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Cytopathology Practice in the COVID-19 Era: Focus on Sample Workload

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Abstract: Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak was declared a pandemic, the magnitude of coronavirus disease 2019 (COVID-19) has continued to grow, putting an unprecedented strain on all medical fields. Its effects on cytopathology workloads have been dramatic. Indeed, despite the implementation of several laboratory biosafety recommendations, cytological screening activities and cytological sampling of patients at low risk of malignancy have been postponed to limit the risk of contagion and to lessen the strain on overwhelmed hospital facilities. In this scenario, a drastic reduction in the total number of cytological specimens has been observed worldwide. This review summarizes the current evidence of the impact of the COVID-19 pandemic on cytopathology practice by focusing on its impact on cytological sample workload.

Keywords: COVID-19; cytopathology; FNA; cancer; screening programs

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic on 11 March 2020. Since then, the magnitude of the pandemic has continued to grow exponentially, creating an unprecedented strain on health systems worldwide [1]. Indeed, the need to increase hospital capacity to meet the surge in COVID-19 patients and the application of stringent safety procedures, such as, for example, social distancing, have dramatically changed the way healthcare is delivered. In this scenario, the field of cytopathology has had to face several technical and diagnostic challenges to cope with the risks of contagion while continuing to deliver efficient cytopathology services. To overcome some of the technical challenges, several safety rules have been put in place to protect laboratory clinicians from the potential presence of the virus in cytological specimens [2–5]. Some of these guidelines include the use of personal protective equipment (PPE) during specimen collection, handling, and processing and the use of a certified Class II biosafety cabinet (BSC) during aerosol-generating procedures, including rapid on-site evaluations (ROSE) [6–8]. Moreover, the guidelines recommend the use of fixative solutions containing >70% alcohol rather than air-dried smears for their ability to inactivate SARS–CoV-2 [6–9].

Similarly, the pandemic has also affected cytopathology diagnostic activity [10–18]. Indeed, since hospitals have been advised to review all scheduled elective procedures to minimize or postpone non-urgent procedures, cytological screening activities and cytological sampling of patients at low risk of malignancy have all been postponed.

Since the beginning of the pandemic, a growing body of literature has investigated the magnitude and the effects of delayed cancer screening and diagnosis. In this review, we will briefly summarize the current evidence of the impact of the COVID-19 pandemic on cytopathology practice, particularly by focusing on the changes in cytology workload.

2. Single-Institutional Experiences

The first study investigating the effects of the COVID-19 pandemic on cytopathology practice was reported by the cytopathology laboratory of the University of Naples "Federico II", Italy, in April 2020 [10]. At the time, Italy was the worst-hit country after China to face the COVID-19 epidemic, soon becoming the country with the highest number of infections and COVID-19-related deaths. A national lockdown was imposed on 9 March 2020; two days later, the WHO declared COVID-19 a pandemic. During the first three weeks of the national lockdown, the Italian study reported a drastic overall reduction (−84.7%) in the total number of cytological specimens compared with 2019. The most affected samples were Pap smears and thyroid fine needle aspiration (FNA) samples, whereas the least affected were samples at higher risk of malignancy, such as breast and lymph node FNAs. These data demonstrate that the implementation of a prioritization policy during a health crisis results in a significantly higher rate of processed malignant samples.

Similar workload trends were also reported in subsequent single institutional experiences. For instance, a few months later, de Pelsemaeker and colleagues provided evidence of the impact of the Belgian anti-COVID-19 measures on the histological and cytological workload of an academic laboratory. They observed a drastic reduction in both cervical and non-gynecological samples in the first trimester of 2020 compared with the corresponding period in the previous years (2017–2019) [11]. Similarly, in September 2020, Rana et al. documented an Indian institutional experience during the national lockdown period, reporting a marked reduction (−90.8%) in cytological samples compared with the pre-COVID-19 era [12]. Moreover, like in the Italian experience, the authors observed a statistically significant increase in malignancy rates. Finally, most recently, in January 2021, Virk et al., who reported data from an academic center in New York, further confirmed a downward trend in the cytology workload (−76%) and an upward proportion of malignant diagnosis [13]. Data are summarized in Table 1.

Table 1. Summary of literature studies reporting single-institutional experiences on the effects of the coronavirus disease 2019 (COVID-19) pandemic on cytopathology practice.

		OVERALL SAMPLE NUMBER					MALIGNANCY RATE (%)	
Author (Ref.)	**Study Period**	**COVID-19 Pandemic 2020**	**2019**	**2018**	**2017**	**Difference (%)**	**COVID-19 Pandemic 2020**	**2019**
Vigliar et al. [10]	3 weeks (9 March to 27 March)	94	615	nr	nr	−84.7	15	5
de Pelsemaeker M. et al. [11]	4 months (January to April)	4921	8152	8513	8174	−39.6; −42.2; −39.8	nr	nr
Rana et al. [12]	9 weeks (24 March to 17 May)	21	230	nr	nr	−90.9	61.9	27.8
Virk et al. [13]	10 weeks (16 March to 15 May)	1372	10,335	nr	nr	−86.7	16	10

Ref.: reference; nr: not reported.

Interestingly, although all these studies highlighted a workload reduction in absolute numbers, the proportion was variable. In fact, the most remarkable reductions were observed in samples with an expected low risk of malignancy among non-gynecological specimens, such as thyroid, and in gynecological samples. The latter evidence was also confirmed by other experiences from American and British laboratories [16].

3. Multi-Institutional Experiences

The first multi-institutional study to reflect the impact of COVID-19 on cytology practice was first published by Wang et al. in September 2020. In particular, the authors

surveyed the workflow and workload of cytology practice in 167 laboratories in the Asia-Pacific region from 1 February 2020 to 20 April 2020 [14]. Interestingly, they observed that most of the participating laboratories had implemented hospital in-house restrictive measures, such as the interruption of elective procedures and surgeries, and the closure of outpatient and emergency departments. They also noticed that half of all participating laboratories had implemented part-time and remote work—measures that inevitably rearranged the entire workforce and cytology workflow. Noteworthy, the survey highlighted that 80% of the participating laboratories experienced a significant decrease in sample volume (>10%) during the study period, compared with the corresponding period in 2019. Overall, although the most remarkable reduction was observed in gynecological samples, even non-gyn exfoliative and aspiration samples were reduced.

The impact of COVID-19 on cytology practice was also investigated in another international, multi-institutional study [15]. The data, collected from 41 participating laboratories from 23 different countries during a four-week period of national lockdown, showed an average volume reduction of 45.3% compared with the corresponding period in 2019. Noticeably, the adoption of restrictive measures led to a substantial reduction in the total number of cases, independently of the specimen type (cervicovaginal tract, urinary tract, breast, thyroid, salivary gland, soft tissue, anal-rectal region, bone marrow, serous cavities, lymph node, respiratory tract, central nervous system, gastrointestinal tract, pancreas, liver, biliary tract); however, the workload decrease was more evident for samples with a lower expected risk of malignancy (e.g., pap smears, thyroid). On the other hand, the adoption of a prioritization policy determined a mild increase (5.56%) in the malignancy rates of non-gynecological samples—a phenomenon that highlights once again the special attention given to patients at higher oncological risk throughout the entire crisis.

4. Molecular Cytopathology

As opposed to elective medical procedures, predictive molecular testing for oncological patients was neither canceled nor suspended throughout the entire emergency phase of the COVID-19 epidemic. Unsurprisingly, studies evaluating the impact of the COVID-19 pandemic on predictive molecular pathology showed little to no variations in the overall workload of molecular testing during the lockdown [19–21]. It is known that, in advanced-stage cancer patients, cytological samples may be the only material available for both diagnosis and molecular biomarker testing to predict patient response to targeted therapies; therefore, molecular cytopathology has emerged as a rapidly evolving field of diagnostic and predictive pathology. Interestingly, as far as molecular cytopathology is concerned, Malapelle et al. reported that the amount of molecular testing performed on cytological specimens (cell blocks and smears) during the national lockdown was comparable to that in the corresponding period in 2019 [19]. Similarly, multi-institutional data focusing on predictive molecular pathology in a non-small cell lung cancer (NSCLC) setting confirmed the continuance of biomarker testing on cytological material, as demonstrated by the increase in absolute numbers in 7 out of 12 European laboratories that detailed the type of tissue samples [20]. The slight increase in molecular testing performed on cytological samples during the health crisis was possibly ascribable to the adoption of minimally invasive diagnostic procedures, such as FNA, to limit the risk of complications requiring hospitalization [22].

In addition to the predictive purposes, molecular profiling of cytological samples is also currently used to further stratify atypical and undetermined cytology classes into low and high malignancy risk categories, such as in the management of uncertain thyroid nodule FNAs. Although, to the best of our knowledge, no studies have focused on the effect of the COVID-19 pandemic on the molecular profiling of thyroid samples, it is reasonable to assume that a reduction in the molecular testing of indeterminate thyroid nodules was due to the decrease in thyroid FNAs seen during the lockdown [23–25]. As opposed to predictive molecular testing in advanced stage NSCLC cancer patients, this phenomenon is consistent with the evidence that most differentiated thyroid cancers are

not considered medically urgent and can therefore be postponed because of their indolent clinical course [26].

5. Ongoing Effects and Future Perspectives

Deprioritization of all elective medical procedures has been an unavoidable effect of the COVID-19 pandemic "emergency phase" in order to maintain the capacity of healthcare facilities and to reduce the risk of infection among patients and medical staff. However, timely diagnosis, treatment, and regular follow-ups for certain malignancies are crucial to prolonging the overall survival of advanced cancer patients [27,28]. After the first wave of COVID-19, single institutions experienced a gradual increase in cytological sample volume thanks to the progressive loosening of restrictive measures [16,18].

Now that the world is still in the middle of the pandemic, cytology practice is still struggling to return to the pre-pandemic levels, as the fear of contagion still permeates people's lives. In this scenario, mass vaccination could undoubtedly be a game changer that could help to revitalize crucial healthcare services, including preventive and diagnostic care services. In the meantime, continuous monitoring of cytopathology practice is paramount in order to guarantee that at least high-risk oncological patients are properly managed. Finally, considering the massive backlog of patients awaiting cytological testing, we expect a rebound increase in screening and diagnostic procedures in the near future [16].

In conclusion, since the beginning of the pandemic, a growing body of literature has investigated the magnitude of delayed cancer screening and diagnosis. As cytopathology is often a first-line procedure in the neoplastic setting, cytopathology laboratories represent a privileged vantage point from which to evaluate the impact of the COVID-19 pandemic on the management of oncological patients. Indeed, despite the implementation of prioritization policies, cytology workloads have been drastically reduced worldwide in order to minimize the spread of infection and to increase hospital capacity for COVID-19 patients. Therefore, continuous monitoring of cytopathology practice is warranted to evaluate the return to pre-COVID-19 levels.

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