

Pathologists and the coronavirus distraction effect

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The current COVID-19 pandemic has imposed sweeping changes in every aspect of life, not least in the way pathologists carry out their practice. Severe acute respiratory syndrome coronavirus 2 spreads quickly from person to person through respiratory droplets released in the air by infected patients. Thus, respecting strict biosafety procedures while handling potentially infected fresh tissues, liquid samples or even air-dried fixed cytological preparations, has become paramount for pathologists. However, the so-called ‘distraction effect’ represents an even more subtle menace to the pathologists than the virus itself.¹ In fact, because of this effect, pathologists run the risk of diverting their attention exclusively toward COVID-19 issues, with a detrimental effect for patients affected by other health-threatening diseases including cancer. Indeed, although rescheduling of non-urgent and elective pathological procedures has become common practice in the wake of today’s pandemic, pathologists should not postpone diagnostic procedures for high-risk patients with cancer.² Likewise, molecular pathologists must continue to perform molecular predictive tests to assure timely selection of patients for targeted treatments.³ In this editorial, now that the peak of the pandemic is over in many countries, we argue that one lesson pathologists would do well to learn is that everyday pathology practice should never be overshadowed by other health concerns, even in the midst of a major health emergency.¹

The report by Vigliar *et al* can be read as an epitomic example of what an effective prioritisation strategy can achieve in cytopathology in times of global health crises.² In our experience, we found that whereas the number of the samples examined during the lockdown was drastically reduced, the percentage of malignant cases was significantly increased, thereby illustrating that cytology is crucial in the diagnosis of patients at high oncological risk.

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By and large, whereas cytological activities for patients at low oncological risk (eg, cervical cancer screening) were all suspended during the critical phase of the COVID-19 outbreak, those addressing patients at higher cancer risk were carried out regularly. However, whether to perform fine needle aspiration (FNA) biopsy, which does not allow for physical distancing, was evaluated on a case-by-case basis, weighing the benefits and risks of each procedure.⁴ In particular, patients at higher oncological risk, like those presenting with enlarged lymph nodes or breast lumps, directly underwent FNA biopsy, provided that several safety issues were addressed. One such issue was to perform rapid on-site evaluation of sample adequacy only when ensuring samples adequacy was an issue, as for ultrasound-guided endoscopic FNAs. Another issue was to make sure that smears were methanol fixed and not air-dried before Diff-Quik staining. The reason is that air-dried smears may generate aerosols and droplets that might contain viable and transmissible viruses.⁴ Lastly, all smears were delivered to the cytopathology laboratories by hand and not by hospital tube systems.

As mentioned above, whereas high-risk patients with cancer were investigated without delays, screenings of patients with unsuspecting presentations were postponed to a later date to avoid the possible risks of COVID-19 exposure during FNA procedures. This is the case of patients presenting with thyroid nodules, when spongiform ultrasound features raise a very low suspicion of malignancy ($\leq 3\%$).⁵ Ideally, the decision to postpone FNAs should be taken by a multidisciplinary tumour board,⁶ evaluating the clinical and imaging data and the patient’s personal history of malignancy. This is because a long and still undefined ‘waiting time’ between referral and FNA generates high levels of anxiety in patients and, in turn, a sense of urgency.

Likewise, during a pandemic, molecular pathologists should remodulate their priorities, as reported in a very recent report by Malapelle *et al*.³ Indeed, if on one hand the temporary interruption of non-urgent molecular assays is regrettable, on the other hand it is wholly conceivable during a pandemic when considering

tests that are not directly associated with increased life expectancy, as those adopted to refine uncertain morphological diagnosis. Conversely, identifying a number of actionable genomic biomarker, which are at the heart of personalised/precision oncology, ought to be carried out without any delay. Germinal *BRCA* testing is a case in point. Indeed, we strongly recommend prioritising this test to select patients for targeted therapies. On the contrary, it should be postponed when it is performed to assess the hereditary cancer risk and prevention of patients’ relatives.⁷ Although Malapelle *et al* did not report significant drops in testing volumes,³ the true impact of COVID-19 on predictive molecular pathology activity is difficult to estimate at present, differing according to the institution and to the local, regional and national epidemiology of the infection. Conceivably, patients’ access to molecular testing was more difficult during lockdown on account of the extraordinary measures taken to observe social distancing. Under normal circumstances, oncologists order molecular predictive testing as soon as a malignant disease is diagnosed; however, when the peak of the coronavirus outbreak hit Europe, such practice was partially suspended owing to the so-called distraction effect. Indeed, if on one hand oncologists were often recruited by internal medicine or emergency departments, hence delaying predictive testing, on the other hand, the slowdown of interventional radiology, endoscopies and surgeries provided far fewer tumour specimens to test.⁸

The ripple effect of this scenario on cytological activities is partially foreseeable. Given that nowadays the outbreak is seemingly less worrisome, it would not be surprising to witness an incoming wave of oncological patients needing predictive biomarker screenings. Undoubtedly, laboratory staff will have to comply with all the safety measures enacted so far to avoid contagion. Indeed, at all times, maintaining social distancing (1m), wearing personal protective equipment and working shifts to minimise the simultaneous presence of people in a laboratory will be crucial to work safely. Furthermore, office activities and implementation of smart working for database updating and clinical reporting will have to be prioritised.

In addition to these safety measures, the use of automated genotyping platforms may also contribute to reducing the amount of time spent in a molecular laboratory. Indeed, these platforms require minimal hands-on work.⁹ For instance, before the outbreak struck,

Malapelle *et al* had been using next generation sequencing (NGS) assays for several years.¹⁰ Only in acute deteriorating patients, when results had to be obtained in a matter of hours, was a fully automated real-time PCR (RT-PCR) platform preferred over NGS.^{11,12} However, during the outbreak, NGS became less sustainable owing to its long hands-on working time and to the need for the involvement of several professionals, including pathologists, biotechnologists and bioinformaticians. Thus, during the lockdown, our laboratory analysed the majority of cases (88.4%) using automated RT-PCR.³ Indeed, the turnaround time (5.3 working days) was optimal and technicians could rotate weekly.³ Not far from now, thanks to technological advances, both RT-PCR and NGS assays will be automatised. In fact, small gene panels are already being run on sequencing platforms to automatise the specimen-to-report workflow and, therefore, deliver results in a single day with minimal hands-on work. Regrettably, upgrading molecular pathology laboratory technologies by promoting automation is a costly process and may not be easily affordable during a financial crisis. In fact, although one may argue that NGS platforms are also expensive, they are not as expensive as fully automated RT-PCR platforms, which indeed require costly cartridges for any single gene assessment. For instance, a detailed genomic analysis (*KRAS*, *NRAS*, *BRAF* and MSI) with an automated RT-PCR costs around €350 for any patient with colorectal cancer, whereas the same analysis with a NGS panel costs only €98.³ Furthermore, laboratories must also factor in the additional costs of providing their staff with disposal protective personal equipment, which must be worn and changed several times a day.

Now that Europe is trying to return to normality, academic research laboratories are being reopened despite remaining understaffed to prevent overcrowding. Obviously, the reopening is crucial not only to keep patients in clinical trials, but also to honour research grant commitments. However, the ripple effects of COVID-19 pandemic will continue to linger in our cytology practice for some time. Indeed, healthcare resources are being allocated outside the molecular predictive pathology field, a phenomenon that may negatively impact our research and

development activities. Equally important, the restricted number of scientists allowed to work simultaneously in the same laboratory to guarantee social distancing may render research laboratories less productive. In such scenario, reshaping research laboratory management and staff organisation may be even more challenging than reorganising the clinical activity. Thus, since patients' care needs innovation, we hope that institutional efforts will be spent to enable academic molecular pathologists to interface with diagnostics and pharmaceutical companies.

As of today, while containment measures are still proving necessary, countries around the world are beginning to gradually ease the COVID-19 restrictions in an effort to restart their economies. Thus, today more than ever before, pathologists should refocus their attention on specific healthcare actions. Indeed, once the postponed cancer screening programmes restart, pathologists should prospectively monitor whether delays in access to healthcare services during the lockdown will translate into an incoming wave of undetected malignancies. Hopefully, this will not be the case, but if it were, one lesson pathologists would do well to learn is that high-risk patients with cancer should never be denied diagnostic procedures or molecular testing for targeted treatments, even in the midst of a devastating global pandemic.

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