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Picture archiving and communication systems in digital cytology

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Summary. The paper describes a fundamental feature of digital cytology relevant to the implementation of the technology in the hospital net services: the electronic recording of the virtual slides (VS) in the hospital information system (HIS) through a picture archiving and communication system (PACS). Starting from the digital cytology (D-CYT) state of art and considering the most important products in the field, particular attention has been devoted in this review to the comparison with the digital radiology (D-RAD). Two main indications emerged from the study: 1. there is not a standard in the digital files relevant to the virtual slides in D-CYT, while in D-RAD the standard digital imaging and communications in medicine (DICOM), introduced by the National Electrical Manufacturers Association (NEMA), has been adopted from several years; 2. the PACS in D-CYT are not standardized from manufacturers. The study makes a proposal of a useful software architecture to improve the PACS integration for D-CYT applications, with potentialities in the HIS.

Key words: telemedicine, digital cytology, tele-pathology.

Riassunto *(Sistemi di archiviazione ed interscambio di immagini in citologia digitale)*. Il lavoro affronta una delle problematiche di base relative all'introduzione della tele-citopatologia negli ospedali: la registrazione elettronica del vetrino virtuale nell'HIS attraverso il PACS. Nella revisione dello stato dell'arte attuale relativo all'introduzione negli ospedali della citologia digitale si è tenuto conto dei diversi prodotti attualmente disponibili. Particolare attenzione è stata inoltre posta alla comparazione con lo stato di inserimento della radiologia digitale. Lo studio ha evidenziato attraverso questa comparazione con la radiologia digitale due importanti problematiche: 1. non esiste attualmente uno standard consolidato relativo ai vetrini virtuali in citologia digitale. In radiologia-digitale lo standard DICOM è stato adottato da diversi anni; 2. i PACS in citologia digitale non sono attualmente standardizzati e cambiano con il produttore. Lo studio termina con una proposta teorica di una architettura software utile a migliorare l'integrazione dei PACS nelle applicazione di citologia digitale con potenzialità nell'HIS.

Parole chiave: telemedicina, citologia digitale, tele-patologia.

INTRODUCTION

Digital cytology (D-CYT) is based on the digital photography of the microscope glass, that is the image of a cytological preparation is digitized, producing the so called "virtual slide" (VS). Up to a few years ago the management of the information in D-CYT applications was exclusively based on the design and construction of a few identical and expensive platforms with microscope units and software tools for both the display and the tele-control (zooming, moving and cutting of pieces of images). Today thanks to the great development of the information technology, the availability of glass digitalization tools and low cost or free visualization tools, the scenario is radically changing. New competitive systems, as those ones based on distributed databases and client-server architectures are today available in D-CYT. Different solutions for D-CYT are available and are based on different equipments such as the ones reported in (which represents a not exhaustive example) [1]: ZEISS (http://www.zeiss.it), NIKON (http://www.nikon.it), OLYMPUS (http://www.olympus.it), HAMAMATSU (http://www.sales.hamamatsu.com), APERIO (http://www.aperio.com), LEICA (www.leica-microsystems.com). To date, the main standardized system for archiving medical digital images is the picture archiving and communication system (PACS) and the main standard for storing and transmitting images is the digital imaging and communications in medicine (DICOM). The PACS is designed to store digital images without the risk of loss or deterioration of their contents and provide

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quick and easy access to all images for all authorized individuals. The DICOM standard is designed for distributing and viewing any kind of medical image regardless of the origin, that is the related peripheral acquisition equipment of a specific vendor. The DICOM allows the transmission of images and related information (*e.g.*, type and patient information). Today, DICOM is used in: radiology, cardiology, oncology and radiotherapy, ophthalmology, dentistry, pathology, neurology, pneumology, surgery. Images are managed by PACS and transmitted by using the DICOM standard.

The D-CYT has the potentiality to change the way of working, offering new chances in tele-consulting and tele-diagnosis in hospitals and also in training [1, 2].

The paper has the objective to study a basic issue relevant to the introduction of the D-CYT in the hospital clinical routine: specifically the production of virtual slides, adequate for clinical diagnosis, the recording, maintenance and sharing of the virtual slides by means of data archiving and management systems, like the existing PACS systems, commonly used in radiology. Starting thus from the status of D-RAD the authors have analyzed the several current limits in D-CYT, taking into consideration what the market today is offering and assumptions from some academic studies in cytology and pathology. Some solutions of images archiving systems were proposed in literature for different purposes, both for building customized archiving systems [3, 4], for images integrating with existing PACS in the hospital, by adapting the format and communication protocol of the virtual slide images [5-7]; some limits of the use of the virtual microscopy in cytopathology were investigated with cytotechnologists [8].

METHODS

An analysis of standardization capabilities of the D-CYT was performed by using a comparison to the D-RAD (that represents a well-standardized practice in the hospital thanks to the European Directives on medical devices and the standardization of DICOM). The analysis also investigates a possible PACS solution based on analogies with a kind of informative system (computer aided equipment CAE; computer aided design CAD; computer aided manufacturing CAM); showing analogies with the problems of maintenance (evolutionary and conservative) of the product for the D-CYT.

DIGITAL CYTOLOGY *VS* DIGITAL RADIOLOGY

Since long time the D-RAD has been based on the standard DICOM [9]. Previously, some attempts of "standardization" before the DICOM were achieved, such as the ACR-NEMA (1985) [10] or the INTERFILE (first version in the 1982 and definitive version in the 1992) [11, 12]; they remained confined respectively to the purely radiological field and in nuclear medicine. The DICOM, developed in 1993 [9], has carried out large innovations:

1. not divisibility between the data of medical image pixel and the data describing the procedure that has been carried out for the formation of the same image;
2. promoting the interconnection in the network between the various typologies of medical devices (CT, NMR, etc.), changing the working activity.

There are several software products that allow to visualize images codified according to this standard (DICOM viewer), some are of public domain and free of charge. During this study phase of review the following free of charge viewers have been deeply analyzed: Rubo Medical, Leadtools, OsiriX, EZDicom, DicomWorks, Aeskulap. The image digitalization played thus an important role in the diffusion of the novel technologies in the hospital applications, in the so called D-RAD. Starting from the radiology rooms with the computers tomography (CT) or the radiological camera up to the rooms with nuclear magnetic resonances (NMR) we have assisted to exceptional revolutionary changes in the management of the data of the exam. The digitalization process in fact meant the introduction of the management of virtual data over the network implying the transmission and the archiving process. Thanks to the DICOM standardization, it was possible to design and construct standardized PACS integrating different imaging equipments. There are still a number of problems hampering the introduction of the D-CYT [13-17] in the hospital:

1) no standardized PACS are currently available; each manufacturer of D-CYT product has designed a proper file standard, for recording and management not allowing an interoperable use as required by telemedicine applications;
2) the use of the DICOM standard is not directly applicable, in fact the virtual slides size exceeds the foreseen image object size limit (2 gigabytes); all the inheritance of the experience of digital radiology, such as the aforementioned visualization tools, are not recoverable. At this moment a Nema Group Working Group (WG) 26 on the digital pathology, in synergy with the NEMA WG 6 responsible for the agreement to the standard, is working on the standardization of digital pathology (and thus digital cytology). The WG 26 DICOM proposed solution for digital pathology is currently under WG 6 discussion in meetings (September 2009 in Florence and in October 2009 in Washington DC) [17-19]; (see also the presentation by Bruce Beckwith in the within of the activity of the WG 26 of the NEMA (http://www.telepatologia.es/9ECT/presentations/Bruce_Beckwith.pdf).

Even though solutions such as those just mentioned are at disposal, manufacturers, to date, preferred to design and maintain a proper standard. Regarding the use of DICOM, we have recently assisted to the efforts of integration conducted by a

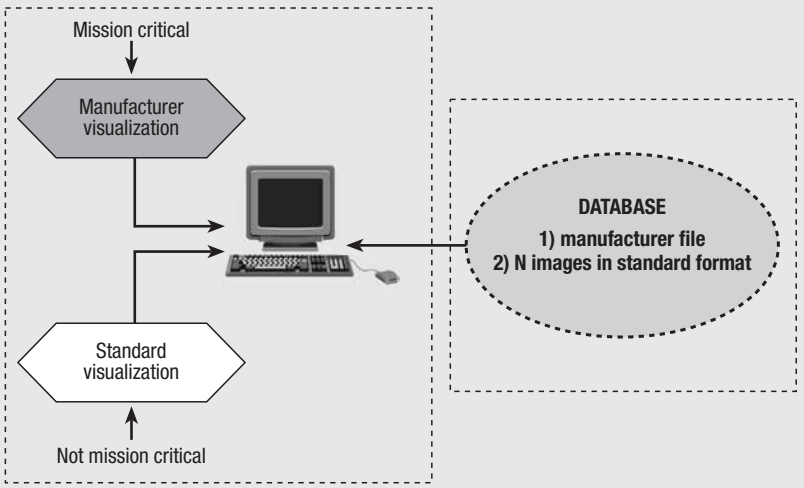

Fig. 1 | *The two ways of constructing database for cytopathology: the "mission critical" of the manufacturer's file and the "no mission critical" of the 15 relevant JPEG files (snaphots).*

leading group of the University of Tampere [5]. The approach used for the integration is based on the JPEG2000 standard and on the interactive protocol JPIP (JPEG2000 interactive protocol) in virtual microscopy. The team has developed a software package based on the JPEG2000 standard, for the image compression, visualization and server applications over the network, suitable for the virtual microscopy applied to the D-CYT and allowing the compatibility with the DICOM standard and thus integrating with existing DICOM-based PACS. The package is available free of charge at the URL (http://jvsmicroscope.uta.fi/). The solution has been successfully tested. However at this stage it has been limited to the academic world.

A POSSIBLE SOLUTION FROM THE CAE-CAD-CAM WORLD

An analogy has been noticed between the problems of recording in the CAE-CAD-CAM informative systems and the PACS in D-CYT. In both technologies the following problems exist:

1) the lack of a standard;
2) the risk due to the market dynamics: a product could exit from the market with serious problems not only for the "evolutionary" maintenance but also for the "ordinary" maintenance. This could lead, in absence of a standard, to the unfeasibility to open and/or manage the recorded files.

Up to date, all the currently vendors' solutions for digital cytology furnish databases of virtual slides based on proprietary file formats (containing images and medical information), this is a point of weakness for the digital cytology and represents a sort of "mission critical" aspect for the routine activity of the laboratories. In addition, the lack of a standard makes the laboratories bound to the vendors and to the market behavior and do not allow the file sharing with laboratories having different database, hampering remote consultation applications. For these reasons, it is hopeful to have a solution "no mission critical" [20], that utilizes files in standard formats and simple to carry out. In planning CAE-CAD-CAM recording and archiving, the solution has been found by recording with the proprietary files of the constructor a further series of files in standard formats of some parts of the design which can allow the reconstruction of the basic elements of the study.

PROPOSAL

The authors propose a simple approach based on common archiving system, capable to ameliorate the integration of the PACS in the cytopathology laboratory, in order to build a local database based on images of standard format (snapshots), constructed on relevant selected images of specific interest from a VS furnished by the commercial database (and not thus on all the VSs).

Figure 1 shows as the solution could come from saving the proprietary file and a number of standard files from the snapshots useful to reconstruct the study (as in the case of CAE-CAD-CAM solutions). The final goal of this operation could be thus to have a digital database, comprehending both the "proprietary database" (PROP-DB) and the standard database (STD-DB) free from the constructor. Such a STD-DB can be reused in the time, for local applications, but also for remote applications, allowing thus to partially overcome the differences among laboratories in the image format. Regarding the D-CYT it has been noticed that fifteen extracted images are sufficient in order to catch up a diagnosis in the case of Pap-tests, as it has been tested by the t-student test in a preliminary study with the statistical significance > 0.1% [21]. The recording of fifteen images in a standard format (like as JPEG, TIFF) seems thus a valid alternative to the vendor's solutions and a kind of narrow-escape from a probable "mission critical" solution *(Figure 1)*. Thus there is the need

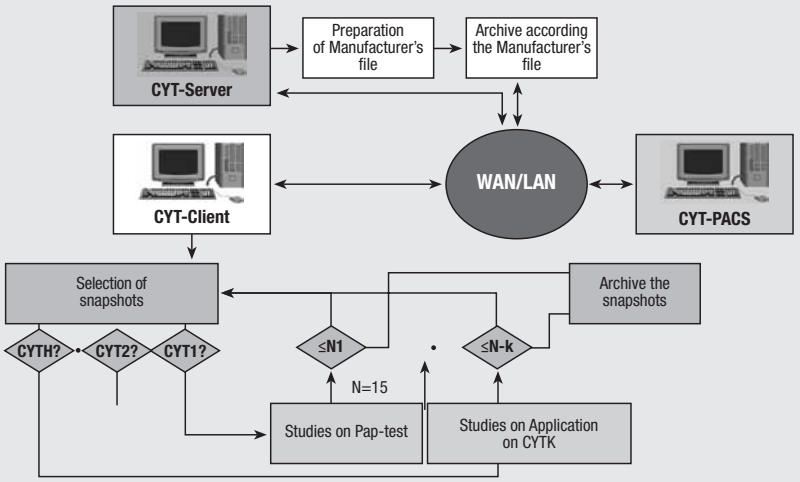

Fig. 2 | *Proposed architecture solution for improving the standardization of PACS in D-CYT.*

to design a local database that allows to manage the snapshots obtained from the region of interest (standard TIFF or JPEG images), usable also in the network. *Figure 2* shows the proposed architecture of archiving taking account of the above considerations. Since all the herein investigated manufacturers allow the extraction of JPEG or TIFF snapshots of selected regions, the realization of the present approach is feasible and manufacturer's independent, representing a kind of mission-critical solution.

Figure 2 shows the proposed architecture for archiving digital cytology studies. CYT-server is the server depositary of the virtual-slides consultable via WAN/LAN from the PC CYT-client of a cytotechnologist. As in the case of digital radiology (where specific guidelines or consolidated studies suggest the optimal number of slices useful to guide diagnosis) also in the case of the D-CYT specific guidelines could be of aid to guide the choice of the optimal number of snapshots to archive on the basis for example of specific studies (in the case of Pap-tests N = 15) [21]. The cytotechnologist selects the snapshots to archive in a CYT-PACS comprehending the vendor's PACS and a PACS containing the snapshots; the number of snapshots are thus selected on the basis of the relevant guidelines for specific applications of digital cytology (CYT1, CYTK).

Figures 3-5 show the proposed solution applied on an Aperio system at the University of Rome Sapienza , 2nd Faculty of Medicine [22].

From a virtual slide furnished in a proprietary format *(Figure 3)*, an operator could navigate through the slide and select a region of interest *(Figure 4)*; the latter region, by means of the snapshot tool, can be saved in a standard format, such as *TIFF* or *JPEG (Figure 5)*. The obtained images can be collected in order to constitute a whole set of information about a specific patient or pathology, allowing

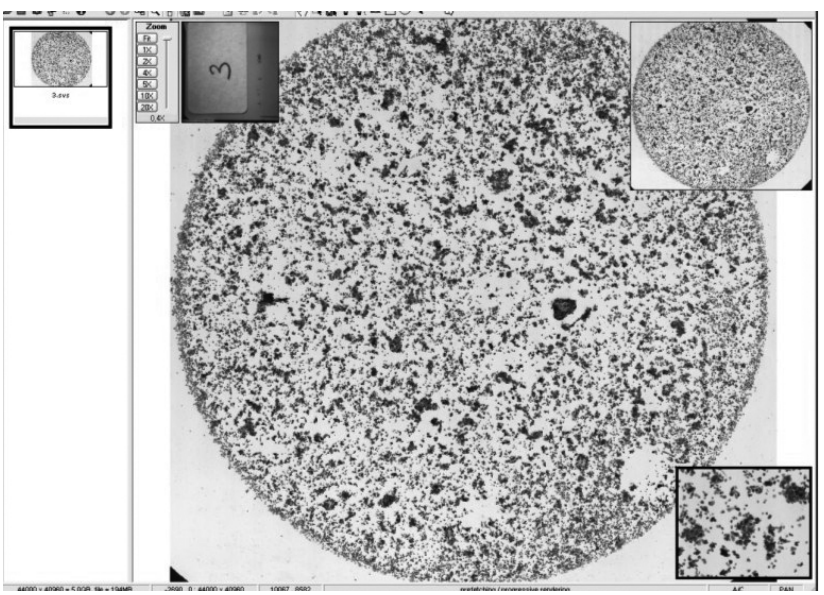

Fig. 3 | *Full view of a virtual slide as it has been obtained by digital cytology application, in manufacturer's proprietary format.*

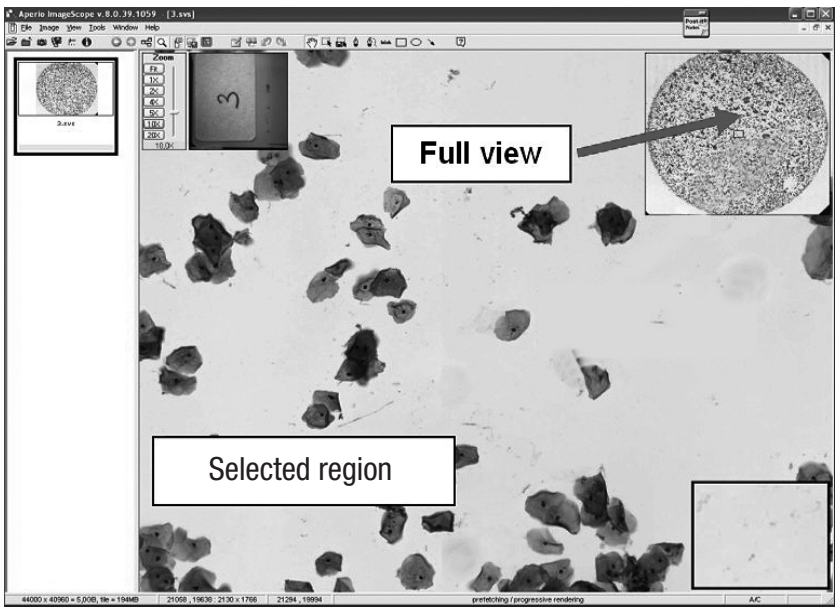

Fig. 4 | *Region selection from the virtual slide: a region of interest can be selected by the operator from the virtual slide and displayed with a suitable zoom.*

different further utilizations for future consultation, local or remote, and/or training and teaching, also by means of e-learning possibilities.

The technological proposal, herein reported, requires to design a local database that allows the operator to manage both proprietary images and standard TIFF or JPEG images, usable also in the network.

During a thesis [22], as a first step, the authors have faced the development of the database, based on Microsoft Access (Microsoft, USA); different set of 15 images were selected from different virtual slides with the aid of clinicians. Medical information regarding patient and pathology was added, in order to build a database adequate to be interrogated to formulate diagnosis and ultimately for tele-consultation and training/teaching purposes. The performed database has been organized for name of patients and each element of the database (identified by the patient name) contained the associated fifteen images and other needed information. *Figure 6* shows the window of the relations between the two main tables of the database ("Patients" and "Exams") and the user interface for managing the database. *Figure 7* shows also a detail of the visualization of the fifteen selected images relating to an element of the database. Furthermore the proposed solution is also easy opened to a conversion process to DICOM when using JPEG format and the software JPG2DCM commercially available

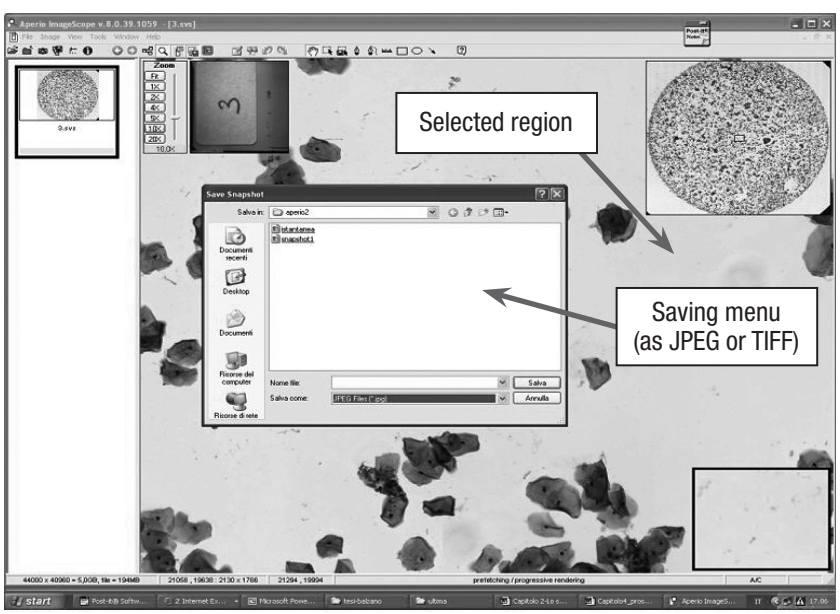

Fig. 5 | *Region saving: the selected region can be saved as JPEG or TIFF format image.*

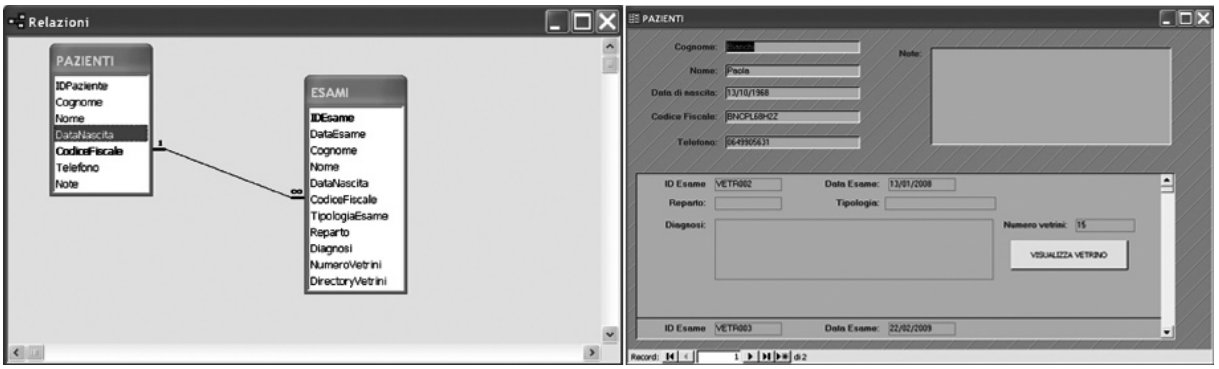

Fig. 6 | *Example of details within the database: the window showing the relations between the two main tables (on the left) and the user interface for managing the database (on the right).*

(www.dcm.org/confluence/display/d2/jpg2dcm) [22] (being the final memory occupancy of the images lower than 2 GB), thus rendering easy the integration within the HIS.

DISCUSSION AND CONCLUSION

In the course of this review we have proposed a solution applicable to the PACS in D-CYT for widening this technology use in the daily routine applications in the hospital.

In fact in the course of the study it has been noticed that there were two issues hampering the diffusion of PACS designed for D-CYT:

1) unavailability of standardized PACS (only proprietary solutions are available) for D-CYT hampering an interoperable use of telemedicine;
2) the use of the DICOM standard is not directly applicable, due to the peculiarity of the digital cytology exam.

The solution proposed could help to improve the integration of the PACS in the hospital; the strength of the solution is that it is based on similar solutions

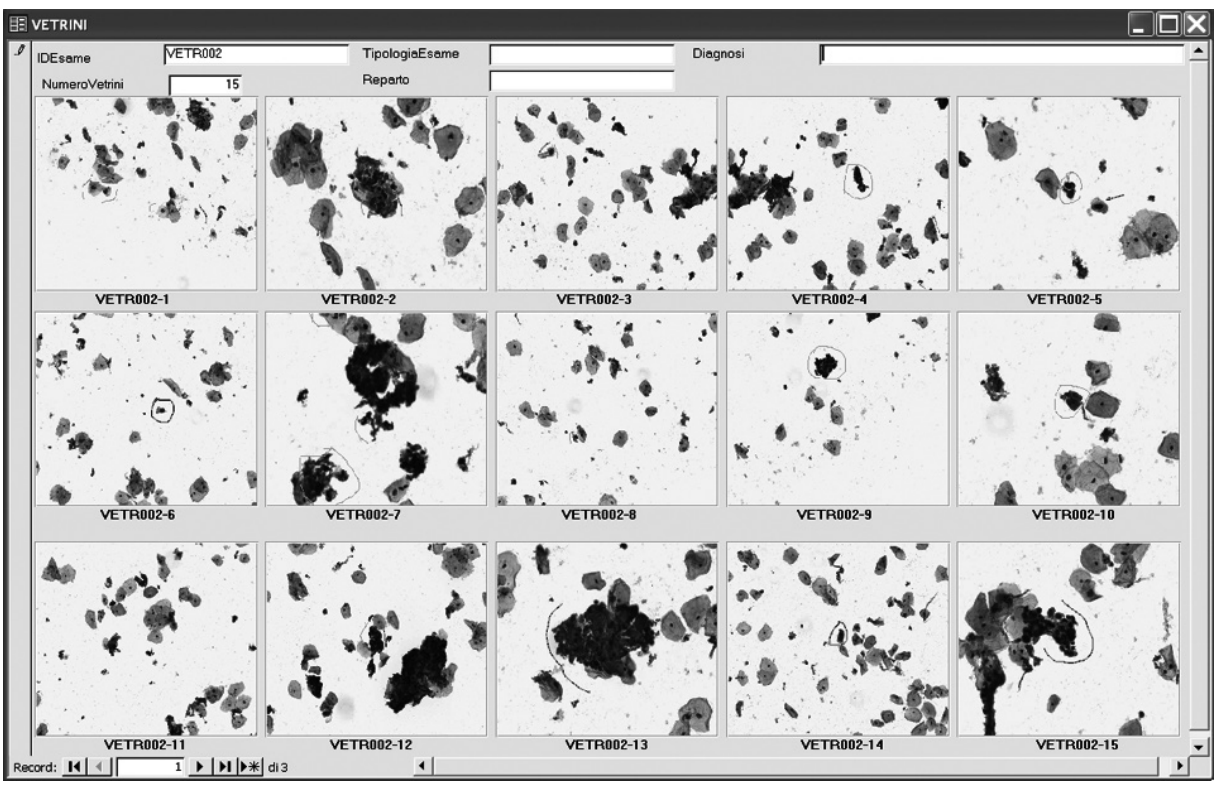

Fig. 7 | *Example detail of the developed database: visualization of the fifteen images relating to an element (a glass) of the database.*

consolidated in the CAE-CAD-CAM environment.

The choice and/or investigation of solutions for D-CYT in hospital should be discussed by all the stakeholders; the scenario offers different opportunities. In a close future, in laboratories where techniques of digital cythopathology are present, the personnel should be able to [1-2]:

- acquire the digitized images from standard glasses;
- select the region of interest;
- record them in a PACS.

Moreover, for all the personnel working in the cytopathology laboratories, the examination on the LCD screen of the digitized image of the virtual slide will be carried out with a different possible visual approach, with respect to that one adopted with the classic optical microscope. This study shows that a standardization of the D-CYT (with particular reference to the PACS) will favour the capillary spread in the territory of the tele-consulting and the e-learning. The laboratory technician will add to his standard competences new competences useful to face the new technology, from the preparation of the virtual slide, to the recording in the PACS.

FURTHER WORK

In the course of this study some further aspects relevant to the introduction of digital cytology in the hospital by using a standard PACS have been pointed out. In particular the authors, have detected some issues of great importance about the full introduction in the hospital of the virtual slide-based technology in D-CYT which should be carefully considered:

1. the resolution and contrast in some cases is not adequate for the investigation of the nuclear-cromatine in the cells [22];
2. the methods of investigation are radically modified for the cytologist; in terms of manner of exploring the glass. The cytologist with traditional microscopy uses a stereo-vision and an archaic instinctive area of the eye (the same used by the primitives men to avoid attacks from animals). Although with virtual microscopy there is the advantage to have an objective tool of visualization, the "monitor", the knowledge of the new strategies of the visual navigation are completely lacking [22].

Hopefully the WG 26 will take in great consideration these aspects relevant for the D-CYT.

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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.

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