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An Analysis of the Impact of COVID-19 Pandemic-related Lockdown Measures on a Large Gastrointestinal Pathology Service in the United States

AEJAZ NASIR, BROOKE HOUGH, CATERINA BAFFA, ARUN KHAZANCHI and DOMENICO COPPOLA

Department of Pathology, Florida Digestive Health Specialists, Florida Research Institute, Bradenton, FL, U.S.A.

Abstract. *Background/Aim: The coronavirus disease 2019 (COVID-19) pandemic prompted global recommendations to delay non-urgent endoscopic procedures to limit the spread of SARS-COV-2, but such delays had unprecedented impact on the delivery of healthcare. Being a large specialty GI Pathology service, we sought to analyze the effect of the pandemic on the frequency of GI malignancies in our department. Patients and Methods: Based on the electronic search of departmental pathology records, we compared the total numbers of cancer diagnoses (primary and metastatic) from various GI biopsy sites during the 12-month pre- and post-pandemic periods. We summarized patient demographics and analyzed pertinent histopathologic data. Results: For all GI biopsy sites, the number of intramucosal/invasive malignancies reported during the one-year pre-COVID-19 pandemic (pre-COVID) and post-COVID-19 pandemic national lockdown (post-COVID) observation periods were 146 and 218, respectively. Among these, 32 and 70 malignancies were reported for the first quarter (representing the earliest post-lockdown period), 29 and 53 for the second, 41 and 54 for the third, and 44 and 41 for the fourth quarter. During the first two quarters of the post-COVID observation period, the increase in malignant diagnoses was most profound, showing 119% post-COVID increase compared to the pre-COVID levels. Of the two main primary histologic types of large intestinal carcinomas [adenocarcinoma (ADC) and squamous cell carcinoma (SCC)], the most profound post-COVID increase was noted in SCCs (136% vs. 58% for ADCs). Conclusion: Compared to the pre-pandemic baseline, the COVID-19 pandemic caused a major increase in biopsy diagnoses of GI cancers in our department. The most plausible explanations for this trend include inevitable lockdowns to minimize the spread of SAR-COV2, which affected GI endoscopy procedure schedules/re-schedules as well as patient response and adaptation to emerging post-COVID GI healthcare patterns. The COVID-19 pandemic's long-term impact on the health of GI cancer patients will need to be determined through systematic analyses by multi-disciplinary teams.*

Correspondence to: Domenico Coppola, MD, Florida Digestive Health Specialists, Department of Pathology, 11505 Palmbrush Trail, Suite 120, Lakewood Ranch, FL 34202, U.S.A. Tel: +1 9417574800, Fax: +1 9417574803, e-mail: domenico.coppola@fdhs.com

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The initial surge of the coronavirus disease 2019 (COVID-19) pandemic prompted national recommendations to delay non-urgent endoscopic procedures and people were advised to avoid surgery centers unless requiring emergency procedures (1-3). As result of these measures, many private practices significantly reduced their endoscopies or completely closed their endoscopic centers. This strategy, while important to limit the community spread of SARS-COV-2, led to significant decreases in endoscopic procedures in the United States and across the globe. As we are experiencing the numerous ways this deadly virus has impacted the delivery of healthcare services, one of the most profound negative impacts of this pandemic on healthcare industry includes delays and cancellations in gastrointestinal (GI) endoscopies, as well as inevitable delays in elective surgical procedures during and after lockdowns.

We, at the Florida Digestive Health Specialists (FDHS) Department of Pathology, support a large network of gastroenterologists across the state of Florida and beyond. The large number of endoscopic GI biopsies reported in our department covers the full spectrum of neoplastic and non-neoplastic gastrointestinal diseases, of which a significant proportion include various GI cancers. In order to achieve

Table I. *Number of malignancies reported by the FDHS Pathology department during 12-month pre-COVID and post-COVID observation periods. Overall, during the one-year post-COVID observation period, there was a 49% increase in malignancies. Most of the increase in malignancies was observed in the post-lock-down quarters (119% and 83% during observation periods 1 and 2, respectively).*

Post-COVID observation periods	Sep 2020-Nov 2020	Dec 2020-Feb 2021	March 2021-May 2021	June 2021-Aug 2021	Sep 2020 through Aug 2021
	Observation period 1	Observation period 2	Observation period 3	Observation period 4	Total cases during 12 months (Post-Covid)
Number of malignancies accessioned/reported (% increase compared to baseline)	70 (119%)	53 (83%)	54 (32%)	41 (-7%)	218 (49%)
Number of malignancies accessioned/reported	32	29	41	44	146
Pre-COVID observation periods	Observation period 1	Observation period 2	Observation period 3	Observation period 4	Total cases during 12 months (Pre-Covid)
	Sep 2018-Nov 2018	Dec 2018-Feb 2019	March 2019-June 2019	June 2019-Aug 2019	Sep 2018 through Aug 2019

the best possible clinical outcome for our patients, our clinical colleagues work in multi-disciplinary settings to manage the large patient population with biopsy-proven cancer diagnoses rendered by our department.

Here, we present an analysis of the increased proportion of cancer diagnoses in our busy GI Pathology service after the COVID-19 pandemic related national lockdown period, with the aim of better understanding the impact of COVID-19 pandemic on the detection and diagnosis of GI cancers. We hope that our analysis will provide valuable insights about the broader clinical impact of the COVID-19 pandemic on similar specialty GI Pathology services in the United States and abroad. This work may also be valuable in planning more effective strategies to triage patients during future spikes in the curve, as the pandemic continues its unpredictable course during 2022 and beyond.

Patients and Methods

This is a retrospective cohort study to evaluate the difference in number of cancer diagnoses before and after the COVID-19 pandemic national lockdown period. We decided to compare the number of diagnosed malignancies over 3-monthly observation periods between September 1, 2018, to August 31, 2019 (pre COVID-19 pandemic observation period; pre-COVID) to those diagnosed over 3-monthly observation periods between September 1, 2020, to August 31, 2021 (post COVID-19 pandemic national lockdown observation period; post-COVID). Electronic surgical pathology records at the Department of Pathology, FDHS, were searched to collect diagnostic data on all patients whose endoscopic biopsies (esophagus, stomach, colon, rectum, and anus) were reported to have invasive or intramucosal carcinoma. Each observation period was divided into four quarterly (3-months) observation periods.

The total numbers of cancer diagnoses (primary and metastatic) from all of the above GI biopsy sites were compared for each quarter during the 12-month pre- and post-COVID observational periods. Cases showing low-grade dysplasia, high-grade dysplasia, adenoma, or Barrett's esophagus without unequivocal diagnosis of intramucosal and/or invasive carcinoma were excluded from this analysis.

Results

The number of GI biopsies accessioned by our specialty GI Pathology service during each quarter for the respective observation periods is summarized in Table I. Comparative analysis of post-COVID trends in malignant diagnoses, as compared to the pre-COVID baseline trend, is shown in Figure 1. Histologic types of malignancies reported during pre-COVID and post-COVID observational periods are listed in Table II.

Collectively, for all GI biopsy sites above, the number of intramucosal and/or invasive malignancies (adenocarcinoma, squamous cell carcinoma, carcinoma, malignant neoplasm, non-Hodgkin's lymphoma) during the pre-COVID and post-COVID observation periods were 146 and 218 respectively, representing a 49% post- COVID-19 increase compared to the pre-COVID baseline (Table I).

Compared to the Pre-COVID-19 baseline trend, cancer diagnoses peaked during early post-COVID-19 national lockdown months. Comparing the pre- and post-COVID numbers of malignant diagnoses made on GI biopsies from all sites, the total number of malignancies reported were 32 and 70 for the first quarter (representing the earliest post-lockdown period), 29 and 53 for the second quarter, 41 and 54 for the third and 44 and 41 for the fourth quarter, respectively (Figure 1). Clearly, during the first and second quarters of the post-COVID observation period, the increase in malignant diagnoses was most profound, showing 119% (70 biopsies from a baseline of 32) and 83% (53 biopsies from a baseline

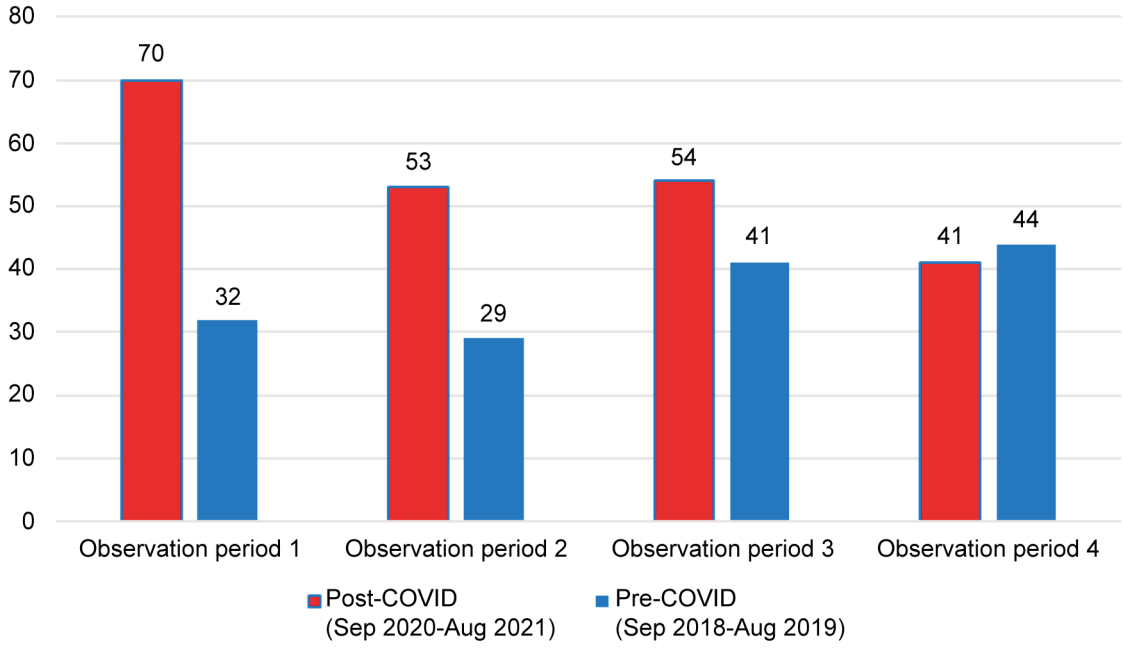

Figure 1. *Comparison of the numbers of gastrointestinal cancer diagnoses made by the FDHS Pathology Department over four 3-monthly pre-COVID [September 2018 through August 2019 (blue bars)] and four 3-monthly post-COVID [September 2020 through August 2021(red bars)] observation periods. As compared to pre-COVID numbers, the relative increase in the numbers of GI cancer diagnoses was most pronounced during first six months of the post-COVID observation periods.*

Table II. *Histologic types of malignancies reported by the FDHS Pathology department during pre-COVID and post-COVID observation periods.*

Observation period	Primary ADC/CA	SCC	IMC	NET	MN	Met ADC/CA	MM	NHL	ADC-SCC	Total cases
Pre-COVID	115	11	13	4	1	2	0	0	0	146
Post-COVID	173	26	11	1	2	2	1	1	1	218

ADC/CA: Colorectal adenocarcinoma/carcinoma; SCC: squamous cell carcinoma; IMC: intramucosal carcinoma; NET: neuroendocrine tumor; MN: malignant neoplasm; MM: malignant melanoma; Met ADC/CA: metastatic colorectal adenocarcinoma/carcinoma; NHL: non-Hodgkin's lymphoma; ADC-SCC: mixed adenosquamous carcinoma.

of 29) post-COVID increases in GI malignancies as compared to the baseline levels during the first and second quarters of pre-COVID observation, respectively (Table I). While still notably higher during the third quarter (54 biopsies compared to the pre COVID baseline of 41), the number of malignant diagnoses rendered during the fourth quarter of post-COVID observation period trended closer to the number of malignant diagnoses during the fourth quarter of the pre-COVID observation period (41 and 44 cases, respectively) (Figure 1).

Compared to the Pre-COVID-19 baseline trend, the most significant increase was noted in squamous cell carcinomas. Overall, during the pre-pandemic year, our department accessioned/reported 146 malignancies while we reported 218 malignancies on GI endoscopic biopsies during the post-pandemic year. The relative numbers of each histological type of malignancy reported are summarized in Table II. Of the two main primary histological types of large intestinal/anal carcinomas (adenocarcinoma and squamous cell carcinoma), the most profound post-COVID increase (136%) was noted in invasive squamous cell carcinomas (SCCs), as compared to a 50% increase in the number of large intestinal adenocarcinomas (ADCs) (Table III).

Discussion

The COVID-19 pandemic has permanently changed our lives in many ways. This includes delivery of healthcare services in various sub-specialties, including diagnosis and management of patients with gastrointestinal disease. The pandemic quickly

Table III. *Frequency of biopsy diagnosis of primary colorectal adenocarcinoma (ADC) and squamous cell carcinoma (SCC) during one-year long pre-COVID and post-COVID observation periods.*

Observation period	Primary ADC	Primary SCC	Total
Pre-COVID	115	11	126
Post-COVID (% increase)	173 (50%)	26 (136%)	199 (58%)

became one of most serious public health emergencies of the modern age. The rapid spread of the COVID-19 and its associated high morbidity and mortality led to sudden lock downs, forcing the elderly and other high-risk populations into isolation while also disrupting many other aspects of the healthcare system. Elective health care services including diagnostics, therapeutics, and elective surgical services were put on hold, leading to delays seriously affecting cancer and non-cancer related services (1).

We have carried out a systematic analysis of our departmental surgical pathology records and found a substantial increase in the number of invasive and intramucosal GI malignancies in our busy GI Pathology service. The trends that we have seen in the frequency of pre- and post-COVID numbers of GI malignancies appear to coincide with the periods of post-COVID national lockdowns. Our data are very informative regarding the negative impact of the COVID-19 pandemic on endoscopic detection of GI cancers during the lockdown and early post-lockdown periods. With the resumption of GI endoscopies in the latter half of the year 2020, the number of invasive cancers diagnosed by our specialty GI Pathology service increased to record levels, remained significantly higher compared to the pre-pandemic baseline numbers in 2018 and 2019, and then gradually came down closer to the baseline over approximately the next six months. Real-life histopathological data like ours will be important to determine the overall clinical impact of the pandemic on GI cancer patient management and follow-up, including systematic assessment of the negative impact of the pandemic on patient outcomes and quality of life measures. At this point, it is difficult to predict the long-term impact of delayed GI cancer diagnoses and follow-up due to pandemic driven lockdowns, although there are increasing concerns expressed by some groups that there may be significant negative impact on long-term patient survival and recurrence rates (2).

In a retrospective analysis of endoscopy procedure data from the GI Quality Improvement Consortium (GIQuIC) registry, the volume of colonoscopies and esophagogastroduodenoscopies (EGD) during the pandemic (March-September 2020) were compared to those before the pandemic (January 2019-February 2020) (3). This study found that across 451 sites, the average monthly volume of colonoscopies and EGDs decreased by 38.5% and 33.4%, respectively, during the pandemic.

A number of investigator groups have evaluated the overall impact of the COVID-19 pandemic on delays in cancer diagnoses and interruptions in specialty care of cancer patients (4-7). In a retrospective analysis at a tertiary academic institution in the U.S., it was shown that 480 non-urgent endoscopic procedures were delayed at the peak of the COVID-19 pandemic (4). Among those, the most delayed endoscopic procedures were colonoscopies for colorectal cancer screening, EGDs for upper GI symptoms, and combined colonoscopy and EGD for suspected bleeding (4). Although 46% of patients with delayed cases ultimately completed an endoscopic procedure, 12 colorectal, pancreatic, and stomach cancers were diagnosed in those patients, highlighting the short-term impact of pandemic-related procedural delays (4). In another analysis, patients with metastatic colorectal cancer diagnosed after the lockdown had a much higher tumor burden compared to those diagnosed prior to the lockdown (5). Median survival was also lower for patients with greater tumor burden compared to those with lower tumor burden (5). These findings suggest that colorectal cancer (CRC) is a major area for intervention to minimize COVID-19-associated diagnostic delays (5). In our analysis, CRC was the malignancy with the highest post-COVID increase in biopsy diagnosis in our department, while other sites were much less frequently involved.

De Vincentiis *et al*. (6) reported that the number of cancer diagnoses in Italy decreased by 39% in the first 6 months of 2020 compared to the mean numbers for 2018 and 2019. The highest decreases in cancer diagnoses were for prostate (75%), bladder (66%) and CRC (62%).

In a national population-based modelling study, Maringe *et al*. (8) used linked English National Health Service (NHS) cancer registration and hospital administrative datasets to estimate that across four major tumor types (breast, colorectal, lung, and esophageal), 3,291 to 3,621 avoidable deaths and an additional 59,204 to 63,229 years of life lost (YLLs) will be attributable to delays in cancer diagnosis alone as a result of the COVID-19 lockdown in the UK. The increase in deaths due to cancer up to 5 years after diagnosis ranged from 4.8% for lung cancer to 16.6% for colorectal cancer (8). These additional deaths are projected to occur as a consequence of the COVID-19 pandemic national lockdown, which has reduced the number of people seeking health care as well as access to and availability of diagnostic services. The authors of this study concluded that urgent policy interventions are necessary to mitigate the indirect effects of the COVID-19 pandemic on patients with cancer (8). They propose interventions such as increases in routine diagnostic capacity, through which up to 40% of patients with cancer are diagnosed, the accurate explanation of the risk of severe illness from COVID-19 in public health messaging, and the

provision of evidence-based information for clinicians to adequately manage the risks and benefits of procedures (8).

Ricciardiello *et al*. (2020) (7) used a meta-analytic approach to analyze time delays to colonoscopy access and estimated the effect on mortality due to the consequent up-stage migration of patients over time by using real-life data from the Italian screened population. This analysis revealed that colon cancer screening delays longer than 4-6 months would significantly increase advanced CRC cases, and also mortality, if lasting longer than 12 months (7). These authors highlight that given the possibility of future COVID-19 or other pandemics, it is imperative to avoid breaking the workflow of colorectal cancer screening beyond 12 months (7). They also recommend alternative strategies for the possibility of future lockdowns and social distancing, the rethinking of test distribution and analysis methods, and the possibility of managing screening-only, SARS-CoV-2–free, dedicated facilities.

In the UK, Sud *et al*. (2020) (9) found that even a modest delay of 3 to 6 months in surgery for cancer may mitigate 19% to 43% of the life-years gained by hospitalization. Lai *et al*. (2020) (10) estimated that approximately 18,000 excess cancer deaths over the next 12 months may be attributed to the COVID-19 crisis. In a population-based analysis, Lui *et al*. (2020) (11) found that while the volume of endoscopies in Hong Kong decreased by more than 50%, the number of patients diagnosed with gastric and colorectal cancer went down by 49.1% and 38.1%, respectively. The authors concluded that the COVID-19 outbreak had resulted in a decrease of available endoscopy services in Hong Kong, with consequent significant delay in cancer diagnosis and in higher cancer stage. They suggested to resume nonemergency endoscopy services as early as possible to balance the risks of delayed cancer diagnosis and the personal safety of patients and staff (11). In a systematic analysis of 62 studies, 38 different categories of delays and disruptions in cancer care were found with impact on treatment, diagnosis, or general health service, including reduction in routine cancer services, cancer surgeries, delay in radiotherapy and delay or cancellation of outpatient visits (12). In another recent study (13), patients with a COVID-19-induced treatment delay had more aggressive cancer behavior, for which rebound medical visits were found to be significant factor, but the individual patient tumors did not seem to progress during the delay.

Going forward, efforts should be focused on following up with patients whose endoscopic procedures were delayed due to COVID-19, helping prevent delayed or missed diagnoses and reduce the progression of GI diseases, especially of GI cancers (4). Furthermore, for all those patients whose procedures had to be delayed, it is essential that their endoscopic procedures are closely tracked and rescheduled once local COVID-19 regulations allow (4).

Various approaches are being proposed to enable healthcare delivery systems to identify medical procedures affected by the COVID-19 pandemic and evaluate the effect of delay, enabling them to communicate effectively with patients and prioritize rescheduling to minimize adverse patient outcomes (4, 14-16). Among these, tailored efforts including multipronged approaches may help reduce the potential public health impact of delayed endoscopic procedures for GI diseases (16). Other potential approaches to minimize the negative impact of COVID-19 pandemic delays in GI cancer detection include triage of patients by family physicians according to standard guidelines (17). In cases of excessive delays in colonoscopy, CT colonography or double-contrast barium enema can be used; there should also be an assessment of tumor grade and pre-operative evaluation of predictive markers like immunohistochemistry for mismatch repair proteins and mutation analysis for KRAS, NRAS, BRAF and PIK3CA, based on their known prognostic value (18).

In addition to rescheduling delayed endoscopic procedures, healthcare institutions can further address these delays through an increase in noninvasive colorectal cancer screening tests, an increase gastroenterology clinical and administrative staffing, as well as by providing evening or weekend endoscopy sessions (4), and by offering improved patient communication and education programs regarding awareness about cancer management during the ongoing pandemic. These proactive approaches are necessary not only to help minimize endoscopy wait times for patients at risk of worsening GI disease but are also critical in averting other public health crises from preventable diseases and exacerbating racial, ethnic, and socioeconomic disparities in GI diseases (15).

Finally, another interesting finding in our study is the remarkably higher frequency in the biopsy diagnosis of anal SCC during post-COVID observation periods, as compared to the other histologic types of GI cancers. Further investigation is needed to evaluate if this finding may be related to the cancers different mean volume doubling times (the SCC mean volume doubling time is 84 days as compared, for example, to the colon cancer mean volume doubling time of 632 days) (19).

In summary, based on systematic analysis of our departmental surgical pathology records, we found a substantial increase in the numbers of cancer diagnoses from the various GI biopsy sites during the earlier phase of the 12-month post-pandemic observation period compared to our baseline departmental trends. Of the two main histological types of large intestinal carcinomas (ADC/SCC), the most substantial post-COVID increase was found in the number of SCCs (136%, compared to 58% for ADCs). The most plausible explanations for the observed trends include inevitable lockdowns to minimize the spread of SAR-COV2, GI endoscopy procedure delays during lockdowns, and patient response and adaptation to emerging post-COVID GI healthcare patterns. The long-term impact of COVID-19 pandemic on the health of GI cancer patients will need to be

closely evaluated by multi-disciplinary efforts by gastroenterology and GI Pathology teams across the globe. In this regard, several specialty practice guidelines (20-22) have been put forward with reference to the most effective management of endoscopic procedures as part of the clinical practice of gastroenterology, including the most optimal use of personal protective equipment, in order to minimize the negative impact of the future waves of COVID-19 pandemic.

Although we designed and conducted the analyses of histopathologic diagnostic data sets with due diligence both during pre- and post-COVID observation periods, a relative limitation of this study is its observational nature, which would not allow determination of statistical significance of the findings presented. It is, however, very well-known in medical literature that in many instances of well-conducted analyses (and studies), clinical, pathologic, biologic, and statistical significance are not necessarily the same. It is, therefore, important for the healthcare community that the findings of each study be interpreted in the appropriate clinico-patho-biologic context and to utilize the appropriate statistical testing/significance as needed, to avoid overinterpretation of the importance of various new data sets/findings.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Domenico Coppola conceived the study and designed the overall analytical approach. Brooke Hough collected and summarized data from department electronic surgical pathology records. Caterina Baffa revised the final manuscript. Aejaz Nasir did extensive literature review, contributed to the analytical approach, analyzed the surgical pathology diagnostic data, prepared tables and figures, prepared/updated bibliography in EndNote and wrote the original and revised drafts. Arun Khazanchi provided expert clinical contributions. All Authors reviewed the original and revised drafts, provided input/expert views and approved the final and revised versions of the manuscript.

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