FROM TELEPATHOLOGY TO VIRTUAL PATHOLOGY INSTITUTION: THE NEW WORLD OF DIGITAL PATHOLOGY

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Summary. Telepathology has left its childhood. Its technical development is mature, and its use for primary (frozen section) and secondary (expert consultation) diagnosis has been expanded to a great amount. This is in contrast to a virtual pathology laboratory, which is still under technical constraints. Similar to telepathology, which can also be used for e-learning and e-training in pathology, as exemplarily is demonstrated on *Digital Lung Pathology* (Klaus.Kayser@charite.de) at least two kinds of virtual pathology laboratories will be implemented in the near future: a) those with distributed pathologists and distributed (≥1) laboratories associated to individual biopsy stations/surgical theatres, and b) distributed pathologists (usually situated in one institution) and a centralized laboratory, which digitizes complete histological slides. Both scenarios are under intensive technical investigations. The features of virtual pathology comprise a *virtual pathology institution* (mode a) that 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 and number of transferred images have to be limited, and usual different magnifications have to be used. The sender needs to posses experiences in image sampling techniques, which present with the most significant information. 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. The first experiences of a virtual pathology institution group working with the iPATH server working with a small hospital of the Salomon islands are promising. A *centralized virtual pathology institution* (mode b) depends upon the digitalization of a complete slide, and the transfer of large sized images to different pathologists working in one institution. The technical performance of complete slide digitalization is still under development. Virtual pathology can be combined with e-learning and e-training, that will serve for a powerful daily-work-integrated pathology system. At present, e-learning systems are "stand-alone" solutions distributed on CD or *via* Internet. A characteristic example is the Digital Lung Pathology CD, which includes about 60 different rare and common lung diseases with some features of electronic communication. These features include access to scientific library systems (PubMed), distant measurement servers (EuroQuant), automated immunohisto-chemistry measurements, or electronic journals (Elec J Pathol Histol, www.pathology-online.org). It combines e-learning and e-training with some acoustic support. A new and complete database 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. At present, telepathology serves as promoter for a complete 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 with exciting diagnostic and scientific perspectives.

Key words: telepathology, smart pathology, virtual slide, virtual pathology institution.

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INTRODUCTION

Diagnostic pathology or tissue-based diagnosis is characterized by its high specificity and sensitivity when compared to other diagnostic medical disciplines such as radiology, clinical pathology, or endoscopic imaging techniques.

It can be considered as the focus of all modern developments in medicine, which can be subsumed under the headlines molecular biology including molecular genetics, electronic or digital communication and computerized medicine.

These two developments in the last decade have altered the daily work of the diagnostic pathologist to a large extent. Molecular biology applications have improved basic knowledge of diseases, and are at present prerequisite for detailed diagnosis of numerous diseases, especially cancer, infectious diseases, or transplant problems. But telecommunication techniques have also become of great interest to diagnostic pathologists (Brauchli *et al.*, 2002; Dietel *et al.*, 2000; Dunn *et al.*, 1999; Kayser *et al.*, 2000).

They have induced intensive communication links between pathologists working all over the world. In addition, they serve for fast interdisciplinary information exchange, for example between small surgical units and large pathology institutions, or between endoscopic departments and institutions of cytology (Kayser *et al.*, 1991; Kayser *et al.*, 1999; Sawai *et al.*, 1999).

The technology of telepathology seems to be matured and fulfils all the conditions of implementation into practical work. In addition, it has opened the door of entering a complete new scene in tissue-based diagnosis, which is now under development.

In this article the roots of telepathology, which go back to trials at the Massachusetts General Hospital in the 1970's (Brauchli *et al.*, 2002; Weinstein, 1986). Its practical applications will be described as well as its future perspectives. These can be formulated in questions such as:

What is the influence of telepathology on completely computerized diagnostic pathology?

What is the standard of a virtual laboratory at present?

What is the influence of telepathology on e-learning?

Is virtual pathology still a vision or already in its childhood?

DEFINITION AND HISTORY OF TELEPATHOLOGY

In the past, telepathology has been defined as "the work of a pathologist at a distance" (Kayser *et al.*, 1999; Weinstein *et al.*, 1990).

At present, this definition still holds true; however, it should be expanded as shown in Table 1, taking into account the development of modern telecommunications and computer technology within the last 10 years.

As stated in Table 1, the definition already includes aspects of performance, which cannot be revealed by conventional diagnostic pathology: it includes a "concentration of information flow at a central (receiver) point, and a contemporary disease classification at several spatial different points (several individual pathologists).

Table 1
Definition and scheme of performance of telepathology

What is telepathology: Telepathology is an electronic, image-related information transfer and classification between 2...n partners either on- or off-line
Conventional technique: image information is provided by one partner, the other(s) classify
Interactive telepathology: all partners contribute to classification, either by providing additional information sources (clinical data, experiences, sampling, etc.) or by image transformation procedures (measurement, filters, etc.)

According to several authors, diagnostic pathology is not only an "information extraction" from a histological slide. To the contrast, it includes a "weighted add" of information gathered from other sources.

These include the patient's history, sex, age, clinical findings (fever, high blood pressure, etc.), or live images and functions (CTs, ECG, etc.) (Kayser, 2002; Martin *et al.*, 1995; Phillips *et al.*, 1998).

Thus, telepathology permits a congruent diagnostic performance at distributed diagnostic centers, and the agglutination of information gathered by different sources (Sawai *et al.*, 1999; Williams, 1998).

This theoretical diagnosis telepathology information network has not been fully implemented to our knowledge until now. Most telepathology applications are performed either in a) fixed point-to-point method, or in b) point-to-distributed points technique.

The point-to-point technique includes fully robotic microscopes, standardized documentation of operation time, features, or analysed image areas (Schwarzmann 1992; Schwarzmann *et al.*, 1995).

It is called on-line telepathology, and most frequently applied for "first diagnosis" procedures, especially for frozen section services. Its characteristics are presented in Table 2.

Interestingly, it is used under local area conditions, for example between small surgical theatres and nearby pathology institutions, and rarely between partners located far away from each other. The Internet serves for open standards.

The necessary equipment is commercially available, however, often specifically bound to the standards of the respective company.

The image quality as exemplarily shown in Figure 1 is sufficient and the diagnostic accuracy nearly identical to results obtained by conventional frozen section services (Nordrum, 1998; Nordrum and Eide, 1995; Stauch *et al.*, 1995; Tsuchihashi *et al.*, 1998).

Table 2
Characteristics of on-line telepathology

On-line telepathology is an electronic, image-related information transfer for intra-operative disease classification
Procedures – Tissue is macroscopically analysed and samples are taken by the surgeon under supervision of the pathologist – Slides are prepared by specialized technicians (frozen sections, close to the surgical theatre) – A robotic telepathology system serves for image transfer and disease classification by the pathologist

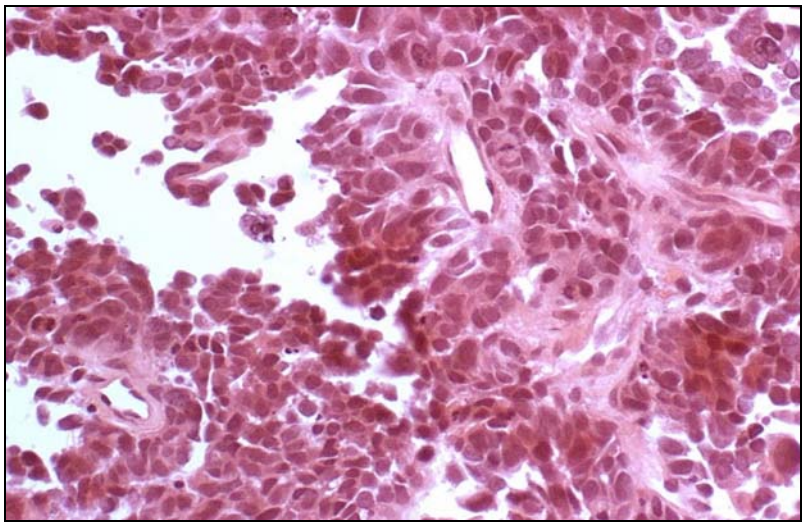

Figure 1 – HE-stained image used for frozen section service by telepathology showing exemplarily the obtained quality (objective ×20, Leica TP system)

The application of the technique listed under b), which is also called off-line telepathology started relatively late, although its technical demands are low compared to the requirements of on-line telepathology. After development and implementation of the Internet with its broadly applicable standards, off-line telepathology is now used worldwide for expert consultation purposes. It can be applied using different procedures, which are listed in Table 3.

Table 3
List of possible procedures to be applied for off-line telepathology services

Fixed partners, fixed platforms: company bound, former remote control, 1992–2000, interactive
Fixed partners, open platforms: Internet, E-mail, 1996–2002
Open partners, fixed platforms: not available
Open partners, open platforms: (specific servers = telepathology consultation centers: AFIP, IPATH, UICC-TPCC; 2000–2002)

At the beginning, expert consultation services were mainly using point-to-point solutions, i.e., fixed partners and fixed platforms (Kayser *et al.*, 1999; Kayser and Kayser, 1999; Weinstein *et al.*, 1995).

At present, this performance has been completely replaced by use of Internet services and the development of specifically designed serves (telepathology platforms) (Brauchli *et al.*, 2002; Dietel *et al.*, 2000; Williams *et al.*, 1998). These telepathology platforms have been implemented at the beginning of this century.

Two systems in use have been placed in the internet: the iPATH server located at the Institute of Pathology, University Basel, and the Telepathology Consultation Centre of the Union contre le Cancre, (UICC-TPCC), located at the Institute of Pathology, Charite, Berlin.

They can be considered as milestones in the history of telepathology, which started as early as 1960 with trials of the National Air and Space Administration (NASA), followed by a specialized medical trials (skin biopsies) at the Massachusetts General Hospital, Boston, USA.

The pioneer work of on-line telepathology with routine frozen section applications was performed in Europe by the telepathology team of the University of Tromsö, Norway (Dr. T. Eide and Dr. S. Nordrum) in 1988 (Nordrum, 1998; Nordrum and Eide, 1995), whereas off-line telepathology trials with multiple contemporary experts' consultation started in Heidelberg, Germany in 1992 (Kayser *et al.*, 1999; Kayser and Kayser, 1999). The first international congress discussing solely telepathology aspects was held in Heidelberg in 1992.

All these trials founded the scientific basis of practical application of telepathology, and acted as strong promoter for further introduction of computerized techniques in diagnostic pathology.

PRESENT STATUS OF TELEPATHOLOGY AND THE VIRTUAL PATHOLOGY INSTITUTION (VPI)

A correct tissue-based diagnosis requires experiences in a broad spectrum of images (diseases). The experiences can be grouped in and simulated by an algorithm, which combines sampling strategies and information association. For example, starting from the light microscopic images taken at low magnification, those areas with the most promising information content will be selected, and analysed again at a higher magnification.

The higher magnification opens more details, and contemporarily shrinks the area of investigation. This procedure can be repeatedly performed for different areas and different magnifications. It is based on the so-called "order of structures" (Kayser *et al.*, 1999).

The progress in medicine induces a greater differentiation of diseases, and increases the number of potential correct diagnoses. At the same time the absolute number of patients increases too, and electronic support is required to handle the

growing amount of data. As discussed above, telepathology is a useful technique to serve for correct diagnosis, i.e., to confirm or readjust the primary diagnosis.

E-learning can serve for an advanced and improved diagnosis quality, i.e., handling the amount of diagnosis. Several of these systems are commercially available; others can be visited on the Internet. They are usually based upon the multi-media techniques, and include acoustic and visual information display.

A good example is the recently published Digital Lung Pathology, which is available at low costs on a CD (www.pathology-online.org) (Kayser *et al.*, 2003).

This electronic textbook includes more than 60 frequent and rare lung diseases. A strict body of disease presentation included live and histological images, and two different training techniques for self-control characterizes it. The start page of the Digital Lung Pathology and its structure are presented in Figures 2 and 3, and the quality of the images is shown in Figures 4 and 5.

All included images can be digitally magnified (zoomed), a set of so-called "descriptors" indicates the significant diagnostic items of the image, self control can be performed by either selecting the correct diagnosis of a presented image (case) from a set of randomly chosen diagnoses, or by choosing the correct images of a diagnosis from a set of randomly presented images.

The list references is limited, and replaced by an automated access to the PUBMED library. Additional Internet links include access to the Europath DNA quantitation server, to the Electronic Journal of Pathology and Histology, as well as to the telepathology consultation systems iPATH and UICC-TPCC. This e-learning and e-training system is still based upon conventional electronic techniques; however, it will be probably implemented into an Internet embedded portal, which permits contemporary learning, practice, quality control, and research.

CONCLUSION

Telepathology can be considered as a successful implementation of electronic technology into the world of tissue-based diagnosis. It is matured in its on-line applications, especially in frozen section services for small surgical units.

The development of the Internet offered new perspectives for off-line telepathology, and has promoted the implementation of telepathology platforms, which permit a distributed access of requesting pathologists to either distributed (iPATH) or assigned (UICC–TPCC) experts. Its consecutive development has created the first virtual pathology institute (VPI), which can be considered as new diagnostic performance in computerized pathology.

The Digital Lung Pathology CD is a characteristic example of electronic teaching and learning in pathology. The experiences of its creation and use are promoting a generalized e-pathology (smart pathology) system, which will include important aspects of telepathology, virtual pathology, and e-pathology.

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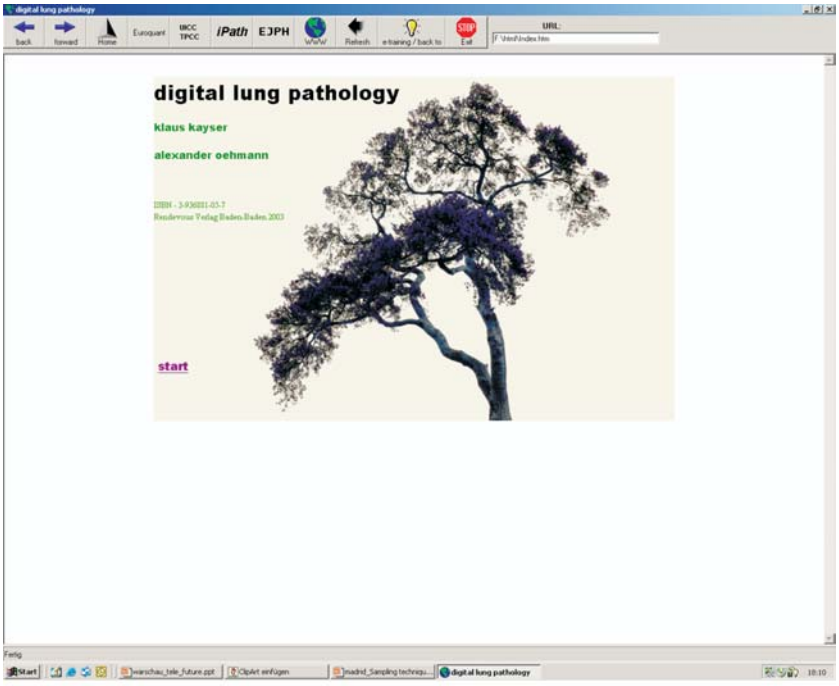

Figure 2 – The start page of the Digital Lung Pathology

Figure 3 – Body of the e-learning and e-training textbook Digital Lung Pathology (underlined items identify links)

Figure 4 – Example of CT image quality of the e-learning and e-training textbook Digital Lung Pathology (alveolar proteinosis)

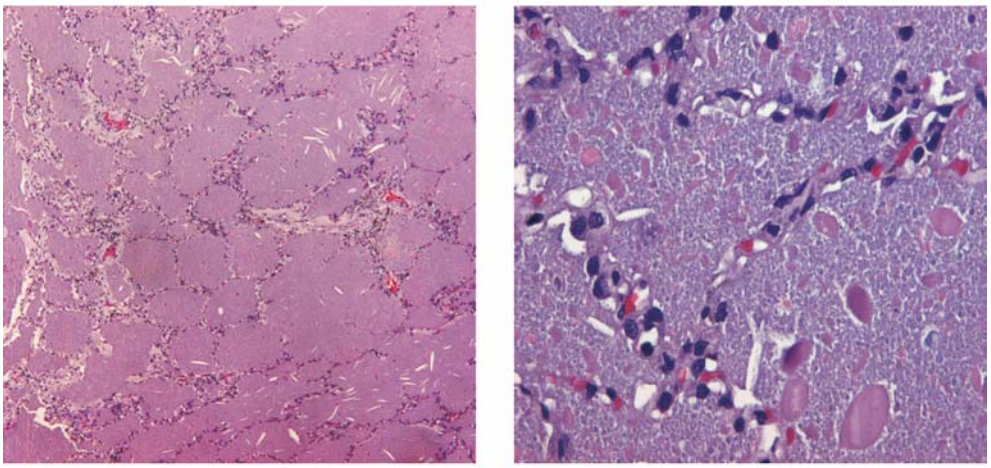

Figure 5 – Example of histology image quality of the e-learning and e-training textbook Digital Lung Pathology (alveolar proteinosis)