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Is The Future of Diagnostic Pathology Digital?

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Abstract

This review explores digital pathology, looking into how it began, how it evolved, and what the future holds for this technology. It also discusses the factors limiting digital imaging adoption and the way they can be overcome.

The main traditional approach for diagnosing diseases in anatomical pathology is light microscopy. Digital imaging was introduced to the field not long ago because of the advent of digital imaging software and hardware developments. Digital imaging technology comprises devices that enable the analysis and subsequent display of digitally captured images, commonly known as whole-slide imaging. Therefore, it can be stored and shared virtually.

Medline, PubMed, and Google Scholar were searched using the keywords “digital pathology,” “whole-slide imaging,” “light microscopic,” “diagnosis,” “review,” and “future.” Articles published between 2007 and 2022 were collected and analyzed.

Based upon a thorough review and analysis of the existing literature, the primary challenges that hinder the adoption of digital imaging technology were identified as the perception that it offers no significant advantages to the field, the cost associated with its implementation and the belief that digital images produced by this technology are inferior to those obtained via conventional light microscopy.

Compared with conventional light microscopy, digital pathology (especially through computer-aided diagnosis) offers many more advantages. One of the main reasons why this technology is becoming more desirable in anatomical pathology is the vital role of digital image analysis, quantification, and teleconsultation.

***Keywords**: Digital Pathology; Whole-Slide Imaging; Light Microscopy; Diagnosis; Review; Future*

Background

As early as the 1980s, along with the advancement of telepathology technology, an interesting invention known as digital pathology emerged in the 1990s. The evolution of virtual slide scanners promoted a shift toward digital pathology. Digital pathology has subsequently substantially advanced clinical pathology and pathological research.

Digital pathology has started to emerge as an optical means. More than 13 types of digital pathology systems exist, including the last telepathology system, whole-slide imaging (WSI). WSI captures multiple images using one or more microscope objectives and high-resolution cameras. These images are then combined using specialized WSI software into a single image that is viewable via a computer screen [1].

The standard methodology for analyzing digital images has seven steps: (a) tissue specimen preparation, (b) image capturing, (c) image processing, (d) image segmentation, (e) processing of segmented images, (f) adoption of a metric calculation for the segmented images, and (g) image interpretation. Each step can be modified as required in [2].

Methods

Medline, PubMed, and Google Scholar were searched using the keywords "digital pathology," "whole-slide imaging," "light microscopic," "diagnosis," "review," and "future." Articles published between 2007 and 2022 were collected and analyzed.

Results and Discussion

Williams., *et al*. [3] mentioned that for digital pathology adoption and acceptance on a wider scale, pathologists and departments conducting diagnosis and regulatory bodies must be assured that WSI or digital pathology is as accurate as light microscopy. One way to accomplish this is to prove by comparison that both diagnostic processes have similar systemic errors.

WSI is useful for initial diagnosis, routine, and clinical practices in oral pathology. Araújo., *et al*. [4] concluded that their work provides original evidence of a good performance of the WSI system in the histopathological diagnosis of oral diseases. This shows the idea that WSI is a viable option for diagnosing oral diseases in clinical practice.

In their systematic review, Goacher., *et al*. [1] observed that the diagnosis concordance between digital pathology and conventional light microscopy was 92.4%, whereas the number of cases repeatedly diagnosed via light microscopy of the same case was 93.4%. Therefore, the authors contend that these data hold great promise for the future and the adaptation of this technology. Due to the increasing demand and workflow, pathology must continuously grow to meet the demands for increased diagnostic accuracy, quality, and safety to improve patient outcomes. These requirements, along with financial constraints, have driven the adoption of a system that facilitates and overcomes these challenges. In addition to the added benefit of easily acquiring a second consultation, digital pathology has various advantages and disadvantages (Table 1).

A systematic study by Araújo., *et al*. [5] revealed significant consistency between WSI and conventional light microscopy (CLM) diagnoses. The included studies validated WSI for general clinical application, confirming that this technology may be used to make initial diagnoses in a range of human pathology subspecialties. The reported challenges with particular findings in certain areas of pathology, such as hematopathology, endocrine, and bone and soft-tissue pathology emphasize the need for validation studies in areas that have not been thoroughly researched.

This digital shift is not new to the medical field. For instance, one of the most successful examples is in radiology. Nonetheless, the rate of acceptance in pathology is lower for multiple reasons, predominantly because whether digital or traditional, the production, scanning, and storage of glass slides are unavoidable, which, in practice, adds an extra step to the flow of prediagnostic work [6]. In radiology, by eliminating hazardous chemical films, processing was more practical and successful.

This new technology can offer more precise and efficient help to pathologists, especially in histoprognostic quantification. In addition, there are benefits of eliminating the time-consuming and costly step of shipping glass slides for consultation, which has the inherent risk of slides being damaged during transport [7].

Shinohara., *et al*. [8] examined 270 cases involving WSIs scanned at 40× for remote consultation. The authors evaluated the impact of WSI-based expert consultation on inconclusive histopathological diagnoses and showed substantial improvement in diagnosis after a remote second opinion. Ninety percent of specialists across subspecialties rated the study's WSIs as sufficient or almost suitable for diagnosis. Two-thirds of pathologists reported no issues reviewing WSIs, with the remaining specialists noting digital image concerns such as trouble recognizing small features on high magnification, inability to precisely focus, and technical challenges, including delayed image loading or out-of-focus areas. Moreover, telepathology could save consultation costs (96%), speed up turnaround (100%), and increase diagnostic quality (96%). Because the WSI scanner is in a laboratory setting, all the earlier benefits will increase consultations by 100%. Most respondents preferred sending and receiving extradepartmental consults digitally. Even though only 60% of professionals used digital pathology, both groups performed similarly. Nevertheless, with all these appealing factors, other considerations restrain digital pathology. For example, infrastructure, process speed, image quality, data management, regulatory approval, and the opinion of pathologists that digital pathology is inferior [9].

Digital Pathology (DP) Feature	Possible Advantages	Possible Disadvantages
In-house telepathology	• Quick second opinion. • Social distancing (COVID-19 pandemic).	• Second opinion overuse (interrupted workflows) • Decreased interpersonal (face-to-face) communication
Extramural telepathology	• Service for remote/understaffed areas. • Specialization through DP in low-volume laboratories • Home-office use. • Healthcare cost reduction through the global histopathology market.	• Social isolation in remote telepathology. • Loss of routine on-site expertise through the home office. • Wage competition in the global histopathology market.
Consultation telepathology	• Quick access is possible. • No physical slide transfers. • Lower threshold for consultation due to shorter turnaround time.	• No tissue blocks are available for additional stains/ molecular assays. • Consulted pathologist unaccustomed to workup (stains/scanner calibration) at the primary center. • Compatibility issues due to the diverse proprietary DP formats. • Possible medico-legal implications due to restricted workup
WSI-general	• No physical slide distribution. • No fading of the stored slides. • No irretrievable/lost slides. • Shorter sign-out time. • Reduced misidentification of slides due to barcoded slides automatically allocated to the case. • Easy dynamic workload allocation • (e.g., management of backlogged work redistribution in case of sick leave).	• The time to evaluable-ready slide increased due to additional scan time. • Integration into a laboratory information system (LIS) for full efficiency gains, leading to possible costs for LIS update. • Regular calibration is required (scanners/displays). • Small particles are omitted by scan, leading to the need for manual checking for rescan. • Artifacts (out-of-focus areas, digital stitching artifacts). • Increased IT dependence (IT downtime) compared with optical microscopy.
WSI reporting/user experience	• Parallel (side-by-side) viewing and digital slide superposition. • Shorter sign-out time. • Quick access to prior slides leads to less immunohistochemistry. • Facilitates slide presentation at the multidisciplinary tumor board. • Easy image sharing in clinical communication. • Computational pathology is possible • Occupational health: less neck strain and more flexible posture.	• Slower evaluation compared with optical microscopes, mostly only single focus plane in routine DP, leading to difficulties with interpretation. • Some structures are harder to recognize on WSI, which requires a glass slide. • Polarization is not possible on DP, leading to the need for a glass slide alongside extra training for safe practice (perceived insecurity on digital sign-out) if not DP from career start. • Easy availability of prior digital slides may shift the medico-legal onus toward more extensive re-examination, leading to increased workload. • Dual infrastructure is generally necessary (glass and digital) • Occupational health: computer vision syndrome

WSI Image Analysis, ML/AI	• Faster, more efficient, and more accurate measurements and quantifications. • Exact quantification of tumor cell content for molecular analyses. • Digital enhancement of the image features • AI for a second-read safety net • Direct link of morphology to clinical parameters "novel biomarkers" beyond human recognition • Inspection and correction of AI app suggestions in development on the WSI viewer: "human-in-the-loop" interaction.	• Benefit of more accurate quantification is not necessarily clinically relevant • Applications beyond human evaluation that is not yet approved/used for clinical management. • AI in transparent ("black box"). • Regulatory oversight challenges with self-modifying (adaptive) AI algorithms and performance not constant over time.
WSI-teaching	• Digital images for presentations and exams are readily available. • Remote teaching and self-study. • Increased student motivation and modern appeal.	• None
Costs and efficiency gains	• Work time is saved through faster turnaround times. • Decreased auxiliary techniques (less immunohistochemistry). • Decreased physical slide transfer costs.	• DP implementation, maintenance, and storage costs add to current fixed costs if productivity gains remain unrealized (fixed work contracts). • Dual infrastructure costs (workstations and microscopes if kept). • Glass and digital storage are still generally deemed necessary. • Technical expert knowledge is required for hardware acquisition.
WSI, whole-slide imaging; AI, artificial intelligence; ML, machine learning.		

Table 1: *Advantages and disadvantages of digital pathology modified from Jahn (2020, p. 12)*

Ghaznavi., *et al*. [10] suggested some strategies to overcome these obstacles, starting with the issue of validation. In support of this, Beaglehole., *et al*. [11] argued that without convincing pathologists that digital pathology is not inferior to light microscopy, this technology will not be widely adopted on the desired scale in pathology. Even if the other barriers are stifled, conducting a well-designed validation study is the main way of achieving wide-scale acceptance.

Jukić., *et al*. [12] compared the diagnostic capability of WSI to that of light microscopy using 900 slides interpreted by three pathologists. They concluded that no significant impact that would affect the accuracy of the diagnosis or the patient's level of care [13]. Similarly, Mooney et al. [14] conducted a randomized study and found no significant difference between WSI and light microscopy ($p = 0.286$).

Moreover, a larger-scale study by Chargari., *et al*. [15] evaluated the pathological performance in detecting cancer in prostate biopsy specimens using both WSI and light microscopy. The authors found no significant difference between the techniques (33.4% using WSI and 34.8% using a light microscope). Additionally, Aswathy and Jagannath [13] emphasized that computer-aided techniques are instrumental, especially in breast cancer analysis and examination, to complement the pathologist's efforts. This was corroborated by the findings of a retrospective study by Fine., *et al*. [16] and a pilot study by Tsuchihashi., *et al*. [17]. Fallon., *et al*. [18] argued that WSI is as accurate as light microscopy, especially in frozen sections in which provided 96% similarity.

Despite all these validation studies favoring the accuracy of WSI, they provided little encouragement to aid the adoption of digital pathology, which raises the question of what is missing. According to Ho., et al. [19], the main problem is the unavailability of guidelines for a much-needed ideal validation study. The authors concluded that designing an ideal validation study is almost impossible.

Future

Madabhushi and Lee [20] argued that for digital pathology adaptation in routine clinical pathology, multiple challenges must first be overcome, including computing and technical issues. However, solving these challenges will be a remarkable add-on to the field, especially in the provision of precise disease image quantification.

Shortly, despite gaining the approval of regulatory agencies, digital pathology will become a crucial part of pathology because of its computer-aided analysis. In support of this, Veta., *et al*. [21] said that computer-aided image analyses of digital pathology will become part of routine practice, particularly in enhancing the workflow and avoiding the time-consuming assistants, including abnormality detection, microorganism detection, immunohistochemical quantification, and tumor grading by counting mitotic figures [3,22].

According to Ghaznavi., *et al*. [10], achieving a comprehensive validation study is the greatest obstacle to adopting digital pathology. Until then, this technology will continue to transform routine pathology practice. In addition, it will establish a more precise computer-aided diagnosis. Furthermore, Griffin and Treanor [23] noted that the operating system of this technology should be improved to provide more fluent and higher safety standards. In the conclusion of their study, the authors argued that digital pathology possesses an appealing reason for a large-scale application in the future.

Hanna., *et al*. [9] outlined that most published guidelines from regulatory or authority figures, including the Royal College of Pathologists and the College of American Pathologists, specifically focused on validation in clinical and academic disciplines. Beginning in 2011, the Digital Pathology Association provided guidelines for pathology retrieval and archiving processes. Following this, the Royal College of Pathologists introduced telepathology guidelines. Subsequently, the College of American Pathologists issued recommendations for digital pathology validation processes, which were subsequently improved by the American Telemedicine Association [24,25].

Gabril and Yousef [26] emphasized how obvious all the presented evidence indicates the future adaptation of digital pathology. Nonetheless, it is a growing field and will eventually play a considerable role in pathology. Furthermore, Sinard [27] predicted that pathologists would no longer use conventional microscopy, which computer screens would replace in the field of pathology. Indeed, the new generation of pathologists is more familiar with WSI technology than with conventional microscopy.

In addition to being subject to stringent regulations, Veremis., *et al*. [28] argued that this new technology will greatly aid pathologists in consultation, telepathology, scientific research, education, quality assurance, and primary diagnosis. Moreover, Al-Janabi., *et al*. [29] addressed the financial limitations of the cost of storage (pathology slides), arguing that it can be solved with digital pathology. They also added that this technology has benefited the field and will continue to be a valuable (if not the best) technique in anatomical pathology.

Bassani., et al. [30] conducted a systematic review to explore the progression of diagnostic methods using artificial intelligence for the diagnosis of head and neck neoplasms. The authors stated that static picture use in digital pathology ushered in the WSI era. Despite some technical and diagnostic challenges, WSI has demonstrated excellent diagnostic concordance compared to conventional light microscopy in anatomical pathology, including cytopathology. Pathology now has access to WSI, allowing AI modalities to be used (Table 2).

Modality	Description
Artificial intelligence	The computer science branch attempting to build smart machines to perform tasks.
Machine learning	The ability of machines to learn information and patterns from data.
Supervised learning	Training machines from labeled input and output data.
Unsupervised learning	Training machines by extracting hidden patterns from input and output that have not been labeled.
Whole-slide image	High-resolution microscopic digital image.
Deep learning	Subfield of machine learning in which algorithms learn without supervision.

Table 2: *AI Modalities Modified from Bassani (2022, p. 3)*

Artificial intelligence (AI) technologies for analyzing histopathology whole-slide pictures have facilitated the improvement and potential automation of pathological diagnosis. These techniques also allow for more effective examination and measurement of tumor microenvironment characteristics [30].

Conclusion

Digital pathology (especially through computer-aided diagnosis) has many more advantages than conventional microscopy. A driver for the desirability of this technology is the vital role of the analysis and quantification of images in anatomical pathology.

Another significant impact has been (and continues to be) how this technology aided virtual pathology, thus facilitating teleconsultation. This, in turn, resulted in better and more accurate patient care [7]. Williams., *et al*. [3] mentioned that this technology could offer more flexibility, higher-quality service, better workflow, and reduced human involvement, including during a period of high demand that requires expedited throughput without impacting quality. Therefore, adopting digital pathology will fulfill these demands [7].

Alzubaidi., et al. [31] claimed that the role of digital pathology would not be limited to WSI analysis but would also play a crucial role in computer-aided diagnosis. Regardless, Kubra [32] argued that despite the great impact of this digital technology, it will never eliminate the role of pathologists. The latter must be included in the development and further enhancement of digital pathology technology. As Bhargava and Madabhushi [33] stated, “The field of pathology is moving toward more informative multimodal tissue imaging, wherein the integration of computer-derived morphologic and functional tissue-based measurements is becoming a central theme. In addition to conventional decision-making, these digital pathology transitions will have a greater impact on telepathology, education, and precision medicine. This progress will require the integration of engineering and pathology at an unprecedented scale” (p. 398).

The magnitude and advancement of digital technology have innovated the practice of pathology. However, the acceptance rate depends on the approval of regulatory bodies and field mass endorsements [34].

Declarations

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