Technical Paper ■

Uses and Benefits of Teledermatohisto-pathology

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Abstract. Teledermatohistopathology is a telemedicine application related to histological diagnosis of cutaneous specimens that works by using the same technology as telepathology. With the aim of providing the most accurate diagnosis, pathologists and dermatologists can work more closely together by means of teledermatohistopathology. The aim of the article is to encourage its introduction into clinical practice and teaching at medical schools in Slovenia. An important step towards this goal was made at the Faculty of Medicine in Maribor, where the first Aperio slide scanner has been operating since 2014. Several other important initiatives are also underway in Slovenia.

Uporaba in prednosti teledermatohisto-patologije

Izvleček. Teledermatohistopatologija je veja telemedicine, ki se ukvarja s histološko diagnostiko kožnih vzorcev in uporablja enako tehnologijo kot telepatologija. Vodi do tesnejšega sodelovanja med patologi in dermatologi ter posledično do postavitve kar najbolj natančne diagnoze. Namen članka je spodbuditi vpeljavo teledermatohistopatologije v klinično prakso ter v učni proces na medicinskih fakultetah v Sloveniji. K temu cilju se približujemo tudi s prvim Aperio skenerjem histoloških preparatov pri nas, ki deluje od leta 2014 na Medicinski fakulteti v Mariboru. V Sloveniji je v teku še več pomembnih projektov s tega področja.

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Introduction

Telemedicine is an emerging field within medicine, which makes use of various telecommunication technologies to exchange medical information over a distance for the purpose of consultation, diagnosis, treatment and teaching. Use of telemedicine can reduce the cost and time of any travel required (by patients, their carers and health care professionals), and leads to a faster delivery of medical services.[1] It has therefore got the potential to revolutionise the delivery of health care in the way that also offers an environmental benefit to mankind.

Teledermatology and telepathology are subcategories within telemedicine, and teledermatohistopathology is a sub-field of both of them. For a better presentation of uses and benefits of teledermatohistopathology it is fundamental to first describe the two of the main telemedicine areas that are affecting it.

Teledermatology

Dermatology is one of the most visual specialties in medicine, making it ideally suited for modern communication and information technology. The application of clinical telemedicine that deals with the practice of dermatology is called teledermatology. Its goal is to provide the best quality of dermatologic care via the latest telemedicine techniques by moving patient information rather than the patient. The specialist care is generally available in larger medical centres in the developed world but quite inaccessible in less developed countries (Africa) as well as in sparsely populated regions (Alaska, Australia). Teledermatology practice brings a solution to overcome this global problem.

The basic option that teledermatology can offer to a dermatologist is to evaluate video or still images of skin disorders along with patient information. There are numerous articles evaluating diagnostic concordance of teledermatology, most of them comparing diagnostic capabilities of teledermatology to traditional face-to-face evaluations. Most experts agree that store-and-forward and real-time video teleconferencing teledermatology is as clinically effective as a face-to-face consultation.[2] Available studies report a rate of 54-95 % (average of 75 %) agreement between store-and-forward procedures using conventional digital cameras and findings from direct physical examination.[3] In the last years new fields in teledermatology have emerged, such as teledermoscopy, which is a promising area for the clinical examination of ambiguous pigmented skin lesions and for melanoma screening. The feasibility of mobile teledermatology and mobile teledermoscopy has recently been proven. These new facilities have the potential to become an easily applicable tool for everyone and may open the door for a new flexible triage system for detection of skin cancer in general and melanoma in particular.[4] Moreover, web consultations in dermatology are a rather new tool that has only become available in the last few years, and teledermatologic services through the Internet offer many possibilities, including continuing medical education, on-line atlases and databases, and specific web applications suited for teledermatology.[5] Another important sub-field is teledermatohistopathology, in which the histological specimen of the skin is evaluated on a monitor screen rather than under a microscope.

Telepathology

Telepathology is the practice of diagnostic histopathology performed on digital pictures.[6] In 1986, an academic pathologist, Ronald S. Weinstein M.D., authored the first paper on telepathology, thereby coining the term “telepathology”. Dr. Weinstein is widely regarded as a pioneer in the field of telepathology and is often cited as the "father of telepathology".[7] Three types of telepathology systems exist: static telepathology, dynamic telepathology (real-time robotic microscopy systems) and virtual slide telepathology ("virtual microscopy"). Dr.

Weinstein invented robotic telepathology systems and telepathology diagnostic networks and was more recently also one of the five co-inventors of the array microscope, which serves as the digital imaging engine for the first ultra-rapid virtual slide scanner that has been recognised as a breakthrough technology by the Wall Street Journal.[7] This technology has been commercialised by more than 30 companies in Asia, the United States and Europe.[8] Europe is involved in big changes in the world of tissue-based diagnostics. Virtual slide implementation in routine tissue-based diagnostics is on its way.[9]

For many years, microscopic details had been stored for archival or teaching purposes in the form of glass slides.[10] Nowadays, virtual microscopy, a type of telepathology that takes place in real time, can be used as an e-learning method to teach histology and pathology.[11] There is an overall increasing tendency at medical schools around the world to digitise microscope histopathological slides for interactive use of teaching resources from anywhere at any time, independent of class schedules.[12] Emerging digital microscopy technology and newly developed scanning light microscopy systems enable histologists to transfer analogue image data of entire slides into digital ones, and to provide them to students in the class with identical contents and quality.[13] Digital slides produced using whole slide imaging (WSI) can be visualized at any magnification and moved along horizontal and vertical axis, which perfectly imitates using a traditional microscope and a glass slide.[12] Digital files are available on a web server that can be viewed anytime with an Internet- or Intranet-connected desktop computer, portable or tablet computer, or even through smartphones.

Potential benefits of telepathology include providing a means of conveniently delivering pathology services in real-time to remote sites or underserviced areas[14] and has already been mentioned above as a new method for teaching. The main aims for introducting telepathology can be summarized as follows:

- Increase of service quality offered to patients due to qualified second opinions;
- Sharing and discussion of interesting pathological cases for increasing professional competence;
- Creation of a permanent and available scientific repository.[15]

Teledermatohistopathology

Teledermatohistopathology, or shortly teledermatopathology, can be defined as a telemedicine application related to histological diagnosis of cutaneous specimens. Its development and implementation around the world is very heterogeneous due to the wide range of existing geographical, social and healthcare conditions.[16] Numerous studies have investigated feasibility and reliability of teledermatohistopathology. Results suggest that telepathology performed by physicians active in dermatopathology may serve as a reliable technique for the diagnosis of cutaneous diseases when experts in dermatopathology are not available locally. Furthermore, teledermatopathology is attractive because it provides an opportunity to obtain timely consultation on difficult cases.[17]

Teledermatohistopathology is not only a sub-field of teledermatology but also of telepathology and uses the same telecommunications technology as the latter. The types of telepathology systems are explained below.

Types of tele(dermatohisto)pathology systems

Static image telepathology is the simplest form of telepathology communication. It functions by capturing selected digital images at one site and thereafter by transmitting them electronically to

the remote site in the form of email attachments or a file transfer protocol (FTP) connection or using a specific web application. This method has some advantages, such as low cost,[10] but the image selection and quality is a major issue.

The second type is dynamic robotic telepathology, which is the transmission of real-time images from robotic microscope so that distant operators have complete control over the received images. The major drawback of this method is its high cost, but its advantages include controlling image viewing with no sampling errors.[10] Components of such a system include a workstation equipped with a high-resolution video camera attached to a remote-controlled light microscope; a pathologist workstation incorporating controls for manipulating the robotic microscope as and a high-resolution video monitor; and a telecommunications linkage.[18]

The third type is represented by virtual slide system (VSS), also called "virtual microscopy" or "remote patchwork". It is a form of static telepathology in which digital imaging technology is used to digitize, store, and view slides. A digital representation of an entire slide at the resolution of a high-magnification objective is designated a virtual slide. The application spectrum of dynamic telepathology is limited by its "live" nature and single user control, whereas virtual slides archived on a network server can be individually controlled and simultaneously viewed by a large number of users.[10] The implementation of virtual slide systems for teledermatohistopathology has allowed avoiding the limitations imposed by conventional microphotography and represents the future in this telemedicine discipline.[5,19]

Several "virtual microscopy" implementations are in use worldwide. The basic system includes a digital camera or scanning system, camera-to-microscope adaptor, microscope, and a computer with an adequate graphics card and monitor. The image in a light microscope is usually acquirable by cameras with CCD (charged coupled device) sensors, producing an analogical signal. The CCD is composed of a large matrix of photosensitive elements (often referred to as "pixels" – picture elements) that simultaneously capture an image over the entire detector surface.[20] The light-intensity information for each pixel is stored as electronic charge and is converted to an analogue voltage by a readout amplifier. This analogue voltage is subsequently converted to a numerical value by a digitiser situated on the CCD chip (or very close to it).[20] The resolution of a camera refers to the pixels that CCD is capable to acquire. For the purposes of teledermatohistopathology, a resolution of 768×576 pixels should be sufficient, but 1024×768 pixels of resolution are recommended with 24 bit of colour.[16] Creating a patchwork may take from several minutes to some hours depending on the area that has to be scanned.[21] The storage of the images is on standard hard drives from 100 gigabytes onwards.

Difficulties in introducing teledermatohistopathology and possible solutions

New facilities in teledermatology have the potential to become an easily applicable tool for everyone and teledermatohistopathology is showing similar potential. The use of teledematohistopathology can increase the healthcare standard and the accessibility to the health care system in developing countries and sparsely populated regions. However, some limitations related to economic, medico-legal and technical issues remain, particularly when dealing with inflammatory skin diseases, as the performance seems to be influenced by the availability of complete clinical data.[16,19] The high cost of the robotic remote telepathology units and VSS is one of the most important reasons why the acceptance of teledermatohistopathology into our daily practice has been delayed.[2,22]

A recent study conducted by Speiser and colleagues from Loyola University Medical Center in Maywood, Illinois, established a novel and cost-efficient solution for those institutions that may not have the budget to purchase either a dynamic

robotic system or a VSS. They found out that telepathology performed via a tablet PC may serve as a reliable and rapid technique for the diagnosis of routine cases with some diagnostic caveats in mind.[8] They used a high-resolution video camera (Nikon DS-L2, version 4.4) mounted on a microscope to transmit digital video of a slide to an Apple iPAD2 (Apple Inc., Cupertino, CA) at the pathologist's remote location via live streaming at an interval time of 500 ms and a resolution of 1280/960 pixels. About 92.5% of cases were diagnosed on immediate viewing (for <5 seconds), with an average time to diagnosis of 40.2 seconds. Of the cases diagnosed immediately, 98.8% of the tele-diagnoses were concordant with the original diagnoses made by conventional light microscopy.[23]

Another solution is represented by smart phones (iPhone, iPod TM Touch, Android, and others), which are widely available and have built-in high-resolution (5 megapixel) cameras capable of still image capture and live video images. They have the ability to connect to network systems via a wireless method (Wi-Fi or cellular network). Adaptors are available (http://www.skylightscope.com/) that allow the smart phone to be connected to the microscope eyepiece. This permits the smart phone built-in camera to view the image in the ocular eyepiece. Static images can be captured and sent via wireless connection to an e-mail address. Live image feeds can be sent wirelessly utilizing the on-site smart phone apps/software (FaceTime™ for Apple, Skype™ for Android/Windows) to the remote viewer. The Apple environment allows for the live image to be delivered to any Apple iOS device (iPhone, iPad, iPad-mini, iPod Touch) and Mac-based system with FaceTime software. Advantages of the smart phone system include portability, no need for a fixed dedicated microscope camera, no need for a hardwired Ethernet connection, and affordability. A simple system could be assembled for as little as a few thousand dollars. Challenges include providing a stable wireless system that can deliver the necessary data to the remote viewer with a high enough quality to provide meaningful interpretation.[24]

Improvements in the diagnostic facility will follow from further development of the VSS, the slide processor, and training in the use of a "virtual microscope". Undoubtedly, as technology becomes even more sophisticated in the future, VSS will overcome the present drawbacks and find its place in all facets of teledermatohistopathology.[19] Currently the economical investment for VSS or real-time teledermatohistopathology equipment may be beyond the reach of most dermatohistopathology practices, but in very near future high-resolution devices will become accessible for most of us.[25]

The beginnings of telepathology in Slovenia

The first Aperio ScanScope CS slide scanner in Slovenia has been operating since 2014 at the Medical Faculty University of Maribor and can be used for healthcare, research and education. The device is a bright-field scanner that digitises whole histology or pathology microscope slides at 20× and 40× magnification and provides very high resolution images (~ 0.5 microns/pixel for 20× and ~ 0.25 microns/pixel for 40× scans). These images can be easily viewed with Aperio's free image viewer (ImageScope), which also allows the user to take snapshots and perform quantitative analysis. Several analysis algorithms are available:

- Positive Pixel Count – allows for the measurement of area and intensities of up to two stains (e.g., measuring the positive DAB staining);
- Membrane – detects membrane staining for individual cells and quantifies their intensity and completeness;
- IHC Nuclear – this algorithm can be used to detect nuclei and quantify their staining intensity;

- Deconvolution – this algorithm is useful for separating and quantifying area and intensity of multiple stains;
- Microvessel Analysis – this is used for angiogenesis measurements;
- Rare Event Detection.

Several major initiatives are currently in progress for introducing online competence and diagnostic decision-making using this version of virtual microscopy.

Traditionally education in pathology has been performed by using textbooks, glass slides and conventional microscopy. Virtual microscopy has created enormous opportunities in pathological training in undergraduate education. Students no longer need to be in the same room as the slides. Furthermore, centralised pathological resources could be delivered to many students simultaneously.

We are testing the same principle in the setting of postgraduate pathology teaching and training. At the Institute of Oncology in Ljubljana, Slovenia, regular slide seminars on difficult cases in tumor pathology have been organized for many years. The currently applied approach with transfer of slides and patient data to participating pathologists in Slovenia, Croatia, Bosnia and Herzegovina, and Italy is costly and time-consuming. WSI will improve this process and substantially reduce the overall turnaround time for slide review.

Virtual microscopy has been recently introduced for central pathology review and diagnostic reproducibility in the National Bowel Cancer Screening Programme in Slovenia (SVIT). In this multi-centric study, the reproducibility of the methods for the assessment of pathological characteristics of several precancerous lesions has not yet been determined. This impedes its use and reporting in routine surgical pathology. We expect that with the use of WSI between the participating pathologist and the central pathology review panel the diagnostic consensus for these lesions will result in improved inter-observer agreement.

The Golnik Hospital started using telepathology 15 years ago by providing consultations for pathologists in developing countries through the *ipath* consultation center for telepathology, which is based at the University of Basel.[26] In 2008, an internal telepathology system was introduced, intended for quicker assessment of the adequacy of cytological samples. They are using a Coolscope II (Nikon, Japan) digital microscope, which offers the possibility of a simple "real-time" virtual microscopy. This way, the Golnik Hospitalhas achieved a decreased in proportion of non-representative samples from 41 to 2 per cent.[26]

Recently, an international telepathology project between Institute of Pathology at the University of Udine, Italy, and the Institute of Pathology at the Izola Hospital, Slovenia, tested a basic digital microscope to verify its performance for occasional remote consultation**.** The system used was composed of a pair of digital microscopes (Leica DMD108, Leitz Microsystems, Wetzlar,Germany) associated to a high-resolution videoconferencing systems (Tandberg 990, Lysaker, Norway). The systems were connected through the Internet. Sixty histology and cytology cases have been collaboratively diagnosed between the two pathology institutes to verify the diagnostic performance of the system in terms of image quality and time needed for diagnosis. No discrepancies between local and remote diagnoses have been identified, with diagnosis time being reasonably close to typical microscope observation times.[27]

For dermatohistopathology we are so far aware of occasional use of virtual slides technology for difficult cases consultation between Italy and Medical Faculty University of Ljubljana.

Conclusion

Skin diseases vary widely from conditions that can interfere with social activity because of cosmetic disorders, such as acne and alopecia, to diseases that affect patient prognosis and quality of life, such as malignant melanoma or basal cell carcinoma, as well as various chronic inflammatory diseases.[28] When the determination of the exact diagnosis and the correct procedure for treatment of these diseases cannot be diagnosed on clinical grounds alone, microscopic findings are crucial to make the final decision. But the problem in Slovenia is that very few dermatologists engage in histopathological diagnosis, and very few pathologists subspecialize in dermatohistopathology. Hence, with the aim to provide a more accurate diagnosis for our patients, pathologist and dermatologist should work more closely together with the use of telemedicine. Furthermore, given the disproportionate availability of physicians and medical facilities at the two University Medical Centres as compared to local hospitals, access to dermatological and pathological care is often woefully inadequate for achieving proper and timely diagnoses. Hence, teledermatohistopathology could offer important advantages for both the pathologist and the dermatologist, and even more so for their patients. In the future every physician will likely be directly or indirectly confronted with telemedicine,[3] so teledermatohistopathology is also going to play an essential role in the future of medical education and assessment.

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