

How to introduce virtual microscopy (VM) in routine diagnostic pathology: Constraints, ideas, and solutions

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Abstract. *Context:* Virtual microscopy which is the diagnostic work with digitized microscopic images in tissue – based diagnosis is in its childhood in being implemented in routine diagnosis. Until today, only a few pathology institutions take use of this new technology, although it is available since several years. Why?

Design: Virtual microscopy requires a new workflow organisation in the pathologist's diagnostic procedure. At a first view, the laboratory workflow seems to remain untouched to a high degree. However, the used laboratory information system (LIS), which is commonly built in a hierarchic order, has to be adjusted at its highest levels, i.e., diagnosis statement, quality evaluation, submission to the clinician (hospital information system), and feedback to the laboratory. Therefore, the laboratory's workflow is involved at all levels too, and the LIS has to be changed or adjusted to the requirements of VM. VM systems are usually equipped with a viewer that mimics the viewing of a conventional microscope, and do not offer access to sensitive nodes of the LIS. Similar, LIS are usually closed and fixed systems because of data security and certification demands. Thus, VM systems have to possess communication access at different LIS levels together with steering commands for the LIS in close association with the diagnostic quality and efficiency (for example demands for additional stains, immunohistochemical or quantitative image methods, etc.), as well as expert consultation, or panel discussion.

Outcome: An implementation of an open and active LIS – VM management system could significantly promote the introduction of VM into routine diagnostic surgical pathology. The management system has to coordinate and translate the demands of VM to LIS (and vice versa), and to assure the communication with HIS. Mandatory features include streaming of the laboratory workflow, feedback commands to LIS, as well as regulation of temporary priority levels.

Conclusion: A successful implementation of VM systems in routine tissue-based diagnosis requires communicative management systems as long as VM is considered to be a “stand alone system” that just mimics a conventional microscope.

Keywords: Virtual microscopy, pathology laboratory workflow, laboratory information system, EAMUS

1. Introduction

Without any doubt, surgical pathology or tissue – based diagnosis is awaiting remarkable changes in the next few years. These will include the diagnostic work with completely digitized glass slides (virtual slides), the application of newly developed mark-

ers for demonstration (visualization) of intra-cellular pathways, and an intensive collaboration with those colleagues who treat the patient, i.e., the oncologist and/or surgeon. The keyword of this new world is called individualized (cancer) therapy or predictive diagnosis [1, 2]. The formal procedure includes a series of steps of tissue examinations in a hierarchical order. It starts with the conventional analysis of small tissue fragments (H&E stained biopsies), followed by analysis of receptors bound to cellular

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membranes and involved in information/recognition processes of cellular division (and apoptosis). The final step includes the analysis of intra-cellular pathways that transfer the extracellular information to the genetic data base (genes) that is responsible for the release of reduplication/apoptosis signals. The series of mandatory examinations is called predictive diagnosis, as its results steer the treatment of the individual patient in close association with the obtained intra- and extracellular functions. An accurate and reproducible as well as efficient implementation of these procedures require in addition to standardized fixation, tissue processing, conventional and immunohistochemical (IH) staining methods sophisticated molecular biology and genetic techniques, and their monitoring [3–5].

A human based interactive judgement of the obtained IH signals still is in use in most of the involved pathology institutions. These are subject to non negligible inter- and intra-observer variations. The same holds true for other procedures, for example based upon fluorescent signals. Accurate measurements are sensitive to digital measurement protocols, they can, however in contrast to observer variations reproducible analyzed and, if necessary, corrected [6–10].

Therefore, the recently developed molecular biology techniques need digital image acquisition and associated analysis programs [11–15]. This performance, on the other hand, will imply remarkable changes in the daily workflow of a surgical pathology institution [2, 3, 16–18].

In this article we want to describe, analyze and judge the necessary, probably unavoidable changes with their benefits and constraint in a surgical pathology institution. Even at this early stage of our article we want to claim that surgical pathology has to follow the new development, if it wants to maintain tissue – based diagnosis in its hands. Otherwise it will lose its competence, and, in addition, non-negligible financial resources.

2. Workflows in routine diagnostic surgical pathology

2.1. Conventional workflow

The workflow of an institute of surgical pathology plays an important role in performance and poten-

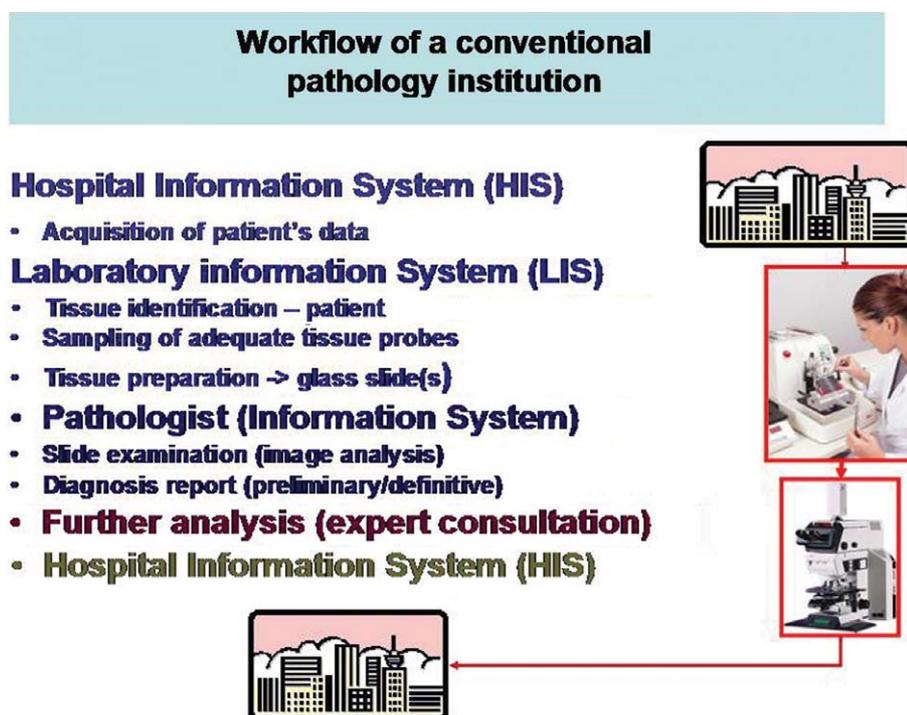


Fig. 1. Workflow of routine diagnostics in a conventional institute of pathology.

tial changes or introduction of new technologies [3, 18]. Its basic features are displayed in (Fig. 1). The components of the workflow include the Hospital Information System (HIS), the Laboratory Information System (LIS), the Pathologist's Information System (PIS) including the pathologist him/herself, and some additional, not mandatory components such as Expert Consultation System (ECS) or Diagnosis Assurance System (DAS) in larger Institutes of Pathology [2, 19–22]. The HIS assures the fast and correct transfer of the patient's data to the Institute of Pathology, and the biunique connection of the tissue with the patient. It is commonly replaced by a so – called patient card in smaller Institutes of Pathology which handle tissue submitted by private medical practitioners. The LIS assures the biunique data transfer between the tissue and the derived glass slides that are viewed by the pathologist. The obtained findings including the derived diagnosis are usually dictated, documented and transferred to the HIS by a specific Pathology Information System (PIS) that also handles the financial aspects (reimbursement) in general. These components are necessary and usually form the general workflow of an effective and structured Institute of Pathology [1, 10, 23–26]. Additional components

include consultation of experts or access to specific cases collections (atlases) in difficult or non familiar cases. The described workflow assures a time effective and “continuous” work of the pathologist who is involved in about 20–60 cases (patients) per day. In addition, VSs are an adequate tool to be applied in intra-operative frozen section diagnosis [27].

How to include virtual microscopy (VM) in a matured and effective workflow?

2.2. Workflow with included (interactive) Virtual Microscopy (VM)

At a first glance, the general scheme of such a workflow differs only minimal from the conventional one (Fig. 2). Only two components have to be added between the LIS and the PIS, namely the Virtual Microscopy (VM), and an electronic storage and retrieval system (ESRS), if we want to include the pathologist's role in a system derived from conventional workflow, i.e., with human – based assessment of diagnosis and without machine assistants. However, these two additional components alter the workflow to a large extent:

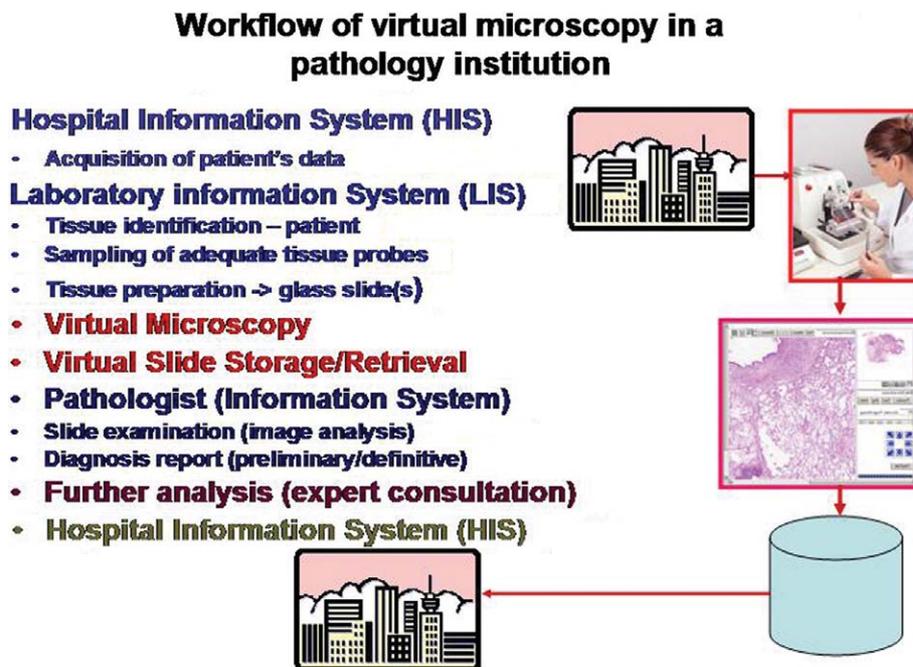


Fig. 2. Workflow of routine diagnostics with included virtual microscopy in an institute of pathology.

Interactive features

Essential: navigation, magnification, adjustment of brightness, white (color) balance, patient's identification (bar code)

Optional: interactive measurement (tumor size, melanoma), labeling, links to experts, laboratory (additional stains), digital textbooks.

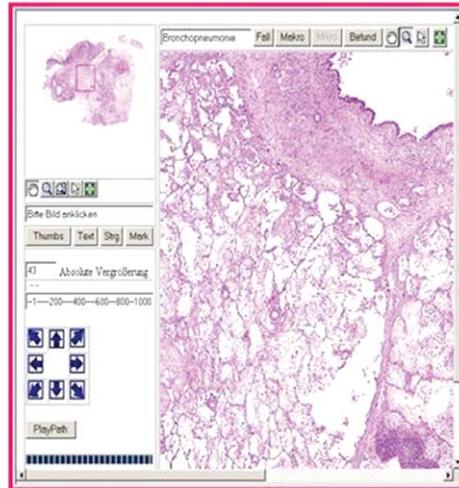


Fig. 3. Essential and optional interactive features in a VM.

VM consists of several components in a time oriented hierarchical order. The first component is the image acquiring system (scanner) that has to be loaded with the conventional glass slides. Most systems require magazines of 20–50 glass slides/magazine [28, 29]. In addition, a bar code is mandatory to assure a correct and automated identification of the obtained virtual slide (VS) with the glass slide. The second component is the fast and error – free transmission of the obtained (usually large, i.e., several GB in size) VSs to an image data bank. The third component steers the presentation of the VSs to the pathologist, i.e., combines VSs of different stains with the patient's data such as clinical history, radiological findings, etc. Some VMs possess components of the PIS such as ordered presentation of the cases, or included digital dictation, others not. In most cases the pathologist has to type in her/his findings and diagnosis. Aspects of reimbursement have not been included in any of the commercially available systems to our knowledge at present.

What are the specific features of such an interactive workflow?

2.3. Specific features of interactive Virtual Microscopy (VM)

VM transfers the stained tissue of a conventional glass slide into an electronic image (VS). The aim of

the pathologists work remains the same: To derive as much information as possible from the image(s) and transfer this information into the medical language which is the diagnosis. Therefore, the principle work using interactive VM is closely related to the work with a conventional glass slide. Essential are navigation, magnification, illumination, and color adjustment (correction) in addition to the patient's data (Fig. 3). However, the digital presentation of the images permits additional interactive assessments such as measurements of size (melanoma), labelling of specific findings (demonstration of giant cells, etc.), crude frequency analysis (counting of mitoses via a grid), overlay or contemporary display of different stains (tumor classification due to cytoskeleton expression), instructions to the LIS (request for additional stains, etc.).

The implementation of interactive VM implies additional work in the laboratory because of loading and maintenance of the scanner and related issues. This additional workload is compensated by digitized storage and retrieval of VS as well as less workload of the pathologist [1, 10, 19, 30–33]. The main constraint of implementation and use of interactive VM are the lower velocity of image screening (sampling) and sometimes the non-appropriate adjustment of image size on the screen as well as missing individual color adjustment [31, 34–36]. Whether one or two screens are more suitable in interactive VM is

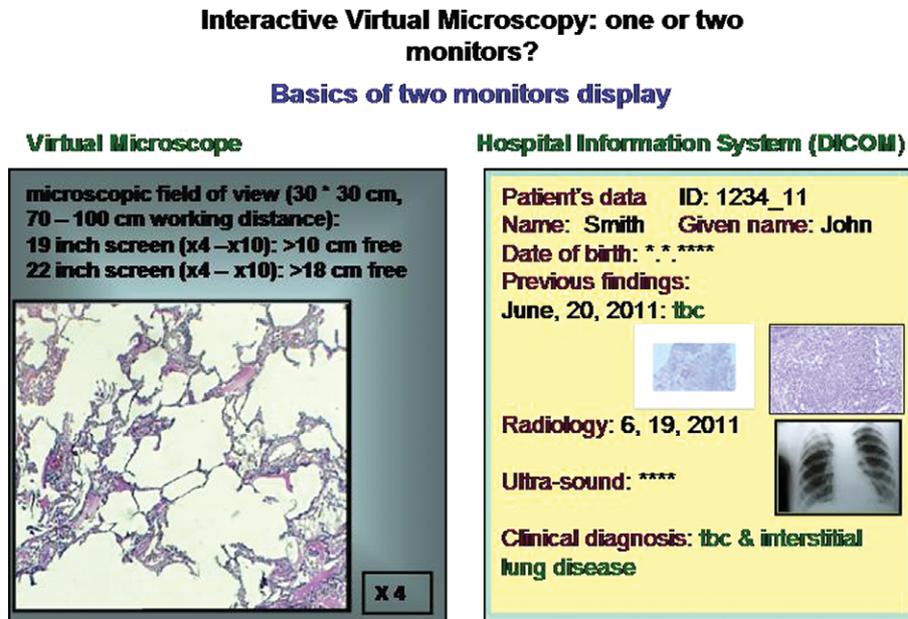


Fig. 4. Basic scheme of information display in a two-monitor VM system.

still under discussion; however, a two screen solution as demonstrated in (Fig. 4) seems to have more advantages.

2.4. Specific features of automated Virtual Microscopy (VM)

Automated VM differs from interactive VM in several points: The aim of automated VM is a support of the pathologist's work by so-called electronic assistants (comparable with those used in other service programs such as corel draw, excel, power point, word or similar programs) [1, 10, 23]. None of these assistants is commercially available to our knowledge at present; however, several successful systems have already been reported. They include "a complete program" of programs arranged in a hierarchical order. They start with analysis (and potential adjustment) of image quality, followed by recognition of region of interest (ROI) and the most appropriate magnification for object segmentation and identification [4, 25, 30, 31, 37–40]. The last step is an automated classification of the "image information carriers" which are derived from objects, structures, and textures [1, 31, 36]. The so – called image content information is then

compared with quality assurance sets that include the already obtained diagnoses and clinical data such as age, sex, symptoms, etc. and the related probability of the electronically evaluated diagnosis [1, 31, 36]. The pathologist's duty would be to judge distinct steps in the described procedure, to assure and finalize the obtained diagnosis.

The workflow of such a system is shown in (Fig. 5), a demonstration of a potential arrangement at a "supervision screen" is depicted in (Fig. 6). Some programs that are included in these algorithms cannot be judged visually. These include the texture analysis and proposed segmentation algorithms which can vary according to the image quality and automated correction [1, 6, 34, 35, 41–45].

3. Perspectives of Virtual Microscopy

Without any doubt, the development of mandatory VM components has made a remarkable progress in the last few years. Commercially available virtual slide scanners have been released that acquire a whole glass slide image in less than 60 sec with a pixel resolution $<0.2 * 0.2 \mu\text{m}^2$. Fast transfer of the several GB measuring images in combination with advanced

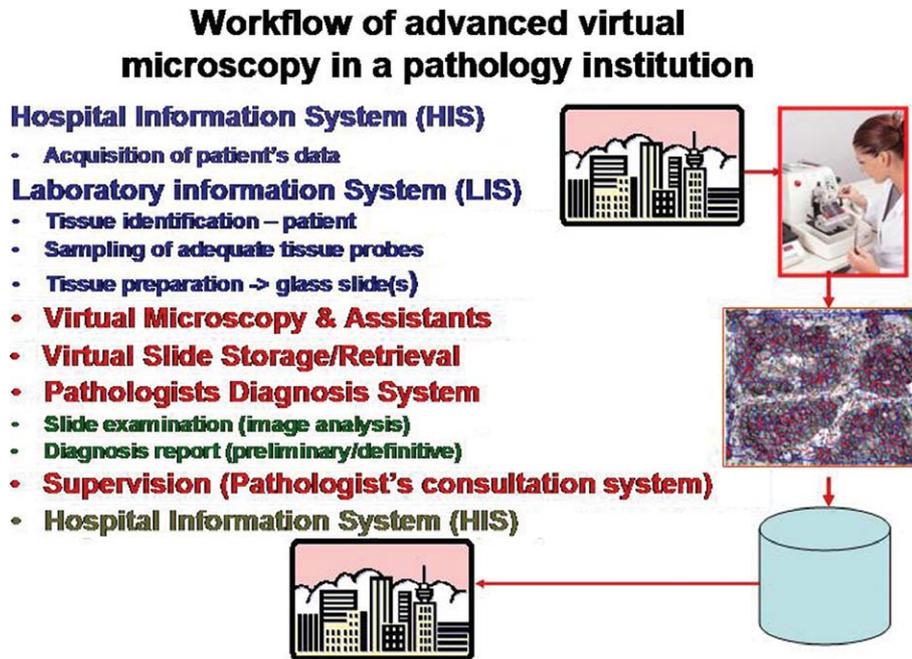


Fig. 5. Workflow of routine diagnostics in an institute of pathology equipped with an advanced VM system.

Automated virtual microscopy monitor display

Maximum field of view about 1500 * 1200 pixels

	Patient's ID: 1234_11	VS no: 1 – 2 – 3 – 4 – 5 – ... n
	Clinical diagnosis: SNO-MED: M83503	ICDO: 8012/3
	Stage of performance: not possible ready started done	
	Image quality	xxx
	Area of Interest	xxx
	Texture analysis	xxx
Chosen objective	Object segmentation	xxx
	Structure analysis	xxx
	Proposed diagnosis	***
X 20	LIS interaction:	xxx

Pathologist's control at:
IQ, ROI, OS, PD
Stage look up (images):
ROI, SA
Confirmed diagnosis:

Expert consultation: on
Statistics: on

Fig. 6. Proposed scheme of monitoring an automated VM by the pathologist.

image compression algorithms is available too [17, 22, 46–49]. Some companies have optimized the related image viewers to the latest communication standards and technology such as FLASH, HTML5/AJAX, (hypertext markup language), asynchronous JavaScript and XML (extensible mark up language), Silverlight, etc. Sophisticated image analysis tools are also available [6, 9, 21, 23, 35, 43, 50, 51]. They mainly focus on immunohistochemistry and “translate” the measured absorption values of the applied visualization dye (DAB, AP, etc.) to the visual judgement of a pathologist (scores) [12, 35, 36, 52, 53]. Some of these systems have already been approved by the US Food and Drug Administration (FDA).

Until today, numerous systems have been sold, and installed in larger pathology institutions to our knowledge. What are they mainly used for?

They all possess components that permit a reliable image acquisition and transfer, a useful tool for teaching and interdisciplinary case demonstration. Nearly all pathology institutes teach students, junior assistants and provide clinical – pathology conferences using virtual slides [54–58]. These issues are the main applications of VM. Its implementation into routine diagnostics remains a slow and hesitating process, and only two European Pathology Institutions (in Sweden and in The Netherlands, both private) have released some information about the experiences. Both of them have implemented a specific surface with the LIS, and both of them are still using conventional microscopy contemporary to our knowledge.

However, the maturation of VM in terms of offering flexible and fast surfaces to different LIS and PIS on the basis of HL7 (Health Level 7), DICOM (Digital Imaging and Communication), and PACS (Picture Archiving and Communication Standard) solutions (standardization) has remarkably increased the interest of larger Institutes of Pathology to implement VM and replace the existing conventional systems [34, 59, 60]. Therefore, we expect that at least in the Western European Countries VM systems that focus on routine diagnostics in surgical pathology (tissue – based diagnosis) will be implemented and matured by corresponding practical experiences in the near future. Such systems will slowly turn from interactive to automated use in order to provide the required cost/efficiency balance which can only be obtained if the otherwise sharply increasing workload of the pathologists will be reduced by this modern technology.

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