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Histopathology during the COVID-19 pandemic: resilience through adaptation and innovation

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Abstract

Histopathology departments have adapted to the challenges posed by the COVID-19 pandemic by a variety of changes including working pattern alterations, technology adoptions and incorporation of techniques. This article summarizes these adaptations and provides references to guide pathologists through the continuing pandemic.

Keywords COVID reaction; digitalisation; pandemic; remote working; research; training

Introduction

In late 2019, many patients in Wuhan, China became ill with respiratory symptoms and required support in intensive care. The organism responsible was a novel coronavirus; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the disease was named COVID-19. It spread rapidly across the globe and declared a pandemic on 11 March 2020. In the United Kingdom, the earliest record of the disease was in Yorkshire (January 2020, several months before the first recorded UK case) where several members of a choir reported COVID-19 like symptoms after a member's partner returned from a business trip to Wuhan.¹

The disease is considerably more transmissible than other coronaviruses and has impacted all aspects of health service. Intensive care units in the UK have been inundated. In the first

wave of the pandemic, there was a dramatic reduction in diagnostic workload in most cellular pathology laboratories as a result of reduction in surgical procedures, and almost complete cessation of routine/aerosol generating samples such as endoscopy. In the second wave, ongoing in autumn 2020, the workload has not been affected as much and some of the digital solutions discussed in this article are being embedded.

General aspects

Histopathology diagnostic services can be broadly divided into three phases – pre-analytic, analytic and post-analytic. In addition to diagnostic activity, cellular pathology departments have commitments to autopsy, screening services, teaching, training and quality assurance. All these aspects have been challenged by COVID-19. Impact on autopsy and cervical screening services have been dealt elsewhere in this issue.

The pre-analytic phase involves handling biological material including fresh tissue for research or frozen sections and formalin fixed tissue and organs of varying sizes. These tissues were concerning as a possible transmission route for SARS-CoV-2. Fresh tissue handling was discouraged by the guidelines produced by RCPATH,² ABPath³ and BAGP.⁴ With resection specimens, longer fixation was advised. Breast surgeons and gynaecologists were encouraged to open specimens whilst in full PPE (personal protective equipment) in order to allow better formalin penetration and reduce risk for pathology colleagues. With the progress of the pandemic there have been no reports of laboratory-acquired infection for SARS-CoV-2 and tensions in handling of specimens have lowered.⁵

The analytic phase has been impacted by reduction in workforce secondary to individuals falling ill with COVID-19, isolation due to personal or contact circumstances and altered work patterns to maintain social distancing. The reduction in workload due to intensive care units being filled with COVID-19 patients resulted in great reduction in major oncological surgical procedures and clinics with reduced attendance resulting in lower numbers of biopsies.

Redeployment

With a reduction in routine diagnostic workload and a spike in deaths in the first wave of the pandemic, an increase in post-mortems was anticipated. The Coronavirus Act (March 2020)⁶ contained emergency legislation relating to certification and registration of deaths. The key guidance was that any medical practitioner with GMC registration could sign the MCCD (medical certificate of cause of death) even if they had not attended to the deceased during their last illness. This allowed redeployment of medical practitioners whose roles did not include direct patient care, to act as dedicated certifiers. Pathologists, particularly those undertaking post-mortems and accustomed to reviewing patient records and completing MCCDs, provided this much needed service. Local flowcharts were set up clearly delineating the new processes involved and teams of consultants and trainee pathologists undertook shifts dedicated purely to ensuring all the processes and documentation required for death registration and cremation were completed at the earliest opportunity, allowing dignified release of the deceased and timely reporting to inform

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national mortality data. Many trainee pathologists refreshed their clinical skills and were redeployed to clinical wards.

Remote working

Working from home (WFH) during the pandemic has been mainly through choice and/or necessity. Reasons for WFH included being clinically vulnerable/shielding, cohabiting or caring for an individual who fell into these categories and isolation/quarantine due to personal or social circumstances. Some pathologists who needed to use public transport extensively and in the areas of high incidence, opted to WFH fully or partly.

Without digital presence

In departments where conventional microscopy is the mainstay of daily reporting, the advice/necessity to socially distance and work from home raised significant logistical hurdles. In non-digitalized situations, pathologists had varied experience of remote working, ranging from a few hours a week dialling into meetings or dealing with emails through to days spent reporting on a microscope at home. For pathologists with no previous experience of home working, governance arrangements relating to the transport and storage of slides and patient information needed to be configured, including the consideration of potential transmission of the virus on slides moving between homes and hospitals. Access to a microscope at home and IT systems to enable reporting, requesting of additional work and participation in MDTs were logistical issues. The process for obtaining and documenting a second opinion from a colleague needed to be agreed to ensure continuing safe clinical practice (Figure 1).

With remote working, visualizing and advising on gross specimens was a challenging task. Whilst most departments had a mechanism for photographing gross specimens, this was not an adequate substitute to physical presence at the cut-up room. Double heading had long been considered the gold standard method of looking at cases with colleagues and trainee pathologists, and WFH without digital support precluded this. The compromise, as necessitated by the pandemic and its implications for individuals, was to agree on site presence by some pathologists, on a rotational basis, in order to maintain all aspects of the service and training requirements.

Digital presence

In all its forms, use of digital resources has been impactful during this pandemic.

Screen-sharing software: a number of screen sharing software applications are now used in the NHS setting, including Zoom, Skype and Cisco Webex - the pros and cons of using each of these in pathology have been discussed.⁷ This article subsequently refers to the use of Microsoft (MS) Teams. Since the start of the COVID-19 pandemic, Microsoft have provided their teleconferencing software (Teams) to enable multisite socially distanced meetings, through the nhs.net secure digital portal. The ability to easily share desktop microscopy (and other relevant data) has been transformative for pathologists, laboratory medicine and clinical colleagues. Setting up MS Teams has been relatively easy for most NHS employees. One can teleconference with multiple

colleagues wherever they are, especially easily if they have an nhs.net email address. Teleconferences can be made from within a prepared 'team' group, or from the chat window by pressing either the telephone or the camera button. The third icon within the chat window is arguably the most useful for pathologists. This allows screen sharing even from outside of an active meeting; when this button is clicked, the user is prompted to share a currently open window or one of their screens allowing sharing of a microscope camera window, report or any other document.

Pathologists may find it time and resource efficient to present from their own office with one's optimized ergonomics, saving on travel time and using relatively unfamiliar systems and a poor-quality MDT room microscope. They can multitask and get on with routine tasks while clinical colleagues are discussing operative approaches or chemotherapy trials.

Whole slide imaging (digital pathology): the cost and logistics of whole slide imaging (WSI) has meant slow adoption in NHS pathology departments but likely to change with NHS Improvement (NHSI) promoting the formation of regional networks and encouraging the future of cross-site reporting.⁸ Using WSI in conjunction with teleconferencing systems, allows digital images to be projected across NHS sites or to homes and mobile devices without concern that the transfer will be blocked by a firewall. Screen sharing technology can introduce a slight time lag in the viewing of WSI remotely but is generally very economical in the use of bandwidth. During the pandemic, laboratories with scanning facilities have been able to use this effectively for reporting, seeking second opinions and training. This way of working however requires a pathologist working at both sites to enable the relevant areas of slides to be shown or shared. In addition, although guidelines⁹ for reporting digitally have been relaxed slightly since the pandemic, most pathologists are not yet comfortable or experienced enough with WSI to report more than a minority of their caseload in this way.

WSI and working from home: home digital pathology using fast 'fibre broadband' networks can be facilitated using a high specification NHS laptop connected to a base station to access NHS servers and applications at home (via a virtual private network). Using the same laptop at home and at work is a 'cost neutral' solution to purchasing a duplicate set of hardware for home working. Large monitors of 'gaming quality' are not expensive to purchase to WFH, and limited self-validation^{9,10} should allow pathologists to provide safe diagnostic service for most cases. Remote working with WSI has some limitations with use of digital images; connectivity with laboratory reporting systems and sometimes limited clinical information should also induce a cautious approach. Given that, at this time, social distancing and local lockdowns seem to be the norm, advice to departments who are in the process of investing in a digital pathology system is to look at the whole process, from end to end, including, a robust link between the image management system [IMS] and the reporting system (in most cases the laboratory information system [LIS]). The real benefits of whole slide imaging pathology are reaped when tracking, extra work ordering, prioritisation and streaming of specialty workloads are all incorporated into an IMS

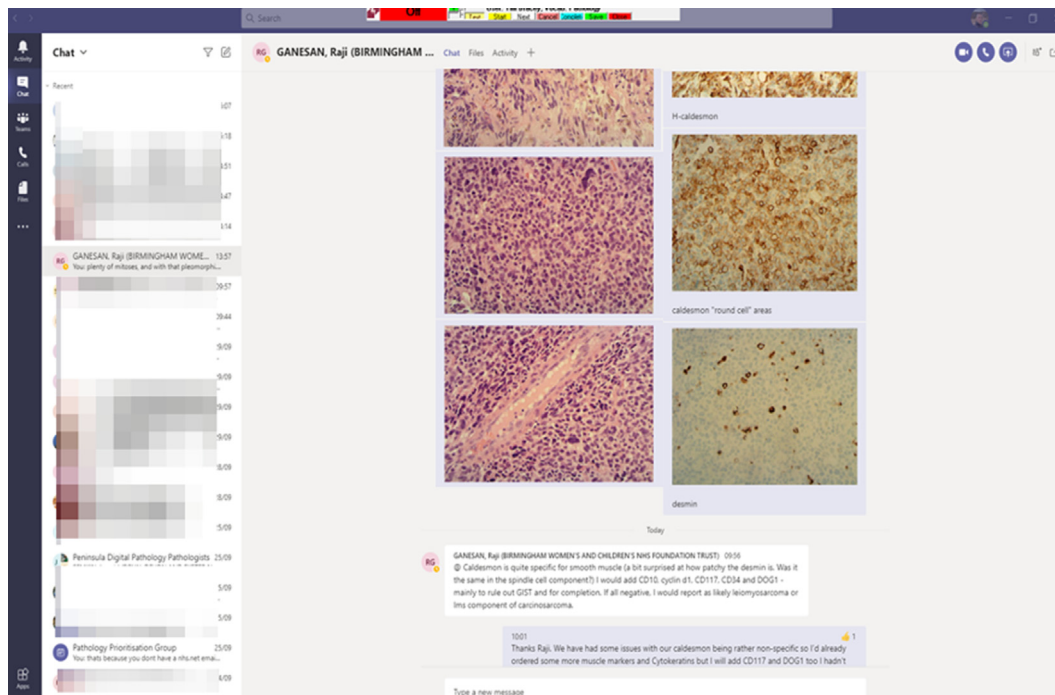


Figure 1 Screen capture of a teleconference between two of the authors discussing a case remotely using Microsoft Teams.

which communicates seamlessly with the laboratory database and ideally the hospital patient information system.^{11,12}

Smartphone microscopy and social media: modern smartphones are packed full of technology enabling easy networking. Some of the more recent phones also have high quality cameras and a host of apps. Social media sites such as Twitter and Facebook are increasingly full of high-quality smartphone images of common to rare pathological entities. The 'Morrison technique'¹³ can be used to take photos. This is a free-hand technique for using smartphones to capture microscopic images without the aid of additional adaptor accessories. It is relatively straightforward technique available to anyone with a smartphone and a microscope, although it requires practice, patience and a steady hand. The last three fingers of the left hand are used to brace against the left eyepiece of the microscope for stabilisation. The smartphone is held between the remaining left fingers and the right hand. The smartphone is then moved slowly closer to the eyepiece until the image comes into focus.

Alternatively, simple mounts can be purchased, and some free software is available to enable 'stitching' of static images to make low quality WSIs for sharing and teaching. Anonymized cases are shared to receive guidance and informal opinions from experienced and knowledgeable specialists around the world, sometimes almost immediately. Although these informal opinions do not replace formal opinions, they can be an excellent alternative and rapid source of ideas and knowledge. As with all forms of image and data sharing, these methods should be considered carefully within the guidelines of local organisation and great care should be taken not to breach patient confidentiality.¹⁴

Clinical prioritisation and impact on pathology practice

Different medical/surgical societies across the globe provided guidance on cancer patients' prioritisation during the COVID pandemic. In breast cancer, the risk of COVID infection with use of neoadjuvant chemotherapy (NACT) was assessed, rationalized and chemotherapy only given to selected patients¹⁵. Data suggest that ER positive tumours can be safely treated by neoadjuvant endocrine therapy (NAET) and surgery delayed for 6–12 months without adverse effects¹⁶ and for early stage ER positive breast cancer bridging endocrine therapy was advised during the COVID pandemic with careful monitoring of tumour response¹⁷. The European Society of Medical Oncology (ESMO) published an interdisciplinary expert consensus for managing cancer patients during COVID epidemic¹⁸ providing a structured and consensus approach to the management of cancer patients. These pandemic related guidelines meant that breast pathologists received larger numbers of mastectomy specimens for aggressive types of breast cancers, such as post NACT triple negative and HER2 positive breast cancer. Wide local excision specimens, particularly following NAET, increased after slowing of the first wave. In order to understand the details of patient management and impact of COVID on breast cancer patients, a UK national audit of patients treated in the period between 16 March-31 July 2020 is currently underway examining the pre-operative, operative and post-operative management of those patients.¹⁹

There was a rapid drop in specimen numbers from gynaecological cancers at the onset of the pandemic, the earliest recovery of oncological surgical procedures was for vulvar cancer followed by endometrial cancers, radical hysterectomies and debulking surgery for ovarian cancers. Lack of intensive care particularly impacted on radical surgery and there was an

increase in requests for hormone receptor assessment and tumour BRCA testing for ovarian cancers, in order to provide patients with non-surgical options. Genomic evaluation of the diagnostic breast core biopsies was favoured during this time and has been shown to be both representative and reliable.²⁰ Clinics for emergency management of gynaecological symptoms, early pregnancy interventions and colposcopy were affected the least.

Rapid intra-operative frozen section diagnosis (FS) is used in early stage ovarian cancer to confirm a diagnosis of malignancy before undertaking radical cytoreductive surgery. Due to the potential aerosol-generating procedure and COVID-unknown status of many patients at the outset of the pandemic, RCPATH² and BAGP⁴ guidance advised against use of FS. At the Northern Gynaecological Oncology Centre in Gateshead (NGOC), pathologists used intraoperative imprint/scrape cytology to great effect. The technique reduces the risk of aerosol production thus minimizing risk of infection to laboratory personnel, without compromising quality of care. Pathologists at the centre had experience of using intra-operative cytology as an adjunct to frozen section. The pathologists and BMSs used PPE (Personal Protective Equipment) kits and specimens were handled under a ventilated hood. Handling large masses under a hood was particularly challenging. Later in the pandemic, in patients who were COVID-negative on preoperative testing, dissection of large specimens was done using a downdraft bench with appropriate PPE. See [Figure 2](#).

Imprint cytology of fresh tissues was first reported by Dudgeon and Patrick in 1927.²¹ Since then the accuracy has been documented as an alternative or as a complement to frozen section.²² The advantages of intraoperative cytology include its simplicity, speed and preservation of cytomorphological details which could be lost due to freezing artefacts on frozen sections. Rapid intraoperative opinion regarding the benign or malignant nature of the tumour was made with attempt at subtyping, where possible. All intra-operative results were given by telephone within 30 min of receipt of the specimen. Diagnostic concordance of rapid intraoperative cytology diagnosis and final diagnosis on permanent sections was achieved.

Multidisciplinary team meetings (MDTs)

Oncology MDTs functioned throughout the pandemic with a combination of remote and minimal in-person attendance. In the situations where attendees are employed by different NHS Trusts, firewalls restricting access to the software used by the Trust housing, remote attendance at the MDT has been challenging. Chairing remote meetings needed a different skill set that was gradually acquired. In optimally resourced settings, teleconferenced meetings facilitated working from home or from individual offices, enabling social distancing allowing even shielded individuals to contribute. After overcoming teething problems with 'muting etiquette' and microphone feedback, team members quickly adapted to the new norm. Just as in conventional MDT discussions, members are encouraged to take their turn to speak and present, with well chaired meetings running most efficiently. In multihospital and multisite MDTs, adoption of an organized method of sequentially discussing patients may result in permanent adoption of this method without intent or desire to return to the previous, non-socially distanced

meeting format (see [Figure 3](#)). Variations in bandwidth slowed live contributions at times.

Research

During phase 1 of the COVID pandemic, there was a need to dedicate all resources to support the clinical activities and to redeploy staff to support frontline services. In the UK, sponsors, charities, universities, NHS institutions and NIHR Clinical Research Network agreed to suspend all non COVID research in March 2020 and to pause the setup of new trials. It was agreed that research time for clinical staff will be instead used for supporting the huge clinical demand of the National Health Service (NHS) during that time. ESMO published guidance on prioritisation of interventional trials from level 1 (highest priority) to level 4 (low priority). Trials with high risk of requiring intensive care facilities were avoided during the pandemic.²³ Those approaches have allowed prioritisation of COVID related research and trials including vaccination and drug discovery.

With the steady fall of COVID positive inpatients, a letter from the CEO of NHS England and NHS Improvement restarting urgent non-COVID clinical activities was sent in April 2020.²⁴ NIHR funded research staff began to return to some research activities and therefore a 'restart framework'²⁵ was produced to facilitate resumption of research activities and setup of new trials while maintaining COVID related research as an integral and important component of NIHR portfolio. This was done within a national framework with local influence whereby trial teams had to demonstrate the viability of their trials, their safety together with capacity and site readiness. Three levels of prioritisation, depending on trial urgency, were proposed, with level 1 being highest priority and including national COVID-19 trials, level 2 including trials with urgent treatments and level 3 comprising all other studies.

In the UK, there has been a differential impact on research activities as a result of the COVID surge with institutions dealing with large numbers of COVID patients, such as in London and Birmingham, more adversely affected compared with institutions in other less affected areas such as the devolved nations. While many institutions recruited well for COVID trials during the pandemic, there has been a significant national disruption to portfolio trials particularly those involving interventions. Restarting trials has also been variable due to workforce challenges with some previously high recruiting research networks lagging behind in restarting of paused trials.

Fresh tissue collection for bio-banking, research and trials has been halted during the pandemic with pathology laboratories encouraged to place specimens in formalin as soon as possible to minimize the risk of transmission to medical and technical staff. Tissue specific guidance, such as the National Co-ordinating Committee for Breast Pathology (NCCBP) and the Association of Breast Pathology (ABP) guidance on breast specimen handling, has been published.³ With easing of the pandemic, fresh tissue sampling has restarted but has not reached pre-COVID levels and may be subject to further disruption with onset of the second wave of COVID.

An example of a successful initiative for supporting research during the COVID-pandemic was the development of Medical Student Volunteers in Research initiative by the West Midlands

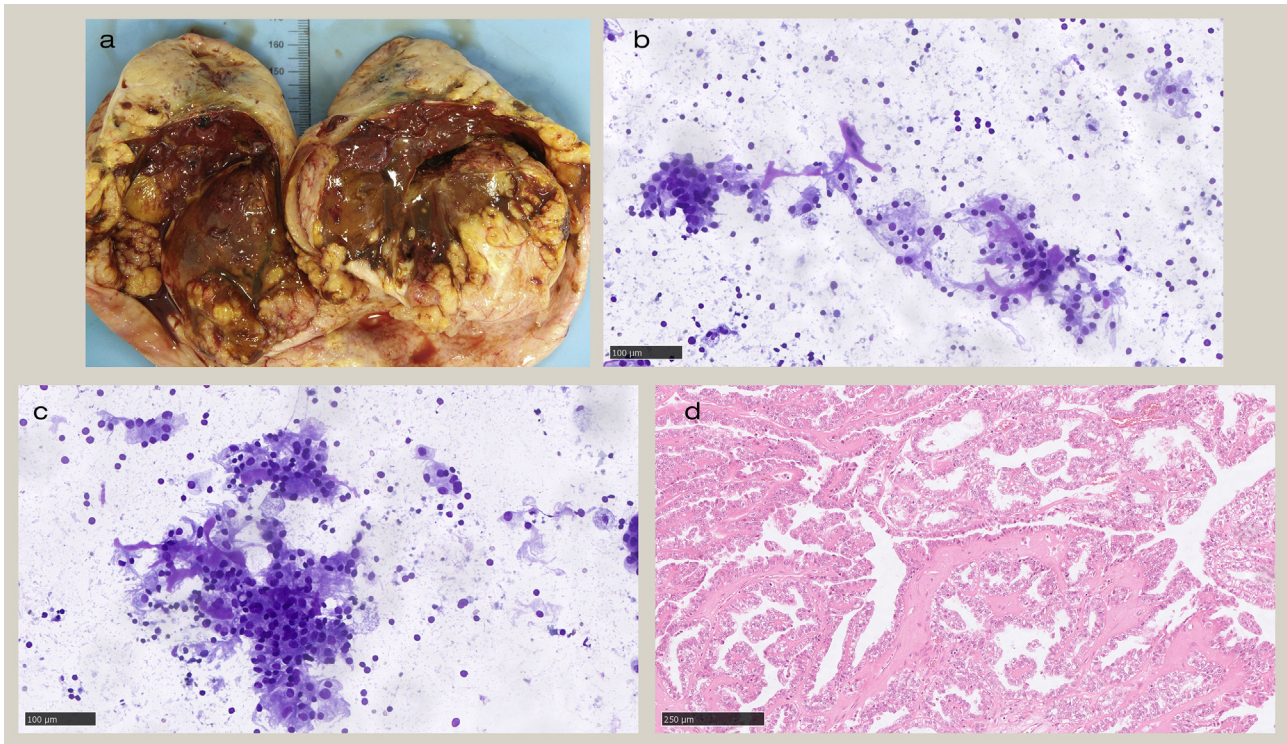


Figure 2 (A) Gross appearance of a haemorrhagic solid cystic tumour with fleshy homogenous slightly spongy appearance and intracystic broad polypoid projections. This suggests a tumour arising in a background of endometriosis. (B, C) Intraoperative scrape cytology (DiffQuik) showing loosely cohesive cells with moderate to abundant fragile, finely granular or finely vacuolated cytoplasm. The nuclei are round, small to medium sized with minimal anisokaryosis. Deep magenta coloured stromal hyaline cores are also present. These features are typical of a clear cell carcinoma. (D) Histological section (haematoxylin and eosin) showing clear cell carcinoma with papillary structures and hyalinized cores. The papillae are lined by non-stratified cuboidal cells with clear or granular eosinophilic cytoplasm and moderately pleomorphic vesicular nuclei with prominent nucleoli.

Clinical Research Network (CRN WM). The scheme encouraged students to volunteer as part of the task force delivering portfolio trials. This included either actual contribution to the research work or helping with particular tasks such as data entry. The scheme was well received by students and helped their learning, career development and mental wellbeing. It also freed some of the CRN staff time to deliver on studies during those exceptional times.

Training

The mainstay of surgical pathology training has been the double-header or multi-header microscope, which only affords elbow-room. Wearing a mask for microscopy is uncomfortable and impractical. Masks cause microscope eyepieces and spectacles to fog. Thus, social distancing is incompatible with conventional surgical pathology training. Screen sharing is being increasingly used for routine reporting with trainees, for regional teaching/training days, 'black box' meetings, and for ARCP (Annual Review of Competency Progression) meetings.

With use of application such as MS Teams, installation of cameras over the cutup benches and high-quality wireless recording headsets remote cut up supervision of trainee pathologists and biomedical scientists, pathologists can oversee dissection and block taking. Pathologists working across sites have also used this technique. Where complex specimens are

involved, remote supervision of cut up has been particularly helpful for the pathologist to have seen a specimen prior to receiving the slides of a complex case for reporting.

Educational meetings

The virtual space has been increasingly used for meetings. The advantages of these meetings are the ease of delegate participation whilst staying COVID-safe and socially distanced. The numbers of delegates can be easily greater than a face to face meeting. In histopathology, scanned material can be shared with this wide audience, providing a very useful practical element to the course. Speakers can be from different time zones around the world, allowing a truly international educational experience. Use of moderators for the virtual meeting allows ease of monitoring of the chat and pose questions for the speakers as well as addressing other organisational and technical queries. The organisational aspects are somewhat different and quite time consuming. As such meetings are novel, the offer of a trial session is appreciated by speakers and requires time. The ongoing possibility of any speaker or organizer contracting COVID-19 makes organizing of week-long meetings quite stressful. During a recent online course of the British Association of Gynecological Pathologists (personal anecdote), healthy children being sent home from school secondary to a fellow student being COVID-positive resulted in a need to reorganize the team managing the course.

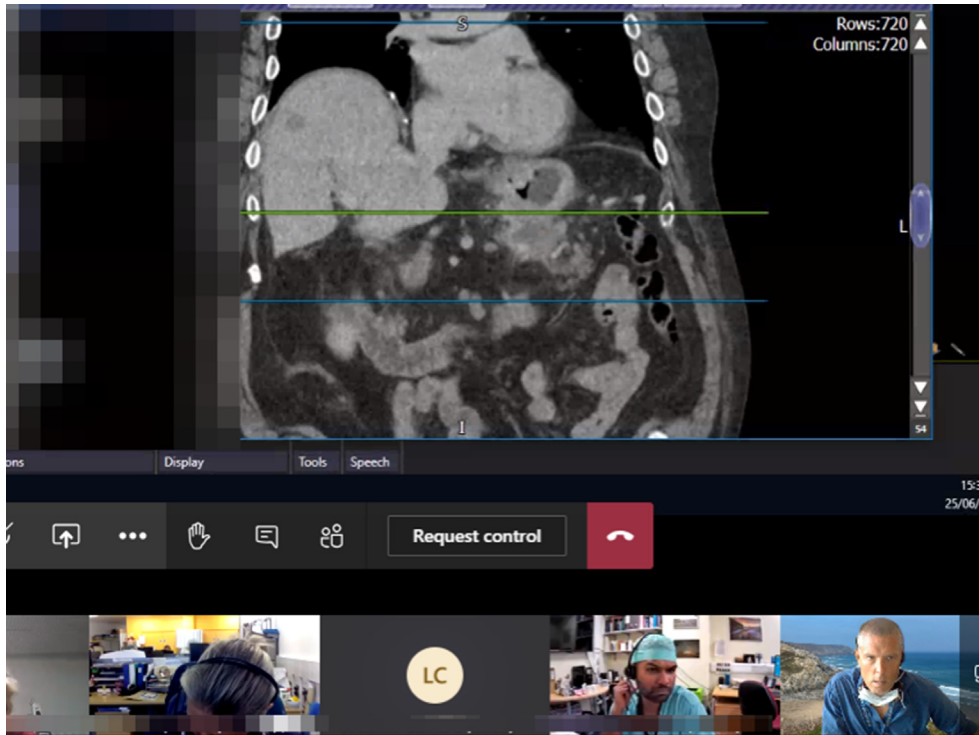


Figure 3 Screen capture of a gastric cancer patient being discussed on MS-Teams during a pan-regional upper GI cancer MDT with representatives from all five hospitals (unmasked pathologist bottom right).

Quality assurance

No quality assurance (QA) visits were conducted during the lockdown period. Other QA activities struggled to be maintained. Internal quality assurance activities like multiheader reviews were reduced or altered in form and amount. Referral and review work were lower taking into account the general drop in activity. With easing of lockdown these activities have resumed with more virtual interaction between pathologists.

Screening

In March 2020, bowel, breast and cervical cancer screening programmes were paused in response to the pandemic to reduce the risk of exposure to coronavirus for healthcare staff and the public. In June 2020, screening services restarted as part of a phased restoration. The pause in screening resulted in a backlog of patients awaiting a screening test and as the capacity of the screening programmes is less than it was pre-COVID due to the increase in infection control measures and social distancing required, it will be some time before services can be resumed at a normal level, although recent data (see Figure 4) suggest that screening activity is starting to increase. QA visits by Public Health England were suspended in response to the pandemic and face to face visits have not recommenced.

The future

Importance of face-to-face communication

In the world of business, remote working and a more flexible approach to work have been established for years. This is a relatively new way of working in medicine in the UK and many aspects

of clinical practice do not lend themselves to remote working. The pandemic has 'forced' us all into working remotely to some degree, and now we know we can, to what extent should we in the future? Whilst virtual communication has obvious benefits – convenience, time efficiency, flexibility, cost saving – the value of face to face communication cannot be dismissed. Anyone who has used video calling will have experienced the awkwardness of people talking over each other or the frustration of trying to get a controversial point across. It is also easier to be distracted by other tasks and diversions resulting in less than optimal engagement in the conversation or meeting. Body language cannot be gauged, facial expressions can be tricky to read and many of the cues we unconsciously rely on to direct our communication are lost. Humans are social creatures. The social element of working in the same space as colleagues - a quick greeting in the morning, a chat during coffee, having lunch together – is a vital part of building connections, engaging as a team and developing a sense of belonging and loyalty. Multiple daily informal *ad hoc* face-to-face interactions reinforce this and support creativity and innovation. The challenge of working remotely and communicating virtually is especially significant for new team members where there is little or no pre-existing parameter to fall back on. Within pathology, team working is crucial for delivering an optimal service - establishing standard practice within a department, facilitating second opinions and training and support of junior colleagues – to name but a few of the elements.

COVID 'grief' – the emotional aspects of the COVID-19 pandemic

An interview was published in the Harvard Business Review in March 2020²⁶ describing how the reaction to coronavirus was a

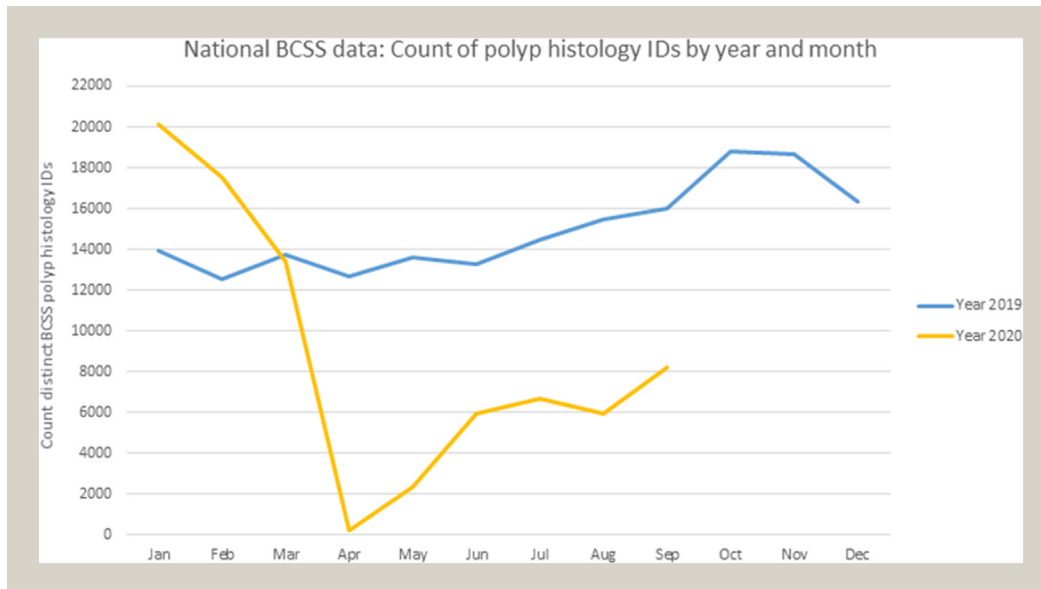


Figure 4 Full roll out of bowel screening commenced in June 2019. On 23 March 2020 the programme was paused due to screening centres diverting resources to the pandemic (data from Public Health England Bowel Cancer Screening Team; used with permission).

form of ‘grief’ – loss of feeling of physical safety, security, sense of ‘normalcy’, personal freedom, routines, jobs, financial security, connection with others and for some the tragic loss of loved ones. There is an anticipatory sense of grieving – the feeling we have about an uncertain future.

This grief follows the Kübler-Ross change curve²⁷ which has five stages variably in terms of order, duration and intensity:

- denial – ‘There’s no crisis. I’m young so I won’t catch coronavirus. It’s happening in another part of the world.’
- anger – ‘Why have I not got the PPE I need to do my job? Why were we not better prepared for this?’
- bargaining – ‘Maybe I can travel to a country where there are no cases.’

- depression – ‘I’m so lonely and feel so isolated not being able to see my family and friends. When will this end?’
- acceptance – ‘I understand what’s going on and will comply with lockdown measures. I will get through it’

Patients and healthcare staff have suffered from varying degrees and stages of COVID grief. Understanding the different stages of the model could provide a greater insight into our behaviour and actions as well as those of the people we interact with at work and home - our colleagues, patients, families and friends – and may help to cultivate the patience and compassion required to reach and maintain a state of acceptance and navigate this unprecedented time (Figure 5).

The pandemic continues to be a global catastrophe and the future will be referenced to before 2020 and the different world left in its wake. As we emerge from the first wave of the pandemic, we have learnt to embrace new technologies. With greater adoption of technology, we can limit viral transmission without sacrificing the quality of safety of our essential work whilst looking ahead to return of personally interactive social existence. ◆

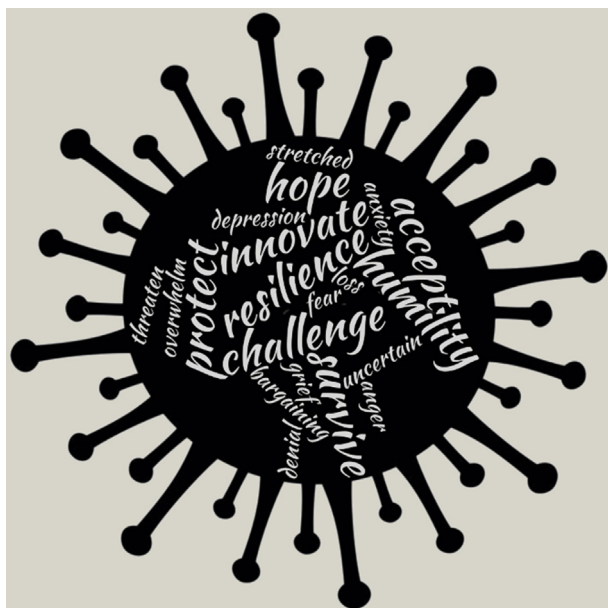


Figure 5 Reactions to the COVID pandemic.

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