E-health and tissue-based diagnosis: the implementation of virtual pathology institutions

Klaus Kayser[1*], Dominik Radziszowski[2], Piotr Bzdy[2], Janina Slodkowska[3*], Izidor Kern[4*], Helmut Sandeck[5*], Rainer Sommer[1], Thomas Schrader[1*], Ekkehard Vollmer[6*], Gian Kayser[7*]

1) UICC-TPCC, Charite, University of Berlin, Berlin, Germany;
2) AGH-UST Krakow, Krakow, Poland;
3) National Institute of Tuberculosis, Warsaw, Poland;
4) Golnik Hospital for Lung Diseases, Golnik, Slovenia;
5) Institute of Pathology, St Olavs Hospital, Trondheim, Norway;
6) Institute of Pathology, Forschungszentrum Borstel, Germany; Institute of Pathology;
7) University of Freiburg, Freiburg, Germany
* Member of VIDI-LUNG (www.pathology-online.org)

Abstract

Monitoring system for grid requires an easy solution for clusters Aims: To analyze the needs, e-health environment, workflow of conventional pathology institutions, and the implementation of tissue-based diagnosis in e-health environment.

Background: Tissue-based diagnosis possesses a low error rate, high acceptance, and broad range of application in modern health care systems. It serves as gold standard in any cancer diagnosis and consecutively, treatment. It is applied for standard diagnosis, estimation of prognosis, response to therapy, potential treatment procedures, and cancer screening programs. The increasing specialization in medicine induces a great number of sub-disciplines with less involved specialists. Thus, communication is mandatory to overcome the modern constraints in medical diagnosis and treatment.

Theoretical considerations. Tissue-based diagnosis uses coloured images in combination with additional information, such as the patients' age, sex or clinical findings. Bias-free communication requires the judgment of original images, and adequate sampling procedures. Despite potential sampling errors, the transfer of still images via electronic communication lines fulfils these prerequisites. Specific systems of diagnostic information transfer have to be open for image access and private data transfer, and to obey mandatory security rules. These aims can be achieved by specific server systems, such as iPATH or UICC-TPCC.

Implementation: Until now, the workflow of "conventional" pathology institutions has been implemented into the e-health scenery by two virtual pathology institutions. These institutions use the iPATH server as tool for electronic primary and secondary diagnosis. They posses a duty schedule of the

experts, and a low number of case - submitting institutions. They are able to work out a diagnosis within 24 – 48 hours, a delay, that is comparable with that of conventional pathology institutions. The third virtual pathology institute is limited to pulmonary diseases, and called VIDI-LUNG (www.pathology-online.org). Its members include well know experts of the field, working in different continents. It is expected that it will significantly promote and distribute specific knowledge, and communicative diagnostic standards in lung pathology. Its start is foreseen for January 1, 2005.

Outlook: Virtual pathology institutions will become familiar to pathologists and e-health care systems within the near future, as they posses strong regulations for service and data protection, members with specific diagnostic knowledge, and a distributed workflow.

1 Introduction

Tissue – based diagnosis is defined as a medical discipline that includes diagnostic statements and procedures based upon any human cellular material [1,9,11,18]. It is usually the task of a surgical pathologist, and, indeed, most of the given diagnosis statements rely on examinations of surgical specimens and biopsies. There are, in addition procedures that are also included in the term tissue based diagnosis, namely cytology, fine needle aspirations, molecular genetic approaches such as fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), chromosome analysis, or polymerase chain reaction (PCR). These investigations are partly performed in pathology institutions, partly in specialized laboratories [25-30]. A tissue based diagnosis statement usually relies on a multi step performance, that begins with the “classical” tissue examination, namely smears and/or histological slides that underwent visualization procedures for nuclei and cytoplasm, and that serve for a solely morphological disease classification [18,20,24,33]. Dependent upon the underlying disorder and upon the needs of for therapy, additional investigations take place, commonly known as genotype and immunotype analyses. These procedures have intensively extended the “range” of a diagnosis, especially in cancer patients. At present, there exist at least four different types of diagnoses, namely

a) classic diagnosis, for example adeno carcinoma of the lung
b) prognosis related diagnosis, for example, favourite outcome due to low proliferation rate
c) response related diagnosis, for example high apoptotic rate after cytostatic therapy
d) risk - related diagnosis, for example high risk for breast carcinoma due to specific gene mutations.

All these diagnoses require human tissue to be assessed. Information about the patient is an additional prerequisite for exact and detailed diagnosis [10-14]. The required “clinical” information depends on the classic diagnosis to a high degree, and, in addition, upon the “therapeutic environment” of the patient. The non-classic diagnoses are usually induced and performed in knowing the classic one, and, thus, require less or even no clinical information [2,16].

The aggregate of all these tissue based diagnoses results in the so-called “final” diagnosis statement, that server for treatment and health care of the individual patient and, in addition, for the implementation of “therapeutic rules” or “standardized therapies” of all affected persons.

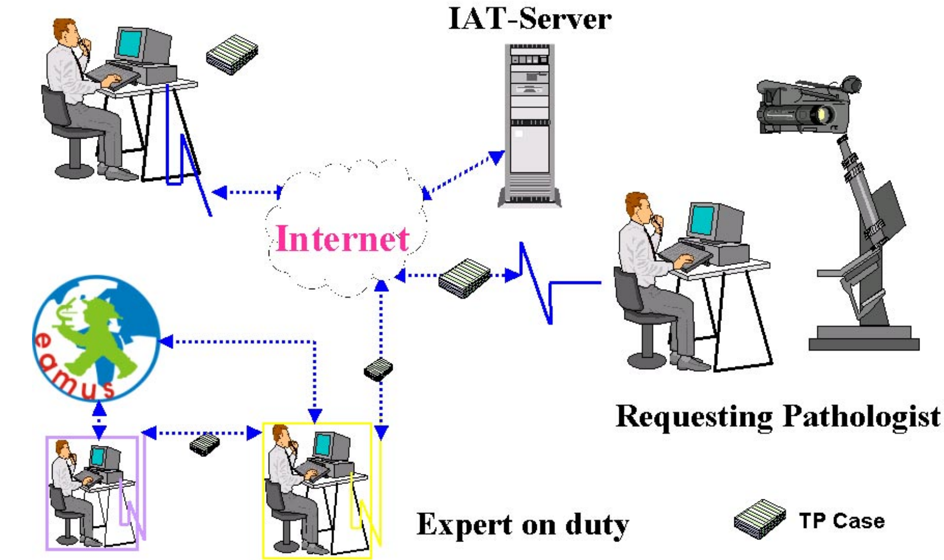


Fig. 1 General scheme of the virtual pathology institution VIDI-LUNG. Note its similarity to that of a common telepathology consultation center, for example UICC-TPCC.

This general principle of tissue based diagnosis has been induced by the progress of molecular biological and genetic technologies. Especially the so-called array technique permits contemporary analyses of several thousand genes or gene products, that will hopefully result in a tailored therapy of individual patients. They require, however, another component of the modern medical world, namely information collection, exchange, and classification. These needs can only be fulfilled by standardized information transfer methods with open and controlled access to information collection and interpretation. Fortunately, a necessary platform does exist, the internet. Therefore, it took only a couple of years to implement specific information handling and performance systems into the world of tissue based diagnosis [5,7,8]. These systems use the results gathered by several groups in using telecommunication purposes in surgical pathology [17,21,23,29], i.e., telepathology. They have replaced the former telepathology systems to a great extent, and can be considered as systems specifically tailored for telemedicine services [31,32]. They can be constructed in a similar manner as “conventional” pathology institutions work, and are then called Virtual Pathology Institutions.

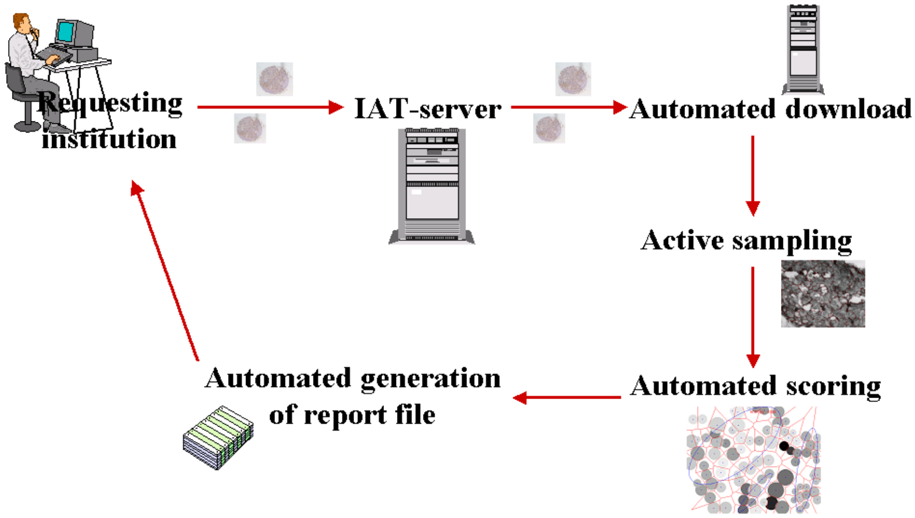


Fig. 2 General scheme of the EAMUS configuration.

In this article we will analyze the theoretical and practical conditions, performance, and practicability of Virtual Pathology Institutions. In addition, some related systems that permit automated and distance independent quantitative analyses of light microscopic images and strategies for automated diagnosis assessment will be discussed.

2 Definition and theoretical considerations

A Virtual Pathology Institute is defined as structured organisation of pathologists who interpret and classify electronic images obtained from human tissue at light microscopic magnification. The expressed statements are equivalent to the diagnoses signed out by a conventional pathology department or institute. However, there are specific working conditions of a Virtual Pathology Institute (VPI) [16]:

a) In contrast to a conventional or national institute of pathology the pathologists working at a VPI have their domicile in several different countries, often with great differences in culture and legal working conditions.

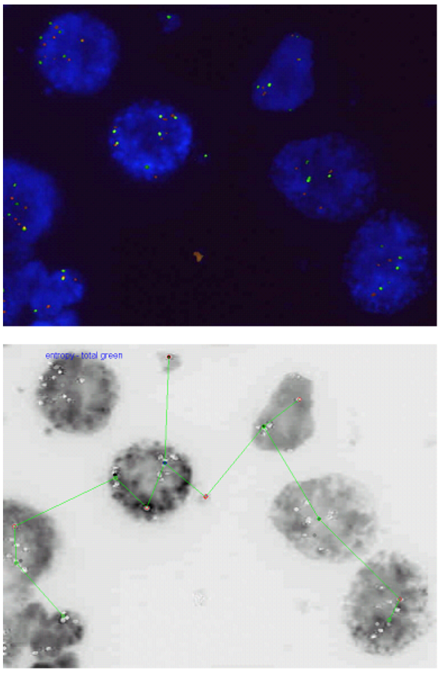
b) They view and judge still images which display only certain compartments of the images seen under a conventional microscope, i.e. they work under specific sampling conditions.

c) They completely depend on the transferred image quality, and cannot “order” new images or new examinations.

d) They have no “final control” of the signed diagnoses, and cannot discuss their statements with the clinical partners.

These specific circumstances induce less responsibility and strict working conditions in terms of liability. However, the strict structure of the VPI can secure a reliability of time schedules (for diagnosis statements), and a higher responsibility compared to a “simple” telepathology consultation center (TPCC).

From the theoretical point of view, both a TPCC and VPI mediate an information transfer that runs from a higher (more secure and detailed) level to a lower one. The (diagnostic) information which is “hidden” in the images to be viewed is released by the VPI and sent to the requesting pathologist or institute. This release is only of practical use, if it can be “understood” by the receiver, and, even more important, can induce adequate reactions in terms of related therapy. The greater the “difference” between the VPI and the requesting institution, the more attractive the VPI is considered, and the more frequently the VPI service will probably be used. Therefore, it seems appropriate to implement a VPI for services of institutions working in countries with high medical standards addressed to those institutions located in countries with low quality health care systems. A closer consideration, however, indicates clearly the limitations of such a service: The practical use for requesting institutes located in countries with poor health conditions is very limited, as the necessary implications cannot or only partly be fulfilled, namely the transfer of detailed diagnosis into the corresponding therapy set ups and schemes. This consideration holds true for both, a TPCC and a VPI, and has been reported in several articles [6,22,31-33]. However, the teaching and education induced by telepathology and its related technologies cannot be underestimated. It induces knowledge of the latest technologies, and, in addition, the “touch” of direct application and the circumstances that require these technologies.



case nr:	3497
Mean no nuclei:	7.3
Size FISH red:	22.1
FISH no red:	2.83
Vv FISH red:	0.002
% nuclei 1 FISH:	0.49
E(MST) red:	0.86
Size FISH green:	28.7
FISH no green:	3.3
Vv FISH green:	0.003
% nuclei 1 FISH:	0.31
E(MST) green:	0.34

Fig. 3 Example of an automated measurement of the EAMUS system.

The creation of a distributed organized network for tissue based diagnosis is not limited to applications that try to close the gap between different levels of health care standards. To the contrast, having implemented such an institution, there are additional tasks obvious, that are directly bound to the diagnosis accuracy and sensitivity as follows:

A VPI possesses the potency to be superior to a conventional institute as it includes only outstanding experts, who are familiar with the corresponding diagnosis details. Its disadvantage is related to its dependence upon the chosen images that form the diagnostic basis. If the selected (or sampled) and acquired tissue slide compartments do not contain the area with most significant information, the derived diagnosis will not be accurate or even wrong. Thus, the major constraint is closely associated with the chosen sampling procedure. According to Kayser et al. [15], sampling within a light microscopic (histological) image can be separated into a hierarchic sequence of chosen image compartments that are acquired at different magnifications. The sampling theory then permits to compute the maximum diagnostic error rate similar to the algorithm that is used by applying Nyquest's theorem in acoustics. This sampling theory can be implemented and applied to digitized images without any difficulties. In addition, it can be reduced to a stratified sampling procedure that allows a fast and effective analysis of images in search for diagnostic relevant items. These include, for example, cancer cells, vascular infiltration, or formation of granulomas.

The sampling theory can be applied in two different ways to improving the diagnostic quality of a VPI:

a) It can be applied prior to the image acquisition and digitalization using an automated microscope table, and selecting only those image compartments for digitalization and further analysis, that fulfil the conditions preset by the sampling procedure (for example certain gray value distribution, size of detected nuclei, etc.), or
b) the whole slide will be scanned and converted into a virtual slide. Afterwards the virtual slide will be analyzed a set of hierarchic sampling procedures as described by Bartels et al. and Kayser et al. [3,4,15,19].

At present, major efforts are undertaken from industry and within different institutions to construct automated scanning machines that can convert tissue slides into virtual slides with sufficient speed and image (pixel) resolution. Theoretically, a pixel resolution of 0.5 mm/pixel is required if all hierarchical steps in a chosen diagnostic algorithm should be digitally assessed [16].

Although all VPIs, to our knowledge, are designed to sign out tissue based diagnoses, and are mainly involved in terms of conventional disease classification, efforts are ongoing to expand this work to genotype and immunotype diagnoses. These efforts require automated and easy to access image quantification technologies, for example measurements of FISH images. The idea is not new, however, all former trials failed due to segmentation difficulties of the images. The recently developed theory of active sampling promises a reliable and stable resolution of this problem [15,19]. The electronic automated measurement user system (EAMUS) that offers automated image quantification via the internet has been successfully tested in first trials, and can be considered as a milestone in the further development of a VPI.

3 Present state of Virtual Pathology Institutions

The idea of a VPI has its origin in providing a tissue based diagnosis service for the Salomon Islands, a country located in the South Sea with about 500,000 inhabitants. No pathologist is working within this state. Promoted by a surgeon working in the Salomon Islands, the telepathology group located at the Institute of Pathology, University Basel, (Dr. M. Oberholzer) designed and organized an internet based diagnosis service that signs out primary tissue based diagnosis of solely electronically submitted cases. The staff members are distributed in Europe, all in all the VPI comprises seven well known pathologists. A second VPI focuses on countries of the far East, especially Cambodia, and is constructed in an identical manner to that designed for the Salomon Islands [5,6].

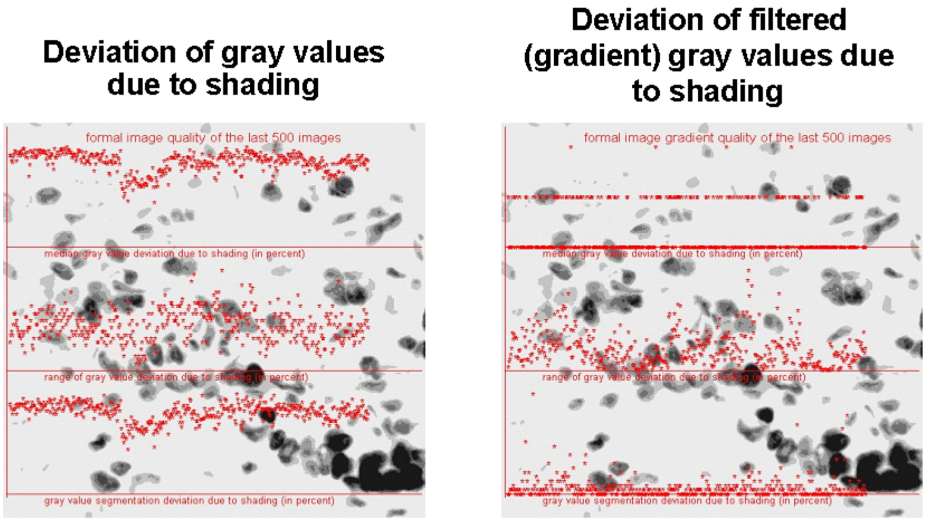


Fig. 4 Continuous image quality monitoring of the EAMUS system.

A third VPI is now located at the UICC-TPCC (Union Contre le Cancre Telepathology Consultation Center) in Berlin. It focuses on lung diseases and is called VIDI-LUNG. The general scheme of VIDI-LUNG that is comparable to that of the other VPIs is shown in figure 1. An administrator organizes the duty plan and controls the transfer of the submitted cases. The pathologist on duty is obliged to handle the transmitted case within 24 hrs at maximum. He can, in addition, contact other colleagues admitted to the VPI prior to signing out the case. If the submitted case contains images obtained from immunohistochemically stained or fluorescent slides, a direct switch to the EAMUS measurement system permits a fast and reliable quantification of these images. This configuration permits a high quality diagnosis that can be expanded in several manners, if the necessary soft ware is available. These expansions mainly include the application of artificial intelligence (AI), for example, “automated extension of the images under consideration, automated changes of displayed colors, etc. The details of these tools are discussed elsewhere [19].

One tool that is included in the VIDI-LUNG VPI is the EAMUS. This automated internet accessible measurement system can also be used independently from the

VIDI-LUNG access. The general scheme of the EAMUS system is given in figure 2. Basically, it is an automated, self-controlling system that consists of two compartments, namely a) an open system that controls access and response via the internet, and a separated, closed measurement system, that periodically interacts with the “open” tool. The “open” tool provides the “closed” tool with necessary standards of images, required information (for example used magnification, applied stains, etc.), and ensures a barrier against misuse such as viruses, worms, etc. The “closed” tool performs the requested measurement, provides a standardized result, and informs the “open” tool once the result is ready for transmission. Additional tools run in the background and serve for adequate documentation of the data and monitoring. An example of the performed measurement is shown in figure 3. The output data belong to a FISH image. As shown, the user can also ask for syntactic structure analysis of his images. These requests are especially useful, if intercellular actions are of interest. As the EAMUS system has several inbuilt self control mechanism, the user is also provided with an automated control of his submitted images, as exemplarily shown in figure 4. The control data reflect to image features that are important for correct segmentation algorithms, i.e., shading and gradient filters. Figure 4 displays a series of more than 500 measurements. The submitted images of measurements 150 – 210 reflect to a significant aberration of shading and deviation of gray value segmentation in comparison to the other images submitted previously and later on.

4 Outlook and perspectives

The e-health environment is characterized by two main features: a) It offers the chance to transfer information from “highly specialized or high quality medicine places” to health care systems working at a “lower specialized level”, and b) it uses basic information sources obtained in institutions that are working at the low specialized level. The prerequisite in performing an efficient e-health care relies on the access to non-biased information sources such as images, basic functional curves (EEG, ECG, etc.). The more basic the information source, the more effective is any e-health application. In tissue based diagnosis, the chosen sampling strategy can be the main constraint in obtaining a non-biased image. The application of virtual slides is an appropriate technique to overcome this potential hazard. It will imply complete new solutions in performing tissue based diagnoses: the implementation of histological or cytological laboratories can be performed even in remote areas. The only requirements are electricity and access to the world wide web. Quality assurance and control can be automatically included using e-health assessment as well as improvement of consecutive therapies. In aggregate, the implemented VPIs are a first step into a new diagnosis world that uses non-biased image information to extract diagnosis and provide the derived treatment for patients living in remote areas.

Acknowledgement: The financial support of the International Academy of Telepathology, Heidelberg, Germany, the Verein zur Förderung des Biologisch technologischen Fortschritts in der Medizin e.V., Heidelberg, IBM, Mainz, Germany, and Microsoft, Munich, Germany are gratefully acknowledged.

References

1. Brauchli K, Christen H, Haroske G, Meyer W, Kunze KD, Oberholzer M. Telemicroscopy by the Internet revised. *Journal of Pathology* 2002; 196: 238-43
2. Brauchli K, et al. (2000) Telepathology: design of a modular system. *Anal Cell Pathol* 21:193-99.
3. Dietel M, Hufnagl P, TN Nguyen-Dobinsky (2000) The UICC telepathology consultation center - a global approach to improving consultation for pathologists in cancer diagnosis *Cancer* 89: 187-91.
4. Dietel M, Nguyen-Dobinsky TN, Hufnagl P. The UICC Telepathology Consultation Center. International Union Against Cancer. A global approach to improving consultation for pathologists in cancer diagnosis. *Cancer* 2000; 89: 187-91
5. Dunn BE, Choi H, Almagro UA, Recla DL, Krupinski EA, Weinstein RS (1999). Routine surgical telepathology in the Department of Veterans Affairs: experience-related improvements in pathologist performance in 2200 cases. *Telemedicine Journal* 5: 323-37
6. Kayser K, Hufnagl P, Kayser G, Zink S (1999) Stratified sampling: Basic ideas and application in pathology Elec J Pathol Histol 5:994-08.
7. Kayser K, Kayser G, Radziszowski D, Oehmann A: New developments in digital pathology: from telepathology to virtual pathology laboratory, in M. Duplaga, K. Zielinski, D. Ingram (edts) Transformation of Healthcare with Information Technologies, IOS Press, Amsterdam, 61 – 69, 2004
8. Kayser K, Kayser G, Zink S. (2000) New technical aspects in telepathology. Elec J Pathol Histol 003-03
9. Kayser K, Kayser G. (1999) Basic aspects of and recent developments in telepathology in Europe, with specific emphasis on quality assurance. *Analytical and Quantitative Cytology and Histology* 21: 319-28
10. Kayser K, Oehmann A Digital Lung Pathology. *Rendevous Verlag Baden Baden*. ISBN 3-936881-05-7, 2003
11. Kayser K, Szymas J, Weinstein R. *Telepathology, Telecommunication, Electronic Education and Publication in Pathology*. New York: Springer Verlag, 1999
12. Kayser K. Kayser G. Becker H. D. Herth F. (2000) Telediagnosis of transbronchial fine needle aspirations--a feasibility study. *Anal Cell Pathol* 21:207-12
13. Lewis K, Gilmour E, Harrison PV, *et al*.(1999) Digital teledermatology for skin tumours: a preliminary assessment using a receiver operating characteristics (ROC) analysis. *Journal of Telemedicine and Telecare* 5 (suppl. 1): 57-8
14. Martin E, Dusserre P, Got Cl, *et al*. (1995) Telepathology in France. Justifications and developments. *Archives d'anatomie et de cytology pathologiques* 43: 191-5
15. Sawai T, Goto K, Watanabe M, Endoh W, Ogata K, Nagura H.(1999) Constructing a local district telepathology network in Japan. Diagnosis of intraoperative frozen sections via telepathology over an integrated service digital network and the National Television Standard Committee System. *Analytical and Quantative Cytology and Histology* 21: 81-4
16. Schrader, T. et. a. (2003) A user friendly Telepathology Service at the Internet – The Telepathology Consultation Center of the UICC *Elec J Pathol Histol* 9:031-007
17. Schwarzmann P, Schmid J, Schnorr C, Straessle G, Witte S. (1995) Telemicroscopy stations for telepathology based on broadband and ISDN connections. *Archives d'anatomie de cytology pathologiques* 43: 209-15

18. Stauch G, Schweppe KW, Puetz M. (1995) One year experience with telepathology for frozen sections. Elec J Pathol Histol 954-08

19. Tsuchihashi Y, Mazaki T, Murata S, et al. (1998) Telepathology and cytology in Kyoto, Japan, to support regional medicine, with special references to their need, accuracy and cost. *Advances in Clinical Pathology* 2: 131-2

20. Vieillefond A, Staroz F, Fabre M, *et al*. (1995) Reliability of the anatomopathological diagnosis by static image transfer. *Archives d'anatomie de cytology pathologiques* 43: 246-50

21. Weinstein R. S., et al. (2001) Telepathology overview: from concept to implementation. *Hum Pathol* 32: 1283-99

22. Weinstein RS, Bhattacharyya A, Yu YP, *et al*. (1995) Pathology consultation services via the Arizona-International Telemedicine Network. *Archives d'anatomie de cytology pathologiques* 43: 219-26

23. Weinstein RS, Bloom KJ, Rozek LS. Static and dynamic imaging in pathology. In: Mun SK, Greberman M, Hendee WR, Shannon R eds. *Image management and communications in patient care: Implementation and impact*. Los Alamitos, California: IEEE Computer Society Press, 77-85, 1990

24. Williams BH, Mullick FG, Becker RL, Kyte RT, Noe A. (1998) A national treasure goes online: the Armed Forces Institute of Pathology. *MD Computing Computers in Medical Practice* 15: 260-5

25. Williams BH. (1998) The AFIP center for telemedicine application - pathology for the twenty-first century. *Telemedicine and Virtual Reality* 3: 64-5

26. Ziol M, Vacher-Lavenu MC, Heudes D, *et al*. (1999) Expert consultation for cervical carcinoma smears. Reliability of selected-field videomicroscopy. *Analytical and Quantative Cytolo*