Ann Ist Super Sanità 2010 | Vol. 46, No. 2: 144-150
DOI: 10.4415/ANN_10_02_07

The virtual slide in the promotion of cytologic and hystologic quality in oncologic screenings

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Summary. A regional experience environment in virtual microscopy and digital pathology comprehending the digital cytology is presented. The project has been conducted in Emilia-Romagna and it has been planned for the promotion and the quality assessment in screening cytology and histology for the prevention of the tumors of uterine cervix, breast and colon-rectum cancers. During the project it has been envisaged the design of a dedicated picture archive and communication system (PACS) for cooperative diagnosis, didactics and training, teleconsulting, documentation of rare cases and pilot experiences; furthermore selected cases are catalogued in the PACS with the aim of the check of the diagnostic concordance in the oncologic screening.

Key words: digital pathology, quality controls, digital slide, PACS.

Riassunto *(Il vetrino virtuale nella promozione della qualità nello screening oncologico in citologia istologia)*. Vengono presentati l'ambiente e le strutture per realizzare una esperienza in microscopia virtuale e patologia digitale che include anche la citologia digitale. Il progetto è stato condotto in Emilia-Romagna ed è stato progettato per la promozione e la valutazione della qualità dell'interpretazione citologica e istologica applicate agli screening per la prevenzione dei tumori della cervice uterina, della mammella e del colon-retto cancro. Si descrive come è stato realizzato un sistema di archiviazione e comunicazione di immagini digitali (PACS) per condivisione di vetrini relativi a casi particolari, per didattica, formazione, teleconsulto e per la valutazione della concordanza diagnostica negli screening oncologici.

Parole chiave: telepatologia, controlli di qualità, vetrino digitale, PACS.

INTRODUCTION

The diagnostic reproducibility assessment is one of the basic parameters of quality control in cytology [1, 2], particularly in the screening for prevention of cervical cancer. The standard set of slides represents the most used method to compare diagnostic proficiency [1], the chance of interpreting microscopic digital photographs provided an interesting alternative to reading whole cytology slides to evaluate the diagnostic reproducibility of borderline Pap-test [3]. In support of preventive screening for cancer of the cervix, breast and colorectal cancer, the Italian Region of Emilia-Romagna enabled control initiatives and promotion of quality in various sectors. The digital images were used to assess the reproducibility in colposcopy [4, 5] but also in cytology, and histology [1]: in 2001 and 2006 two CD-ROMs were packaged containing microscopic images of cervical diseases along with programs to observe and record the diagnostic interpretation and send the results to the regional center of coordination [6]. The data are discussed in a final consensus meeting [7]. Piemonte and Trentino Regions have experienced dynamic telepathology applications with the possibility of consultation and online discussion of pathologies observed in the cancer prevention screening in a teleconference with pioneering live microscopy [8, 9]. The Region of Tuscany employs digital images for proficiency tests and for teaching screening [10].

The modern concept of telepathology is expressed today in the whole-slide imaging digital pathology [11], where all the information on conventional sample are then transferred into a file, easily archived, catalogued, duplicated or advice for quality control, but is especially available at a distance and from multiple locations simultaneously with drastic reduction of time needed to achieve proficiency test reproducibility [12].

Problem definition

The production of digital slides with modern scanners is relatively simple and quick. All suppliers offer publishing services into private or public networks server [11] and software able to track scanned cases comprehensive database to build large casuistry archives on the net [13].

While tools are already available for a teleconference discussion of cases with vision of cytological preparations in line [14, 15], educational programs with integrated digital slides are poorly developed

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nor self-evaluation or proficiency tests for continuing education and professional updating are easily accessible. On this field, only scattered experiences have been recently reported and they are mainly addressed to specialists [16, 17].

Aim of the work

The objective of this study is to describe a management system for cytological and histological whole-slides digital images and related clinical data, to build a PACS among pathologists of the Emilia-Romagna Region. This must be backed by software for the realization of network slide seminars to perform periodic tests of diagnostic reproducibility and proficiency test. The cases, collected and properly catalogued in an online, extensive and systematic digital archive of slides, easily accessible, with diagnosis discussed in clinic-pathological audit and validated by experts, can be used as diagnostic reference tool (casuistic atlas online).

MATERIALS AND METHODS

The pathology PACS consists of functional units with components and programs.

Scanning stations

Function: to create digital slides in various laboratories.

Hardware: two Aperio Scanscope XT scanners were installed in two different locations.

Software: Scope program to operate the scanner and create whole-slide digital images.

Servers and network

Function: connect to each other scanner, workstation and server that contain the memory disks.

Hardware: HP server with two disks for a total of 6 TB; a high speed, optic fibers cabled local area network (LAN) is available in the intranet connection between the scanning position and servers.

Software: Microsoft Server 2003 operating system, Apache web server.

The two scanners and a server are connected together by a private network (intranet), even if located in buildings physically distant. The second server is exposed to the public network (Internet) and connected with a secure connection to the first server *(Figure 1)*.

Subsequent functional units are represented by programs that exploit the hardware shown above; the access to the various functions is controlled by a password that also defines the user's rights of participating/examination/editing.

Digital slides Internet publication

Function: it makes available the large images of whole slides in emulation microscopy, that is to make available for diagnostic interpretation through the network connection. The publishing service allows clients to explore limited areas of the image without downloading the entire file; the function is analogous to the exploration of maps in navigation systems or network (Bing Maps or Google Maps).

Software: Multiple Aperio Services Manager (standard equipment of XT Server) in support to Apache web server. The connected clients can see the digital slides through conventional Internet browser (Explorer, Mozilla etc. with Adobe Flash Player v.8 installed) or microscope emulation programs such as Aperio ImageScope or universal digital microscopes (*e.g* Digital SlideBox, www.digitalslidebox.com).

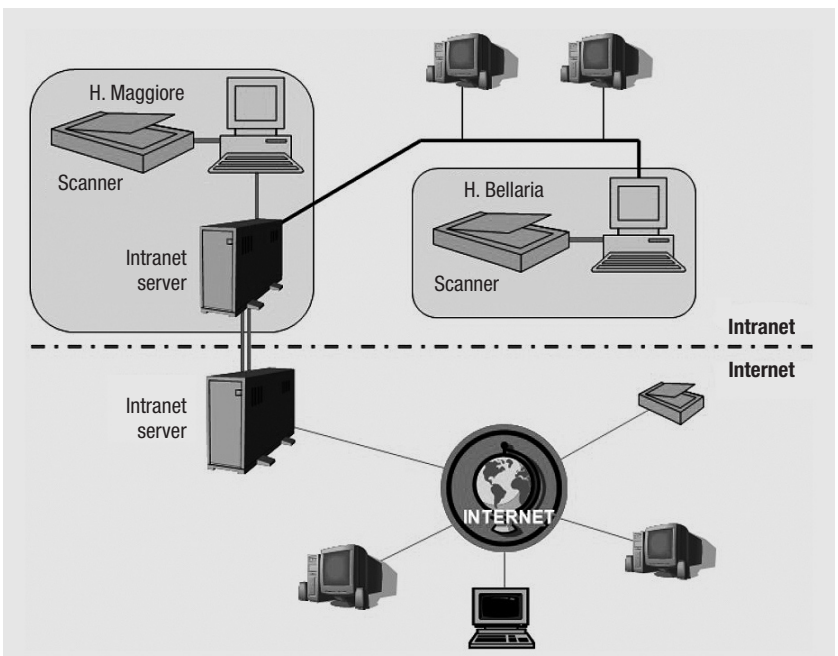

Fig. 1 | *Network scheme: two scanners are in an intranet environment with a local disk server, connected to an Internet server where the public products are stored.*

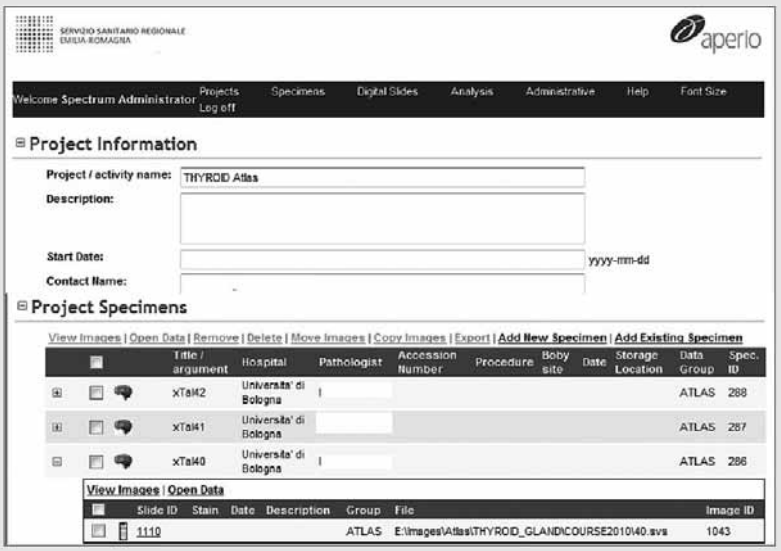

Fig. 2 | *The Aperio Spectrum interface, with the three hierarchic levels of organization: this interface is used to record cases, specimens and slides information into the database.*

Cases archive

Function: organize digital slides into logical units available.

Software: Spectrum Aperio program provides three levels of hierarchical organization, [Project or Case] ⇒ [Specimens] ⇒ [Digital Slides], in a tree structure: a project can contain many specimens and each specimen may be connected to several slides. File attachments is allowed at any level: images, documents, tracks, broadcasts.

From an information technology (IT) perspective, the spectrum program is written in PHP, a popular open source language, which uses a relational database as popular as MySQL.

Proficiency tests

Function: provides tests, questionnaires or quizzes based on the interpretation of digital slides, specimens or histological/cytological clinical cases stored in the archive, giving eventually an assessment of supplied diagnosis, allowing to build comparison scheme with other received advices.

Software: we analyzed different systems of e-learning open source, to find one that is fully compatible and integrated with the Spectrum program. The Docebo platform (www.docebo.org) has been chosen, a complete suite of online learning, flexible and configurable, as it uses the Spectrum development environment, PHP and MySQL. Improvements were made so that among learning objects Docebo can handle cases, specimens and digital slides stored in Spectrum to build questionnaires, examinations and proficiency tests based on these.

Slides seminars

Function: to collect and record adequate cases with histological documentation to be discussed in seminars of diagnostic consensus and in clinic-pathological audits.

Software: the slides are scanned and the clinical data are inserted in the spectrum database, then Docebo renders them in a windows and built a simple proposal form to collect differential diagnoses, anonymously if preferred by the participant. During the observation of cases and slides the examiner is not allowed to see the diagnosis nor the opinions of other contributors.

Finished collection of diagnostic interpretations, cases are discussed in consensus meetings (seminars audit) with the possibility to employ teleconferencing systems.

Consultation atlas

Purpose: to organize cases, specimens and slides according to logical diagnostic hierarchies, with directories to simplify search of concepts and diagnoses in order to create an atlas of digital slides for consultation, covering a wide range of histopathology, especially cancer.

Software: a program was developed that uses indexing and search cases, specimens and slides rare ecorded in digital Spectrum. The cataloging and indexing is performed with NAP codes, a Nomenclature derived from SNOMED [18], which contains terms in Italian and English and encompasses extensive synonyms and complex searches.

Cases are presented with data and attachments provided in the Spectrum environment, with a friendly user configurable layout.

RESULTS

Scanning system, network and servers operate on the parameters of commercial supply and are satisfactory for the purpose of this work.

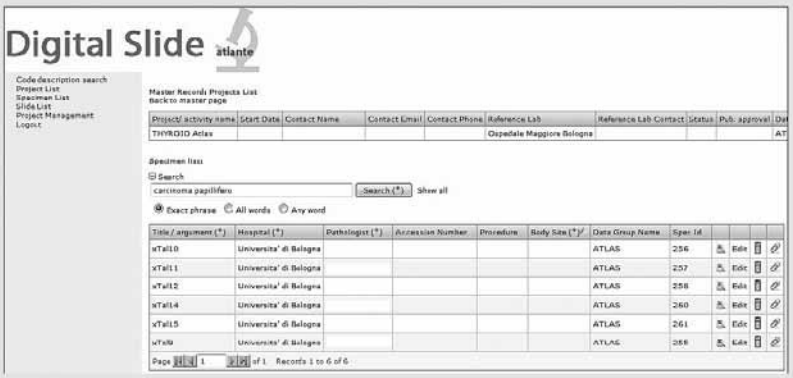

Fig. 3 | *The cases atlas environment shows the same cases recorded in the Spectrum database, and with the possibility to apply diagnostic filters. In the search field the term "papillary carcinoma" would have had the same results as "carcinoma papillifero", inserted here.*

Cases archive and consultation atlas

The Spectrum program provides a good digital archiving of slides organized into hierarchies of specimens and projects. The cases firstly are saved into the archive with the Spectrum Aperio interface *(Figure 2)* and then viewed and coded according to NAP system using an appropriate developed form *(Figure 3)*.

Retrievals to find slides and cases associated with a coded diagnosis are very simple and can be made either in Italian or English language *(Figure 4)*. Once selected a case, the related digital slides can be viewed online *(Figure 5)*.

Slide seminars and proficiency tests

Questions and test preparations in the modified Docebo environment are associated with appropriate digital slides: the scheme used to collect responses is a unique selection from a preset list, both for histology and cytology *(Figure 6)*, similar to what was done in ordinary reproducibility test using standard sets of conventional slides [19].

The results of proficiency test are exposed and discussed elsewhere: the aim of this paper is to describe the environment and the programs suitable for the screening quality promotion and control.

The acceptance of cytologists and pathologists of this way of operating was rather good: the major objection was on exploring whole-slide digitalized conventional pap smears: it was even more boring and time consuming than on glass slide! For this reason the more representative areas of conventional Pap smears have been marked with large circles to orientate and speed reading.

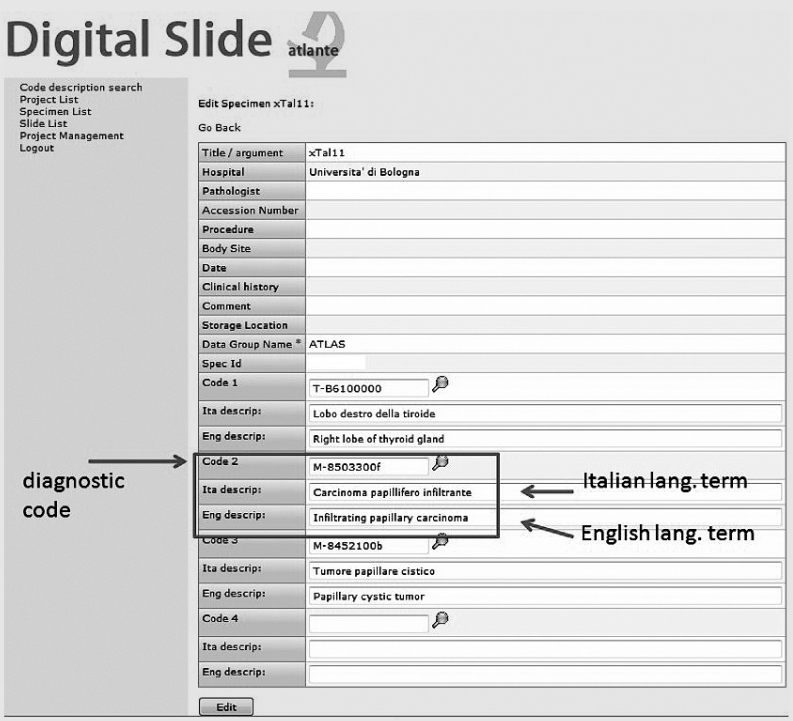

Fig. 4 | *Diagnostic code entering form: up to 4 codes can be associated to a case. Retrieval can be performed in Italian or in English language.*

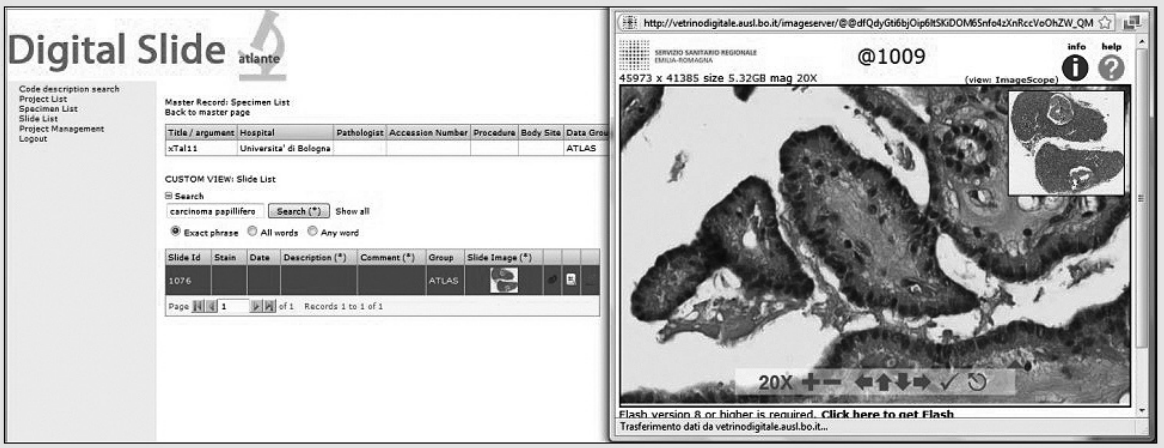

Fig. 5 | *The cases atlas at the slide level: selecting the tile in the case bar, the "digital microscope" is opened.*

DISCUSSION

Previous experiences on exploiting digital images for diagnosis reproducibility tests in the cancer screening environment [6, 7, 20-28] naturally evolved in the whole-slide digital image, that nowadays can be the considered the best tool to promote and control quality [16] and built a diagnostic reference atlas for histo and cytopathologists.

Digital slides over the Internet can offer much more besides the quality control [15] but until now the so called virtual histology is more current in research and morphology teaching [29].

Digital macro and micro images on line shown in the clinico-pathologic audit or seminars can give to pathologists the opportunity to explain and argue morphologic findings, opening the horizon of pathology, bringing it closer to the other diagnostic specialties that can demonstrate and discuss their findings straight in front of clinicians. Some authors argue that pathology is becoming digital in the same way that did radiology 20 years ago [15, 30]; maybe this will happen in the near future but there is a fundamental difference with the story or radiology: there, digital is instead X-ray plates, whole-slide image must be besides the glass slide, that will remains an essential step.

Big digital slide repository have been proposed [13, 15] but nowadays hard disks are still not convenient if compared to storing glass slides. Satisfactory images of rare cases can be consulted on line for diagnostic purposes: some web sites expose histological images for this use (www.raretumours.org): the biggest challenge in this field is to find and look at the right slide-file just when you look for it. We identified the key for this task in building a diagnostic coded index, based

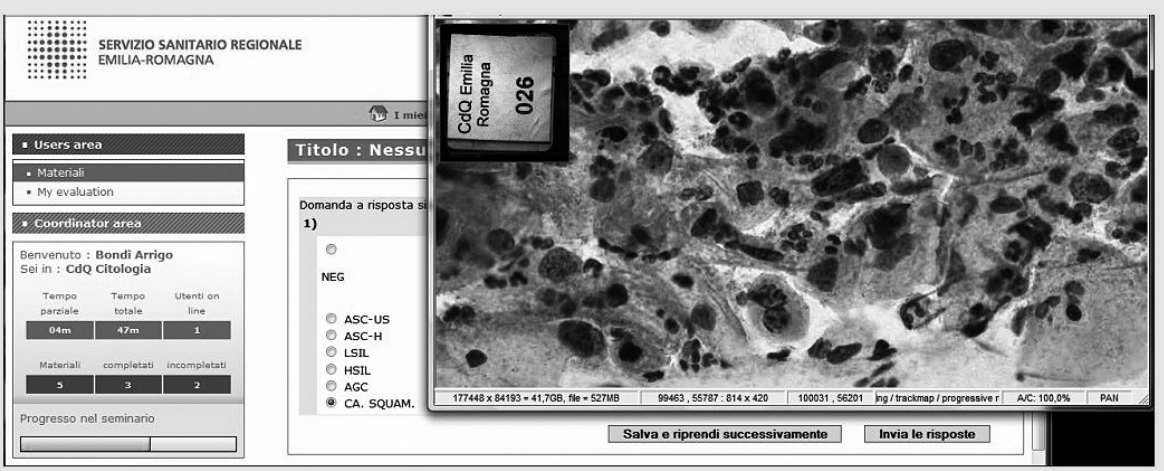

Fig. 6 | *Cytology proficiency test: digital slide shown in a ImageScope window over the answering form. Slides are the same recorded in the Spectrum database.*

on multicode endowment to each case exploiting the NAP nomenclature, a clone of SNOMED. This seems efficient.

Another significant aspect of the software developed in this project is the fully interconnection with the Spectrum Aperio database, that maintains a wide compatibility with the many Aperio archives scattered in the internet and offers an efficient interface with the e-learning environment Docebo, that permits to built questionnaires for proficiency test and slide seminars.

Many of these tools are involved in the open source philosophy that promote access to the end product's source materials: in slide imaging Della Mea, *et al*. produced the eSlide suite, an open source software system for whole slide imaging [31].

We have produced an integrated environment that includes many of the modern aspect of digital pathology that can be shared with the PACS system in many laboratories in the region, including quality promotion and control of image interpretation in cytology and histology applied to cancer prevention screening.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Submitted on invitation.
Accepted on 5 May 2010.

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