Digital Pathology in Latin America

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Short Report

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Abstract

Background: Digital pathology (DP) adoption in Latin America has expanded slower than in developed regions, probably due to many barriers not seen in the latter areas. This article aims to present the current scenario in the region, highlighting barriers and possible solutions to encourage its adoption in Latin American countries.

Methods: An expert panel of 9 Latin American medical pathologists and 1 information technology specialist participated in an online modified Delphi panel, utilizing a third-party platform (iAdvise, Within3, USA). Thirteen pre-prepared questions were answered interactively.

Results: Experts' observations confirm the paucity of labs in the region that utilize digital pathology technology. The panel ranked obtaining second opinions and presenting images remotely as the main benefit of a digital pathology system, although many others were cited as well. Cost of implantation was the main barrier mentioned by the experts, and payers' and decision makers' lack of awareness of benefits ranked second as a barrier to DP implementation. Internet infrastructure was also mentioned as a concerning issue in the region. Besides diagnostic pathology services, proposed revenue incomes included commercialization of digital services to other institutions, loan agreements of equipment and software, and organizing courses for pathologists or residents. The need for alternative reimbursement methods for diagnostic services was also mentioned. A regional network of collaborating institutions was also suggested as a viable solution to reach distant areas and laboratories lacking the technology.

Conclusions: The benefits of DP are clear to the expert panel, but cost and lack of awareness of its benefit may be hampering its widespread adoption in Latin America.

Introduction

The practice of pathology in the developing world presents numerous challenges in terms of limited resources, shortages of subspecialists and trained laboratory personnel, and lack of continuing education programs[1]. Widespread adoption of digital pathology (DP) in Latin America has been hindered by its lack of reimbursement, due to the low level of information of its value throughout the scientific community and among decision-makers and payers. The unfamiliarity with this technology has negatively impacted its implementation in Latin American laboratories, putting the region at a significant efficiency disadvantage and distance from the developed markets.

Digital pathology can be defined as the set of tools and systems to digitize pathology slides and associated meta-data, their storage, review, and analysis together with the necessary infrastructure[2]. The DP process encompasses acquisition, retrieval/storage, manipulation, sharing, and analysis of the information in the glass slides[3].

In pathology, digital images can be used to make primary diagnoses, offer second opinions (telepathology), execute quality assurance (e.g., re-review and proficiency testing), provide education, be

used in academic presentations, perform research, and be published. Marketing and business purposes, and tracking (e.g., audit trail of how an image was viewed), are also possibilities when using digital systems[4].

A recent systematic review and meta-analysis showed that DP is equivalent to conventional light microscopy regarding clinical concordance (98.3% (95% CI 97.4 to 98.9), although some discrepancies were described[5]. Furthermore, individual studies have shown that DP can be time[6] and cost-saving[7].

The evidence described above seems insufficient to foster DP's implementation in Latin America, and a deeper inquiry into its utilization in the region may provide insights to understand this gap.

The main objective of this article is to present the current experience of Latin American pathologists with digital pathology, highlight barriers to its implementation in Latin America and propose solutions to achieve its adoption in the region.

Methods

A modified Delphi method was used to prepare an algorithm using the iADVISE platform (Within3, OH, USA). Ten experts from Latin American countries iteratively answered 13 questions (Supplementary Table 1) online for two weeks about the use of digital pathology, its applications, and barriers for implementation in the region. The questions were written by an experienced pathologist and a medical oncologist with high expertise in the area and reviewed by the multidisciplinary panel. The experts also met for 28 days to write and revise the manuscript using the iADVISE platform.

Results And Discussion

Current DP uses in Latin America

Digital Pathology systems have been used in Latin America for morphometric analysis[8], histology[9], histochemistry[10], immunohistochemistry[11 12], neuropathology[13], medical education[14 15], and reproducibility research[16]. Besides those reports, the experts in the panel also report utilizing DP systems for measurements of cancer invasive borders, static cytometry, intra-operatory biopsy analyses, creation of digital archives, telepathology, research, publications, and videoconferencing.

Digital Pathology Systems

The digital pathology ecosystem has two main components: the information systems (hospital information systems, electronic medical records, laboratory information systems, and others), the digital pathology system (hardware and software), and its tools[3].

Whole slide imaging (WSI) involves digitizing or scanning glass slides to produce "digital slides" for viewing by humans or subjecting them to automated image analysis[17]. Whole image scanners (WSS)

were developed in the 1990s[3] and are currently capable of producing high-resolution digital images at multiple magnifications and focal planes[17].

A white paper from the North American Digital Pathology Association[18] presents an overview of WSI technology. It demonstrates several immediate applications of WSI that support pathology practice, medical education, research, and collaboration.

Routine workflow in a digital pathology lab may be divided into pre-scanning, scanning, and post-scanning tasks. For a review of workflow details, its implementation, and some drawbacks, see the review by Hartman[19]. Stathonikos et al.[20] described the experience of implementing a fully digital lab in the Netherlands and all the hurdles and successes encountered during the process.

Implementation of DP systems

Before implementing any DP system, a thorough analysis of its attributes and the laboratory requirements must be performed. Fast image scans and the production of high-quality images are the main attributes the panel describes as essential features for a digital pathology system. Table 1 shows other characteristics needed for the ideal DP system.

Table 1
Ideal features of a Digital Pathology system

User friendly
Versatile reader
Robust cloud/fast server and web viewer
Affordable cost
Small size, low weight and low noise when scanning
Low heat generation
Low failure rate
Remote viewing
Adequate storage capacity
Automatic scanning
On-site technical support
Easy integration with the LIS
Continuous flow of production
Data integration with hospital databases

The cost was the leading topic when discussing the current barriers of digital pathology implementation in Latin America. In 2017, Griffin and Treanor [21] estimated that, for implementing a fully digitized university hospital histopathology lab in the UK, the initial cost would be £1,4 million, and maintenance costs would be £250,000.00 per year. For a 10% increase in efficiency, the cost would be repaid in 2 years; for an increase of 15%, it would be in 1 year. A recent study analyzed the cost-saving benefits of a fully deployed digital pathology lab at the Memorial Sloan Kettering Cancer Center [7] . The authors demonstrated that, when comparing operational costs before and after the implantation of DP, five-year projected savings would be US$ 1,3 million after installation.

Two reports show that DP may save time and increase the efficiency of the workflow. Baidoshvili et al.[6] reported saving an average of 19h of a workday in five different workflows. The highest savings was in routine diagnosis and multidisciplinary meeting workflows. Savings of 19 h/day translated into 2.63 full-time-equivalent laboratory staff (36-h working week), corresponding to €120 000/year. Studying consultation times before and after DP, Vergani et al.[22] showed that the turnaround time of consultation diagnostic reports significantly differed from conventional (mean 12 days; range, 3 to 45) to digital (mean 1.4 days; range, 1 to 2) workflows. The overall cost switched from 3365 per conventional report to 300 euros for the digital system.

Experts in the panel believe that most pathology labs in the region lack the resources to implement complete systems and that payers and decision-makers overlook the benefits such systems can offer. Table 2 shows the main barriers experts encounter when trying to implement or adopt DP systems. Initial costs for DP implantation seem a very significant impediment for small or medium laboratories. Another important barrier is the reimbursement of routine diagnostic workups due to complex negotiations with payers and providers. One expert commented that implementing DP in most labs in Latin America could be challenging due to the lack of infrastructure in the current scenario. Concern about possible wage reductions for the pathologists was also mentioned, although no reports describing such reductions could be found.

Table 2
Main barriers for the implementation of a digital pathology system

Costs of implementation and maintenance
Payers and decision makers overlook the benefits
Lack of support for Pathology areas by Hospital administrators
Lack of adaptation and acceptance by doctors
Lack of standardization
Cost of digital storage is greater than the physical storage
Lack of an adequate strategy for the digitization of images
Low proportion of laboratories with technical quality certification
Pathologists are not aware of its benefits
Lack of reimbursement
Complexity of use
Lack of guidelines for validation of diagnostic methods
Fear of job replacement

Use of digital images in practice

Ninety percent of the experts agreed that DP might contribute to increasing diagnostic efficiency in pathology labs. Reasons for this increase are presented in Table 3.

Table 3
Reasons for increased efficiency when using Digital Pathology systems

Images are remotely shared with multiple pathologists and viewed simultaneously
Review cases anytime, anywhere
Don't waste time preparing for shipping or fighting with courier services
Not having to move boxes with slides to home or to other hospitals, which is cleaner and safer
Reduce shipping times
Greatly improve teaching activity
Decrease interobserver variability with certain markers
Offer multi-magnification assessment, diagnosis, archiving, easy access, special studies with defined algorithms
Pathologists may subspecialize since they can concentrate cases from different institutions
Standardize quantitative techniques and lesion detection
Improve productivity of pathologists
Improve workflow in the laboratory and therefore decrease response times
Increase in number of samples (biopsy type)
Pathologists may focus initially on simple, easy-to-train algorithms and subsequently dedicate time to cases of greater complexity.

According to the panel, patients would also benefit, mainly because of better access to second opinions and case sharing with other experts. Other benefits for patients are shown in Table 4.

Table 4
Benefits of DP for patients.

Better access to second opinions and sharing with other experts
Standards are guaranteed in labs that use algorithms and AI
Consensus diagnoses in problem cases
Greater access to companion diagnostics and targeted therapies
Reduced time for diagnosis
The possibility of sending digital images when a patient is referred to another institution, reducing waiting times in the delivery of material (blocks and sheets).
Reduces the possibility of loss or damage of the material
The digitized image could be delivered to patients, thus reducing the risk of damage to the slide
Academy and research
Contribution in precision and standardization especially in quantitative techniques
Development of collaborative research studies with international working groups

The ease of consulting with other experts for a second opinion was also ranked as a significant benefit for pathologists, followed by the possibility of working remotely and using DP as a tool for medical training. Table 5 shows other benefits for pathologists mentioned by the experts in the panel.

Table 5
DP benefits for pathologists

Enable participation in accreditation and quality programs
Facilitate management of pathology labs, leading to greater efficiency
Improve archiving with digital files
Share images of the lesions in oncology meetings, bringing the pathology closer to other specialists and avoid having to take photos for these meetings.
Allows the use of algorithms and AI for research
Quantify antigen expression more objectively and accurately
Quantify volumes of structures allowing a much more precise biometric morpho analysis
Make the art that is pathological anatomy more objective
Optimize slide storage space and migrate easily accessible and referenced footage to digital storage
Optimization of work time
Image traffic and what we can do with training
Digitized files for multiple purposes (research, teaching, clinical forums)

Non-routine uses

Telepathology and second opinion

The panel ranked the ease digital pathology offers in obtaining second opinions and presenting images remotely as the main benefit of a digital pathology system.

Telepathology has been validated by the American Telemedicine Association[23] and approved by the FDA for primary diagnosis in surgical pathology when using a specific system[24 25 26]. The approval did not exclude the need for local validation when labs can identify other (e.g., histology-related) issues specific to their laboratory that may need to be addressed to optimize workflow and/or image quality for diagnosis by WSI[25].

Telepathology has the potential to address the problem of insufficient anatomic pathology expertise[27]. A study in Tanzania showed a potentially high diagnostic validity, especially for selected groups of diseases[28]. Another report from Northern Italy[29] demonstrated that working remotely during the COVID-19 pandemic was feasible and considered an essential tool to maintain the reporting activity in a pathology unit.

Fischer et al. described barriers to the widespread adoption of telepathology in low-income countries[30]. They include inconsistent internet connectivity, high initial costs depending on image type required, lack

of laboratory technical quality certification, the limited number of companies that provide laboratory information systems, expertise in slide preparation, and equipment maintenance[30].

Education

Several initiatives taken before and during the COVID-19 pandemic showed that digital pathology systems could be used effectively for training purposes[31]. The experts mentioned training medical residents as one of the more important uses of digital pathology in Latin America. The primary concerns when using WSI for training are centered on connectivity issues[32].

Recent articles and reviews have described learning curricula for medical training[31 32 33 34] and reviewed resources that may be helpful when implementing a digital pathology education system[35 36].

Academic or hospital meetings

Presentation of pathology findings in clinical conferences, academic meetings, and tumor boards are frequent events in academic or hospital settings, and the use of WSI has increased in the last few years[37]. Traditional microscope projection was compared in a small study[37] to oil-immersed WSI regarding processing and presentation time and clinical team satisfaction. There was no statistical difference in preparation and presentation times. The clinical team considered the use of WSI as better overall ($p=0.0004$), to have better image quality ($p<0.0001$), to be more efficient ($p<0.0001$), and to be more helpful for clinical decision making ($p=0.007$).

Other advantages mentioned by the experts in our panel are more straightforward access to previous images and other samples, time saved from taking microphotographs for presentations, and more interactive and dynamic discussions because of the ease to show areas of interest and change the magnification of slides.

Image analysis and artificial intelligence algorithms

Computer-assisted diagnosis (CAD) comprises technical procedures using digital algorithms to assist medical diagnoses. During the past 25 years, CAD has evolved into a frequently used research tool and is becoming one of the major research areas in medical imaging[38].

Computer-assisted analysis of histological images seems to simplify the workflow because of automation and consistent interpretation[38]. The combination of computational power, high-quality digital cameras, and WSI scanners, together with the improvement of image analysis algorithms, offer robust quantification of protein expression, objectivity, and reproducibility[38]. The most crucial advantage of computational pathology is to reduce errors in diagnosis and classification[39]. The use of artificial intelligence algorithms in digital pathology is an area of extensive research and can improve the sensitivity and accuracy of the diagnoses and improve turnaround time[39].

WSI is ideal for collaborative studies of rare diseases, such as uveal melanoma[40] or malignant peripheral nerve sheath tumors[41], where images may be analyzed using a standard protocol. Cancer registries and other biorepositories may use WSIs and clinical metadata to perform large clinical studies on prognosis and treatment, using machine learning protocols[3]. The generation of high-quality images is also a feature of digital systems[18], which aids the pathologist when publishing research results.

Utilization of Digital Pathology in the routine diagnostic workflow

Primary diagnosis in digital pathology refers to making the final reported pathology diagnosis when reviewing WSI, without first looking at the glass slide[3]. Scanners can perform whole slide imaging in different imaging modes such as brightfield, widefield fluorescence, confocal, structured illumination, multiplexing, and/or multispectral[42]; brightfield scanning emulates standard brightfield microscopy and is the most common and cost-effective approach[18].

Immunohistochemical studies are particularly suited to digital image analysis, with some biomarkers approved for quantification using the specified reagents and software[3]. Breast cancer biomarkers are by far the most prominent clinical application of digital image analysis in surgical pathology[43].

A companion diagnostic device is a diagnostic tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product[44]. The accurate assessment of immune checkpoint inhibitors predictive markers in different tissue compartments is critical to select the best therapy option for an individual patient. Software-assisted tools might play a crucial role in the stratification of patients to specific therapies in the age of immunotherapies and beyond[45]. A list of approved USA FDA tests can be viewed at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Seventy percent of the experts agreed that DP might support and increase the implementation of CDx tests in routine practice among pathologists. The digitization of slides can facilitate access to predictive markers and enhance personalized medicine once respective therapies are approved and reimbursed in Latin American countries.

The experts perceived digital tools to provide a remote diagnosis intra-operatively as a significant advantage of DP. A systematic review[46] of 56 intraoperative telepathology studies showed a concordance rate between DP and the reference standard of 96.9% (range 68.8 to 100%). This review included studies performed in the 1990s utilizing older techniques, which may explain the wide range in the concordance rate. Preanalytical factors such as poor tissue sampling, staining, slide preparation, and lack of knowledge of gross findings were common causes of discrepancies reported. In another systematic review[47], the same group reported that DP diagnosis from a specialist resulted in a better diagnosis than what would have been reported by a general pathologist using conventional microscopy.

Literature focusing on digital cytopathology is still scarce. The tridimensional distribution of material, the multiple stains used in routine practice, and the lack of tissue reference are some of the cytology-specific challenges that make standardization of the technique more difficult[40]. Kumar et al. published a recent review[16] concentrating on this issue.

Suggestions to overcome implementation barriers

The decision to implement a digital system in a pathology lab must consider several factors, including costs, time, and effort spent in the transition[48]. The Digital Pathology Association published a guide[48] for conducting a thorough and complete assessment of the needs of pathology laboratories before the implantation of DP.

The expert panel suggested several ideas to facilitate the adoption of DP in Latin American labs and increase revenue (Table 6). Suggestions included the commercialization of digital services to other institutions, loan agreements of equipment and software, and organizing courses for pathologists or residents, among other ideas. One recurring suggestion was the creation of a collaborative network of pathologists in the region that could provide more efficient use of resources, offering services to distant areas and generating opportunities for training and education.

Table 6
Ideas for adoption of DP and increase revenue

Commercialization of digital services
Paid consultations in distant institutions
Web of pathologists specialized in DP
Training courses for pathologists and residents
Alliances with universities, hospitals and state institutions
Lending of equipment and software
Access to complete solutions (antibodies, scanners, software, laboratory systems, etc.

Other revenue opportunities include WSI-based image analysis, computational pathology, precision medicine, drug development, clinical trials, and big data[48].

Before adopting DP in the region, the experts recommend that important factors be addressed, such as pathologists and staff training, optimization of the internet infrastructure, availability of companies that provide and support complete digital pathology workflows, and awareness and education of payers reimbursement issues.

Alternative reimbursement models to facilitate DP adoption and commercialization in Latam

Most laboratories in the region follow traditional payment systems where every procedure is billed (fee-for-service, personal observations). Innovative payment systems include value-based agreements[49], and merit-based incentive systems[50], among others. Value-based agreements offer payments based on quality over quantity, while the costs are based on historical expenditures and value for patients. Merit-based systems were implemented in the USA in 2017[50] and include 4 distinct categories, quality, advancing care information, improvement activities, and cost, each contributing to a score that defines the final payment.

Homeyer et al.[51] wrote a review about the implementation of artificial intelligence in pathology and discussed some economic aspects of such enterprise. Of note, the review presents several ideas and concepts that may be useful for those planning to adopt digital solutions in the pathology lab. The authors suggest the creation of a business model canvas, defined as "the rationale of how an organization creates, delivers, and captures value." A value proposition for customers is at the heart of a business model, and in the case of artificial intelligence in pathology, it includes cost reduction, quality improvement, and innovation[51]. Cost structure, key partners, key resources and activities, customer relationships, and revenue streams are also part of a business model that needs to be defined before launching a new solution in the market. Knowledge of regulatory approval procedures in each country is essential for the successful implementation of DP systems.

Conclusions

During the latest pandemic, pathologists have been working remotely in many circumstances to protect themselves, colleagues, family members, and the delivery of clinical services[52]. Digital pathology has been shown to contribute to maintaining the workflow in pathology labs[28 29], even with the social distancing restrictions. This article described the experience and expectations of Latin American pathology experts regarding DP implementation in the region.

The adoption of digital systems offers opportunities for increased cost-efficiency in pathology labs around the world[7 21]. However, the initial costs of implementation may be a great barrier for laboratories in developing regions such as Latin America. Another way to demonstrate DP cost-efficiency in Latin America would be through performing HEOR (Health economic & outcome research) studies, which would bring real-world data to show its economic value.

Digitization in pathology is presently less common and still less standardized than in other areas of medicine. Still, the development of advanced CAD-based applications will provide a massive potential for cost-saving measures through increased efficiency and patient safety[38]. Several issues need to be resolved to guarantee the region-wide implantation of digital pathology systems, such as internet infrastructure, professional training, and reimbursement problems.

In association with other stakeholders, a Latin American network of pathologists might be able to overcome some of the barriers, providing the benefits of DP to laboratories, pathologists, and patients.

This Latin American network may pave the way for this unavoidable change that will transform how pathological diagnoses are interpreted, reported, and used for clinical decision-making.

Abbreviations

CAD – computer-assisted diagnosis

CDx – companion diagnostic tests

DP – digital pathology

LIS – laboratory information system

TP – telepathology

WSI – whole slide imaging

WSS – whole image scanner

Declarations

Conflicts of Interest

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