Original Article

Whole-Slide Imaging Allows Pathologists to Work Remotely in Regions with Severe Logistical Constraints Due to Covid-19 Pandemic

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Abstract

Introduction: In this study, we report on our experience using digital pathology to overcome the severe limitations imposed on health care by the Covid-19 outbreak in Northern Italy. Social distancing had a major impact on public transportation, causing it to run with reduced timetables. This resulted in a major challenge for hospital commuters. To limit the presence in our hospital of no more than two pathologists at a time out of four, a web-based digital pathology system (DPS) was employed to work remotely. **Subjects and Methods:** We used a DPS in which a scanner, a laboratory information system, a storage device, and a web server were interfaced so that tissue slides could be viewed over the Internet by whole-slide imaging (WSI). After a brief internal verification test, the activity on the DPS was recorded, taking track of a set of performance and efficiency indicators. At the end of the study, 405 cases were signed out remotely. **Results:** Of 693 cases, 58.4% were signed out remotely by WSI, while 8.4% needed to be kept on hold to return to the original microscope slide. In three cases, at least one slide had to be rescanned. In eight cases, one slide was recut. Panel discussion by WSI was necessary in 34 cases, a condition in which all pathologists were asked for their opinion. A consultation with a more experienced colleague was necessary in 17 cases. **Conclusions:** We show that WSI easily allows pathologists to overcome the problems caused by the severe social distancing measures imposed by the Covid-19 pandemic. Our experience shows that soon there will not be alternatives to digital pathology, given that there is no assurance that other similar outbreaks will not occur.

Keywords: Covid-19, digital pathology, pandemic, whole-slide imaging

Introduction

The Covid-19 pandemic is showing just how fragile our societies, economies, and national health-care systems can be. The delivery of health care that fits the definition of a complex system,[1] is now facing staff and supply shortages as hospitals are being overwhelmed with patients hit hard by the Covid-19 outbreak. Health-care logistics is one of the main aspects of a complex system,[2] primarily because it includes a broad range of stakeholders. Besides devices, medicine, and reagents, the supply chain must include doctors who are more vulnerable than ever to logistical shocks. Coronavirus pandemic in Italy represents exactly that kind of a shock to the system as public transport timetables have been scaled back to <50% capacity to comply with social distancing requirements.

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Patient one, the first Italian to contract the disease, moved into the intensive care unit on February 20, 2020, in the Northern region of Lombardy, Italy's hardest-hit.[3] On March 4, the first Covid-19 patient was admitted to the hospital of Biella (Piedmont) which is 41 km from Lombardy [Figure 1]. From then on, Lombardy and the neighboring regions, including

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Piedmont, activated stringent restrictions, prohibiting residents from going anywhere besides the supermarket or pharmacy. On March 20, the Italian government extended those restrictions to the entire country, including emergency measures such as travel limitations and a ban on public gatherings. Furthermore, because of the risk that health-care workers may be exposed to Covid-19 on the job, most public health systems provided specific recommendations for when an employee, not showing symptoms, should be constrained to self-quarantine at home. In the present article, we share our experience with deploying and using digital pathology for remote reporting to limit the presence at the Biella Hospital to no more than two pathologists at a time. One of the main reasons for this reorganization is to adapt to the evolving threat since most pathologists of our institution commute from a distance of 40–80 km, by bus and train. Moreover, one of the authors, sub-specialized in hematopathology, works at a different institution >100 km away (Milan). Digital pathology for primary diagnosis has been available in our diagnostic pathology service since 2018 and the main use of it, for the time being, was aimed at building a vast repository of virtual slides for the real-time recovery of the histological history of patients, multidisciplinary team discussions, and second opinions. However, even before the Covid-19 epidemic, as others have done in the past,[4] our system was often used for remote reporting of urgent cases when the referring pathologist was not physically present in the hospital. Now, things have dramatically changed, and we thought it useful for us, and any colleague interested in using digital pathology for viewing virtual slides on the web to save on a shared database a set of quality indicators of every single action taken during the entire remote reporting process. It must be clear that when we take into consideration whole-slide imaging (WSI) transmitted across the Internet for primary diagnosis actually, we are not dealing just with a scanner but with a complete integrated system by which a laboratory management program, the software that drives scanning equipment, a powerful archiving device, and a webserver are interfaced in a complete digital pathology system (DPS) so that a virtual slide can be viewed and studied.[5] It is important to stress this point because many institutions that claim to have digital pathology only possess a scanner for a few slides and are unable to process the workload of a daily histopathology routine and share it on the network.

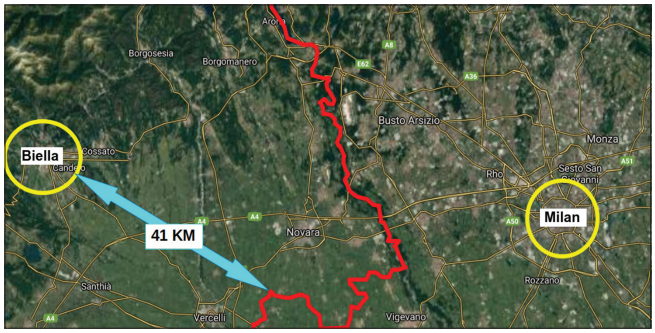

Figure 1: The map shows where Biella and Milan are placed in Northern Italy. The double arrow shows the distance between Biella, which is in the region of Piedmont, and the border of Lombardy, traced in red. Lombardy is the region where the first cases of Covid-19 where detected

Subjects and Methods

Study design

The Pathology Unit of the Biella Hospital has four permanent pathologists on staff, one cytologist, and a consultant hematopathologist. Our unit handles about 10.000 histology requests annually (biopsies and resection specimens) in a hospital of 482 beds. In this report, we do not take into consideration cytology since our DPS is not yet certified for traditional smears or pap tests. The laboratory technicians of our unit were local and not limited by any sort of travel restrictions, for some, however, a temporary reassignment in the clinical laboratory is underway to cope with the overload of Covid-19 tests. We decided to reduce the presence of pathologists in the workplace to two to guarantee frozen sections and gross consultation services during surgery, while the other two would contribute by remote reporting. From March 9 to March 27, 15 working days, the activity of our DPS was recorded, and 405 cases were signed out remotely at the end of this study. Of these cases, six criteria were used to monitor the reporting activity of each pathologist: (1) back to the microscope slide, (2) rescan, (3) recut, (4) panel discussion among all pathologists by WSI, (5) consultation (case referral to a more experienced colleague before signing out), and (6) review (case referral after signing out). A panel discussion of a digital case was accomplished by a WhatsApp group chat (WhatsApp Ireland Limited, Dublin, Ireland) that we called "Biella Pathology" where case numbers were posted, and a final diagnosis through a collective contribution could be reached. For privacy policy in the chat group, demographic data were never posted except for the patient's age, gender, and essential clinical data.

System

The histopathology laboratory is equipped with a two-dimensional (2D) barcode (Datamatrix)-based tracking system (Ventana Vantage, Roche, Milan) and a high slide capacity scanner (Nanozoomer-XR, Hamamatsu Photonics K.K., Japan) able to rapid automatic processing of up to 320 slides, dynamic focus, and image quality judgment functions. The scanner is connected to the hospital network and its software receives slides data from the anatomic pathology laboratory information system (APLIS) (Winsap, Engineering, Turin, Italy) utilizing SOAP (Simple Object Access Protocol) a standardized XML-based web service protocol used for exchanging data between applications and systems. Scanned slides are saved as NDPI files in two network-attached storage systems with a 21 TB capacity (Dell EMC2) and a RAID-6 data recovery to protect user data against repository failures. A web platform (Cloud Pathology Group, Milan, Italy) for remote access to virtual slide trays allowed case searching by the unique case number or by scanning 2D codes on the requisition forms (Hyperion scanner, Honeywell International Inc.).

A WSI viewer enables the rendering of histological images up to a 40X resolution, but images can be further enlarged by an interpolation algorithm. Access to the web served virtual slides was not limited by the workstation geographic location and was platform independent from the point of view of the operating system (Windows, Apple, Linux, etc.) and the kind of graphical web browser used (Google Chrome, Mozilla Firefox, Internet Explorer, and Safari were tested). Normally in hospital, each operator used dual-monitor workstations, one of which was a medical-grade 27" Barco display (Kortrijk, Belgium) with a 3280 × 2048 pixels resolution. However, remote reporting was performed using common personal computers. In fact, three pathologists used notebooks with 15.6-inch displays and two a desktop pc with 22" and 27" monitors at a 1920 × 1080 pixel resolution [Table 1]. All users had Internet connections by fiber optics with download speeds ranging from 20 to 120 MBps and upload speeds of 20–25 MBps. The scanner and its workstation were placed at the end of the histology laboratory workflow to optimize slide loading on the racks and focusing options settings by each operator. Breast cancer prognostic and predictive biomarkers were performed using the Benchmark staining system (Ventana Medical Systems, Inc.). Ki-67, estrogen, and progesterone receptors scoring was performed with the Immunoratio plugins of ImageJ,[6] a public domain software. Measurements were done with the built-in options available from the viewer. Since our APLIS was not a web application, remote access to the hospital workstations was accomplished by two different means. The first using a terminal server technology (RDS, Microsoft, Redmond, Washington) through a VPN SSL tunnel (GlobalProtect, Palo Alto Networks, Santa Clara, CA). The second by a widely used remote access software (TeamViewer version 15.3, Germany GmbH) which is platform-independent since one of the pathologists has adopted the GNU/Linux operating system (Ubuntu 19.04). Gross specimen imaging was performed with an 8 Megapixel USB webcam with a 2.8–12 mm lens (Ailipu Technology Co., China) mounted in a grossing hood, interfaced through the USB port to the APLIS workstation. From the APLIS, remote users had full access to the saved digital images of surgical specimens. All requisition forms providing patient's clinical data were scanned as PDF files and saved in a shared directory of the Pathology Unit network that, for privacy, was only accessible to authenticated users. A web-based application provided online access to imaging data and radiology reports (View Motion, Carestream Health, Inc., Genova, Italy).

Table 1: Laptops and monitors used in this study for remote reporting. Resolution and screen size are indicated

Type	Model	Resolution (pixels)	Screen size
Laptop	HP 250 G7	1920 × 1080	15.6"
Laptop	Lenovo Essential V145	1366 × 768	15.6"
Laptop	ASUS M509BA-BR001T	1366 × 768	15.6"
Monitor	Philips 226V4LSB	1920 × 1080	22"
Monitor	HP 27e	1920 × 1080	27"

Verification test

Prior to remote reporting, each pathologist had to undergo a brief verification test with a training set of five prostate needle biopsy cases scanned at × 40. For each case, an average of 12 slides was available with three sections on each one. Four cases had a previously diagnosed adenocarcinoma with a Gleason grade 3 + 3 or 3 + 4[7] in a single biopsy and one was negative for prostate cancer. This test aimed to reproduce on a smaller scale, an ongoing regional trial on low-grade prostate cancers based on digital slides.[8] However, each one of our pathologists since 2018 had already undergone several informal validation tests comparing glass slides to whole-slide images, using our WSI repository as a common internal quality control procedure. In fact, since all accesses to the DPS platform are logged, we could verify that around 5% of all cases were previously viewed both on slides and by WSI. If we take into account that in our unit the DPS has been available for 2 years (since 2018) and that over 10,000 cases are signed out each year, we can estimate that about 1000 cases have been read both on the slide and digital; therefore, College of American Pathologists (CAP) guidelines for validations were followed.[9]

Results

If one takes into account that in 2019, the mean number of cases scanned monthly in our pathology unit was 843 (3030 slides); at the end of March 2020, the volume of histopathology cases has been steadily dropping. In the time frame of this report, however, 693 cases have been signed out, corresponding to 2462 virtual slides. At the end of the brief internal verification test based on five prostate biopsies, all four pathologists detected the acinar adenocarcinomas present in a single-needle biopsy of four cases and correctly scored the fifth case as negative. A minor discrepancy on the Gleason score was recorded for one of the readers on a single case [Table 2]; kappa statistics, however, was good with a value of 0.68 (95% confidence interval 0.36–1.00).[10] Our consultant hematopathologist had already provided second opinions remotely using our WSI system in several cases without any problem. In the single case that he reviewed in the present study, a lesion of a parotid gland, his diagnosis perfectly matched ours. This brief test, together with the experience of 2 previous years, convinced us that most of the tissue histologies could be viewed remotely by WSI. In the short time frame indicated in this report, a significant proportion of slides were read by two pathologists from home, while, as noted, alternatively, two remained in the hospital taking turns for grossing and frozen sections. Of 693 cases, 405 (58.4%) were signed out remotely by WSI [Table 3]. Six key indicators were used to monitor this diagnostic activity and the results are shown [Table 4]. In our experience, as average, 3–4 slides per case were systematically scanned and of 405 cases signed out remotely, 30 slides (7.4%) needed to be kept on hold to return to the microscope. Of the cases that had to be diagnosed with glass when the histology

Table 2: Brief verification test with a training set of five prostate needle biopsy cases scanned at ×40. For each case, an average of 12 slides was available with three sections on each one

Pathologist	Case				
	1	2	3	4	5
1	Pos (G 3+4)	Pos (G 3+3)	Pos (G 3+4)	Pos (G 3+3)	Neg
2	Pos (G 3+4)	Pos (G 3+3)	Pos (G 3+4)	Pos (G 3+3)	Neg
3	Pos (G 3+4)	Pos (G 3+3)	Pos (G 3+4)	Pos (G 3+3)	Neg
4	Pos (G 3+3)	Pos (G 3+4)	Pos (G 3+3)	Pos (G 3+3)	Neg

Kappa statistic: 0.68, SE of kappa: 0.166, 95% confidence interval: 0.36–1.00. Pos: Positive for adenocarcinoma, Neg: Negative for adenocarcinoma, G: Gleason grading

Table 3: Of 693 cases, 405 (58.4%) were signed out remotely using digital pathology

	Number of cases	DP	Percentage
Head and neck	42	22	52.4
Breast	49	31	63.3
Gastrointestinal/hepatobiliary	102	71	69.6
Gynecology	192	97	50.5
Genitourinary	112	69	61.6
Skin	75	57	76.0
Hematopathology	93	44	47.3
Lung	13	7	53.8
Soft tissues	15	7	46.7
Total:	693	405	58.4

DP: Digital pathology

Table 4: Six key indicators were used to monitor remote diagnostic activity

Indicator	*n* (%)
Back to slide	30 (7.4)
Rescan	3 (0.7)
Recut	8 (2.0)
Panel discussion	34 (8.4)
Consultation	17 (4.2)
Review	1 (0.2)

was deemed acceptable, four were gastric biopsies and seven cervical biopsies. In those cases, dysplastic fields needed cytological details of nuclear abnormalities that digital images were unable to render. In three cases (0.7%), at least a single slide had to be rescanned for a more appropriate choice of focus points. In 8 cases (2.0%), one slide had to be recut. Panel discussion by WSI was necessary in 34 cases (8.4%), a condition in which most of the pathologists were asked for their opinion on a problematic diagnosis. It is significant to note that no problems were reported over the resolution or color quality of virtual slides rendered on the screens available at home. A call for a panel discussion was generally posted on the WhatsApp group by the pathologist that had in charge the case. A "consultation", that is a review by at least one additional pathologist before sign-out, was done 17 times (4.2%), and that in general occurred whenever a younger pathologist remotely asked his more experienced colleagues a question on a particular area of interest that could be easily marked with the viewer's annotation tools. In the course of this study, a single review (0.2%) was asked for a second opinion by a subspecialist pathologist. All breast cancers (16 of 31 breast cases) were signed out using digital pathology since in our unit, assessment of distance from margins and predictive biomarkers is performed with automated image analysis softwares.

Discussion

Since February 20, 2020, when the first patient in Italy positive for Covid-19 developed respiratory failure, hospitals in the hard-hit Italian northern regions have started to put off surgeries or procedures that were not urgent in their bid to free doctors, nurses, and beds for the most critically ill patients. At the time of writing in Italy, >100,000 people were affected by Covid-19 and 10,000 died of the disease. For these reasons, since the beginning of January, the number of histopathology cases has been dropping. The new rules imposed by the government to stop the spread of the disease and the severe limitations to commuters forced our pathology unit to adopt radical changes in its organization. Therefore, it was decided that as many as possible of the pathology reports had to be signed out remotely. The brief internal verification test based on prostate biopsies was not formalized, as many equivalency and efficiency studies have already been published by large academic centers.[11,12] The test was mainly done to give us a measure of how reliable our DPS was and to reassured us that routine histopathology could be carried out without any problems. Even though, as expected, grading was not perfectly reproducible, the results were good as all the malignant lesions were correctly detected. In fact, it is well known that among general pathologists, not specialized in genitourinary histology, the distinction between Gleason 3 and Gleason 4 glands can be challenging.[13] As it became apparent that working remotely was not only feasible but also the only possible solution to the problems caused by the social distancing measures, this approach was chosen to guarantee the proper functioning of the service. Studying histological patterns on WSI was not new to us as it is common practice to follow online pathology courses for continuous medical education programs generally based on WSI. For most of us, working from home in the past was on a voluntary basis and not as part of a weekly shift schedule. To improve

the quality of home working, we took into account some of the main factors that could have affected the remote productivity of pathologists. The percentage of cases that went back to the original slide or that needed a rescan can be easily explained. First of all, digital pathology, although ideal for histology, is not yet the best tool for the cytological assessment of fine details such as nuclear chromatin and shape. However, any pathologist is fully aware of these limitations exactly as he is aware when his microscope has resolution problems. Second, none of the participants in this study could use a costly medical-grade monitor at home. However, in our opinion that is shared by the Royal College of Pathologists,[14] the current generation of modern consumer-grade displays, evidently not recommended for radiology applications, often has high specifications, sufficient for WSI.[15] One of the problems that lead to return to the original microscope slide was not the screen resolution or the scanning technology but the insufficient quality of some of the original microscope slides due to wrinkles and folding of tissue sections that affected the correct focusing and degraded the final virtual images.[16] Notably, the image quality was regarded as optimal, both on histochemical (i.e., hematoxylin and eosin and Giemsa stains) and immunohistochemical slides to render a detailed assessment of morphologic features and diagnosis of a hematolymphoid neoplasm (in the case given, corresponding to extranodal marginal zone B-cell lymphoma with lymphoplasmacytic differentiation). It is quite evident that also the histopathology laboratory has to be adjusted for WSI and should apply rigorous control procedures and constant attention to the quality of microscope slides before scanning. Paradoxically, one thing that emerged is that viewing virtual slides actually induced a more collaborative work among pathologists. Remote users took advantage not only of WSI but also of social media to reach, in 8.4% of the cases, a final diagnosis through a team (panel) discussion. For the same reason, discussion of a case with a more experienced colleague was also frequent so that in >12% of the cases, the slides were seen by at least two pathologists increasing the quality of the final reports. The present study only depicts a restricted time window of intensive use of WSI to overcome the severe limitations imposed to face the coronavirus epidemic.

However, it is quite evident that the Covid-19 crisis will permanently change all the perspectives on how national health services will be organized from now on, once that this pandemic will be over. It is remarkable that our approach is now shared and actively supported by the CAP[17] who in a letter dated March 13 signed by CAP President Patrick Godbey and CAP Council on Accreditation Chair Richard Scanlan requested to give local laboratories the discretion to work remotely. On this issue, CAP has recently made available a guideline to promote remote sign-out to regulatory agencies.[18]

Conclusions

As expected, our experience has shown that WSI easily allows pathologists to work remotely for primary diagnoses. Most importantly, in the critical time frame of our study, digital pathology was an essential tool to maintain the reporting activity of a pathology unit to an acceptable level. The problems caused by the severe social distancing measures have made it evident that soon there will not be any credible alternatives to digital pathology since there is no assurance that other similar Covid-19 outbreaks will not occur.

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Conflicts of interest

There are no conflicts of interest.

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