the CLIA rules, pathologists are now required to authenticate patient reports sent by a certified laboratory using electronic methods. During the 2019 pandemic from a novel coronavirus, this guideline might have made pathologists, colleagues and family members vulnerable to infection. Relaxing some of the rules allowed pathologists to work from non-certified locations on pathology samples. Remote microscopic diagnoses are now possible with digital pathology, even though a full confirmation of accuracy has not been documented yet. In order to digitize all the glass slides used for routine clinical diagnosis in many surgical pathology fields, they were scanned using a powerful digital scanner set at a magnification of $\times 40$ (makes each pixel 0.26 micrometers). There were twelve pathologists involved in nine medical specialty areas and they all worked remotely through a safe network connection to review and report complete pathology cases online from different locations. Whole slide images were added to the laboratory information system and examined using a vendor-independent custom whole slide image viewer. Users worked with personal devices (computers and displays of different sizes and resolutions) that were connected to clinician stations inside the organization using a virtual private network. All glass slides were then looked at using a conventional microscope by the pathologists in the official department. It was studied to what degree the key points of reporting—such as primary diagnosis, margin status, lymphovascular or perineural invasion, pathological staging and ancillary test results—were in agreement among the pathologists. Standard digital file size was 1.3 GB, it took an average of 90 seconds to scan a slide and the area of each scanned tissue was 612 mm². Signout sessions presented 108 cases with a total of 254 specimens and 1196 slides. Consistency in findings was strong at 100% for the major categories and 98.8% overall (251 out of 254). The study confirmed that primary diagnostic review and reporting of full pathology cases from remote areas could be done in a public health emergency. We found that the major diagnoses on remote cases were in perfect agreement (100%) between a review of glass slides and a review of digital images. This study using a digital pathology system proved that it can be applied remotely to support the review and reporting of cases, showing it to be operational, effective and user-friendly.

Keywords :- Remote digital pathology, Diagnostic concordance, Whole slide imaging, Public health emergency.

Access this article online		
Home page: https://mcmed.us/about/abs	Quick Response code 	
Received:05.01.2020	Revised:12.01.2020	Accepted:28.01.2020

INTRODUCTION

The main parts of a digital pathology platform are a scanner for whole slides, software to see the images and monitors. Digital pathology makes it easier for

pathologists to review and analyze pathology slides with a digital workflow. With this method, pathologists can review and issue diagnoses in a new way, gain new

knowledge and manage patient specimen slides electronically. It has been shown through many studies that WSIs agree with results from reading traditional slides [1–25]. Studies show that reporting in an anatomic pathology lab can easily include using WSIs. Digital pathology can also assist in creating and improving a digital workflow for pathologists. In specialized cancer centers, experts in different areas of pathology look after the patients. Digital pathology has helped pathologists by making their work easier and saving costs [3]. The law requires that certified laboratory patient reports be checked and authenticated by a pathologist electronically [26]. Yet, when there was a pandemic because of a novel coronavirus, complying with this requirement could endanger both pathologists and their trainees, their relatives and their colleagues. Besides, during a public health crisis, when pathologists are banned from being physically at the workplace either by sickness, quarantine or by order, there may be gaps in patient care and delays in getting reports. Many pathologists have strong remote access (using virtual private networks) through network firewalls, making it possible to access hospital data systems, including laboratory information and medical records, from a distance such as home. Because of this, digital pathology now enables exploring and applying new digital tools for use outside of regular pathology areas. This study examines and confirms the use of a digital pathology system in a major academic institution greatly affected by the COVID-19 pandemic. Glass slides made from both formalin-fixed paraffin-embedded and frozen tissues were scanned and stained with hematoxylin & eosin, immunohistochemical and special stains. There were glass slides used for in-house studies as well as for consulting cases sent by other institutions. The process involves checking glass slides before imaging, using a scanner to create digital images and assuring quality of these images after imaging. A digital file for viewing is made by capturing high-resolution images from every glass slide and merging them to look like seeing a slide and regular glass images under a microscope. A type of software is now available to help pathologists in making diagnoses. Here, whole slide scanners made by several manufacturers and customized viewing software have been added to assist with medical workflows. This study sought to (1) judge if remote digital pathology was workable for routine cases, (2) test how feasible and convenient it was for remote pathologists to review cases and (3) confirm that the system could be trusted for primary pathology diagnosis done remotely.

MATERIAL AND METHODS

An evaluation was done first to check whether the department had everything in place to use remote sign-out. All of the clinical members, faculty and

trainees, were surveyed to obtain their responses. A team chose patient specimens in advance from a prominent tertiary academic cancer center. remote digital sign-out was used for some days when pathologists were working outside of the office. The team performed operations on biopsied, resected and external departmental specimens according to the usual accessioning rules. Each pathologist was given a worklist matching their assigned clinical service day which composed the entire clinical work for the day in their area of expertise. Pathologists looked at and assessed all the slides and various levels from biopsies, immunohistochemical stains and special stains sent with the consultation. The frozen sections were studied and reviewed with the matched frozen section control slides following the department's regular schedule. Another pathologist who was not taking part in the sign-out checked to see that all the cases for each pathologist were put on their respective worklists and were scanned properly. Specimens acquired by the institution itself (known as "in-house") were handled in the same way: accessioned, examined by gross pathology, sectioned into cassettes/blocks, processed, embedded, sliced, stained and covered with cover slips. The study used all patient samples that each pathologist reviewed on their assigned review date. From the time a patient case is accessioned, through processing and distribution of slides, is highlighted in Fig. 1. By using Leica Spectra instruments, staining of slides, mounting and drying the media were all done. Leica Universal Slide racks are used with the Aperio GT450 whole slide scanner. When the staining and coverslipping was done, lab workers then placed the slides on the Aperio GT450 scanner. A native $\times 40$ objective lens was used to scan the sample at $\times 40$ equivalent magnification ($0.26 \mu\text{m}/\text{pixel}$). If the slides for consultation come from external medical centers, the site prepares the slides, ships them to our institution and they are added to our laboratory information system. Every consult slide had a departmental consult barcode applied and they were arranged into Leica Universal Slide racks during the accessioning process. In the pathology accessioning area and histology laboratory, there were places for picking up patient specimens and dropping off the histology slides. The digital scanning team often took racks of consult slides to the quality control and scanning areas. All pathology materials (including containers, blocks, slides) were marked with 2D data-matrix barcodes. The introduction of the glass slide barcode made it possible for the AperioSlide manager database and the laboratory information system (Cerner CoPathPlus) to work together. Images from whole slides were accessed in CoPathPlus through PICSPlus and opened in a special whole slide image viewer. Laboratory slides, belonging to histology or accessioned samples, were all scanned, whether or not they were part of the validation study.

Slides not involved in the study were scanned and analyzed to make sure the GT450 scanner functions properly and to measure its quality.

Control and organization of image scans and the use of WSI Viewers

The software used for whole slide images (WSI) is an official platform that works with all vendors. Per the process for scanning medical institutions, potential clinical samples are scanned digitally and recordings added to the laboratory information system. All pathologists have, for the past three years or more, been using this viewer to analyze both recently scanned and existing WSIs. The case viewer is launched inside the Cerner solution and all stored WSI images are instantly displayed. You can control the way you move using your mouse and your keyboard. Using the web-based viewer means it works in the pathologist's default browser and has fingerprint image previews, slide labels, zoom, pan options and the ability to load various slides together. You can use annotation tools to measure distances, see what you have looked at, view a map with the areas you have looked at, take screenshots and write notes.

Signing out patients with digital or glass slides.

As soon as the scanning of glass slides was done, all WSIs could be found in the laboratory information system in the order of the cases and glass slides. Before a faculty pathologist reviewed them, the trainees (fellows) prepared reports on all the cases. Participants helped manage the cases using both glass and digital slides which helped keep social distancing at the event. Students handled physical slides and was also provided with digital slide access at the same time. After reporting the preliminary information, cases were sent to pathologists for investigation. Pathologists went over each case separately on their screens, doing so remotely and using safe VPN connections and double checking access. Standard workstations used by the hospital (3.2 GHz CPU, 8 GB RAM, 64-bit processor) were connected to remotely through browsers like Google Chrome or Internet Explorer 11. Laboratory information systems allow pathologists to look at requisitions and examine WSIs. Once the digital review was done, the final reports were fed into the system but remained stored locally. Checking the slides again was performed in-person using Olympus BX series light microscopes, imitating the original digital review. Digital and glass reviews were done quickly (mean time of 2 days) to keep the reporting turnaround time under control. Routine workflows were used to report, allowing for free-text, template and synoptic formats. All identified prior pathology information and WSIs were at hand before the sign-out decisions. Metrics were gathered after every

session. Remote monitoring equipment gathered info on the computer's hardware, network internet speed, what browser the customer used, monitor dimensions and resolution, CPU and RAM. Problems related to technology were listed. All participating pathologists were given a questionnaire after having completed the signout session.

Concordance

A "read" describes a result after a diagnosis is made for a specimen section; a case may have many specimen sections and lab slides. With each completed signout, we logged the subspecialty, type of specimen (biopsy, resection, in-house or consultation), organ site, number of slides and any extra tests, called ancillary tests (for example, H&E recuts, immunohistochemical staining and special stains). The collected information contained primary cancer classification, the condition of the border of cancer cells (margin status), invasion of nearby blood and nerve vessels or channels, pathological tumor (pT) stage, nodal (pN) stage and any discrepancies between the digital and on-glass interpretations. The same pathologist compared paired WSI and brightfield microscopy reads on each tumor case. There was a calculation of how often two doctors agreed or disagreed on the same diagnosis. Using the glass slide diagnosis was the standard by which the tests were evaluated. Criteria developed from approved studies on digital pathology systems by the FDA [2, 3, 27, 28] were used to set the concordance thresholds [2, 3, 27, 28]. Findings were seen as major discrepancies when one modality caught clinically important findings that the other failed to detect. Minor findings had no effect on patient care. An uninvolved pathologist checks whether the two readouts of the cancer match. Technical staff or the referee pathologist looked at the WSIs to ensure accuracy as part of quality assurance before a final report was signed. The standard methods used in handling tissues (including accessing them, looking at larger specimens, processing, embedding, microtomy and staining) did not change. First, each artifact was assessed under low magnification (macro) before moving on to scanning. It was required by quality control guidelines that the slides be stained properly and completely dried, not be damaged, not have any stray ink marks and that the coverslip should fit well and be free from air bubbles or overhang. All slides used wore barcodes which were tracked and scanned in the laboratory system after passing through a barcode reader. Original barcodes that couldn't be scanned were replaced by newly-made labels. If the quality during scanning fell below expectations for barcodes, tissue, focus or image, the slide scanner gave alerts to the operators. Despite pending errors, WSIs were briefly reviewed through thumbnails and checked visually to see all tissues were

scanned and that their barcodes were read successfully. When I used the touchscreen, it instantly showed me if I needed to rescans. Through the built-in viewer, pathologists could point out issues with the slides and this would inform the scanning team to rescan them (Fig. 2). If artefacts were found, pathologists could ask the machine to repeat the scans.

RESULTS

The testing included a thorough examination and confirmation of digital pathology procedures using the Aperio GT450 scanner with many pathology subspecialties. In all, 2,135 glass slides which consisted of both in-house and consultation materials, were scanned and careful attention was paid to keeping the quality controlled. There were relatively few technical issues (26 barcode failures, 5 cases of missing tissue detection, 7 detection errors, 4 lacking macro focus and 11 image quality complications) with the scanner, proving it was dependable for specimens in genitourinary, dermatopathology, breast, thoracic,

neuropathology, gastrointestinal, head and neck, breast and gynecologic pathology. The most common types of specimens were those from the genitourinary system (prostate and bladder) with 140 and 25 specimens and breast and dermatopathology samples (18 and 33, respectively). Several body tissues in head and neck and gynecologic areas were studied, creating a fair workload for validation. Comparing digital whole slide images (WSIs) to diagnoses made on glass slides across 16 sessions found very high agreement. Most of the parts compared showed good agreement, with only minor differences (four cases) and only a single major difference highlighted in session 7. It becomes clear that digital pathology and traditional microscopy are equal, so digital pathologists can use digital images for primary diagnosis. Based on the statistics, proper equipment management and strong quality checks allow digital pathology tools to evaluate slides as well as glass slides, enabling faster remote signout and helping improve workflow efficiency without lowering diagnostic reliability.

Table I: Technical evaluation of Aperio GT450 glass slide rescans.

Department	Case Type	Total Slides Scanned	Barcode Failure	No Tissue Detected	Tissue Detection Failure	No Macro Focus	Image Quality Issues
GU	In house	320	2	0	0	0	0
GU	Consults	385	14	2	0	1	2
Derm	In house	125	0	0	0	0	0
Derm	Consults	50	0	0	3	0	0
Breast	In house	110	0	0	0	0	0
Thoracic	In house	70	0	0	0	2	0
Thoracic	Consults	35	0	0	0	0	0
Neuro	In house	85	0	0	0	0	0
GI	In house	40	2	0	0	0	0
GI	Consults	18	1	0	0	0	0
H&N	In house	25	0	0	0	0	0
H&N	Consults	30	3	0	0	0	0
All	In house	45	0	0	0	0	2
All	In house	90	1	0	0	0	0
All	In house	380	0	3	4	0	5
All	In house	175	0	0	0	0	0
BST	In house	55	0	0	0	0	0
BST	Consults	15	0	0	0	0	2
GYN	In house	70	0	0	0	0	0
GYN	Consults	5	0	0	0	0	0
Totals		2135	26	5	7	4	11

Table 2: List of specimens in each respective subspecialty

Breast	Genitourinary	Head & Neck	Gynecologic
Breast	18	Prostate	140

Lymph node	6	Bladder	25
Lymph nodes	12	Thyroid	3
Bone & soft tissue	Kidney	11	Urethra
Bone	8	Testis	4
Soft tissue	4	Tonsil	2
Ureter	2	Adrenal	1
Dermatopathology	Other	12	Other
Skin	33	Lung	15
Eye globe	2	Lymph node	7
Gastrointestinal	Thoracic	Bone	3
Liver	6	Brain	4
Stomach	3		
Colon	3		
Small bowel	2		
Rectum	2		
Gallbladder	2		
Spine	2		

Table 3:Concordance between whole slide image and glass slide reads for all reader sessions.

Validation Performance and Equivalency	Total Parts	Part: Minor Discordance	Part: Major Discordance
Session 1	48	1	0
Session 2	50	0	0
Session 3	20	0	0
Session 4	9	1	0
Session 5	6	0	0
Session 6	5	0	0
Session 7	28	0	1
Session 8	6	0	0
Session 9	13	1	0
Session 10	11	0	0
Session 11	30	0	0
Session 12	7	0	0
Session 13	12	0	0
Session 14	3	0	0
Session 15	8	0	0
Session 16	7	0	0

Figure 1:Aperio GT450 Performance by Department Success rates across 2,135 glass slide rescans

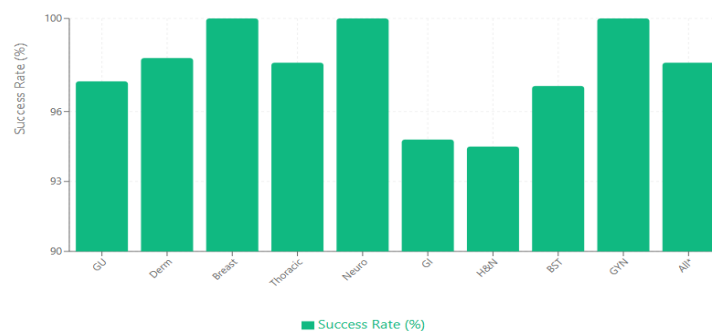


Figure 2:Specimen Distribution by Subspecialty Pathology specimen types across different subspecialties

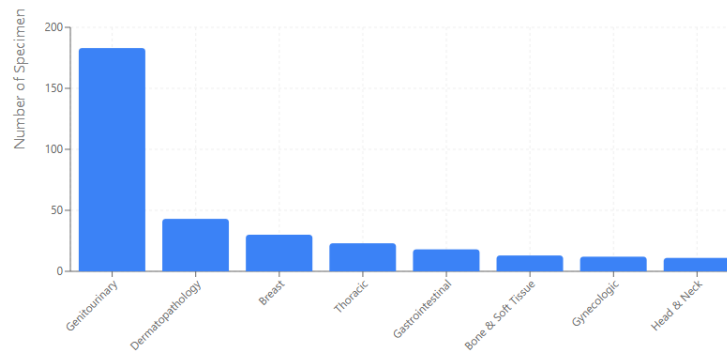
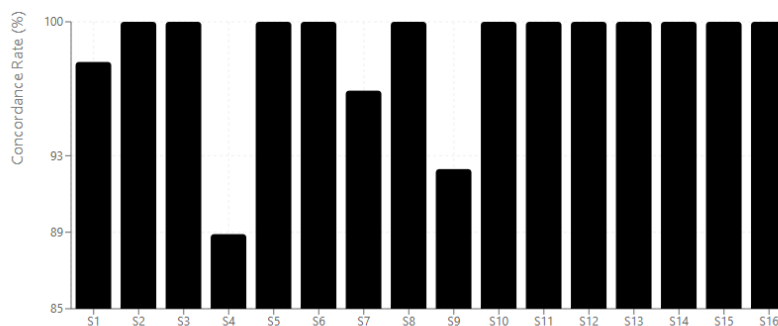


Figure 3: WSI vs Glass Slide Concordance Rate by Session Validation performance across 16 reader sessions (263 total parts)



DISCUSSION

A digital pathology system was evaluated in remote primary diagnosis, including workflows for preparing glass slides in formalin, paraffin, frozen tissue and stained with hematoxylin & eosin, immunohistochemical and special stains (4). Every specimen was checked by attending pathologists remotely via digital means and then they looked at the glass slides under brightfield microscopy in the certified center. It proved that using remote pathology review and reporting is possible and that it works smoothly and can be conveniently used for primary sign-out. What we observed agrees with studies showing that both whole slide imaging and slide viewing provide the same diagnosis and this is the first research to demonstrate consistency in using digital platforms to diagnose disease in a non-certified remote place (5). Because of the recent worldwide health emergency, people are paying more attention to digital pathology so that healthcare can continue and personnel can be protected. Most regulations require pathology reports to be generated in certified laboratories which prevents regular use of digital pathology systems from a distance. Emergency

measures have temporarily let pathologists report on WSIs remotely, without requiring them to be directly linked to previous systems. Regulatory advice directs laboratories to closely validate remote digital pathology methods and allows flexibility in using unapproved systems when needed during emergencies. Because of the strong validation, it is now possible to rely on digital pathology for reviewing patient materials without needing a microscope. Professional guidelines directed the study which covered surgical pathology samples like frozen sections and additional stains, showing that the process from accepting the case to the final report complies with requirements. There were no significant differences in the diagnoses given by both specialists and most cases of disagreement were minor. Even though digital and glass slide diagnoses are the same in most cases, certain situations might require polarized light or higher resolution for proper examination of microorganisms. Even so, many pathologists described good experiences with remote sign-out, using different equipment and internet connections. Suggestions regarding easier navigation tools and comfortable work configuration were made. All in all, digital pathology

sign-out was proven feasible and secure which allows it to be used even after the emergency period. The remote access worked well and allowed trials involving digital pathology to be conducted in a manner prepared for its use in routine care and resulted in worldwide updates to guidelines.

Conclusion

Remote digital pathology for sign-out using whole slide imaging (WSI) was successfully proven to be reliable and efficient for this public health emergency. Because scanned slides and glass slides gave the same diagnosis with a rate of 98.8%, remote digital pathology is just as accurate as traditional in-person microscopy. A strong digital pathology system, capable of high-resolution scanning, being vendor-independent and integrating with the laboratory information system, made sure everything ran smoothly as we maintained high quality. Because COVID-19 prevented many pathologists from using approved laboratories, this research pointed out that adapting guidelines and digital solutions allowed

pathology work to carry on smoothly. Looking at cases remotely, pathologists were still able to keep their diagnoses on track across a range of surgical pathology subspecialties like frozen sections and round-the-counter reviews. Significantly, there were not any major findings that would have changed patient care, showing that remote digital pathology is reliable. People using remote sign-out were generally positive about the experience, yet there were mentions for improvements in navigation tools and better office furniture. It is also highlighted in the study that using remote digital pathology meets important clinical standards, speeds up processes, shortens delays and offers additional safety for medical workers during infections. Now, since the use of digital pathology in emergencies is successful, it can be introduced into daily use, broadening availability of expert pathology no matter where someone is located. Such changes should make diagnostics better, encourage cooperation and help healthcare systems respond to future problems while continuing to look after patients properly.

REFERENCES

1. Borowsky AD, Glassy EF, Wallace WD, Kallichanda NS, Behling CA, et al. Digital whole slide imaging compared with light microscopy for primary diagnosis in surgical pathology: a multicenter, double-blinded, randomized study of 2045 cases. *Arch Pathol Lab Med*. 2020.
2. Mukhopadhyay S, Feldman MD, Abels E, RaheelaAshfaq, Beltaifa S, Cacciabeve NG, et al. Whole slide imaging versus microscopy for primary diagnosis in surgical pathology: a multicenter blinded randomized noninferiority study of 1992 cases (pivotal study) *Am J SurgPathol*. 2018;42:39–52.
3. Hanna MG, Reuter VE, Hameed MR, Tan LK, Chiang S, Sigel C, et al. Whole slide imaging equivalency and efficiency study: experience at a large academic center. *Mod Pathol*. 2019;32:916–928.
4. Al-Janabi S, Huisman A, Nap M, Clarijs R, van Diest PJ. Whole slide images as a platform for initial diagnostics in histopathology in a medium sized routine laboratory. *J ClinPathol*. 2012;65:1107–1111.
5. Bauer TW, Schoenfield L, Slaw RJ, Yerian L, Sun Z, Henricks WH. Validation of whole slide imaging for primary diagnosis in surgical pathology. *Arch Pathol Lab Med*. 2013;137:518–524.

Cite this article:

Dr. Veeravalli Sudheer Kumar. Strategies For Better Antibiotic Use In Pediatrics From Direct Implementation. *Acta Biomedica Scientia*. 2020;7(2):303-309.



Attribution-NonCommercial-NoDerivatives 4.0 International