

COVID-19 Disruptions to Endoscopic Surveillance in Lynch Syndrome

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ABSTRACT

Disruptions in cancer screening due to the COVID-19 pandemic may disproportionately affect patients with inherited cancer predisposition syndromes, including Lynch syndrome. Herein, we study the effect of the COVID-19 pandemic on endoscopic surveillance in Lynch syndrome through a prospective study of patients with Lynch syndrome at a tertiary referral center who were scheduled for endoscopic surveillance during the COVID-19 pandemic shutdown between March 16, 2020 and June 4, 2020. Of our cohort of 302 individuals with Lynch syndrome, 34 (11%) had endoscopic procedures scheduled during the COVID-19 pandemic shutdown. Of the 27 patients whose endoscopic surveillance was canceled during this period, 85% rescheduled procedures within 6 months with a median delay of 72 days [interquartile range (IQR), 55–84 days], with identification of an advanced adenoma or gastrointestinal cancer in 13%. Individuals who did not have a rescheduled endoscopic procedure were significantly younger than those with

a rescheduled procedure [age 35 (IQR, 26–43) vs. age 55 (IQR, 43–63), $P = 0.018$]. Male sex was also suggestive of increasing likelihood of not having a rescheduled procedure. Taken together, our study demonstrates that the COVID-19 pandemic shutdown led to delayed endoscopic surveillance in Lynch syndrome, with potentially impactful delays among young patients. These data also emphasize the importance of timely surveillance in Lynch syndrome during this current, as well as potential future, global pandemics.

Prevention Relevance: The COVID-19 pandemic has led to unprecedented disruptions in cancer screening, which may have disproportionate effects on individuals at increased cancer risk, including those with Lynch syndrome. Herein, we show that the COVID-19 pandemic led to significant disruptions in Lynch syndrome surveillance with potentially impactful delays, thus highlighting the importance of ensuring timely surveillance among this high-risk cohort.

Introduction

The COVID-19 pandemic has led to unprecedented disruptions in medical care, including cancer screening. While it will take years to realize the true consequences of these disruptions, the immediate effects are increasingly apparent with an estimated 86% reduction in colonoscopy screenings during the height of the COVID-19 pandemic; with the diagnostic delay following the pandemic resulting in an estimated 16% increase in colorectal cancer-related deaths (1, 2). These disruptions may disproportionately affect individuals at increased

cancer risk, including those with Lynch syndrome, the most common inherited colorectal cancer risk syndrome with an estimated prevalence of 1 in 279 (3). Lynch syndrome confers a significantly increased lifetime risk of colorectal cancer, with accelerated carcinogenesis, emphasizing the importance of frequent endoscopic surveillance in this population (4, 5). Current guidelines recommend that individuals with Lynch syndrome have colonoscopies every 1–2 years, which has been demonstrated to significantly reduce colorectal cancer risk (6, 7). While *MLH1*, *MSH2*, and *EPCAM* carriers are generally recommended to start surveillance at age 20–25, recent guidelines have recommended starting surveillance in *MSH6* and *PMS2* carriers at an older age of 30–35 given the lower colorectal cancer risk associated with pathogenic variants in these genes (6).

Given increased colorectal cancer risk and need for frequent endoscopic surveillance in Lynch syndrome, it is critical that these individuals undergo regular and timely surveillance. However, how COVID-19 pandemic-related disruptions will affect cancer surveillance in Lynch syndrome remains uncertain. Herein, we examine endoscopic surveillance disruptions in individuals with Lynch syndrome caused by the COVID-19 pandemic, the efficiency of rescheduling these important procedures, surveillance findings, and factors associated with decreased likelihood of rescheduling in this high-risk group.

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Materials and Methods

This was a prospective cohort study of individuals with Lynch syndrome followed at our tertiary care center. This study was conducted after approval by the University of Pennsylvania (Philadelphia, PA) Institutional Review Board and was conducted in accordance with the U.S. Common Rule. A waiver of informed consent was granted by the Institutional Review Board. We identified and collected data on those individuals who had an endoscopic procedure canceled, scheduled, or performed during the COVID-19 pandemic shutdown. This shutdown was defined as the time from initial implementation of procedural restrictions on March 16, 2020 through June 4, 2020, which was the beginning of the yellow phase of reopening in our region. Data were subsequently collected through December 4, 2020, 6 months after our region's yellow phase of reopening. At our institution, all individuals with endoscopic procedures canceled during the COVID-19 pandemic shutdown were added to an administrative rescheduling list. Once routine surveillance procedures began to be scheduled again, attempts to contact and reschedule individuals on this list were made by administrative staff via either phone call and/or communication through the electronic medical record. Individuals not rescheduled during the study period were contacted by phone by a single staff member who inquired via similar open-ended questioning as to the reason why the endoscopic procedure was not rescheduled, and offered assistance in rescheduling if desired by the patient. Descriptive statistics were presented as medians and interquartile ranges (IQR) or as percentages. We compared characteristics between those who rescheduled endoscopic procedures and those who did not. Continuous and categorical variables were compared using Wilcoxon rank-sum and Fisher exact tests, respectively.

Logistic regression was used to estimate the odds of rescheduling as a function of variables retained with a $P < 0.05$.

Results

Of the 302 individuals with Lynch Syndrome followed by our center, 34 (11%) had an endoscopic procedure scheduled during the COVID-19 pandemic shutdown between March 16, 2020 and June 4, 2020. Of these 34, 7 (21%) had procedures performed as scheduled whereas 27 (79%) had procedures canceled. Six months after entering the yellow phase of reopening, of those who had canceled procedures, 4 (15%) had not yet rescheduled their procedures whereas 23 (85%) had procedures rescheduled and completed. Of those who completed their rescheduled procedures, the median delay in procedure completion was 72 days (IQR, 55–84; **Table 1**). Three individuals (11%) with canceled procedures were outside of a 2-year surveillance window, which is often considered the upper surveillance interval limit for Lynch syndrome in the United States (6). Conversely, among individuals who completed their rescheduled procedure and were within a 2-year surveillance window, the median time remaining prior to reaching a 2-year surveillance interval was 246 days (IQR, 230–287 days).

Individuals without a rescheduled endoscopic procedure were significantly younger than those with a rescheduled procedure [age 35 (IQR, 26–43) vs. age 55 (IQR, 43–63), $P = 0.018$; **Table 1**]. Of note, there were no individuals in this cohort under age 35 with pathogenic variants in *MSH6* or *PMS2*, and therefore none whose age of surveillance initiation may have been affected by recent guideline changes (6). Apart from age there were no other statistically significant differences between the groups, however male sex was also suggestive of increased likelihood of not having a procedure rescheduled

Table 1. Characteristics of individuals with Lynch syndrome who had endoscopic procedures canceled during the COVID-19 pandemic shutdown.

Variable	Had a rescheduled procedure N = 23	Did not have a rescheduled procedure N = 4	P
Days between canceled and rescheduled procedure, median (IQR)	72 (55–84)	—	—
Outside of 2-year surveillance window	2 (9%)	1 (25%)	0.40
Age, median (IQR)	55 (43–63)	35 (26–43)	0.018^a
Male sex	6 (26%)	3 (75%)	0.093
Race			1.00
Asian	1 (4%)	0 (0%)	
White	22 (96%)	4 (100%)	
Personal history of any cancer	14 (61%)	2 (50%)	1.00
Personal history of colorectal cancer	8 (35%)	1 (25%)	1.00
Pathogenic gene variant			1.00
<i>EPCAM</i>	2 (9%)	0 (0%)	
<i>MLH1</i>	4 (17%)	1 (25%)	
<i>MSH2</i>	9 (39%)	2 (50%)	
<i>MSH6</i>	4 (17%)	0 (0%)	
<i>PMS2</i>	4 (17%)	1 (25%)	

^aStatistically significant at the alpha = 0.05 level.

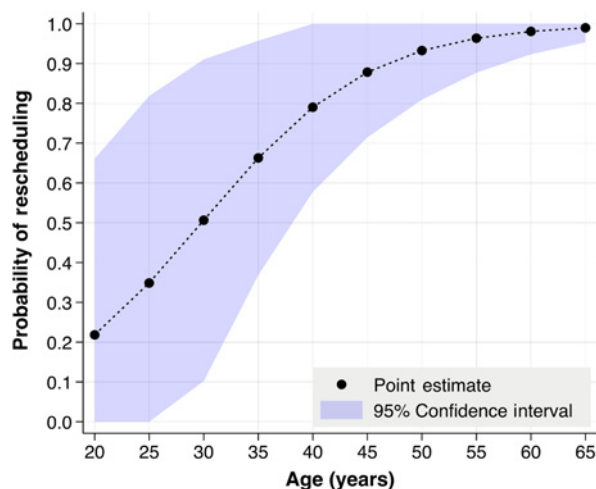


Figure 1. Relationship between age and probability of rescheduling surveillance endoscopic procedures in Lynch syndrome.

(75% of those not rescheduled were male vs. 26% of those rescheduled, $P = 0.093$; **Table 1**). In logistic regression, the odds of rescheduling increased by 92% per 5-year increase in age (95% confidence interval, 1.02–3.59; $P = 0.04$). Predicted probabilities of rescheduling as a function of age are shown in **Fig. 1**. The four individuals who did not have rescheduled endoscopic procedures were contacted by phone, with two of them not feeling comfortable about coming in for a procedure during the pandemic given COVID-19–related concerns, one being unaware that a procedure needed to be rescheduled, and one who was delaying the procedure until completion of recently initiated chemotherapy.

Of the 23 individuals with rescheduled and completed procedures, clinically significant endoscopic findings were

identified in 8 (35%) individuals. Increased age was associated with increased likelihood of identifying a clinically significant endoscopic finding (**Table 2**). The identified clinically significant findings included colonic tubular adenomas/sessile serrated lesions in seven individuals, including two individuals with advanced adenomas, and identification of a previously unknown gastric cancer recurrence. Of those individuals with advanced adenomas, neither had a history of colorectal cancer; however, both had prior advanced adenomas. Specifically, a 14 mm tubular adenoma was identified in a 61-year-old female with a pathogenic variant in *MSH2*, 400 days after her previous surveillance colonoscopy. This individual had a history of 11 prior tubular adenomas including one prior 15 mm tubular adenoma. In addition, a 12 mm tubular adenoma was identified in a 48-year-old male with a pathogenic variant in *MSH2*, whose previous surveillance colonoscopy 185 days prior had identified a 30 mm tubular adenoma with high-grade dysplasia.

Discussion

Lynch syndrome is a high-risk cancer predisposition syndrome, and therefore it is critical to identify the magnitude of the delays in preventive care ensued during the COVID-19 pandemic and identify subgroups in this cohort who may be disproportionately affected. Our study demonstrates that the COVID-19 pandemic shutdown led to delayed endoscopic surveillance in Lynch syndrome, with potentially impactful delays among young patients.

While most individuals with Lynch syndrome in our cohort had endoscopic procedures successfully rescheduled in an expedited manner, 15% of those with canceled procedures had not yet rescheduled 6 months after movement of our region to the yellow phase of reopening. We found younger patients were less likely to have a rescheduled procedure, indicating that this demographic may benefit from dedicated outreach to ensure

Table 2. Characteristics of individuals with rescheduled endoscopic procedures.

Variable	No clinically significant endoscopic findings <i>N</i> = 15	Clinically significant endoscopic findings <i>N</i> = 8	<i>P</i>
Age, median (IQR)	51 (36–59)	62 (57–66)	0.02^a
Male sex	3 (20%)	3 (38%)	0.62
Race			0.35
Asian	0 (0%)	1 (13%)	
White	15 (100%)	7 (88%)	
Personal history of any cancer	9 (60%)	5 (62%)	1.00
Personal history of colorectal cancer	8 (53%)	1 (13%)	1.00
Pathogenic gene variant			0.87
<i>EPCAM</i>	2 (13%)	0 (0%)	
<i>MLH1</i>	3 (20%)	1 (13%)	
<i>MSH2</i>	5 (33%)	4 (50%)	
<i>MSH6</i>	3 (20%)	1 (13%)	
<i>PMS2</i>	2 (13%)	2 (25%)	

^aStatistically significant at the alpha = 0.05 level.

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rescheduling is completed. These data are consistent with other studies looking at uptake of cancer screening, which was lower in young people (8). Our data also demonstrated that men may be less likely to have rescheduled endoscopic surveillance; however, this trend did not meet statistical significance, possibly on the basis of small sample size. Men have been shown to be less likely to undergo genetic testing for cancer susceptibility (9) as well as less likely to undergo cancer screening (10, 11), consistent with the results we observed in this Lynch syndrome cohort. Finally, we explored why individuals may not have a rescheduled procedure, finding that half of individuals without a rescheduled procedure were not comfortable coming in for an invasive procedure during the pandemic. Apart from COVID-19–related concerns, there are many other reasons that may factor into not rescheduling such as not knowing surveillance is due and higher priority medical treatments, both of which we also observed. Other potential reasons that may be related to the ongoing pandemic include financial hardship, loss of insurance, or change in child/family care responsibilities within one's family, which may also affect an individual's ability to undergo a rescheduled surveillance procedure (12).

It is also important to consider whether this delay in rescheduling procedures is of any consequence. Most current guidelines in the United States support up to at least a 2-year interval for colonoscopic surveillance in Lynch syndrome (6), while some studies have proposed that up to a 3-year interval is acceptable (13, 14). We found only 11% of our cohort was outside of the 2-year surveillance interval, whereas the remainder of the cohort had a median of nearly 8 months (246 days) prior to reaching their 2-year surveillance interval, indicating that some of these individuals may have been able to further delay their procedures and would still be within the recommended surveillance interval of current guidelines (6). However, given the rapid progression from polyp to malignancy in Lynch syndrome (5), the potential impacts of even relatively short delays in cancer screening may be of larger consequence in individuals with Lynch syndrome compared with the general population.

We also show that of those who rescheduled and completed their procedures, 35% (8/23) demonstrated neoplastic endoscopic findings, including 13% (3/23) with either an advanced adenoma or gastrointestinal cancer identified. Of note, those individuals with advanced adenomas identified on their delayed surveillance procedures had a history of prior advanced adenomas, indicating they were at increased baseline risk. While the short procedural delay caused by COVID-19 likely did not play a significant role in the development of these neoplastic lesions, these findings underscore that high-risk lesions are identified during Lynch syndrome surveillance, thus reaffirming the importance of timely endoscopic surveillance in this high-risk population, especially in individuals with a history of high-risk endoscopic lesions.

There are important limitations that we acknowledge. This is a single institutional cohort with limited racial diversity, and

therefore the results may not be generalizable to all institutions. The small group size without a rescheduled procedure may have limited our ability to detect other statistical differences. In addition, some individuals who follow with our program undergo endoscopic surveillance procedures outside of our institution, and therefore we are unable to capture their procedural cancellation and rescheduling data. However, despite these limitations, this study provides insight into a high-risk group of patients for whom no data are currently available about pandemic-related surveillance disruptions. Furthermore, given the unique nature of the current pandemic and its disruption to cancer screening, our findings underscoring the importance of ensuring endoscopic follow-up for patients with Lynch syndrome may be applicable across other high-risk groups as well. Future studies in this area will require analysis of larger, multi-institutional Lynch syndrome cohorts to determine other factors that may predict likelihood to reschedule, as well as longitudinal studies to determine the long-term outcomes of these surveillance delays.

With the possibility of additional shutdowns in the future, either related to resurgent COVID-19 or future global pandemics, it is important to recognize and actively target the groups at highest risk of cancer development resulting from postponed surveillance, including Lynch syndrome. In the event of canceled procedures due to COVID-19 or other future events, endoscopy practices should strive to maintain a record of all procedural cancellations, and work efficiently with administrative staff to reschedule these procedures once it is deemed safe to do so. Although this may require extensive administrative effort, it is also important to ensure that individuals who are not successfully rescheduled are provided additional outreach to facilitate this process. Finally, those at the highest risk should be prioritized for rescheduling once rescheduling resumes. Among individuals with Lynch syndrome, endoscopy practices can consider prioritizing patients for surveillance rescheduling who have the highest risk of cancer, including those with a history of an advanced adenoma or prior gastrointestinal cancer, carriers of a pathogenic variant in *MLH1* or *MSH2/EPCAM*, and those overdue for surveillance at baseline; however, all patients with Lynch syndrome should be considered high-risk compared with the average-risk colorectal cancer screening population.

Much of the current literature has focused on persons at highest risk of COVID-19, as well as alternative methods of health care delivery during this pandemic (15, 16). While individuals with Lynch syndrome are not considered “high-risk” for COVID-19, they are a group that requires frequent health care contacts for cancer surveillance, and illustrate the complex and far-reaching effects of the pandemic. Finally, the ongoing nature of the pandemic underscores the delays in care that high-risk patients are incurring and emphasizes the importance of ensuring that delays are minimized. As we continue to monitor COVID-19–related procedure delays worldwide, special attention should be paid to those with Lynch syndrome to ensure that these individuals have their

endoscopic procedures rescheduled and performed in an efficient manner.

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Authors' Contributions

D.B. McKenna: Data curation, writing—original draft, writing—review and editing. **C.M. Dudzik:** Data curation. **S. Kumar:** Formal analysis, methodology, writing—review and editing. **N. Mahmud:** Formal analysis, methodology, writing—review and editing. **B.W. Katona:** Conceptualization, resources, supervision, methodology, writing—original draft, project administration, writing—review and editing.

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