Current Status of Whole Slide Imaging in Education

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Abstract

Conventional light microscopy (CLM) has classically been the basic tool to teach histology and pathology. In recent years, whole slide imaging (WSI), which consists of generating a high magnification digital image of an entire histological glass slide, has emerged as a useful alternative to CLM offering a myriad of opportunities for education. Navigation through the digitized slides closely simulates viewing glass slides with a microscope and is also referred to as virtual microscopy. WSI has many advantages for education. Students feel more comfortable with its use, it can be used in any classroom as it only requires a computer with internet access and it allows remote access from anywhere and from any device. WSI can be used simultaneously by a large number of people, stimulating cooperation between students and improving the interaction with the teachers. It allows making marks and annotations on specific fields which allow specific directed questions to the teacher. Finally, WSI supports are cost-effective compared with CLM. Consequently, WSI has begun to replace CLM in many institutions. WSI has shown to be an extremely useful tool for undergraduate education (medical, dental, and veterinary schools), the training of residents of pathology, tele-education, and in tumor boards.

Background and historical perspective

Basic skills in histology and pathology are an essential component of the education of undergraduate students, not only at medical schools, but also at schools of dentistry, veterinary medicine and biology. Residents and fellows in pathology demand more advanced training and certified pathologists require continuing education. This training has to be provided increasingly more frequently to participants located in distant sites. Until a few years ago, the only tool that fulfilled these needs was conventional light microscopy (CLM). CLM was introduced as a diagnostic and teaching tool nearly two centuries ago and became the basis for teaching histology and pathology [1;2]. However, CLM has many limitations, not only in conducting the classes, but also in assessing the skills of the students. One of the main disadvantages of using CLM is that it does not allow simultaneous viewing of the slides by multiple students. Secondly, rooms with multiple microscopes are expensive and require continuous maintenance. A third important disadvantage of CLM is the need to generate glass slides and store them, which entails a significant economic cost and the loss of specimen material.

In the early 20th century the emergence of projectors facilitated the training of students because it allowed displaying the histological images to a number of participants at the same time. The introduction and development of initially analogic and later on digital videocameras boosted the use of CLM in multiple teaching settings. However, these devices allowed moving the slide only to one person, and consequently, served as a teaching supplement but did not allow the replacement of CLM.

In the 80s the first digital images were generated from histological slides, although it was not until later, with the advent of personal computers with sufficient memory capacity, that digital microscopy progressed rapidly to the technology we know today. A few years later imaging converter programs and servers appeared, which allowed uploading the virtual slides to the web and permitted viewing the images and using zoom [1].

Whole slide imaging (WSI), also referred to as virtual or digital pathology, consists of generating a virtual image of the entire histological glass slide. The process is performed by WSI scanners, robotic microscopes capable to automatically generate digital images from the glass slide. Current scanners are able to use different optical objectives (x10, x20, x40, x60) depending on the specific needs and allow scanning the whole slide or a particular portion of the tissue. Specific software allows viewing digital slides online from computers without the need for a CLM. At present there are numerous systems prepared to generate good quality virtual images of histological sections obtained from paraffin blocks or frozen tissue as well as from cytological smears. Image browsing is performed with a mouse or a joystick, which allows moving through the different areas of the slide and permits zooming the image, thus simulating the optical objectives of a CLM [3]. Software viewers have multiple tools to make measurements and annotations on the images, and may contain additional patient information, thus providing a complete view of the cases [4]. The information is adequately protected because, although students and residents can access the virtual slides from any computer, access is controlled by the use of a specific password and registered in the system.

WSI is an extremely useful teaching tool because it allows displaying the histological slides on a computer monitor and solves many of the problems of CLM. Indeed, WSI has been used for many different educational activities (Table 1).This technology is rapidly expanding as a teaching tool, either as a complement of CLM or completely replacing CLM. In many centers the transition from CLM to WSI has already occurred either gradually or suddenly. This review focuses on the applications of WSI (or virtual microscopy) in education.

Advantages of WSI

WSI has brought about an important change in the way of understanding teaching in histology and pathology, allowing the introduction of some actions and capacities that were previously not possible. The main advantages of WSI are summarized in table 2.

Some of the advantages of WSI are related to the change in the physical tool itself. WSI allows any computer to work as a CLM, and consequently reduces or eliminates the need for conventional microscopes. It has been clearly shown that students feel more comfortable with the use of the WSI because they all have prior knowledge of computers (almost all students are currently digital natives) [5-10]. An additional advantage of WSI is that the slides are always in focus. Thus, the students very quickly get used to the tool and can concentrate immediately on the histological features of the slides and not on the management of the microscope [6;9;10]. WSI can be used in any classroom, because it only requires a computer with internet access [1;11]. Moreover, WSI allows access from any device, either in or outside the facilities of the Institution. This implies that the students can review the histological slides at any time and

from anywhere, thereby facilitating their study and eliminating the restrictions of access to the laboratory of microscopy after class hours [1;6;10;12-14]. As a consequence, the very expensive and costly to maintain laboratories of microscopy become unnecessary leading to a significant reduction of costs [9;15]. With an appropriate bandwidth virtual microscopes can be used simultaneously by an large number of people, thereby surpassing the restrictions related to a limited number of CLMs in a laboratory [4;9;12;16;17] and stimulating cooperation between students [9;12;15;17-19]. Moreover, the interaction between teachers and students is improved by viewing the same image at the same time in the classroom, which allows bringing up questions easily and facilitates the learning [15;18;19].

The second group of advantages of WSI is related to the characteristics of the viewer. The presence of a thumbnail indicating the area shown on the screen (Figure 1) promotes better orientation when the student browses the slide [12]. Digital viewers allow seeing the slide at a very low magnification, which also helps the student to be orientated in the tissue. Teaching tools based on WSI allow completing the information of the histological slides with clinical data, imaging studies (conventional radiology, CT scan, ultrasound scan, magnetic resonance), macroscopic images, as well as histochemical or immunohistochemical stains (Figure 2), which, in turn, allows a more complete picture of the study cases [16;17]. Many viewers allow simultaneously displaying several slides on the screen, thus facilitating the interpretation of immunohistochemical techniques by comparing them with the conventional hematoxylin and eosin stain (Figure 3) [1]. Another feature of WSI viewers that is particularly helpful for teaching purposes is the possibility to make marks and

annotations on specific fields of the digital slides to show the key features that allow the recognition of the lesions. This tool facilitates solving specific doubts and improves the interaction between the teacher and the student. With the annotations made by the teacher the students can easily identify the key areas on a slide allowing them to focus on the diagnostic clues of a specific lesion. Annotations and marks made by the students allow them to ask the teacher about specific doubts. Indeed, annotations seem to improve the final results of the students, and several studies have shown that the students who had notes on the slides have better scores than those who do not make any annotation [1;12;14;20-22].

The third set of advantages of WSI is related to the histological slides. Digital slides always have the same quality. They never break, get lost or deteriorate with time. Thus, it is not necessary to replace them by re-cutting and staining new slides every certain period of time, with the subsequent impact on costs and preservation of the frequently highly valuable tissue from the paraffin block [17;20]. WSI homogenizes the material available to students. All students have exactly the same digital slide, which eliminates the variability in quality among different glass slides. Creating selections of interesting cases to students becomes extremely easy because there is no need for additional histological sections [10;17;22]. The easiness to prepare collections of cases with a high number of slides from each organ or pathology allows randomly showing many different cases to the students. This makes the student learn to recognize the histological characteristics of the organ or the lesion and not remember the slide because of other features, such as the size or shape of the tissue [17]. These features enhance learning, and are especially useful during

the evaluation test because the results are totally dependent on the knowledge of the student [23].

WSI allows using cases with very scant material and consultation cases, even when the material has to be returned to the referral center. WSI allows immediate accessibility to old cases, without the need for technical staff to retrieve the slides or paraffin blocks from the archive. WSI also allows using cytological images while preserving the original slide [22]. Finally, WSI permits introducing FISH or immunofluorescence slides, which previously had to be shown on static images because of the deterioration and loss of fluorescence.

Weaknesses of WSI

The main disadvantage of WSI is the initial economic investment for the acquisition of the scanner and the complete WSI system [1;12]. The high resolution WSI images are associated with very large size files, which means significant needs in terms of disk memory for their storage. Thus, high capacity servers to store and distribute the information are needed, and regular maintenance of the servers is required. Proper functioning of the system requires high speed Internet connection [4].

However, the tool can be used for different subjects and, thus be shared by different departments at the school (histology, pathology, medical specialties). A possible solution to this problem is the use of scanners already working at the institution for pathological diagnosis and using free or low-cost software to view the virtual slides [1]. Several vendors offer renting systems that include the digitalization of a set (or a few sets) of slides, the use of teaching software and a number of terabytes in a server. This option eliminates the

investment in the equipment and reduces the costs associated with servers. In any case, computer classrooms are much more versatile than laboratories of microscopy, and all the initial economic disadvantages of WSI are rewarded with time, because the investment in computer equipment and maintenance is much less than that of the costs associated with a laboratory with optical microscopes [9;15].

Another possible disadvantage is that in the centers that only use WSI the students do not learn how to use the CLM. Nonetheless, this is a minor problem since most medical students almost never use the microscope after finishing their training. Indeed, it is more important for them to recognize histological patterns and lesions than to learn how to use the tool [8;15;24].

Finally, the use of these computer-based tools may result in a dramatic reduction of the personal contact between teachers and students. Actions promoting face-to-face meetings should be considered to avoid the depersonalization associated with the spread in the use of computers. On the other hand, periodic quality control of WSI is highly recommended. This should include a comparison between virtual and glass slides, an evaluation of the use of the system outside the course schedule and the registration of what virtual images and which areas in these virtual images are most often seen by the students [1].

WSI in undergraduate teaching

The number of centers using WSI in undergraduate teaching, either as a complement to or as a substitute of CLM has markedly increased over the last few years. Many studies have shown excellent results with WSI, not only for

medical students, but also for students of biology, dentistry, parasitology and veterinary medicine [2;7;8;23;25-30]. Many of these centers have evaluated the opinion of the students after the introduction of WSI, and all have reported very positive feed-back [9;26;30;31]. One of the most valued advantages is the improved accessibility to the slides with WSI, allowing the student to access the slides at any time and from any place [10;14;19]. Several studies have shown that this is one of the most appreciated features of WSI, and this was the most prized feature in a study conducted at our institution [10]. Indeed, data obtained from the audit of accesses to the navigator at our institution showed that over half of the accesses are made on holidays and over one-third after working hours (Figure 4).

Students consider the use of WSI to be easier than that of CLM. WSI allows them to concentrate on the tissues and lesions and not on handling the microscope [8;15;32]. All studies agree that WSI improves collaboration between students and self-learning [6;9;16;24;33;34]. Teachers also positively evaluate WSI because, although there is initially a significant increase in the time related to the preparation of the material, in the end it results in a significant reduction of time spent in the preparation of the lessons [19;35]. WSI provides a more complete approach to the cases by adding clinical information, radiological imaging, macroscopic images, immunohistochemical stains and molecular data to the virtual histological images [33;36]. This can more accurately simulate the actual diagnostic practice and seems to be associated with better final results. Most studies agree that the image quality is better with WSI than with CLM, because the microscopes used for undergraduate teaching

are, in general, of poor quality [20]. Images generated at a 200x magnification are of sufficient quality for undergraduate teaching.

The negative evaluations are basically related to technical aspects such as the speed in loading the images or compatibility problems with some computer models. A high speed internet connection and a server with sufficient capacity are required, especially when many students view slides at the same time [12]. Some centers have solved the problem of storage space by giving the virtual images on a DVD support or scanning only the portion of tissue they want to view, thus saving space in relation with the whole slide [37]. There is still some controversy about whether WSI can totally replace CLM, because students using WSI do not learn how to handle the CLM. The students' opinions about this issue are divided. Most studies reveal that the teachers think that it is more important for the students to use their time in learning histology or pathology than in getting familiar with the technical aspects of the management of the microscope [2].

Finally, the evaluation process using WSI offers choosing between numerous slides, and allows the homogenization of the test, because all the students can visualize the same slide. The use of WSI evaluates only the knowledge of the student, obviating the influence of their ability to use the microscope [32]. Students positively evaluate the use of WSI in the tests as long as the practices are carried out in the same way [30]. Indeed, it is strongly recommended that the same system be used to perform the practical lessons and the exams. There is major reluctance to completely abandon CLM when lessons are taken with WSI and the tests are performed with glass slides. In contrast, if WSI is also used for the evaluation, the students do not feel the need

to use CLM during the course [30]. On comparing the final results of students using WSI with those using CLM (either in the same year or in previous years) no differences have been observed or they were better among those using WSI. Moreover, students using WSI seem to recognize histological patterns better [5;31;38;39].

In summary, studies assessing the use WSI by students have shown very positive results. WSI does not seem to affect the final knowledge or may even improve it [10;40-42].

WSI in post-graduate training (residency and fellowship programs)

One of the first uses of WSI was to create series of interesting cases for residents or fellows in pathology and other specialties that require histological recognition of normal and pathological tissues [17]. Preparing virtual slides prevents the loss of biopsy material in making sections for teaching, thus making the collection of interesting cases much easier. Many residents can view the same image at the same time, with the possibility of working outside the center facilities and at any hour. These features provide an optimization of time and generate more comfort for residents and fellows.

The presence of annotations on the virtual slides also represents a major improvement because it facilitates learning. A study comparing results between residents of dermatology and pathology who visualized the same virtual images, and a group with annotations made by teachers and the other without them, showed a better score in residents whose preparations had annotations, because the learning was more directed towards the most characteristic histological changes that led to the correct diagnosis [21].

WSI has also successfully been used to measure the learning level reached by residents. Several initiatives, such as the European Association of Pathology Chairs and Residence Program Directors, aim to homogenize the knowledge of residents all over Europe evaluating them by performing a test containing virtual slides [17]. WSI is well evaluated by residents in the studies, although the final results comparing abilities reached with WSI and CLM differ from one study to another [43-45]. The presence of clinical and radiological information and previous practice using WSI seem to influence the results [36].

Some studies point out the relevance of establishing the steps involved in the diagnostic process, stressing that residents should learn not only what the correct diagnosis is, but also what the logical sequence to achieve this diagnosis is. These studies use eye-tracking cameras that pick up eye movement during the diagnostic process. The difference between senior pathologists and residents are established by examining which fields are more often viewed, the time spent in these fields and the order in which the slide is observed. Residents spend much more time evaluating the slides than experienced pathologists. However, experienced pathologists are slower in choosing the field in where they will zoom and they do this more frequently in areas outside central (foveal) vision than residents. Thus, there are two kinds of slide evaluation: one more dispersed and time consuming and another more targeted and effective [17;46].

Although WSI is currently mainly a complement to CLM, in the future it is expected to almost completely replace CLM as the use of WSI in routine diagnosis expands in laboratories of pathology. Studies to determine the impact of training pathologists without exposure to actual glass slides are warranted.

WSI in schools of cytopathology

The homogeneity in the quality of the images displayed to the students is a highly appreciated feature of WSI and represents a major advantage in cytopathology, because it allows many students to use the same slide simultaneously without the risk of breaking or losing the slide. In addition, annotated digitized slides are very useful for teaching cytomorphology to cytotechnologists. The use of annotations for evaluation has excellent results, allowing comparison between expert cytologist and students [47].

However, the implications of the relatively low resolution of some WSI systems at low (screening) magnification still need to be solved. Moreover, viewing through a CLM may provide a different perceived field width than what is seen on a monitor. WSI has more difficulty in generating appropriate images due to the difficulties in focusing the images at different levels [48]. This problem can be solved with the use of software packages that allow focusing the different levels of the virtual slide thereby more closely simulating the daily practice of cytology.

In conclusion, although WSI has significant educational advantages, a number of technical problems should be solved before it can confidently be used to teach cytology.

Tumor boards

Many hospitals have tumor boards where clinicians meet for multi-disciplinary case presentations. Pathologists are often required to present the pathology findings at the board presentations. WSI is currently successfully used for this purpose at several institutional tumor boards [49;50]. The use of

WSI in tumor boards and interdisciplinary sessions also helps to bring histology knowledge to residents of medical or surgical specialties who do not have much contact with the laboratory [22].

Tele-education and e-learning

The use of e-learning and tele-education is expanding extraordinarily because it allows providing continuous medical education in a practical and convenient way, markedly reducing costs. Virtual workshops avoid the need to travel to meetings, providing significant economic savings and more flexibility. WSI allows easy visualization of the cases and eliminates the requirement of sending the glass slides, saving time and the costs of courier service. Moreover, the system avoids the risks of loss of or damage to the glass slides [22]. Different online services permit the access to on-line teaching with the objective of sharing virtual slides (e.g., PathXchange,vMicPathorama, Slide2Go) [51].

The use of this technology is markedly spreading, and numerous Institutions promote web-based learning. The Unites States and Canadian Academy of Pathology (USCAP), the American Society of Cytopathology (ASC), and the International Academy of Cytopathology (IAC), among others, have virtual atlases that include numerous cases with educational purposes [52]. Currently there are several collections of cases aimed at teaching residents such as the Dr. Juan Rosai collection (www.rosaicollection.org) (approximately 20,000 cases from 1945 onwards), the collection of the Pathological Society of Great Britain (www.pathsoc.org) or other collections intended for the general public (www.virtualpathology.leeds.ac.uk) [17;22;53]. Virtual slides and seminars are offered by the USCAP´s online academy (more than a 100 virtual slides from different organ systems). The number of journals

that allow access to WSI examples to illustrate the articles, thus improving the content of the publication, is also on the rise.

Perspectives for the future

CLM has been used in pathology departments, as well as in the laboratories of the schools of medicine, biology, dentistry and veterinary medicine for decades. Its replacement by new technologies represents a major challenge. However, increasing needs of education and growing evidence indicating that the results of WSI in teaching undergraduates and pathologists are very positive is resulting in a significant expansion of this tool. Comfort in use and the ability to display the same slide anywhere and at anytime by several people simultaneously, makes this technology much more convenient than CLM. However, the high cost of maintenance of the laboratories of microscopy and optimization of the time of teachers and students with the use of WSI is likely to push most training centers towards the replacement of CLM by WSI. WSI is also extraordinarily expanding as a tool for tele-education and e-learning. Further investigation is necessary to improve the existing WSI applications specifically designed for education and to develop ergonomic tools that improve the navigation of virtual slides. It is possible that in the near future textbooks will have the option to visualize WSI, which will be facilitated with the use of portable devices like tablets or smartphones [22].

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Table 1. Major educational uses of whole slide imaging (WSI).

Undergraduate teaching (medicine, veterinary medicine, biology, dentistry)

Pathology training (residency and fellowship programs)

Schools of cytotechnology

Tumor boards

Tele-education, e-learning and virtual workshops

Table 2. Advantages of whole slide imaging (WSI) for teaching purposes.

Related to the equipment

- Students feel more comfortable with the use of the virtual microscope because they have prior computer knowledge.

- It can be used in any classroom: it only requires a computer with internet access.

- It allows remote access anywhere and from from any device.

- It can be simultaneously used by an unlimited number of people.

- Several students can use the same computer at the same time, stimulating cooperation between students.

- It improves the interaction between teachers and students by viewing the same image at the same time.

- Eliminates the need for investing in the creation and maintenance of the microscopic laboratories.

Related to the viewer

- The thumbnail in the viewer facilitates better orientation when the students browse through the slide.

- The information of the histological slide can be completed with macroscopic images, immunohistochemical stains, radiological images and clinical data.

- Several slides can be simultaneously displayed on the same screen, facilitating the interpretation of immunohistochemical techniques.

- It allows marks and annotations to be made on specific fields which facilitate specific directed questions to the teacher.

Related to the digital slides

- Digital slides do not deteriorate with time and do not have to be replaced.

- Homogenizes the material available to students.

- Eliminates the need for additional histological sections.

- It allows using cases with scant tissue or consultation material.

- FISH or immunofluorescence digital images do not lose fluorescence.

- It allows immediate accessibility to old cases, without the help of technical

  staff searching for the files in the archive.

Figure 1. The viewer displays a thumbnail that indicates the area shown on the screen. This promotes better orientation when the student browses the slide.

Figure 2. Teaching tools based on whole slide imaging (WSI) allow completing the information of the histological slides with clinical information, imaging studies (conventional radiology, CT scan, ultrasound scan, magnetic resonance) macroscopic images, as well as histochemical or immunohistochemical stains.

Figure 3. The viewer allow displaying simultaneously several slides on the screen, thus facilitating the analysis and interpretation of immunohistochemical techniques

Figure 4.A) Number of accesses to the virtual slides from the opening of the website to the day of the exam. The X axis shows the day of accession in relation to the exam (day 0). The Y axis shows the absolute number of accessions. Red columns identify accessions on weekends/holidays (Saturday, Sunday or other holidays). Blue columns indicate work days. **B)** Time of accesses to the virtual slides during the day. The X axis shows the time of the day and the Y axis shows the absolute number of accessions
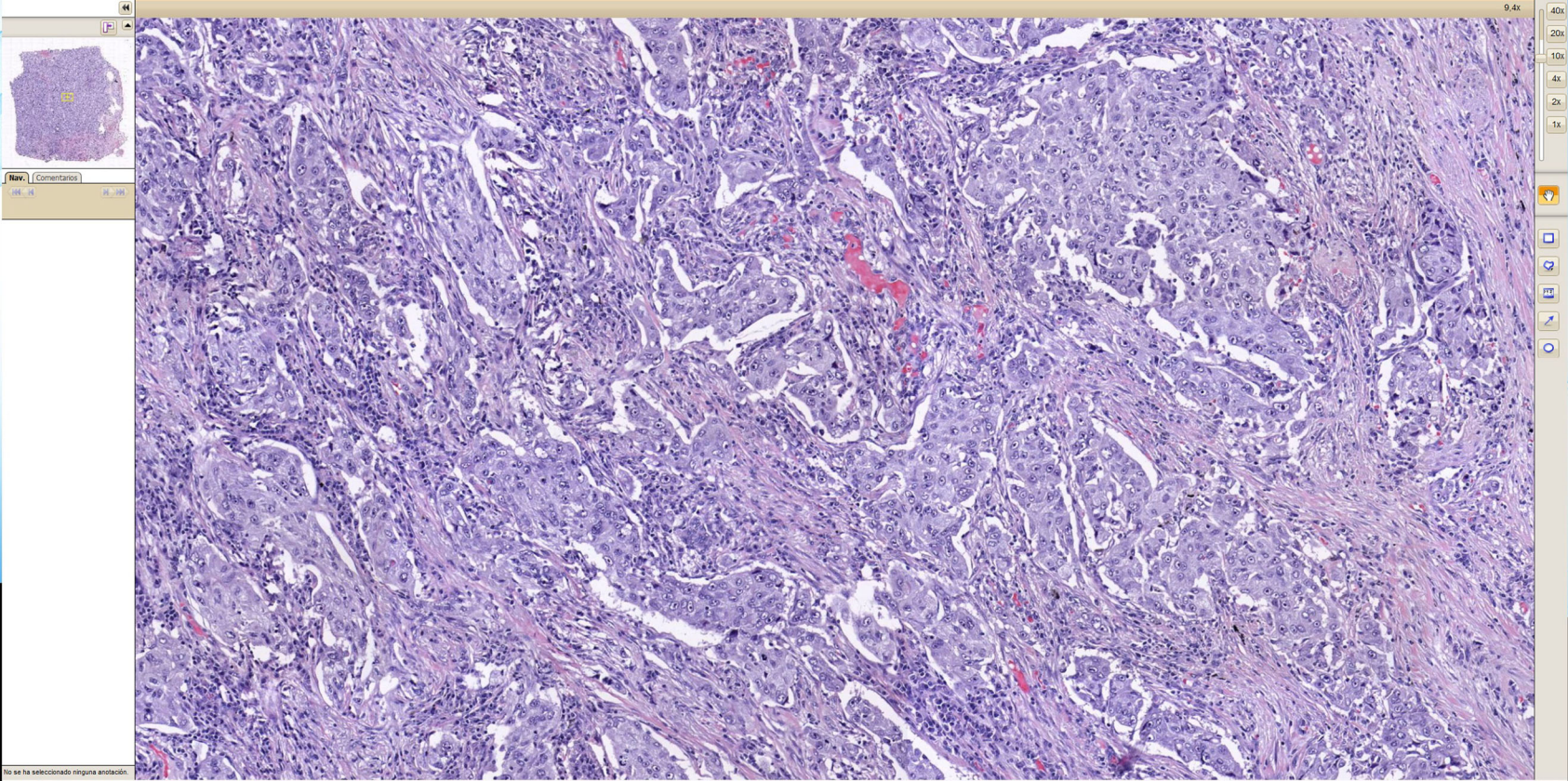
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Tags:
Pathology
69 years old man, ex-smoker, consulted to the hospital for 2 week history of hempotysis. The patient had a pathological history of hypertension and hypercholesterolemia. The image explorations evidenced a 6 cm mass in the right upper lung lobe.
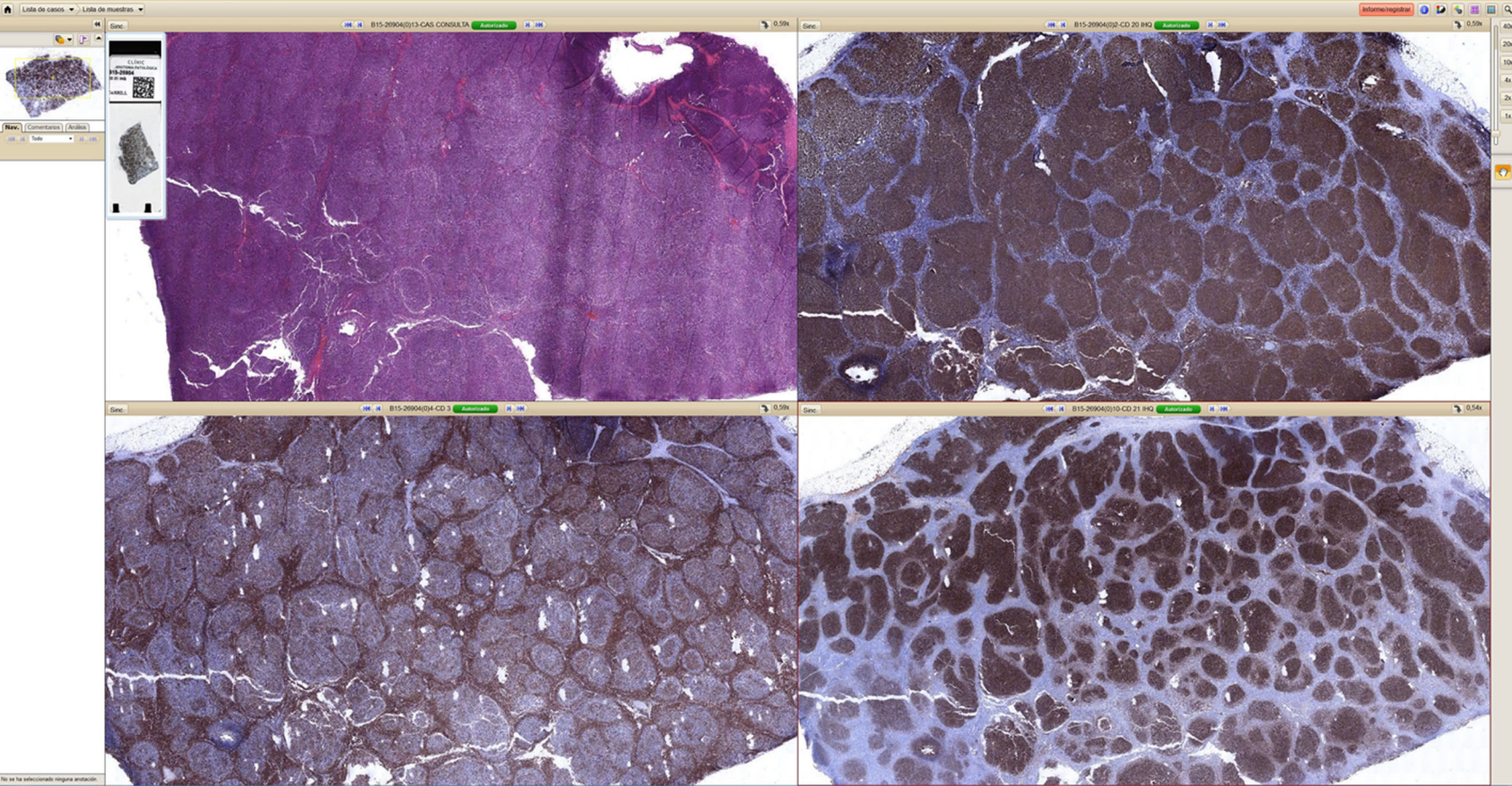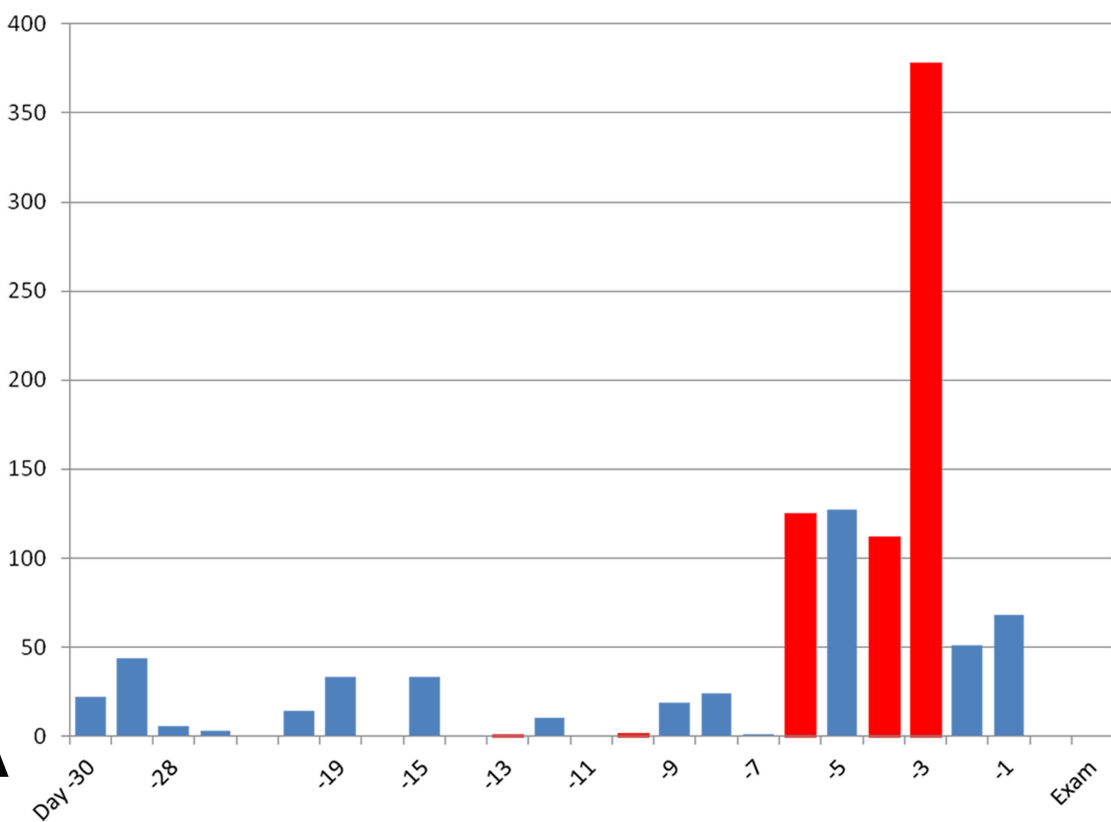Privacy: public
Age:
69

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