Review Article

Digital cytopathology

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Abstract The advancements in the fields of technology and networking have revolutionized the world including the fields of medicine and dentistry. Telemedicine and its various branches provide a broad platform to medical professionals for consultations and investigations and can also act as a valuable educational aid. This review highlights the components, methods employed, clinical applications, advantages, disadvantages of telepathology and telecytology.

Keywords: Digital cytopathology, telecytology, telepathology, virtual microscopy, whole slide imaging

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INTRODUCTION

Pathology forms the foundation of modern medicine. Although the practice date backs to the Greek Physician Hippocrates, pathology's impact on health has relied heavily on a steady stream of technological advances. The advancements in the field of technology and networking led to the advent of telemedicine.

The WHO defines telemedicine as "the delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evolution and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities."[1]

Telepathology is a subtype of telemedicine which is often used among the medical and dental personnel.[2] It provides a broad platform to medical and dental professionals for further investigations and consultations.

DEFINITIONS OF TELEPATHOLOGY

Earlier, Weinstein in the year 1986 defined telepathology as "the practice of pathology over long distance."[3] Later, John Sinard stated it as "the use of any of the telemicroscopy technologies to make the primary diagnosis for the specimen from a remote site."[3] At present, telepathology has been defined as "the practice of transmitting digital pathology images of microscopic or gross findings through telecommunication networks to remote viewing locations for diagnosis, storage or education."[4]

HISTORY OF TELEPATHOLOGY

Telepathology has a diverse history spanning over 40 years. In the year 1960, telepathology was first demonstrated by the National Air and Space Administration.[5] In 1968,

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the first formal trial was done when black and white microscopy images of a blood smear were transmitted from Logan Airport in Boston to Massachusetts General Hospital.[5] In the year 1986, Ronald S Weinstein, "Father of Telepathology," coined the term telepathology and in a medical journal outlined requirements to create remote pathology diagnostic services.[6,7] In the same year, color video was used to demonstrate telepathology between Texas and Washington DC through satellite. In the year 1989, a National Telepathology Program was implemented for frozen section services in Norway. The complete telepathology system hardware became available only in the year 1994. In the year 2000, whole slide imaging (WSI) was introduced. In the year 2009, the Food and Drug Administration panel gathered to address approval for the use of digital pathology for diagnosis.[8]

Today, telepathology finds uses in several fields including telecytology. Telecytology refers to "diagnostic cytopathology performed on digital images."[9] Telecytology was first used with mainly cervical smears, and since then, its scope has expanded manifold.[10] In the field of dentistry, smears from potentially malignant lesions can be made and sent to distant places for obtaining expert opinions. Figure 1 depicts the various branches of telemedicine.[11]

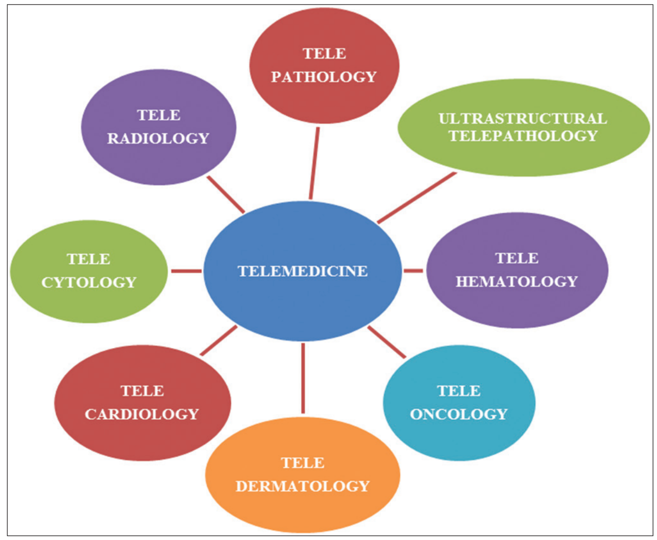

Figure 1: Different branches of telemedicine

Digital cytopathology now finds varied applications in various areas such as clinical practices, intraoperative consultation, education purposes and to overcome the problem of nonavailability of pathologists.[12] This review highlights the components, methods employed, clinical applications, advantages and disadvantages of digital cytopathology.

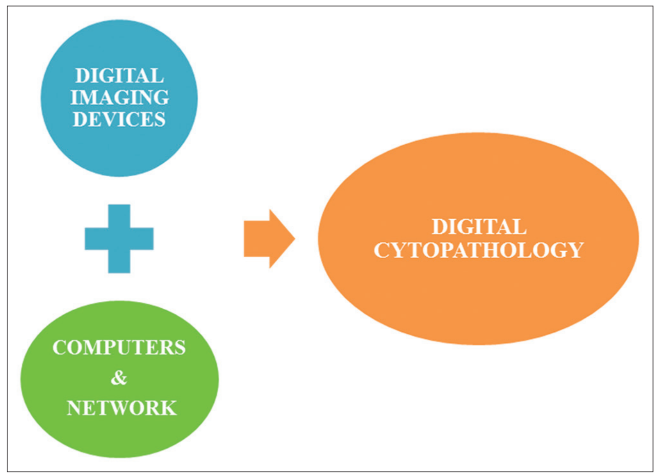

Figure 2: Components of digital cytopathology

COMPONENTS OF TELEPATHOLOGY/ TELECYTOLOGY (DIGITAL CYTOPATHOLOGY)

The entire process of digital cytopathology depends mainly on the conversion of optical information obtained from the eyepiece of a microscope into a digital image and then transmitting it remotely. This is done by the digital imaging devices (digital camera and WSI scanners), computers and networks.[13] Figure 2 represents the three main components of digital cytopathology.

Digital imaging process

A digital image in a computer comprises two-dimensional (2D) array of numbers, each element of which represents a pixel.[14] The process of digital imaging has four key steps: Capturing the image (image acquisition), saving, editing and viewing the image (storage and management) and finally, display or transmission of images.[8] Figure 3 shows the sequential steps involved in the process of digital imaging.

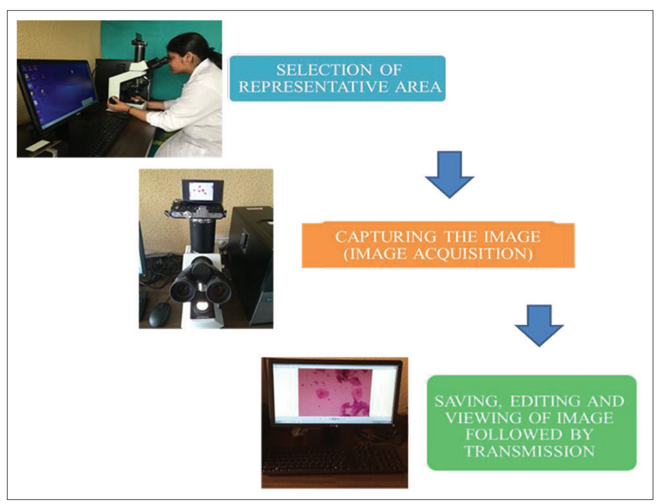

Figure 3: Steps involved in digital imaging

Three types of microscopic digital imaging

(a) Static (Still Images)

It is also called as the store and forward type of digital imaging and is the simplest of all techniques.[8,15-17] Here, the sender (pathologist) preselects the areas, captures the images with a camera and then digitizes the images, which are then transmitted to a remote personnel through e-mail or internet.[18]

Advantages

- Low cost
- No requirement of any special software
- Minimal equipment requirement (microscope with camera attachment, internet).[3,19]

Disadvantages

- Chances of missing an area of diagnostic significance since only a few areas are imaged and transmitted
- Areas to be imaged differs with the observers, hence resulting in observer bias which may also result in sampling errors
- Recipient has no control over the magnification and focusing of slides
- Extensive manual labor is required for scanning the entire slide and selecting the representative areas which accounts for ergonomics.[19]

(b) Dynamic (Real-time/Live/Robotic Microscopy)

It finds application mainly in frozen-section telepathology and understaffed areas.[20,21] Here, direct transmission of microscopic live images is done to the recipient by means of live telecommunication.[20,22]

Advantage

Robotic microscope recipient is capable of controlling the magnification and slide.

Disadvantage

This system is difficult and expensive as it requires charged coupled device video camera, high-resolution video monitors, special softwares, high-performance computers and most importantly a stable, broad bandwidth telecommunication link between the sender and recipient.[20]

(c) Whole Slide imaging/Virtual Microscopy

This method simulates light microscopy and involves the process of slide digitization (scanning and conversion of glass slides into digital images). Here, scanning of the slide in various fields and adjustment of the magnification can be done using specialized software. Moreover, this software also allows simulation of panning around and zooming in or out using a conventional microscope.[8] The current WSI technology provides us with virtual microscopy that can be accessed anywhere in the world using the internet.

Methodology

WSI involves two steps. First step involves generation of a large representative digital image using a specialized hardware (scanner). Second step utilizes specialized software to view and analyze the digital files.

Various scanners are commercially available in the market with a wide range of appearances and functionality. Some scanners can scan only a limited number of slides while other larger instruments can accommodate several glass slides. A WSI scanner comprises the following essential components: (i) a microscope with lens objectives, (ii) light source, (iii) robotics to load and move slides, (iv) digital cameras, (v) computer, (vi) software to manipulate, manage and view the digitized slides. Manual or automated scanning of the slides can be done. Speed of scanning varies from 1 to 3 min per slide, depending on the objective magnification and the plane of focus acquired.

Once the camera captures the digital data, a computer uses specialized imaging software to generate a virtual slide using either tile-based or line-based scanning. Tile-based scanning obtains large number of square image frames, which are assembled into a mosaic pattern, auto-correlated for proper alignment and then stitched into a single, seamless image. In line-based scanning, slide stage moves linearly in a single axis to obtain images in long, uninterrupted strips or lines. This method is more commonly used since it simplifies the image alignment process. The image resolution of the scanner is determined by the microscope objective, numerical aperture of the objective and the quality of camera photosensors.[23,24]

After generation of the virtual slide, software is applied for image acquisition, viewing, management, sharing and analysis. File formatting is done to attenuate the size of acquired raw, uncompressed whole slide image file. Since WSI files are significantly larger, compression-decompression methods are employed to archive the virtual slides, which gets stored as several image files in multiple folders. These files are reconstructed into a multilayered pyramid, enabling optimized viewing across multiple resolutions. Image viewer is the software utilized to navigate the digital slides, which allows the user to view, pan and zoom the virtual images on a digital screen.[25,26]

Figure 4 gives a step-wise representation of methodology employed in WSI.

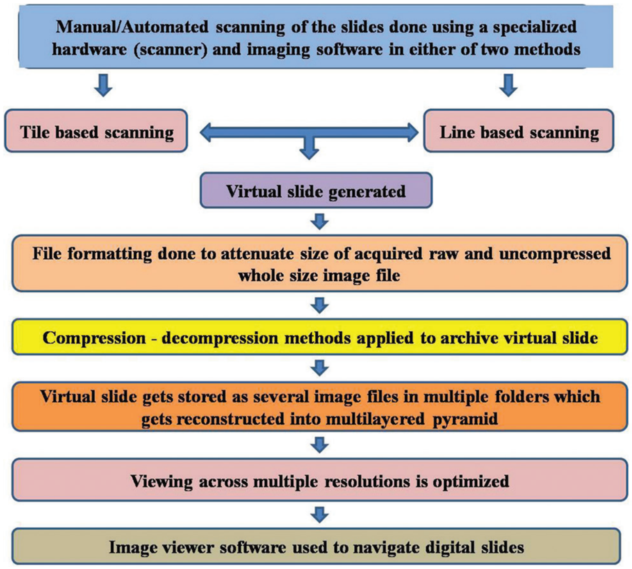

Figure 4: Methodology of whole slide imaging

Advantages

- Entire slide is scanned; hence, chances of missing out on any diagnostic information are very less
- With the advent of Z-stack function, three-dimensional scanning can be done
- Manual focusing can also be done
- More interactive
- Easily shared
- Questions or doubts can be cleared on the spot
- Helps in creating virtual slide boxes which could include a wide range of cases without the fear of loss, fading or breaking of the glass slides
- It can also be used for quality assurance, online cytology proficiency testing, online board examination or certification, providing cytopathology services to remote hospitals and for synchronous consultation.[13]

Disadvantages

- Entire method is very costly due to the scanners and softwares employed
- Requires specialized training
- Scanning the entire slide takes a long time
- As the entire slide is scanned, the size of the file increases and hence difficulty while sending as well as storing the images
- Lacks standardization due to the multiple softwares and vendors available
- Bandwidth limitation of network with area may not allow completion of the process.[13]

Computers and network

Computers with fast processors, high storage capacity and internet with high data rate (large bandwidth) are required.

CLINICAL APPLICATIONS OF TELEPATHOLOGY

It can be used in clinical practices for interactive discussions over difficult cases and for consultation by transmission of images from areas with limited resources.[27] It can also be used for intra-operative consultation with a pathologist away from the place of surgery. Thus, by combining the process of imprint biopsy, frozen sections and digital imaging, it is possible to obtain tumor-free margins and prevent unnecessary excision.[22,28] Moreover, second opinion services on frozen sections can be done which would limit unnecessary patient transfer. Telepathology also finds wide application in the field of education, wherein it provides significant advantages over the traditional method. It provides the advantage of multiple viewing at the same time and provides a wide platform for discussion and in keeping permanent records of a variety of cases.[13]

CLINICAL APPLICATIONS OF TELECYTOLOGY

The applications of cytopathology can be broadly classified into primary opinion, second opinion, third opinion and distance learning. Most commonly, it is used to obtain second opinion, i.e., expertise in cytology by transmission of images from areas with limited resources or by speeding up consult process.[29] Digital imaging has been employed in evaluation of gynecologic material obtained by cytobrush technique (PAP tests)[30,31] and nongynecologic material (aspirates of breast, thyroid, pancreas, pleural fluid specimens).[32-35]

Telecytology has also been used as a tool for quality assessment and improvement in the evaluation of thyroid fine needle aspiration specimens (fine-needle aspiration cytology).[24] Moreover, it can also be used for archiving and presentation of rare and unusual cases, classical examples of entities which would be of high significant value. WSI of slides could be made a part of patient electronic medical record and would facilitate rapid transmission of images between institutions and help in obtaining secondary opinion without the use of glass slides.[9] It can also be employed in distance-based continuing education with the use of teleconferences using images accompanied by lectures, real-time microscopy sessions. It also finds application in cytology proficiency testing and various research purposes.[36-39] In future, use of artificial intelligence and data mining can also be implemented in the field of digital cytopathology.[17]

Diagnostic cytology-on-a-chip technique rapidly detects potentially malignant disorders and oral cancers with high specificity and sensitivity. Bringing both molecular and morphological analysis in oral exfoliative cytology on a single nano-bio-chip platform will enhance its utility in clinical diagnostics.[40] Diagnostic cytopathology can also be implemented in the field of "Biobanking" which would help to access a wide variety of collected and well-annotated specimens.[41] In the field of dentistry, telecytology would prove to be an important tool when needing second opinion for smears of potentially malignant disorders obtained by cytobrush technique, malignancies or in cases of suspected recurrent malignancies or in patients where biopsy is a relative or absolute contraindication. Moreover, it could also be used for obtaining opinions regarding aspiration biopsy contents obtained from cystic, vascular lesions or tumors and for gaining any additional information on microbiological samples obtained from various diseases of microbial origin manifesting in the head and neck region. Consultation between armed forces dentists and specialists on patients' status can be facilitated by this digital revolution. This would provide easy and cost-effective access of dentists to specialists, thus providing improvement in the quality of care and aiding in better decision-making.

DIAGNOSTIC ACCURACY OF TELECYTOPATHOLOGY

Kim *et al*. used real-time dynamic telecytology to perform rapid assessments of pancreatic fine-needle aspiration biopsies and found no significant disagreement between routine on-site and telecytology interpretations.[42]

Kerr *et al*. reported 97% concordance and 99% accuracy using a locally controlled real-time system for rapid assessment.[43]

Alsharif *et al*. analyzed 400 cases and found 1.8% discrepancy rate using a real-time telecytology system, compared to a 3.1% discrepancy rate for routine glass-slide rapid evaluation, when each was compared to the final diagnosis.[44]

Heimann *et al*. used real-time telecytology for a variety of rapid fine-needle aspiration assessments and compared it to on-site rapid interpretations and found that 95% and 97% of all specimens were concordant with the final and on-site rapid interpretations, respectively.[45]

Galvez *et al*. analyzed the specific cytologic features identified in breast fine-needle aspirations and noted that all features assessed could be identified in both the static images and under the microscope.[46]

Della Mea *et al*. reported that using static images sent by e-mail achieved a satisfactory result in 84% of cases.[47]

Ayatollahi *et al*. reported 83%–87% accuracy for the interpretation of static images from pleural effusion specimens as compared to the final diagnosis versus 89% accuracy for interpretation of the glass slides.[35]

Jialdasani *et al*. reported a "clinically useful" diagnosis in 91% of cases using static-image telecytology.[48]

The above-mentioned studies show good overall diagnostic agreement between the various methods employed in digital cytopathology and glass slides, thus making it a promising diagnostic, educative and consultative tool in the near future.

ADVANTAGES OF TELEPATHOLOGY AND TELECYTOLOGY

The implementation of telepathology and telecytology has some very useful aspects. In histology, if the slides are defective or damaged, a tissue block is kept for potential recuts. However, every cytology slide is unique and irreplaceable. No two cytology slides even if obtained from the same site of the same patient demonstrate exactly the same features. Consultation over difficult images would reduce the time and cost factor. Digital imaging can be used to keep permanent digital copy which would diminish the need to physically send slides over large distances which could result in damage to the slides. Moreover, it could provide a unique teaching aid. A universally accessible database with ideal, varied digital images of various cases from different parts of the world can be made for the benefit of pathologists and cytologists everywhere.[13] Kumar *et al*. designed a randomized crossover trial to evaluate the quantitative and qualitative impact of WSI and virtual microscopy adaptive tutorials with traditional glass slide and textbook methods of learning cytopathology. They found that learning cytopathology with WSI and virtual microscopy adaptive tutorials was as effective as and was perceived as more efficient than learning from glass slides or textbooks.

LIMITATIONS

In spite of the long history of attempts to establish telepathology and telecytology in the mainstream, it still finds very limited applications and acceptance mainly due to the difficulty in making suitable imaging systems which could accurately reproduce the entire slide content. Moreover, difficulty is encountered in imaging the entire cytological material due to the three-dimensional element of these images contributed by cell clustering or artifact production. Cytological material tends to be more distributed throughout the length of the glass slide; hence, intensive screening of the entire slide is required which is difficult to screen and transit. In cytology, individual cell features and background are more focused on and this requires higher magnification and good quality images. Finally, the requirement of complimentary staining in cytology contributes to increased number of slides to be examined for providing a definite diagnosis.[13] These factors make cytological material imaging difficult. Moreover, the new technology is costly, subjected to observer bias, not useful for finding artifacts and chances of missing critical diagnostic areas such as early stromal invasion are high.[49]

CURRENT CHALLENGES

Current challenges in acceptance of telecytology and telepathology include high cost and complexity, low rate of acceptance due to the chances of missing significant details, security issues as the protection of electronic data has to be taken into consideration, legal ethical issues such as physician licensing issues, indemnification issues, insurance issues and other contractual issues, lack of standard protocol of specimen processing, lack of infrastructure and lack of training among medical personnel.[17,50,51]

NEWER TECHNIQUES, RECENT ADVANCES AND FUTURE PROSPECTS

Biobank

A biobank refers to collection of biospecimens in the form of tissues, smears and imprints that have been ethically collected and stored using the standard operating procedures. They represent a highly valuable resource for potentially malignant disorders and oral cancer biomarkers translational research along with cancer drug discovery. This technology includes next generation sequencing, circulating tumor cell characterization, single-cell RNA sequencing and circulating DNA analysis. Moreover, the availability of a large number of well-annotated biosamples is crucial to fully exploit these technological advances which can lead to quicker development of new therapies and to tailor existing therapies to molecularly defined populations.[41,52] Digitization of biobanking technology can be useful in research, education and consultation purposes.

Nano-biochip sensor

Nano-biochip sensor is a novel technique that combines cytomorphometric analysis with quantification of tumor biomarkers providing a rapid oral cytology assay.[53] The oral-cytology suspension is first delivered to the sensor using pressure-driven flow, wherein cells larger than the membrane pore size are retained on the membrane surface.[52,54] The captured cells are then stained with fluorescent dyes and immunoreagents to distinguish the cytoplasm, nucleus and cancer biomarkers. Finally, the stained cells are subjected to a 3D fluorescence-microscopy scan of the membrane surface which is followed by automated image analysis.

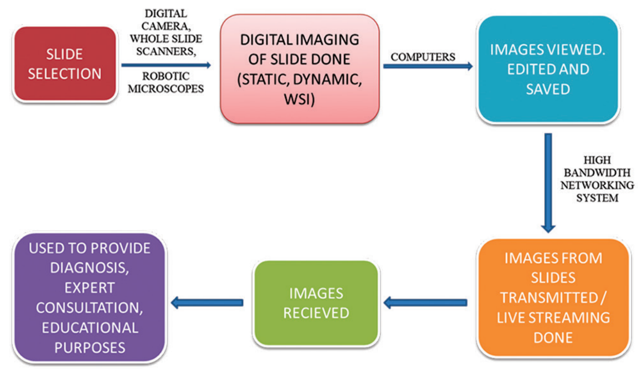

Figure 5: Process of digital pathology

Picture archiving and communication system

It is a medical/dental imaging technology which provides storage and convenient access to images from multiple modalities.[55] Electronic images of cytological smears, X-rays, computed tomography scans, histopathology slides and reports are transmitted digitally which eliminates the need to manually file, retrieve, or transport. Picture archiving and communication system can be used to deliver timely and efficient access to images, interpretations and related data.

CONCLUSION

The steps involved in digital pathology are summarized in Figure 5.

Telepathology and telecytology are the recent technological innovations in the medical and dental field which allows the practice of pathology and cytopathology over a distance by transmission of digital pathological and cytological images using telecommunication networks. It provides a wide platform for discussion and hence obtaining expert opinion. It can also be used for slide archiving and as a very lucrative educational tool. Factors such as further advancements in technology, adequate training of cytopathologists and evolving regulatory and legal guidelines would determine if digital pathology would replace the conventional method of reviewing glass slides.[9] To conclude, pathology informatics is likely to revolutionize the role of a pathologist into a diagnostic specialist.

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Conflicts of interest

There are no conflicts of interest.

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