

New Developments in Digital Pathology: from Telepathology to Virtual Pathology Laboratory

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Abstract. *Aims:* To analyse the present status and future development of computerized diagnostic pathology in terms of work-flow integrative telepathology and virtual laboratory.

Present status: Telepathology has left its childhood. The technical development of telepathology is mature, in contrast to that of virtual pathology. Two kinds of virtual pathology laboratories are emerging: a) those with distributed pathologists and distributed (≥ 1) laboratories associated to individual biopsy stations/surgical theatres, and b) distributed pathologists working in a centralized laboratory. Both are under technical development. Telepathology can be used for e-learning and e-training in pathology, as exemplarily demonstrated on *Digital Lung Pathology Pathology* (www.pathology-online.org).

Features of virtual pathology: A virtual pathology institution (mode a) accepts a complete case with the patient's history, clinical findings, and (pre-selected) images for first diagnosis. The diagnostic responsibility is that of a conventional institution. The internet serves as platform for information transfer, and an open server such as the iPATH (<http://telepath.patho.unibas.ch>) for coordination and performance of the diagnostic procedure. The size of images has to be limited, and usual different magnifications have to be used. A group of pathologists is "on duty", or selects one member for a predefined duty period. The diagnostic statement of the pathologist(s) on duty is retransmitted to the sender with full responsibility. First experiences of a virtual pathology institution group working with the iPATH server (Dr. L. Banach, Dr. G. Haroske, Dr. I. Hurwitz, Dr. K. Kayser, Dr. K.D. Kunze, Dr. M. Oberholzer,) working with a small hospital of the Salomon islands are promising. A centralized virtual pathology institution (mode b) depends upon the digitalisation of a complete slide, and the transfer of large sized images to different pathologists working in one institution. The technical performance of complete slide digitalisation is still under development and does not completely fulfil the requirements of a conventional pathology institution at present.

Virtual pathology and e-learning: At present, e-learning systems are "stand-alone" solutions distributed on CD or via internet. A characteristic example is the Digital Lung Pathology CD (www.pathology-online.org), which includes about 60 different rare and common lung diseases and internet access to scientific library systems (PubMed), distant measurement servers (EuroQuant), or electronic journals (Elec J Pathol Histol). A new and complete data base based upon this CD will combine e-learning and e-teaching with the actual workflow in a virtual pathology institution (mode a). The technological problems are solved and do not depend upon technical constraints such as slide scanning systems

Perspectives: Telepathology serves as promotor for a new landscape in diagnostic pathology, the so-called virtual pathology institution. Industrial and

scientific efforts will probably allow an implementation of this technique within the next two years.

Introduction

At the beginning, telepathology has been defined as “the work of a pathologist at a distance” [1,2]. In accordance with this definition at least two main applications can be distinguished: a) its use for primary diagnosis, and b) its use for secondary diagnosis [3-6]. The scope of primary diagnosis in telepathology is mainly covered by its application in frozen section services, and consecutively called on-line telepathology [1]. Specific remote control microscopes with fixed partners have been developed, working either on an individual or an open platform, i.e., the internet [7]. Whereas nearly all applications of on-line telepathology in frozen section services are related to a bilateral application (client – server configuration), the implementation of open standards to these systems offers, at least theoretically, the involvement of several pathologists located at different institutions in primary diagnosis services.

Similar to the history of on-line telepathology, the use of telepathology for secondary diagnosis started with point to point solutions [1]. However, already in the first trials of telepathology for second opinion services the necessity of an open platform has been realized [8-10]. The development of the world wide web as a common telecommunication standard, therefore, promoted the application of off-line telepathology to a large extent, and the internet served immediately for transfer of the client’s request and the expert’s answer [11]. Frequently, several experts are involved in reviewing a difficult case instead of consulting only one outstanding colleague [12]. Thus, again, the scenario of telepathology, as given by the above stated definition, has changed. Therefore, at present telepathology should be defined as an electronic, image related information transfer and classification in diagnostic pathology between 2...n partners, either on-line or off-line [13].

This extended definition includes, in addition, the possibility, that several clients (or information sources) might be involved in the process of diagnosis findings. The latter can be seen in image segmentation and measurement procedures, retrievals for logic evaluation of potential diagnosis, or adding clinical information from different data bases [14].

The use of the internet for consultation and primary diagnosis services has lead to the construction of specific servers, which replace the simple “letter-oriented” information transfer of e-mails with attached forms and still images. At present, three different server types have been installed, namely a) that of the Armed Forces Institute of Pathology (AFIP) {<http://www.afip.gov>}, b) that of the Institute of Pathology, University Basel (iPATH) {<http://www.telepath.patho.unibas.ch>}, and c) that of the Union contre le Cancre at the Institute of Pathology at the Charite, Berlin (UICC-TPCC) {<http://pathoweb.charite.de/UICC-TPCC/default.asp>}. The principal differences of these server in terms of structure and potential application have been discussed in detail elsewhere, and can be summarized as follows: The AFIP server possesses the highest diagnostic responsibility and most strict organization, that of the UICC-TPCC is equivalent to an intermediate realization of the mentioned teleconsultation services, and the iPATH is the most flexible system with the lowest diagnostic responsibility [15-21].

Based upon the recent development of telepathology systems, in this article we will describe the potential implementation of these systems into the daily workflow of a diagnostic pathology institution. The technical progress in digitising complete glass slides and implementation of artificial intelligence (AI) into these systems serve as additional parameters in judging and estimating the future “way of telepathology”, which will probably lead to a new environment in pathology, the world of so-called digital pathology.

1. The Virtual Pathology Institution (VPI)

The outstanding majority of in telepathology trials results in diagnostic quality which is equal to or only to an insignificant lower level inferior to the conventional performance in frozen section service or in expert consultation [1,2]. For example, the only randomised frozen section service study on breast cancer describes nearly identical results of both the on-line telepathology or the conventional frozen section service [22-24]. Thus, telepathology is mature to be introduced into a pathology laboratory, which can be performed in two different ways: a) on distributed pathologists associated to different individual biopsy stations or surgical theatres, and b) on distributed pathologists working in only one pathology institution. The first scenario can be practically used for institutions working in developing countries or for surgical theatres without associated pathologists. It results in the assessment of a group of pathologists who diagnose only on an electronic display, and otherwise follow the conventional conditions of a pathology institution. These include the set up of a “duty plan”, i.e., time schedules of the involved pathologists’ availability to diagnose submitted cases, their individual responsibility, and an intra-institutional case discussion. The technical prerequisites for such a system are internet connections of each participating pathologists, and a system which handles the administration and management of the submitted cases and the diagnoses. This system has to be open and flexible. It has to administer the submitted cases, the availability of the pathologists, the information of the client, and an adequate documentation system. To our knowledge only one virtual pathology institution is working at present. It includes several well-known pioneers of telepathology (Dr. L. Bannach, Dr. G. Haroske, Dr. K. Kayser, Dr. K.D. Kunze, Dr. M. Oberholzer, and others) and uses the iPATH for administrative purposes. The cases are submitted from a small surgical institution which is not equipped with a local pathologist, namely, from the Honaria Hospital of the Salomon Island. More than one hundred cases have been analysed until now without major difficulties.

The second scenario, which focuses on different pathologists who are working in the same “umbrella institution” has not been implemented solely at a virtual basis to our knowledge. In contrast to the distributed VPI the local VPI might still be based upon conventional glass slides, from which selected still images at moderate and higher magnification are acquired and transferred to a combined image – case documentation system. Most of these systems are only extensions of the common pathology documentation systems, and have no or only minor principal advantages when compared to conventional pathology documentation systems. They might, however, additionally be associated with distinct measurement or diagnosis support systems, such as quantitative immunohistochemistry or neural networks. These extensions are of real clinical value. They need, however, an adequate artificial intelligence system (AI) to improve pathology diagnosis performance [26,27].

The final VPI as defined in the second scenario is based upon complete digitised glass slides (virtual slides). In principle, virtual slides possess several significant advantages in comparison to “normal” glass slides: Theoretically, these include easy documentation, storage, and retrieval, contemporary diagnosis of several pathologists, contemporary quality assurance and evaluation, fast performance of additional staining, or construction of large distributed VPIs. The general technological constraint is based upon the necessity to digitise a complete glass slide into a virtual slide. These virtual slides amount to several Giga Bytes in size, and are, thus, not easy and fast to handle at present. The parameters of the virtual slide technology, which is commercially available today, is listed in table 1.

Table 1. Features of commercially available slide scanners (based upon 3DHistech) and those needed for practical online use

General features (implemented)	
input format	standard microscopic slides
scanning region	20 * 50 mm
tissue finding	automatic
focus	automatic

<i>Parameters</i>	<i>available</i>	<i>needed</i>
scanning time/slide	appr. 5 min	< 10s
slide load/night	appr. 300 slides	>1000 slides
image size	appr. 3 – 4 GB	> 4 TB
network interface	< 1Gb/s	> 10 Gb/s

As shown in table 1, the “practical necessity” is still a great distance away from the commercially available technology at present. A digitalisation of approximately 300 slides over night, and the use of digitised slides for implementation of a virtual slide data bank (image data bank) seem to be the only practical application until now.

In principle, a pixel resolution of 0.5 $\mu\text{m}/\text{pixel}$ is required if a region of a complete glass slide should be scanned, and if all magnifications afterwards should be performed digitally. The best display available possesses 9 million pixels presented at a density of 200 pixels/inch. (IBM, flat screen T221). By a simple mathematical computation we can, therefore, display 0.1 mm to 1 inch on this screen, or, in other words, an area of 2 mm * 2 mm on the whole screen. This is the size of a normal biopsy. In addition, the areas of tissue arrays or fine needle punctions measure about 0.5 – 1 mm in diameter, and can, thus, scanned, computerized, and visualized as a whole. One need an array of approximately 16,000 pixels in order to display a complete biopsy on this screen without a patchwork procedure for digitalisation.

The technology, which is available at present, is, however, sufficient for additional practical use only if AI is implemented, too.

2. Introduction of AI

The technical development of image acquisition and storage induces image sizes which are difficult to handle, and even more difficult to transfer from the point of acquisition or storage to clients who are viewing or manipulating images. The image size of a complete glass slide measures several Giga Bytes. Image compression procedures might reduce the size by factor 10 however, do not result in an adequate size for normal application, such as viewing or performance of actions, which are based on viewing an image. The most appropriate solution can be seen in the application of artificial intelligence (AI), which takes into account the aim of the client. For example, if the client wants to perform relative measurements of image objects, the transmission of the objects might be sufficient instead of transmitting the whole image. If this is not possible due to segmentation problems, appropriate sampling might be another solution.

The prerequisite of AI application is to focus on the “aim of the user”, i.e., the knowledge, what the user wants to do with the image. If this application has been defined, the original large sized image can be analysed in relation to these aims, and only the

interesting compartments will be transferred, stored, or searched for the information wanted.

In practice, the simplest method is to perform an adequate sampling. Little has been published on “adequate sampling”. Therefore, some basic aspects are presented here. As shown in table 2, in general, five different sampling techniques can be distinguished.

Table 2. Principles of different sampling techniques

<i>Sampling procedure</i>	<i>Performance (pixel selection)</i>	<i>Application</i>
Random	Random start point	Stereology
Stratified	Object related start point	Diagnostics (cancer cell)
Passive (random or stratified)	Fixed segmentation procedure	Conventional stains
Active (random or stratified)	Local segmentation procedure	Immunohistochemistry
Functional	Evaluation of rare events	Molecular Pathology

Random sampling is the most frequently performed sampling procedure. Its roots go back to the earliest days of stereology. A simple grid is superimposed to the image, and the hits of the grid points with segmented image points are counted. As the relationship between the grid starting points and the image points is random, this technique is a bias-free and easy to apply technique. It is used to calculate spatial and volume related fractions of the objects (volume fraction, surface/volume fraction, etc).

Stratified sampling requires a knowledge of object features which are searched for. Only those objects are taken into account, which fit into the predefined scale of the objects' scales. Stratified sampling is frequently used on cytology smears in search for rare events, i.e., cancer cells or cells with similar predefined features.

Both random and stratified sampling procedures can be further distinguished by the “relationship (function) of the “hits” between the grid points and the segmented image points. If this relationship is fixed, i.e., if the selection function $f_s = \{1,0\}$, we have only points which hit and those, which do not. This relationship is fixed for the whole image. This procedure is called *passive sampling*, and is the most frequently used sampling technique.

Active sampling has to be performed, if the segmentation procedure requires a local function, for example, dependent upon the staining intensity. The selection function can then be described by $f_s = \{g(x,y)\}$, whereas $0 < g(x,y) < 1$. In practice, this procedure leads to a secondary transformation of $g(x,y) \rightarrow \{0,1\}$ dependent upon additional features of the selected object. It is an appropriate technique to search for the best fitting segmentation threshold in immunohistochemical images, and can standardize variations in staining intensity or slide thickness.

Functional sampling tries to define the “biological significance” of segmented rare events, and to distinguish artefacts from those with real potential meaning. It is based upon syntactic structure analysis, i.e. an analysis of segmented rare objects in spatial relation to their environment, i.e., frequent objects with different features. Its is a useful technique for analysis of relationship between different (immunohistochemical) markers, such as proliferation (e. g. MIB-1) and expression of receptors (e. g. galectin-1, galectin-3), or for molecular pathology data [28].

The implementation of AI based upon the discussed sampling procedures induces new aspects of telepathology and the establishment of virtual laboratories. It can, for example, significantly diminish the time needed for primary diagnosis in telecytology [26].

3. E-Learning and e-Teaching in Pathology

AI seems to be, in addition, necessary when establishing a customer – oriented e-learning system in diagnostic pathology [29]. These systems have to meet a conclusive information agglutination in diagnostic medicine, based upon histological images. The “Digital Lung Pathology” CD gives a good example of the present status of the technique [30]. It presents a selection of about 60 rare and frequent lung diseases. It contains a regular structure based upon the experiences of the textbook “Analytical Lung Pathology” [31].

The electronic medium, however, permits a user-friendly presentation of all headlines related to an included lung disease, an easy fresh-up of the latest literature, and a suitable control of the user’s diagnostic knowledge. Electronic zooming is possible on all included radiological and histological images, as well as rapid “jumps” to related diseases or information content by use of prepared links. The presented structure of any included disease are shown in table 3.

Table 3. Disease structure of the Digital Lung Pathology CD (www.pathology-online.org)

<i>Definition:</i>	
<i>Incidence/Epidemiology:</i>	<i>Clinical Presentation:</i>
<i>Prognosis:</i>	
<i>Endoscopy:</i>	<i>Images</i>
<i>Radiology:</i>	<i>Images</i>
<i>Pathology:</i>	<i>Gross</i>
<i>Histology:</i>	<i>Images</i>
<i>Image descriptors:</i>	
<i>Special stains:</i>	
<i>Genotype and cytogenetic analysis:</i>	
<i>Hallmarks of Diagnosis:</i>	<i>Differential Diagnosis:</i>

4. Search for References (National Library)

The unique structure permits a user friendly information presentation and lookup. For each disease, at least four different histology images at different magnifications are included. The radiological images consist of normal chest X-rays and computed tomography images. To provide clinicians with adequate gross in vivo images, endoscopic images have been included as well.

The training scenario permits a test of the user’s knowledge from two points of view: a) to assign a diagnosis to a given histological image (or a complete set of images), and b) to choose the correct image associated to a given diagnosis. The training procedures can be chosen from each “stage” of the CD independently from the selected disease or information source. Exemplarily, the training set up for disease recognition is given in Figure 1.

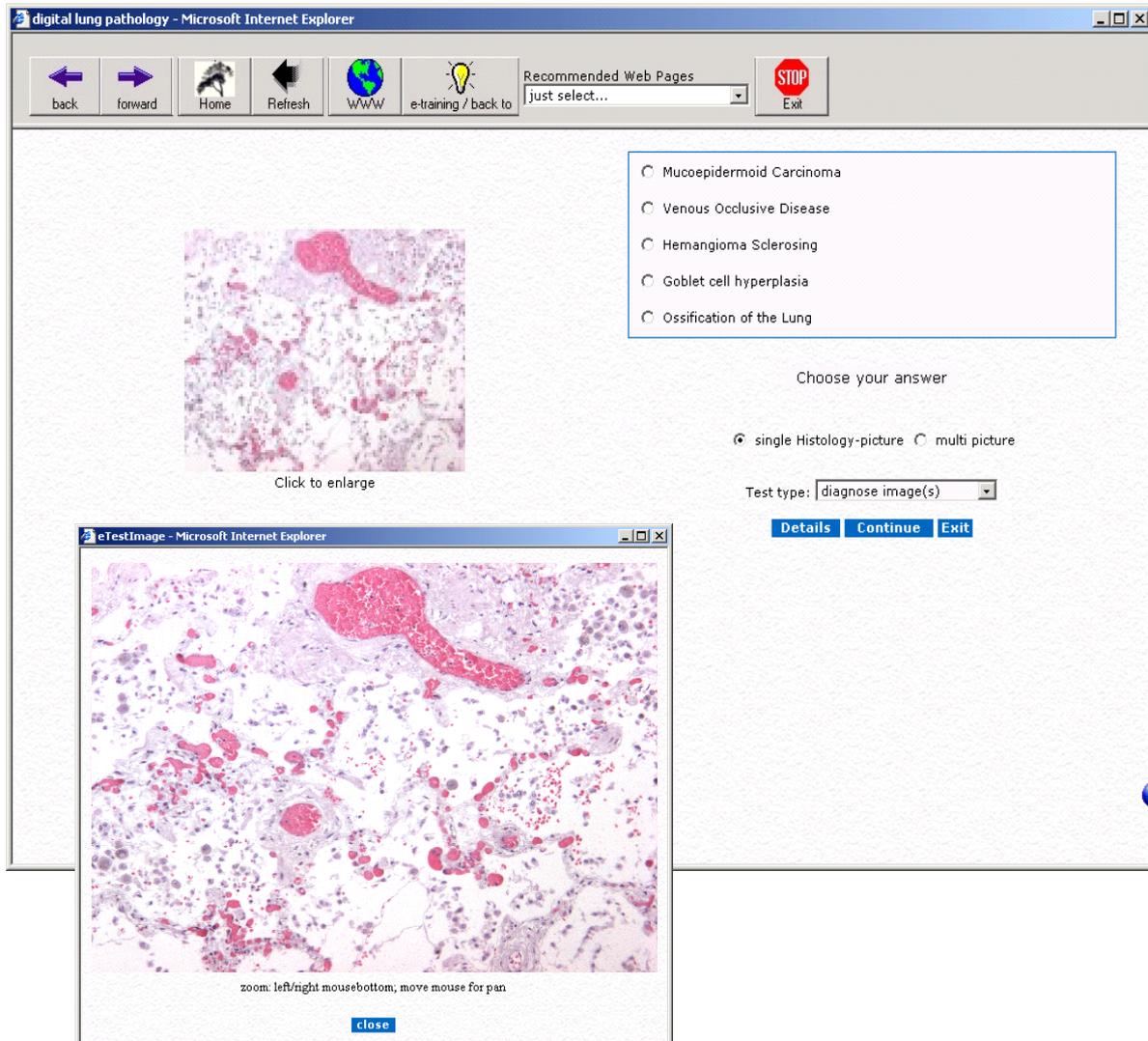


Fig. 1. E-training with “Digital Lung Pathology”

The thumbnail image can be enlarged, and the corresponding disease has to be selected from the presented five different choices. Another training presents a choice of five images, and the correct one has to be selected in accordance with the given disease. All choices of selection are randomly prepared in order to avoid a “memory” effect.

In addition to the disease presentation, several links are included, such as access to the Europath server, to the UICC-TPCC and iPATH servers, to the Electronic Journal of Pathology and Histology, and the home page of the International Academy of Telepathology (IAT).

All in all, the Digital Lung Pathology CD is a state-of-the-art-tool for e-learning and teaching. It offers simple expansion to be used as

- histopathological electronic textbook,
- open image data basis
- integrated training and knowledge test
- presentation with wireless internet access
- training set during the daily workflow
- integrative tool for virtual slide technology.

In the near future, these e-learning and e-training tools will become integrated into the daily work of a diagnostic pathologist, and will, in combination with the algorithms used for automated image analysis [32-35], permit contemporary disease classification, expanded learning, and – which is not discussed here – distribution of acquired knowledge, i.e. associated scientific publication.

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