Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The practice of cytopathology during the era of COVID-19: challenges and changes

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Abstract

This paper reviews the challenges faced by cytology laboratories during the COVID-19 pandemic. Various safety guidelines regarding collection, handling, transport and sampling in cytology laboratory are presented. A brief literature overview of adapted changes regarding new safety techniques, processing, sampling techniques implemented by the cytology laboratories in this part of the world is presented. The use of cytology in COVID-19 patients is discussed. The authors have also tried to present the challenges and changes faced for training and education during this time. Migration from multi-headed scope in-person sign-out to digital based platforms were adapted to continue medical education. The potential long-term implications of these adaptations on cytology services are also touched upon.

Keywords challenges; changes; coronavirus disease-19; COVID-19; cytology; education

Introduction

It has been not much longer than a year since the world was hit by the pandemic caused by the novel Sars-Cov-2 (Covid-19). The global impact of Covid-19 has far exceeded initial estimates with significant challenges posed to almost every area of life. The medical communities in general, and pathology laboratories, were not immune either. It remains more essential now than ever for cytology laboratories to function optimally diagnostically and without compromising the health of their fellow cytotechnologists, pathologists, trainees and administrative professionals. Some of the challenges faced by cytopathology laboratories are unique in comparison to other laboratories in general. Cytology laboratories around the world adapted accordingly with some innovative measures to combat the effects of the pandemic and ensure safe delivery of essential cytology services.

Impact of COVID-19 on specimen collection, handling, transport and processing

The initial phase of COVID-19 pandemic response started with strict lockdown in most countries throughout the world. Guidance evolved as the pandemic developed, and countries varied in their approach and handling of how best to contain and minimize the effects of the virus. Laboratories struggled to implement/update the safety guidelines and ensure the safety of their staff. Many organizations at regional, and country level published their recommendations/resources to be adapted by a cytology laboratory. Some helpful resources are listed in Box 1.

In the United States of America (USA), the Centre for Disease Control (CDC) recommends any specimens coming to the cytology lab from suspected or confirmed COVID-19–positive patients to be transported as UN3373 Biological Substance Category B.[1] The packaging for UN3373 consists of 3 components: 1) a leak-proof primary receptacle, 2) a leak-proof secondary packaging, and 3) an outer packaging of adequate strength with at least 1 surface having minimum dimensions of 100 mm × 100 mm. The primary container should also have a patient label and the laboratory request form should be in outer packaging. Use of pneumatic tube systems should be discouraged and all the specimens with suspected or confirmed COVID-19 should be hand delivered. The personnel who transport specimens should be trained in safe handling practices and spill decontamination procedures. As the virus can survive on paper up to 24 h, efforts should be made for paperless electronic request transmission. [2]

From the literature published so far, it is clear that the major routes of transmission of COVID-19 are person-to-person transmission through air droplets, close contact with an infected individual or touching fomites that have been contaminated.[3] Since many of the cytology specimens have a high likelihood of generating aerosols or droplets, for example all respiratory specimens (such as Broncho alveolar lavages, bronchial brushings, bronchial washings, sputum, pleural fluids, EBUS-guided FNAs, and touch imprint slides from lung core biopsies), appropriate Personal Protective Equipment (PPE) should be worn prior to handling any specimen. PPE includes gloves, surgical masks, water resistant gown and eye protection (goggles or

Resources and guidelines for cytology labs in the COVID-19 pandemic.

- http://www.britishcytology.org.uk/go/covid19-resources
- https://www.cap.org/laboratory-improvement/news-and-updates/cytopathology-laboratory-considerations-during-the-covid-19-pandemic
- http://www.jcytol.org/article.asp?issn=0970-9371;year=2020;volume=37;issue=2;spage=67;epage=71;aulast=Srinivasan
- https://www.pathologica.it/issue/download/11/PATHOLOGICA_2_20

Box 1

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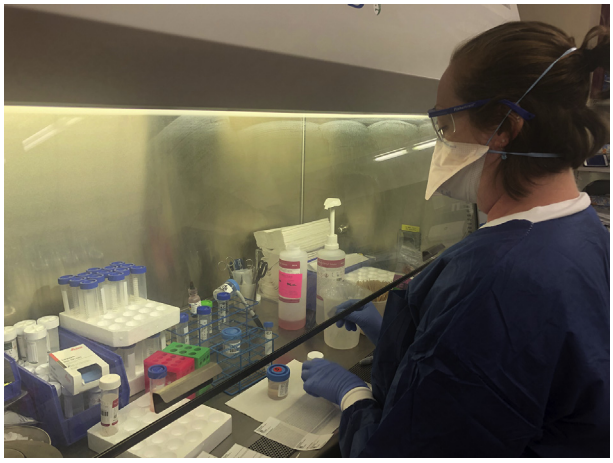

Figure 1 Cytotechnologist wearing appropriate PPE (N95, Goggles and gloves) to for processing sample in Biosafety Cabinet-II. Photograph courtesy of Teresa L. Friedman, CT (ASCP).

face shield) while processing specimens in a certified Class II Biosafety Cabinet (BSC) (Figure 1). When a Class II BSC is not available or when handling samples from patients with suspected or known positive COVID-19, surgical mask and/or face shield or other physical barriers, like a splash shield are advocated; centrifuge safety cups and sealed centrifuge rotors can be used to reduce the risk of exposure to laboratory personnel. Given the variability in the clinical presentation of COVID-19, all specimens received in a cytology lab should be considered as a high-risk specimen. Respiratory specimens collected in appropriate containers can be stored at a temperature of 2oC—8oC for a maximum period of 72 h before processing. If it needs to be stored for longer, World Health Organization (WHO) recommends the use of -200C and to ideally dry ice pack (-70 °C) for storage until the test is performed.[4] In addition, CDC recommends performing site and activity-specific risk assessment to determine if additional biosafety precautions are warranted 1. Recommendations on safe handling of specimens of suspected COVID-19 patients were released by various organizations including WHO,[4] USA Center for disease control CDC,[1] European CDC,[5] the United Kingdom (UK) Government,[6] and various countries from Asia (Taiwan and China) in Chinese, an excerpt of which is summarized by Chen et al.[7] in their commentary.

Some of the general practices in cytology laboratories required modification and changes to prevent contagious spread of COVID-19. It was recommended to avoid making air-dried smears at the onset of the pandemic when knowledge about the virus was rudimentary. Quick stains like Hema 3 and Diff Quik do not utilize alcohol-based fixatives for air-dried smears. 95—99% alcohol is added to the regime of air-dried smear staining protocol specifically for all respiratory tract and oral specimens since alcohol is more effective against COVID-19 than methanol.[8] Though formalin and most of the fixatives with >70% of alcohol are effective against inactivating COVID-19, other fixatives that use weaker alcohol as used in Liquid Based cytology (LBC) media such as PreservCyt, Cytolyt (Hologic,Inc) and SurePath (Becton, Dickinson and Company), are unknown in their ability to adequately inactivate Severe Acute Respiratory Syndrome-Corona Virus- 2 (SARS-CoV-2), the causative agent for COVID-19.[9] Straccia et al.,[10] studied cytomorphological changes after adoption of a new protocol: the addition of 95% ethanol of at least an equal volume to the amount of the material for ThinPrep liquid based cytology specimens of urine, thyroid, cerebrospinal fluid, lung/mediastinal FNA, Broncho alveolar washings and body cavity effusions prepared by automated ThinPrep processors. Their study found increased background fibrin for FNA biopsies and less clear nuclear details mostly in not-well preserved cell clusters. No significant difference was found in the immunohistochemical staining pattern. The new technique did not significantly impact on making cytologic diagnosis overall.

Cytopathology specimens can be categorized into three groups: high-risk, intermediate-risk, and low-risk for COVID-19 infection. Formalin fixation and paraffin embedding can inactivate SARS—CoV-2, and as such cell blocks can be categorized as in the low-risk group. The high and intermediate-risk samples should be processed in a Class II BSC with appropriate PPE. Processing for any low-risk samples can be performed using standard good microbiological practices and procedures.[7] The bigger cytospin preparator which does not fit into standard biosafety cabinets is not being used at many laboratories. While this can increase the specimen handling workload and turnaround time of specimen processing in the cytology lab, the safety of cytotechnologists must be taken into consideration. Since cytology glass slides are usually manually processed by multiple people before arriving at a pathologist's desk for reporting, wearing gloves to avoid contact can be a solution. Dipping the slides in 95% alcohol can be another alternative, but the disadvantage is the alcohol might erase any screening marks put on the slide by the screeners.[9]

COVID-19 virus has been shown to persist on a variety of surfaces for up to 72 h. Hence, all the surfaces and equipment used in the cytology lab should be frequently decontaminated. The most commonly used and most effective decontaminant are freshly prepared 0.1%—0.5% Sodium hypochlorite solution, 70% ethanol and 0.5% hydrogen peroxide. UV disinfection or a manual spray device can also be used.[2]

Cytology specimen sampling, diagnosis and COVID-19

Cytology laboratories quickly saw a drastic reduction of screening and diagnostic cytology specimens like pap/cervical smears, fine needle aspiration cytology of thyroid smears, urines and effusions due to lockdown enforced at most of the places in early spread of the disease. In the initial three weeks of Italian national lockdown, a single institutional study done at cytopathology laboratory of University of Naples 'Federico II', reported a significant reduction of number of thyroid FNAs ($p < 0.001$) from n = 229 (37.2%) to n = 12 (12.8%) and pap smears (n = 216, 35.1% vs n = 18, 19.1%; p = 0.003).[11] The experience in our laboratory at University of Pittsburgh Medical Center, USA with Pap smears is also similar from 200 a day to 15—20 a day for the first month of lockdown. Labs in the UK also noted well over a 50% reduction in diagnostic cytology and a reduction to almost

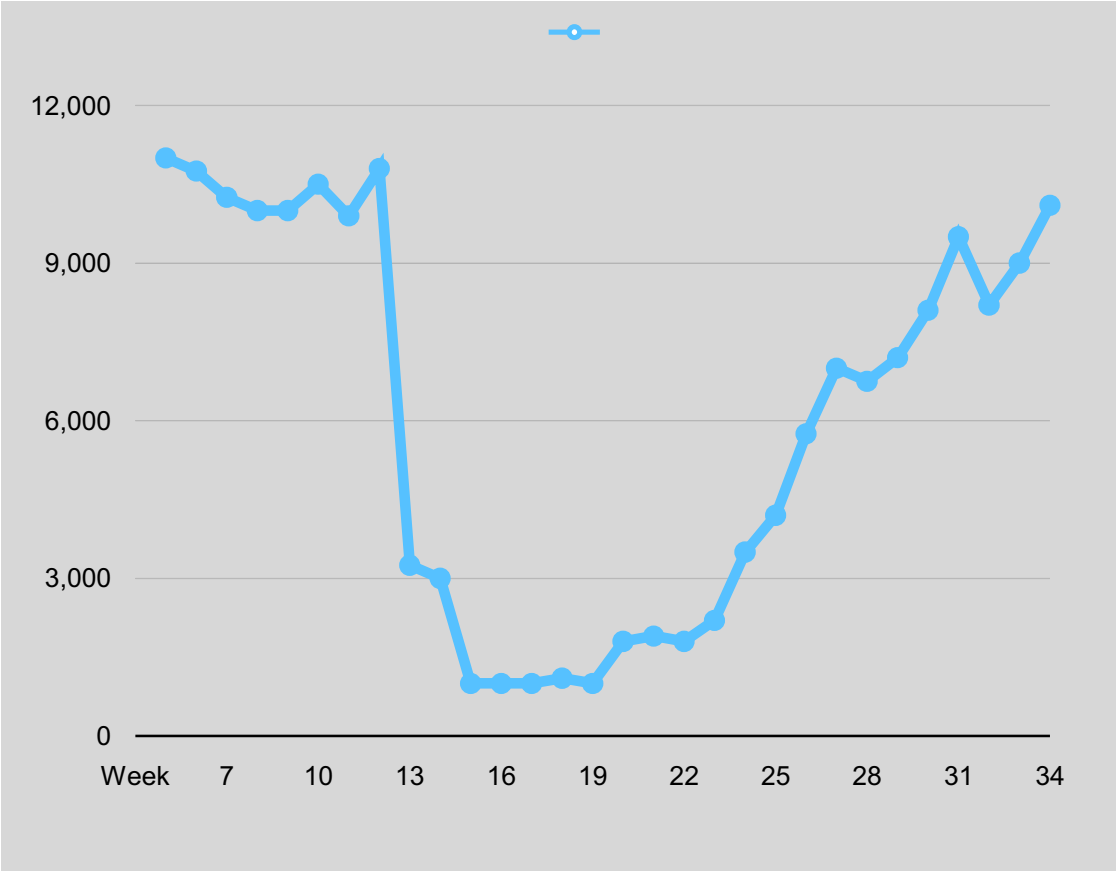

Figure 2 Graph of cervical cytology daily workload numbers and fall off during COVID-19 lockdown period and rebound of work as lockdown measures are relaxed (from one of the author's laboratories, PAC). UK lockdown commenced from about week 13 and began to be relaxed from about week 24 onwards.

zero for routine cervical cytology screening samples (PAC, personal experience; Figure 2). It is also necessary for the cytology labs to prepare a mitigation strategy for a rebound increase of these diagnostic and screening cases soon as and when services start to resume to more pre-COVID levels.

The initial decrease in specimen numbers gave an opportunity to the cytology laboratories to evaluate their staffing need, maintain social distancing among the workforce and formulate a plan to optimally operate the lab while meeting the social distancing guidelines. Some laboratories, akin to clinical teams, split their staff into teams and had an alternating on site approach, so that the staff was effectively split into two identical teams, to try and minimize exposure and maximize staff resources and availability.

WHO recommended the establishment of a blame-free environment for laboratory staff to report incidents, encouraging self-assessment and symptom reporting, and arranging appropriate work hours with breaks. If a worker is infected with COVID-19 due to exposure at a work place WHO, further recommends honoring the right to compensation, rehabilitation and curative services and considering it as an occupational exposure, henceforth treating as an occupational disease with adequate emotional support by the management.[12] Current challenges for cytology laboratories are summarised in Box 2.

Cytology laboratories: challenges.

- More stringent implementation of safety precautions for the cytology samples
- Provision of enough PPE including N95 masks and respirator masks for laboratory personnel exposed to high-risk specimens
- Provision of suitable fixatives and disinfectants
- Significant reduction in volume of cervical screening cytology cases
- Necessity to continue rapid on-site evaluation of possibly aerosolizing procedures like EBUS/EUS guided FNAs and FNAs performed by pathologists
- Facilitate quarantine to the laboratory staff in instances of exposure to COVID-19
- Adoption of newer sampling procedures (e.g. FNA instead of core biopsy in breast and oral lesions)
- Validation of ancillary techniques for confirmation of SARS-COV-2
- Maintain social distancing during reporting and during on-site evaluations in FNA clinics
- Facilitate training and education of residents, medical students and cytotechnologists students through virtual teaching sessions.

Box 2

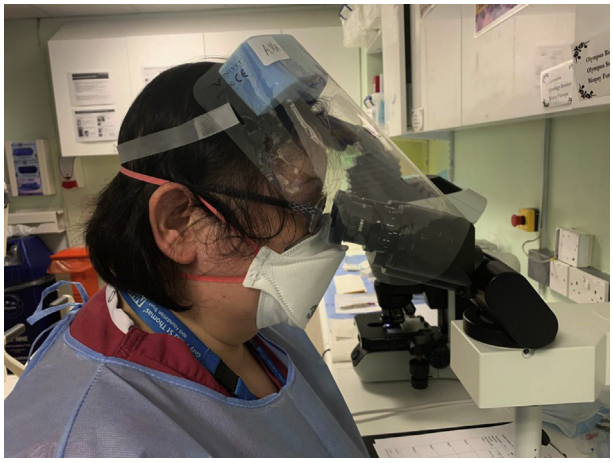

Figure 3 Cytotechnologist wearing appropriate PPE (N95, face-shield, disposable gown) for ROSE. Photograph courtesy of Alicia Ma, Cytopathology (BMS).

It has been a challenge to continue rapid on-site evaluation during the COVID-19 outbreak by our cytology frontline staff. However, rapid on-site evaluation (ROSE) helps immediate evaluation of specimen adequacy and triage which is specifically important in the deep-seated lesions accessed non-surgically using radiologic guidance like endoscopic ultrasound (EUS) guided fine needle aspirations (FNAs) and endo-bronchial ultrasound (EBUS-TBNA) guided transbronchial needle biopsies. ROSE or FNA procedures require strict implementation of advanced biosafety policy to prevent transmission, since COVID-19 can be aerosolized and viral particles may be transmitted through respiratory droplets in contaminated samples and equipment. Chen et al.[7] recommends use of a dedicated sonography room and associated equipment to decrease the risk for transmission from patients that have suspected or confirmed COVID-19. For both EUS-FNA and EBUS-TBNA, contact and droplet precautions should be implemented, standard pre-procedural and post-procedural hand hygiene should be performed; and appropriate PPE (Figure 3) (surgical masks, eye protection, water-resistant gowns or waterproof aprons, and gloves) should be used and discarded at the end of each procedure. However, some services have avoided this risk by resorting to the use of histology samples (immediately fixed in formalin) to reduce such issues.

WHO recommends recognizing the importance of adequate ventilation, the presence of the minimum required people in the procedural room and use of respirator masks adequately fitted for procedures at risk of aerosolization like EBUS-TBNA. For EUS-FNA, the recommendation is 60L/person of natural airflow to ensure adequate ventilation and since EBUS-TBNA has an even greater risk for exposure to the virus, the recommendation is for natural ventilation airflow of at least 160L/person or the use of negative pressure rooms with at least 12 air changes per hour.[13]

Implementation of telecytology for ROSE decreases the number of people to a minimum at the procedural site. Where this is already in place, cytotechnologists attend the procedure, prepare and drive the slide under the microscope and the consultant and trainee can review the slide from their own offices.[14] FNAs performed by pathologists are also considered high-risk, especially if an FNA is of the head and neck region, because of the pathologist's close approximation to the patient's respiratory droplets. The decision to perform such FNAs should be taken at the discretion of the performing pathologists based on the clinical urgency, diagnostic and therapeutic implication. When it is required to perform such FNAs, COVID-19 should be ruled out in the patient by screening for symptoms and undergoing the available COVID-19 screening tests. Pathologists should also wear proper PPE and maybe work in pairs to limit the time spent at an FNA clinic to the minimum. Where the decision is to postpone an FNA, speaking with the patient by phone to evaluate the patient's urgency of getting the procedure is important. It can also be used to assess if the patient has any potential COVID symptoms that may require investigation and reduces the risk of exposure to the pathologist.[15]

Cytologic findings in COVID-19 cases

The cytologic features of COVID-19 have not been well reported in literature yet. Those that have been reported so far suggest that COVID-19 infection does not produce specific diagnostic changes that are pathognomonic of this infection, but rather those of marked reactive changes. However, it is important to be aware of some of the suggestive features of the presentation of COVID-19. Furthermore, a cytologist's simple observation of respiratory specimens might give a clue to diagnose atypical presentations to treating physicians. A bronchoalveolar lavage (in a patient positive for SARS-CoV-2) showed predominantly large numbers of activated plasma cells (CD138+) with occasional plasmablastic features on the cytologic preparations and immunostaining. Occasional intranuclear cytopathic inclusions and nuclear clearing of alveolar macrophages attributable to SARS-CoV-2 were also documented.[16] The exuberant plasmacytosis implies immune activation which has also been frequently reported in extrinsic allergic alveolitis, drug-induced pneumonia, aspergillosis, lymphomatoid granulomatosis and primary effusion lymphoma. Another case report with bronchoalveolar lavage cytology, in a 34-year-old male with an atypical presentation,[17] did not reveal similar findings. However, the cytologic impression was of significant marked reactive changes in pneumocytes, with lymphocytes, histiocytes, and occasional fibroblastic balls lined by pneumocytes. The reactive pneumocytes can be a major diagnostic pitfall in cytology specimens of cases with diffuse alveolar damage and it is important to note the distinctive pinched shape of reactive pneumocytes ("Napoleon hat" sign)[18] so as not to over diagnose them as malignancy.

Another frequent post-mortem finding reported in the literature in association with COVID-19 is pleural effusion. Pleural effusion was reported in up to 60% of post-mortem in confirmed COVID-19 cases. Cell blocks of pleural effusion cytology showed reactive mesothelial cells in a mild inflammatory background as described by Calabrese et al.[19]

Although the respiratory system seems to be prime harbinger for COVID-19, extra-pulmonary manifestations are more

frequently being reported. The extra-pulmonary organ involvement that has been reported includes renal, cardiac, central nervous system, skin and gastrointestinal.[20] Hence, cytology labs should be careful and consider that all the specimens they receive as potentially at risk and process them with appropriate safety measures and precautions.

A novel cytologic technique described in the literature that can be potentially a non-invasive method to study neurotropic manifestations of COVID-19 is nasal brush cytology. A study of 18 nasal brush cytology from Italy, done in COVID-19 positive patients with symptomatic upper respiratory tract infections, showed rarefaction of supranuclear stria and neutrophils in all cases. While these findings need to be replicated in larger cohort studies, this might be a potential area for further exploration.[21] Changes of clinical practice to help make diagnoses were also adapted during this era. One lab in the United Kingdom reported FNA of accessible sites for oral lesions instead of surgical biopsies to make diagnosis and therapeutic decision. Transoral FNA and p16 immunohistochemistry, HPV ISH studies were requested frequently to replace tonsillar/palatal biopsies and to diagnose and make therapeutic decisions in primary and metastatic head and neck oropharyngeal cancers.[22]

Ancillary techniques for tissue diagnosis of SARS-COV-2 have also been reported. There has been a case series of use of SARS-COV2 immunohistochemistry and in-situ hybridization[23] for tissue diagnoses and different organ involvement. Stand-alone cytology laboratories need to develop standard operating protocols to use these ancillary techniques which can be a helpful tool for diagnosis.

Whilst patients may present as potentially COVID-19 related, we must remain alert to the many other infective and other co-existing clinical conditions that may present clinically or cytologically.

COVID-19 and trainee education

Due to implementation of social distancing, multi-headed microscope teaching, in-person grand rounds, journal clubs, inter-departmental consensus meeting, and many national and international pathology meetings have all had to be canceled. This has hugely impacted on trainees' education and understanding of pathology. This is especially seen for trainees in their earlier phase (first-year residents and cytotechnologist students) who learn a lot with in-scope teaching as regards basic cytomorphology and helpful clues to clinching cytology diagnoses. However, after almost six months of the COVID-19, many technologies have been visited to continue education, teaching and learning and collaboration. Many institutions have eliminated double or multi-headed microscope sign-out and have opted instead for more independent interpretation by the trainee first who enters their interpretation into the pathology laboratory information system (LIMS) software, followed by review by the attending pathologist. It is important more than ever to close the loop by giving feedback to the trainee about their initial interpretation, in the form of written comments on the trainee's working draft or the case is returned to them after signing out by the attending pathologist. Some institutions (such as UPMC) also utilize secured video-based platforms to review the slide together with trainees especially for challenging cases.

The remote learning of cytopathology microscopy is further complicated because of unique issues pertaining to cytology like the three dimensionality of the cells which needs multiple focal planes (using z-axis), more frequent use of 40x to make a confident diagnosis and focal scattered nature of diagnostic cells. It also needs more time for the early learners and trainees to get acquainted with cytopathology slides. The attending pathologist teaching trainees need to be aware of these issues and take time to focus the cells of interest. The trainees also need to spend additional time looking at cytology cases, even when not on a cytology rotation.[24] Chiou.[25] described a remote ecytology tool that they utilized at their institution at New Jersey, USA for teaching cytotechnology students. Their experience is based on the use of easy video teaching and communication platforms Zoom conferencing (San Jose, California) and Canvas (Salt Lake City, Utah) as their online tools for lectures, microscopy sessions, and tests. Remote multi-head sessions were also conducted at their institutions by attaching a mobile device to the microscope to transmit live videos like the tele cytology Rapid On Site Evaluation (ROSE) concept.

Many of the institutional grand rounds, weekly didactic teaching, journal clubs, tumor boards and consensus meetings have also moved to virtual platforms. Some of the secured platforms that are being used to conduct these are: Microsoft Teams, Zoom, Cisco WebEx or Jabber and Skype. Many of these platforms are being used through institutional subscription; however, some of them like Skype and Zoom with limited number of users and time (100 users and 40 min for Zoom) are available for free. Some organizations, such as the UK National Health Services (NHS), have indicated preferred systems (such as Windows Teams) but inter-institutional connectivity may still be problematic.

To compensate for the decrease in work volume and the many trainees who were forced to stay at home or in quarantine in order to comply with social distancing guidance, many organizations throughout the world came up with self-paced online didactics which were live and many of them are archived, free

Cytology laboratories: changes.

- More stringent implementation of safety precautions for the cytology samples
- Screening of all laboratory staff everyday while entering the hospital
- Free of cost COVID-19 testing in instances of symptoms or exposure to known COVID-19 patients
- Use of adequate PPEs while performing ROSE for EBUS/EUS guided FNAs and FNA performed by pathologist
- Novel samplings: nasal brush cytology, intra-oral fine needle aspirations
- Use of SARS-COV-2 ancillary techniques for diagnosis
- Migration to digital platforms for sign-out and trainee education
- Adapt to unique features of digital cytopathology
- Utilization of social media for education:
- Webinars, virtual lectures, virtual grand rounds, and virtual presentation series.

Box 3

and easily accessible. Some of them are: CAP virtual pathology didactics (#CAPVirtualPath) with capacity of 1000 attendees, Virtual pathology grand round (#VirtualpathologyGR), founded by few pathologists, Path Cast, Royal College of Pathologists and British Association for Cytopathology webinar series, International Academy of Cytology (https://www.cytology-iac.org/educational-resources) and American Society of Cytopathology webinar series (available on YouTube).

There are also many free whole slide image repository websites which trainees can access. For example: Massachusetts General Hospital https://learn.mghpathology.org/

Some free slides databases available for cytology case access are web pathology (https://www.webpathology.com/atlas_map.asp?section=19), and John Hopkins University unknown conference of cytology cases set http://apps.pathology.jhu.edu/cyto/, Case of the month by Papanicolaou Society of Cytopathology (http://www.papsociety.org/case-of-the-month/) and University of Pittsburgh Medical Center https://path.upmc.edu/. The American Society for Clinical Pathology (ASCP) has many educational offerings online, many with CME credits.

A marked increase in the use of social media for education has also been noted after the onset of the COVID-19 pandemic. Many people utilize Twitter, Instagram, Facebook, Periscope and made many educational YouTube videos to bridge the gap in their training and education.[26] These all allow for rapid sharing of good quality images, and for real time interaction and online discussion.

Conclusion

At this point, COVID-19 appears to be here to stay for months, if not years. Many clinical practices and pathways have been altered and may never return to pre-COVID ways. This is also the way for pathology laboratories. Cytology laboratories have had to alter many of their practices (Box 3). Not all that has been changed is for the worse, and many of the new ways of working are superior and are probably here to stay. Cytology must ensure that any changes are based on best evidence, and that if clinical and laboratory practice is to be altered, no detriment to quality or diagnostic accuracy must occur. We must also be aware that events such as COVID-19 may, and potentially will, occur again given the modern world in which we live. Much of what we have learnt and implemented should not be forgotten. Cytology labs should also start preparing for a rebound increase in workload. As we continue to adapt, it is important to not to compromise the education of our trainees and cytotechnologist students. ◆

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Multiple choice questions

A middle-aged male presented with acute chest pain, fever and shortness of breast. A chest-xray revealed mass-like infiltration of left middle lobe of lung. A bronchoalveolar lavage cytology was performed. What features would suggest likely COVID related pneumonia

- **a Atypical cells with pinched shape and multinucleation**
- **b Ground-glass nuclei and multinucleation**
- **c 3D clusters of goblet cells**
- **d Keratinized cells with nuclear pleomorphism**

Answer: A.

All of the high-risk samples (respiratory specimens) received in a cytology laboratory should be processed in

- **a Bio Safety Cabinet-II (BSC-II)**
- **b Bio Safety Cabinet-II (BSC-III)**
- **c Should not be processed**
- **d Can be processed without Bio Safety Cabinet**

Answer: A.

Digital cytology is unique because of

- **a Three-dimensionality**
- **b Focal diagnostic cells**
- **c Use of high power for diagnosis**
- **d All of the above**

Answers: D.