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Authors

Kolb, Jennifer
Davis, Christian
Hochheimer, Camille
et al.

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Time to Therapy May Not Impact Diagnosis Upstaging in Patients Referred for Management of Luminal Gastrointestinal Neoplasia

Jennifer M Kolb, MD MS[1,2], **Christian Davis, MD**[3], **Camille J Hochheimer, PhD**[4], **Sarah Beilke, MD**[3], **Irvin Ma, MD**[3], **Charlie Fox, MD**[5], **Jazmyne Gallegos, BA**[6], **Jack O'Hara, BA**[6], **Wyatt Tarter, MS**[4], **Sachin Wani, MD**[6]

[1]Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA

[2]Division of Gastroenterology, Hepatology and Parenteral Nutrition, VA Greater Los Angeles Healthcare System, Los Angeles, CA

[3]Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

[4]Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado-Denver Anschutz Medical Campus, Aurora, CO

[5]Division of Gastroenterology, Hepatology, & Nutrition, University of Utah

[6]Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Abstract

Background—The COVID-19 pandemic dramatically impacted endoscopy practice. Recommendations were to postpone elective cases, including procedures for removal of luminal neoplasia. This provided a natural experiment to evaluate outcomes related to these decisions and the impact of time to procedure on change in histology.

Aims—The primary aim is to examine time to endoscopy for therapy of colorectal polyps and BE with dysplasia and oncologic outcomes during the COVID-19 pandemic.

Methods—This was a retrospective cohort study of individuals referred for endoscopic therapy of advanced colorectal polyps and dysplastic Barrett's esophagus between July 2019-January 2022. Multivariable logistic regression was used to evaluate whether time to therapeutic exam was associated with a change in histology. Time from index to therapeutic exam before versus after the start of the pandemic (March 20, 2020) was compared using a Cox regression.

Corresponding author: Sachin Wani, MD, Professor of Medicine, Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Center, Mail Stop F735, 1635 Aurora Court, Rm 2.03, Aurora, CO 80045, USA, Fax: 720-848-2749, sachin.wani@cuanschutz.edu.

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Results—There were 310 patients (56% male, mean age 65) who were referred for colon polyps (n=256) and BE-related neoplasia (n=54). The median time to therapeutic exam was 78 days (range 4–718). Time to therapy was shorter for colon polyp cases completed after versus before the pandemic (HR: 1.49, 95%CI 1.14–1.96). The pandemic was not associated with a difference in time to exam for BE. Change in histology from index to therapeutic exam was noted in 51 cases (16.5%) and was mostly upstaging (70.6%). There was no association between time to therapeutic exam, sex, or timing related to the pandemic on the probability of being upstaged for colon polyps or BE.

Conclusions—Fewer than 1 in 5 cases had a change in histology from index to therapeutic exam and there was no delay related to the COVID-19 pandemic. These findings suggest that procedures for removal of advanced colon polyps or dysplastic BE can potentially be postponed with minimal impact, helping guide triaging decisions going forward.

Keywords

Colon cancer; Barrett's esophagus; colon polyp; COVID-19; pandemic

Introduction

The COVID-19 pandemic dramatically impacted medical practice in the United States and had a major effect on gastroenterology with significant reductions in procedural capacity.[1] In the early stages of the pandemic, endoscopy was designated as an aerosol generating procedure with accompanying multilevel recommendations to postpone all elective non urgent cases in March 2020.[2] This unprecedented situation led professional GI societies to issue guidelines on what constitutes elective versus urgent versus emergent procedures. Although some were obvious (cholangitis should not be delayed >24 hours, chronic abdominal pain can be deferred), other clinical scenarios were more nuanced. One such clinical challenge was how to triage procedures intended for the evaluation and treatment of luminal GI neoplasia.

Endoscopic management of esophageal and colorectal neoplasia posed a unique challenge given the paucity of evidence to inform safety and outcomes of postponing these procedures. A consensus statement issued at the time using the Delphi method suggested to "defer and reassess timing in >8 weeks" for treatment of Barrett's esophagus (BE) with dysplasia or large or histologically advanced colon polyps.[3] This guidance was helpful in the initial phase but as the pandemic dragged on longer than expected it was clear that stronger data beyond expert opinion was needed. There was also considerable disagreement among endoscopists on priority and timing for endoscopic procedures.[4] It is unknown if the time between index examination and completion of the therapeutic procedure to remove premalignant or malignant lesions affects the final histology. This is a common clinical scenario and question that is universally relevant even outside the pandemic. The aims of this study are to evaluate the association between time to endoscopy for therapy of colorectal polyps and dysplastic BE with oncologic outcomes, with a focus on the impact of the COVID-19 pandemic on procedural delay. The information gleaned from this analysis will inform evidence-based recommendations to guide clinical decision making and triaging of procedures.

Methods

Cohort Identification and Inclusion Criteria

This is a retrospective cohort study of all individuals referred for an endoscopy or colonoscopy between July 2019 – January 2022 for therapy of either 1) advanced colorectal lesions:[5] colorectal tubular adenoma ≥2cm *or* with villous histology *or* at least high-grade dysplasia *or* a sessile serrated polyp with any degree of cytologic dysplasia and 2) BE with any dysplasia. The rationale for excluding nonadvanced colon polyps and nondysplastic BE is that natural history data indicate these may take years to progress, and these are seldom referred to a therapeutic endoscopist.[6, 7] Patients were identified through a list of all referrals to the interventional endoscopy section at a tertiary care center (University of Colorado Hospital). Duplicate patients were removed from the list and referrals were filtered by procedure type (upper endoscopy, colonoscopy, and endoscopic ultrasound) then by diagnosis to remove hepatobiliary and pancreatic cases. Manual chart review confirmed eligibility and patients with a pathology report demonstrating the above-mentioned histology were included. Patients with therapeutic exams prior to 2019, those missing the primary outcome, and those who did not receive a therapeutic exam were excluded. For BE cases where expert pathology review was performed by the center receiving the referral, this new interpretation constituted the histology (e.g., if referral for high grade was then downgraded to low grade, this was classified as index histology of low-grade dysplasia). Reclassifying index histology according to local pathology read was implemented to reduce misclassification bias. This study was approved by the Institutional Review Board.

Data Collection and Variables

Information collected from the index examination and therapeutic examination included date of procedure, intervention performed, histology, and recommendations. Additional objective data regarding clinical care during this time were collected including whether the patient was seen in clinic and whether there was central pathology review. The following histology hierarchy was used to determine whether a change in diagnosis was upstaged or downstaged: 1) Colon polyps: tubular adenoma < villous/tubulovillous adenoma < high grade dysplasia, intramucosal carcinoma < invasive carcinoma and 2) Barrett's esophagus: non dysplastic < low grade dysplasia (LGD) < high grade dysplasia (HGD) < intramucosal carcinoma (IMC) < invasive carcinoma. A *clinically meaningful* upstage in diagnosis was defined as a change to intramucosal or invasive carcinoma since this would presumably result in a change in patient management or prognosis. For BE related neoplasia, the index histology accounted for any modifications that were made during expert pathology review. Time to therapeutic endoscopy was measured as a continuous variable from the index examination to the therapeutic examination for lesion removal.

Outcomes

The primary outcome was change in histology of colorectal polyps and dysplastic BE and its association with time to therapeutic endoscopy. Secondary outcomes were 1) clinically significant change in histology, 2) time to therapy measured in relation to the COVID-19 pandemic, and 3) polyp characteristics associated with a change in diagnosis.

Statistical Analysis

We calculated the difference in days between the index exam (accounting for secondary pathology review for BE) and the therapeutic exam and created a binary outcome of whether the change in histology was an upstage. Therapeutic exams taking place before March 20, 2020 were considered as pre-COVID and those taking place after that date were considered post-COVID. Relevant patient characteristics were summarized overall and by lesion type. Then, a Cox proportional hazards regression was used to compare the time to therapeutic exam in patients with therapeutic exam dates pre vs. post the onset of the COVID-19 pandemic within each lesion type. We evaluated whether days to therapeutic exam and lesion type were associated with the outcome of upstaged diagnosis using multivariable logistic regression within each lesion type, with our primary analysis being that within colon polyps and our secondary analysis being that within BE. These models also included patient characteristics associated with the outcome with a p-value less than 0.2 in bivariable comparisons as well as an indicator for whether the therapeutic exam took place before or after the onset of the pandemic should the hazard ratio be significant in the Cox regression. Final model results were interpreted at the 5% significance level.

Results

The initial list returned 26,190 referrals which was filtered down as described by procedure type and diagnosis and subsequent chart review to confirm eligibility. A total of 310 patients were included in the study (56.1% male, mean age 64.9) (Table 1). The cohort included 256 colon polyps (80.6%) and 54 dysplastic BE (17.4%). (Figure 1).

Change in histology- upstage or downstage

There was no change in histology from index to therapeutic exam in 210 cases of the overall cohort (80.5%) whereas 36 (13.8%) were upstaged and 15 (5.7%) downstaged. (Figure 2). Of the 207 colon polyps with available index histology, a total of 37 had a change in histology that were mostly upstaged (n=27, 13.0%) with 10 (4.8%) downstaged. When looking at specific polyp characteristics, polyp size was significantly different across groups with larger polyps more likely to be upstaged (Kruskal-Wallis rank sum test p=0.008). (Supplemental Table 1).

There were 54 cases of dysplastic BE referred for evaluation and 38 underwent secondary expert pathology review. This resulted in 5 cases being upstaged and this more advanced diagnosis replaced the baseline histology. After therapeutic examination, 14 cases had a change in histology with 9 upstaged (16.7 %) and 5 downstaged (9.3%).

Change in histology- clinically significant upstage

A total of 29 cancers were found in the cohort. Of these, IMC or invasive carcinoma was present in 12 at the index exam, and 2 changed from invasive at index biopsy to intramucosal carcinoma at resection. The remaining cancers were classified as having a clinically significant upstage to intramucosal carcinoma or invasive carcinoma: 10 colon polyps (3.9% of all polyps) and 6 Barrett's cases (11.1% of BE) (Figure 1).

Time to therapeutic exam and delays

The median time to therapeutic exam was 78 days (range 4–718) (Table 1). For colon polyp cases, the pandemic impacted the time from index to therapeutic exam. This time interval was significantly shorter for cases completed after the onset of the pandemic compared to prior (HR: 1.49, 95% CI 1.14–1.96, p= 0.004) (Figure 3). There was no significant difference in time from index to therapeutic exam for BE (HR: 1.38, 95% CI 0.76–2.50, p=0.3) (Figure 3)

Based on the survival analysis and bivariable results, sex and COVID timing were included in the multivariable model for colon polyps in addition to days to exam. There was no association between time to therapeutic exam and upstaged diagnosis (OR 1, p= 0.77). The model for BE was the same except COVID timing was not included. Days to exam was not associated with a difference in the probability of an upstaged diagnosis (OR = 1, p=0.92). Using these same models to assess the association with clinically meaningful upstage in histology for colon polyps and BE, no significant predictors were detected.

Discussion

In this cohort of 310 cases of luminal neoplasia, only 51 cases (14.4% of colon polyps and 25.9% BE related neoplasia) had a change in histology, with most being upstaged. Only 13% of 256 colon polyps were upstaged after resection and very few (3.9%) had a final diagnosis of IMC/cancer. This study also evaluated time from index endoscopy to therapeutic resection and found that longer time to therapy and the COVID-19 pandemic did not impact histology outcomes. These results suggest that removal of advanced colorectal polyps and dysplastic Barrett's esophagus can potentially be postponed with minimal impact. These valuable insights can inform future triaging decisions and prioritization as needed.

The change in practice patterns surrounding the pandemic provided a natural experiment to study the clinical outcomes related to these triage decisions. A survey study of 11 centers across 4 continents reported that 55% of procedures for endoscopic resection of neoplastic lesions were deferred due to COVID-19, and certainly in the US this was recommended.[3, 8] The impact of these decisions was largely unknown at the time. A retrospective study from the UK (n=111) compared procedural timing of endoscopic resection of colon polyps 1 year prior to the pandemic (March 2020) and 6 months post and found longer delays related to the pandemic (median 16 vs 8 weeks) with possible negative impact.[9] Our US based study did not find significant procedural delays which may be a result of measuring a longer post-pandemic period (March 20, 2020 to January 2022) and reflect improved triaging practices as the pandemic progressed.

Our findings suggest that referrals for removal of advanced colon polyps are not time sensitive and can be postponed if needed without consequence. Among a large cohort of 256 advanced colorectal polyps, only 10 (3.9%) had a clinically significant upstage to IMC/cancer. Natural history data indicate that colon polyps take years to progress, so this is not surprising. These data are supported by a multicenter colon endoscopic mucosal resection cohort study in the UK (n=268) that showed similar rates of malignancy and outcomes despite pandemic related procedural delays and longer time to resection.[10]

Importantly, our study adds support that these therapeutic exams can be safely delayed without progression. The more likely explanation for histology change after polyp removal is an “error” or misclassification on the part of the initial endoscopist or pathologist.[11] This concept underscores the questionable clinical utility of a pre-resection biopsy, which are subject to sampling error and may negatively impact the subsequent procedure through fibrosis, longer procedure time, and lower en-bloc resection rates.[12, 13] Polyps should be examined closely using non-invasive technologies such as virtual chromoendoscopy paired with standardized classification systems to describe polyp morphology (Paris classification) and surface pattern, and only biopsied if there is suspicion for deep submucosal invasion or cancer.[14–16] Triaging based on polyp characteristics would be more meaningful than according to biopsy results which may be flawed. It is notable that in our study, more than half the cases referred did not include descriptions of the polyp using the Paris classification, highlighting the need for ongoing education in high-quality practices among endoscopists.

This study provides novel data on the impact of procedural timing for BE-related neoplasia. Early in the pandemic, the recommendation was to postpone radiofrequency ablation for BE with LGD/HGD and postpone EMR for nodular HGD (confirmed by expert pathologist).[3] These recommendations may have led to a decrease in the diagnosis of BE, BE related dysplasia requiring RFA, and EAC.[17–19] Additionally, a retrospective study in Northern Ireland found the diagnosis of BE declined by nearly 60% and EAC declined by 27% during the pandemic.[20] Our study population reflects this trend with 38 cases of BE identified before the onset of the pandemic and 16 cases during the pandemic. Importantly, our results showed that time to endoscopic therapy had no meaningful impact on histology for BE related neoplasia. It is also notable that 25.9% of referred BE lesions had an upstage in diagnosis either at the initial expert pathology review (n=5) or after endoscopy (n=9). Furthermore, 6 cases (11.1%) had a clinically significant upstage. There are several possible explanations for this that are well described, including 1) inadequate initial exam with failure to detect visible lesions, 2) lack of adherence to recommended sampling strategies to use Seattle protocol along with targeted biopsies,[21] and 3) pathologist discordance for dysplasia diagnosis.

Contrary to our hypothesis, time to therapeutic exam was significantly shorter for colon polyp cases that took place after compared to prior to the pandemic. These results were surprising considering other data showing COVID related delays in clinical encounters and cancer care with subsequent negative outcomes.[22] We suspect the shorter time to endoscopy may be related to institutional policy and reflects our triage protocol where high risk lesions or advanced resection cases were prioritized, and more routine cases were delayed. Given the significant ongoing impact on healthcare related to personnel staffing shortages, patient related unemployment and insurance barriers, changes to individual overall health and priority of gastrointestinal procedures relative to other medical issues, these results provide guidance for timing of resection procedures even beyond the pandemic. Due to small sample sizes after the onset of COVID, we were unable to analyze within distinct phases of the pandemic.[19]

Our study is inherently limited by misclassification bias and measurement error. For example, a colon polyp may have been designated tubular adenoma at the time of referral

and found to be tubular adenoma with HGD which may not signify progression but rather misclassification at the index examination. However, this is consistent with real world endoscopy practice and known limitations of sampling bias. To mitigate this, in cases of BE related neoplasia we considered the central pathology review as the index exam histology, consistent with guidelines. As this was a retrospective study some data was missing, including information on Paris classification (126 polyps without this data) and polyp size (25), as well as the *number* of biopsies on the index exam; however, these circumstances are reflective of real word experience. In the event of another global pandemic requiring postponing procedures, a prospective study could investigate the correlation between an initial optical diagnosis and subsequent histologic diagnosis. This study was underpowered for the analysis of *clinically relevant* upstaging to IMC/cancer, which would be an interesting primary outcome for a multicenter study. Additionally, this study uses a single-center cohort, so it is possible that the impacts of the COVID-19 pandemic were more pronounced in other regions of the world which could have led to more procedural delays than were represented in this cohort. Finally, since time to exam was not associated with change in histology, this study does not provide a threshold beyond which you will see a negative impact on outcomes.

In conclusion, time to therapeutic exam and the COVID-19 pandemic were not associated with changes in histology for advanced colorectal polyps or BE related neoplasia. These results provide valuable information to assist in triaging procedures and clinical decision-making both for current practice and to inform responses to future pandemics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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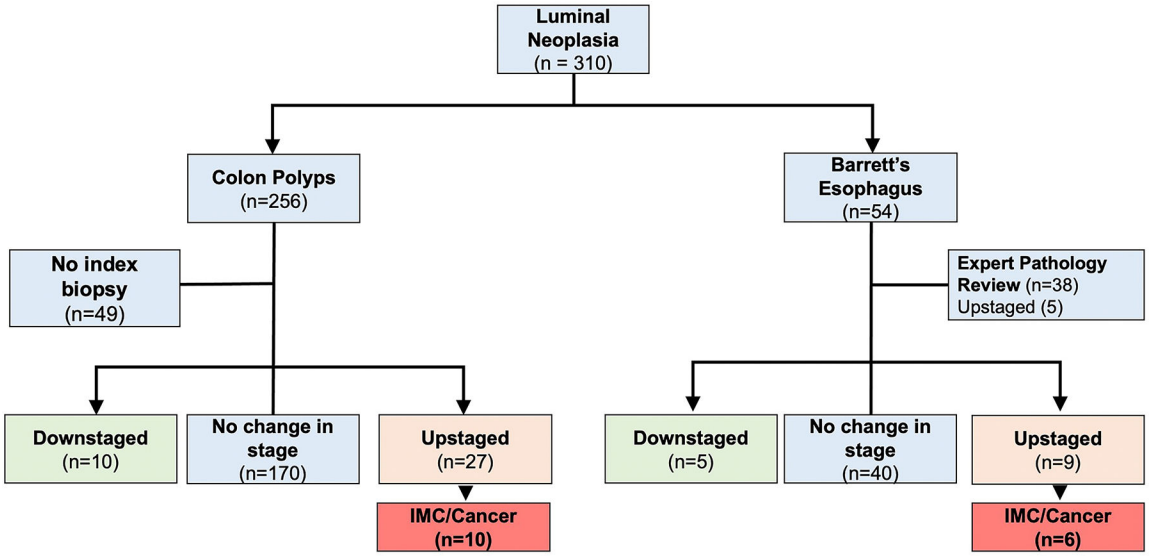

Figure 1:
Flow chart of change in histology and clinically meaningful upstage

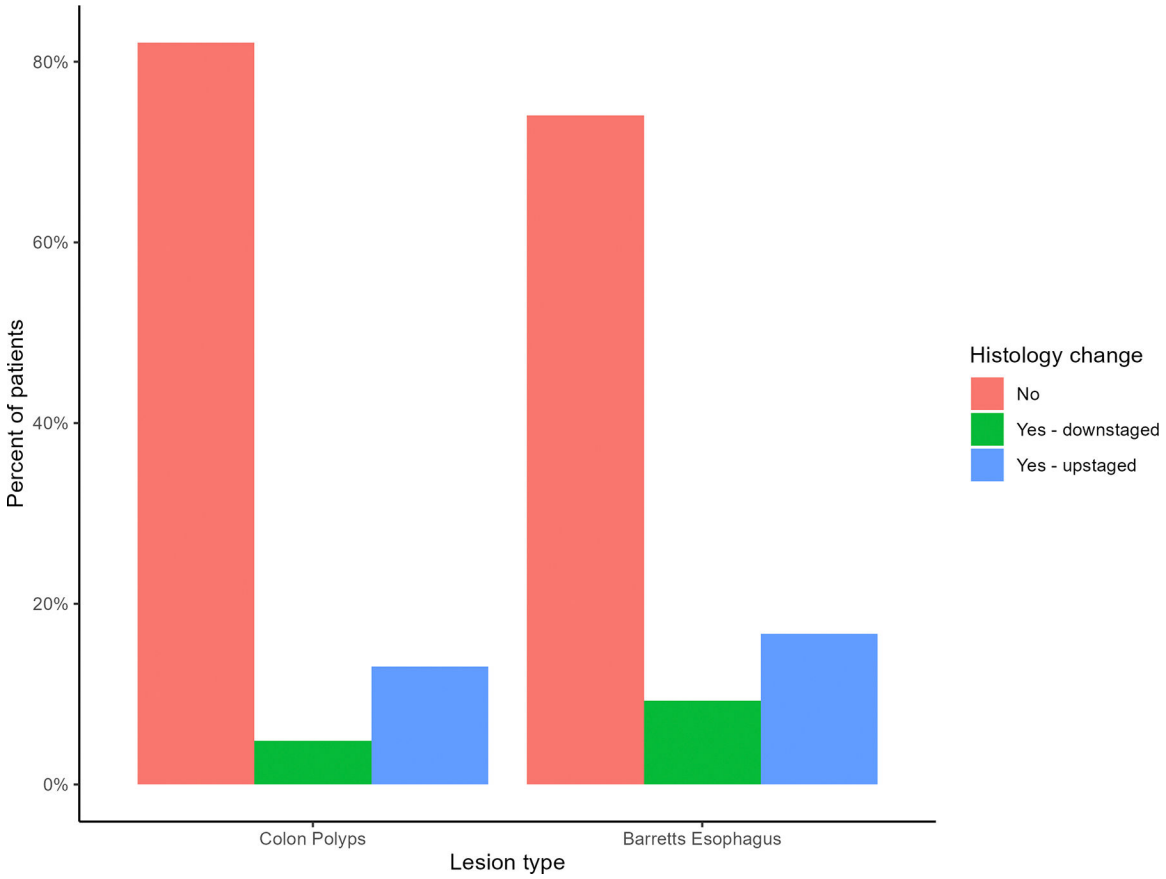

Figure 2:
Histology change by lesion type

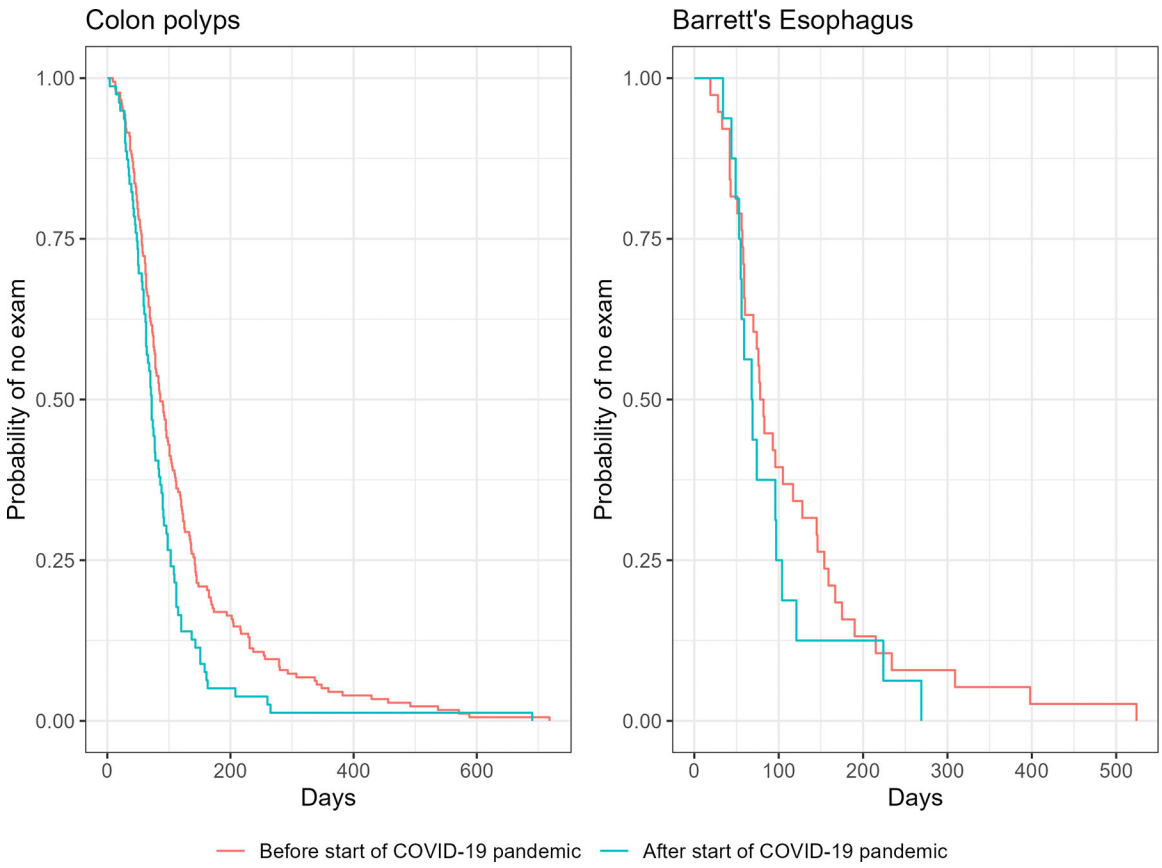

Figure 3.
Time to therapeutic exam before and after the COVID-19 pandemic

Table 1.

Patient characteristics overall and by lesion type

Characteristic, n (%)	Colon Polyp N = 256[1]	Dysplastic Barrett's Esophagus N = 54	Overall N = 320
Sex, Male	127 (49.6%)	47 (87.0%)	174 (56.1%)
Age, mean (SD)	64.3 (10.7)	67.6 (10.6)	64.9 (10.7)
Race			
White	227 (88.7%)	50 (92.6%)	277 (89.4%)
Black	8 (3.1%)	0 (0.0%)	8 (2.6%)
Asian	5 (2.0%)	1 (1.9%)	6 (1.9%)
American Indian or Alaska Native	1 (0.4%)	1 (1.9%)	2 (0.6%)
More than one race/Unknown	15 (5.9%)	2 (3.7%)	17 (5.4%)
Ethnicity, Hispanic or Latino	26 (10.2%)	1 (1.9%)	27 (8.7%)
Family history of GI cancer	51 (19.9%)	8 (14.8%)	59 (19.0%)
Histology change from index to therapeutic exam			
No	170 (82.1%)	40 (74.1%)	210 (80.5%)
Yes – downstaged	10 (4.8%)	5 (9.3%)	15 (5.7%)
Yes - upstaged	27 (13.0%)	9 (16.7%)	36 (13.8%)
Clinically meaningful upstage [2]	10 (33.3%)	6 (66.7%)	16 (41.0%)
Time between index to therapeutic exam, days, median (range)	80 (4–718)	76 (19–524)	78 (4–718)
Timing of procedure			
Before start of COVID-19 pandemic	177 (69.1%)	38 (70.4%)	215 (69.4%)
After start of COVID-19 pandemic	79 (30.9%)	16 (29.6%)	95 (30.6%)
Therapeutic exam delayed	37 (14.8%)	13 (26.0%)	50 (16.7%)

[1] n (%); Mean (SD); Median (Range)

[2] This proportion is calculated out of all upstaged diagnoses