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Review

HISTORY OF THE EUROPEAN CONFERENCE SERIES ON DIGITAL PATHOLOGY: MEMORIES AND PERSPECTIVES

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Abstract

Background: Digital pathology is based on both quantitative analysis of microscopic images and electronic communication (telepathology). Herein we report its development in close relationship to the European conference series on telepathology, virtual slides, and digital pathology that started in Heidelberg 26 years ago.

Telepathology, Virtual Microscopy and Digital Pathology: The author founded the conference series in Heidelberg in 1992, and has participated in all of them. This report can give an insight of conferences' information and data exchange in relation to available technological and medical knowledge.

The digital world was still in its childhood at the date of the first conference. Most pathologists were not aware of its medical, technologic, and financial power at that time. Technological research and medical application investigated in electronic communication and digital acquisition of colored pictures. Frozen section services and its need for fast information transfer between different institutes and the surgical theatre dominated the application of technological development. Consecutively, all issues of telepathology were in focus at the start of and the following conferences. The pioneers of that time tried to convince their colleagues of the promising perspectives and the increasing technological influence on pathology.

It took several conferences in this series until the majority of or nearly all pathologists recognized the power of this new technology. Retrospectively, some conferences remained at the scientific level of their preceding meetings, whereas others substantially promoted electronic (digital) knowledge and application in research and routine pathology.

Perspectives: At present, digital pathology is well implemented and mainly used for education and enhancement of molecular biology methods such as next generation sequencing, predictive diagnosis, or risk associated investigations. Implementation in routine diagnostic pathology (virtual slides, etc.) is on its way.

Digital pathology seems to move forward to explore still unknown areas in surgical pathology, and tissue – based diagnosis. These include considerations on morphology, function and order

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of structures, which can detect potentially endangered factors or repair of live threatening breakdowns, as well as biostatistics, data mining, or self recognition algorithms.

Keywords: European Conference on Telepathology; Digital Pathology; Telepathology; Virtual Slides

Introduction

The first trials of telepathology range back to 1976, when Ronald S. Weinstein reported its successful application for emergency [1-7]. This period was completed by T. Eide and I. Nordrum, who performed the first telepathology application in routine surgical pathology diagnosis (frozen section service) [8-10]. Contemporary the first "complete" theory of quantitative image analysis, called stereology was founded [11-13]. The names of Gundersen, Mall, and Weibel have to be mentioned who tried to implement a reproducible statistical approach of sampling and derived microscopic image analysis [14 -18].

A different approach of structure analysis based on graph theory was reported by Kayser, Prewitt, and San Feliou [19-23]. None of these methods was applied in routine diagnostic practice even though all investigations were scientifically founded, of low laboratory burden, and resulted in useful clinical information [21, 24]. The reasons remain unclear. There were no (electronic) tools available that could bridge the quite complex nature of understanding and practical application. In addition, they did not permit an easy performance. As long as new methods require specific theoretical understanding and associated complex practical performance they will probably not become routine tools in medicine or pathology.

However, new methods are always reported in scientific meetings, and attract colleagues, who are curious and interested in. Contemporary with or shortly after technological development the stillborn tools serve for new fields of application, such as improvement of specificity and sensitivity, lower costs, or increased details of medical information [25].

The series of European Conferences on Telepathology, Virtual Microscopy and Digital Pathology offers the unique opportunity to judge the gap between technological progress and its medical application, to analyze conference characteristics that mirror innovation and data confirmation, and to search for reasons that hinder or promote routine application.

History of Telepathology, Virtual Microscopy and Digital Pathology

The history of digital pathology and its related fields is summarized in <Table 1>. In addition to the first NASA trials (National Air and Space Association) in 1960 telepathology and its practice became aware to pathologists between 1976 – 1995 [26-32]. Application for frozen section services, especially of breast cancer surgery was in focus [33-35]. The bridge of space between a small department of surgery and a main pathology institute was of priority. The bridging of

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time (expert consultation) as well as asynchronous transfer protocols and open access (internet based) platforms were implemented some years later [33-39]. The details of the history of telepathology have been already described by several authors and can be read elsewhere [40-43].

History of telepathology

- 1960 and later first trials of NASA
- 1976 skin biopsies, Logan Airport (on-line)
- 1986 urinary bladder biopsies (NBCG, USA, reference)
- 1988 breast biopsies (Tromsö, T. Eide, I. Nordrum, on-line)
- 1992 reference (lung: M. Drlicek, K. Kayser, W. Rahn; breast: J McGee)
- 1995 and afterwards, frozen sections (on-line) and expert consultation (off-line, internet), continuous education
- 1996 EC project EUROPATH (G. Brugal, KD. Kunze)
- 1998 Euroquant (telemeasurements, G. Haroske, KD. Kunze)
- 2000 UICC-TPCC (consultation center, Charite, Berlin)
- 2001 IPATH (flexible expert consultation, M. Oberholzer)
- 2001 implementation of AI in telepathology, (K. Kayser)
- 2005 VIPI Virtual International Pathology Institute (K. Kayser)
- 2008 Open Access Journal (2014) www.diagnosticpathology.eu

Table 1: History of digital pathology and its related fields.

The series of the European Conferences on Telepathology, Virtual Microscopy and Digital Pathology is depicted in <Table 2>. It started in Heidelberg, June 1992, and was continued biannually until today (May, 2016, Berlin). The conferences took place at different European cities including Berlin, Budapest, Heraclion, Paris, Toledo, Udine, Venice, Vilnius, or Zagreb. Around 120 colleagues participated at the first conference, and about 200 participants at each of the following events. The industrial exhibitions and the organization, however, changed remarkably. The first congress was completely organized by the local staff in contrast to the congresses of the new century. All conferences of this century were organized by professional congress organizing companies. Industrial partners financed these conferences and became a substantial compartment not only for financial reasons, but, in addition, for transferring knowledge and ideas between both parties pathologists and exhibitioners.

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Table 2: Series of the European Conferences on Telepathology, Virtual Microscopy and Digital Pathology.

Development of Technology and Digital Pathology

Development of research and science starts either with a new, innovative idea or explanation of otherwise not understood experimental results, or with new technologies that are implemented in new fields of application. Einstein's theory of relativity is an example of a new complex idea that altered our understanding of nature. Digital pathology is an example of a new application field of a technology that has been created for quite different approaches. Search for fast communication lines in terms of broad band signaling and the development of fast and large charge coupled devices resulted in accurate digital cameras, mobile phones, and powerful computers [40, 42, 44-46]. All of these items are consumer oriented. Therefore, they are easy to handle (at least in majority), and cheap in price due to mass production. In principle, there is no intensive training necessary to use a personal computer (PC), a smart phone or a tablet, and medicine is an attractive commercial market. Radiology and surgical pathology are the most attractive medical fields to implement new electronically based technologies, because they provide image oriented and accurate diagnostic information of numerous diseases.

The development of electronic technology and its spread to digital pathology is summarized in <Table 3>. Video cameras became commercially available in 1980. It took another ten years until

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they have been used in routine online telepathology services [47, 48]. Integrated services digital network (ISDN) allowing broad band width connections were introduced in Europe in 1990. Remote control telepathology started four years later only [49-52]. The implementation of communication standards (internet) induced the greatest progress of all types of communication. It opened the entrance into a new world of information transfer such as social forums, open access publication, chat, hospital information systems, big data analysis, distributed networking, etc. All these applications are based upon interactive communication instead of one way information transfer only [37, 53-55]. Immediately, the server technology matured and can handle big data issues as well as complex iterative computations that provide forecasting of systems' development with incredible accuracy and velocity [5, 55-57].

Technology & Digital Pathology

Technology		Digital Pathology
1980 Video camera	> 1990	Routine frozen section telepathology
1990 ISDN	> 1994	Remote Control
1995 Internet	> 1998	Euroquant (remote cytometry)
2000 Social networks	> 2001	iPATH
2005 Wireless phones	> 2010	Virtual slides
2010 Glass Fibers	> 2014	Big data, automated measurements

Conference focus

- 1992 – 1998 > Issues of tele-pathology (diagnosis assurance, reliability, routine problems)
- 2000 – 2006 > Open access items, tele-measurements, whole slide technology, tele-education
- 2008 – 2014 > Virtual pathology institutes, image quantification, digital pathology, virtual slides, electronic publication

Table 3: Development of electronic technology and its spread to digital pathology.

Conference focus

The series of the conferences covers a period of 26 years, a period of broad changes in the technical and medical world. The main focus of the telepathology conferences is also depicted in <Table 3>. Issues of accuracy, technological and medical constraints and their overcome dominated the conferences in the last century. They are still subject of discussions in the recent sessions, however, issues of the virtual image information such as virtual slides, regions of interest, image content information, automated measurements, or diagnosis assistants are in focus now-a-days.

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In addition, innovative ideas and research ruled some of the conferences. For example, telepathology was the dominant subject in 1992 – 1996, and virtual slides were in focus at the conferences of 2002 and 2004. The participants of conference sessions that took place between and after these dates were more interested in consolidation and confirmation of recently published research results than in the presentation of present innovative ideas. An overview of innovation and cessation in the conference series is shown in <Table 4>.

The latest conference which took place in Berlin in 2016 was dominated by all aspects of digital pathology. Telepathology, open access and closed forums have found their historical place of digital pathology. There is no doubt that virtual microscopy results in the same diagnostic accuracy when compared with conventional microscopy. Open access networks and communication can provide sufficient reliability and transfer velocity that is needed for virtual microscopy. Tasks and questions how to expand virtual microscopy to take advantage of digitalization, or how to combine recent biomolecular and biogenetic knowledge with virtual microscopy pose the challenges in our days.

Dates of Innovation and Cessation

Scientific conferences do not always focus on new, innovative ideas. Often they relax and serve more for reputation than for innovation. What about this conference series?

Dates	Innovation	Cessation
• 1992 - 1996	Telepathology	
• 1998		Consolidation studies
• 2000 - 2004	Virtual slide, internet	
• 2006 - 2008		Routine service
• 2010 - 2014	Digital pathology Image content information	

Table 4: An overview of innovation and cessation in the conference series.

Do pathologists resist to implement digital pathology?

The statement that “pathologists are conservative (some say stubborn) and not brave enough to implement new ideas in their daily work” was said at all conferences in this series, and frequently followed by the question: “How long, if at all, it will take that pathologists perform

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telepathology, use forums or virtual institutes for expert consultation, quantify image properties instead of crude judgments? Some facts that might answer these questions are presented in <Table. 5>. It displays the history of former innovative techniques which have without any doubt found their routine application in surgical pathology. The first report of immunohistochemistry (IHC) was published by Albert Coons in 1941, that of in situ hybridization (ISH) by Mary Lou Pardue und Joe Gall in 1969 [36, 58]. It took about the next 30 years to introduce IHC and the next 25 years to implement ISH in routine microscopic diagnosis. Both methods became a substantial refinement of microscopic diagnosis.

Stereology, 3-D reconstruction and syntactic structure analysis never became part of routine diagnostics, if we neglect rare exceptions. However, the implementation of telepathology, internet applications and expert consultation are frequently in use by larger pathology institutes today. The applications include frozen section services, continuous education, and clinical pathological interdisciplinary conferences. These data indicate that in addition to financial considerations appropriate tools of good performance are a prerequisite of application in routine services.

Quantitative Pathology & Routine Tissue – based Diagnosis

- It has been said: Pathologists hesitate to implement new ideas. Is this reality?

Date	Tool	Routine Tissue Diagnostics
1941	Immunohistochemistry	yes, appr. 1978
1969	In situ Hybridization	yes, appr. 1995
1995	DNA sequencing	yes, appr. 2010
1961	Stereology	no
1970	3 – D reconstruction	no, trials 2014
1975	Structure analysis	partly, since 1990
1980	DNA cytometry	yes, 1984, until today
1984	Telecommunication	yes, 1988, until today
2000	Internet forum	yes, 2001, until today
2000	Virtual Slides VS	yes, 2008, until today
2005	Automated measurements	no

Table 5: History of former innovative techniques and their routine application in surgical pathology.

Perspectives

The forecast of technological and medical development should be based on both history and recently obtained results of research and sciences. Financial aspects contribute too. They are,

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however, of minor significance as long as the financial environment remains constant and industry invests in the needed technology.

The development of the respective main topics of surgical pathology is listed in <Table. 6>. One of the dominating topics in the past, autopsy, is of no longer significance in clinical practice, and has been replaced by live imaging (computed tomography, nuclear resonance images, ultra sound images, etc). Autopsies are rarely performed in Western pathology institutes. They usually serve for education of medical students. This is a fact, and it is useless to discuss advantages and constraints of autopsies. Their time is gone.

History influences Future ?

- Fate of pathologists main tissue domains

Date	Domain	Future ?
1850 – 1975	autopsy	gone, residues remain*)
1950 – 2016	biopsy	still increasing
1950 – 2016	cytology	constant
2000 – 2016	tissue bank	increasing
1850 – 2016	OP tissue	constant – slightly decreasing
2012 – 2016	liquid biopsy	increasing**)
2010 – 2016	in vivo mic	increasing**)

*) replaced by in vivo imaging; **) mic = microscopy, will probably reduce biopsy and cytology

Table 6: Development of the main topics of surgical pathology.

Tissue examinations of biopsies, cytology, and surgical specimens dominate the scenario of surgical pathology today. Biopsies by far outbalance surgical specimens. They form the financial background of any institute of pathology, especially when combined with IHC and molecular examinations. However, will their time last forever? They are at least endangered by recently developed techniques, namely liquid biopsies and in vivo endoscopy. Liquid biopsies analyze DNA fragments of the peripheral blood that are characteristic for certain diseases, especially cancer. Localization, size and type of the disease (cancer) define the treatment strategies.

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In vivo images (CT, NMR, etc.) display information of size, localization and related features. Liquid biopsies characterize the molecular features of the disease under consideration. In vivo microscopy can detect histological features in vivo.

Thus, the question arises: Will conventional tissue biopsies including their quite complicated processing methods hold their dominating role? History tells us: probably no longer than for 10 – 20 years. The number of surgical specimens will probably decrease too despite the technological progress of surgical intervention on aged patients. The main key of the proposed development is again the progress of molecular technology and associated examinations.

What will be the remains of surgical pathology in future? Digital and integrative pathology might be a factor of influence. They bridge the distances between the different levels of biologic tissue orders, which start at the level of macromolecules and finally reach the level of organs, species and social properties. There is hope that medical information of the cellular level cannot completely be replaced by information that has been collected from genes and macromolecules.

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