Accepted Manuscript online: 2023-03-06 Article published online: 2023-05-09

Extended delay in endoscopic mucosal resection is not associated with adverse outcomes: Findings from the COVID-19 pandemic

OPEN ACCESS

Authors
Eddie Liu[1], Cassandra McDonald[1], Surim Son[2], Jeffrey Hawel[3], Nadeem Hussain[1], Nitin Khanna[1], Brian Yan[1], Vipul Jairath[1,2,4], Michael Sey[1,4]

Institutions
1 Division of Gastroenterology, London Health Sciences Centre, London, Ontario, Canada
2 Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada
3 Division of General Surgery, London Health Sciences Centre, London, Ontario, Canada
4 Lawson Health Research Institute, London Health Sciences Centre, London, Ontario, Canada

submitted 14.10.2022
accepted after revision 2.3.2023
published online 6.3.2023

Bibliography
Endosc Int Open 2023; 11: E474–E479
DOI 10.1055/a-2048-1433
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Corresponding author
Michael Sey, MD, MPH, FRCPC, London Health Sciences Centre-Victoria Hospital, 800 Commissioners Rd. E., London, Ontario, Canada, N6A 5W9
Fax: +519-667-6820
msey2@uwo.ca

ABSTRACT

Background and study aims The aim of this study was to investigate the impact of delayed endoscopic mucosal resection (EMR) of colorectal polyps on health outcomes.

Patients and methods A bidirectional cohort study was completed. A baseline group consisting of all EMRs performed within a 15-month period before a province-wide, government-mandated cessation of EMR procedures due to the global pandemic was compared to EMRs impacted by the shutdown, defined as the COVID-19-delayed group. The primary outcome was the incidence of malignant polyps. Secondary outcomes included technical success, polyp recurrence at follow-up colonoscopy, advanced polyp histology, probability of meeting endoscopic criteria for adequate resection for malignant polyps, metastatic colorectal cancer, and complications.

Results A total of 268 EMR procedures were included in the study cohort, of which 208 formed the baseline group and 60 were in the COVID-19-delayed group. The median (IQR) patient age was 72 (13.0) and 113 (41.2%) were females. The median (IQR) wait time was 92 days (87.8) in the baseline group and 191 days (127.8) in the COVID-19-delayed group ($P<0.001$). Overall, there were no significant differences in the incidence of malignant polyps, technical success, polyp recurrence on follow-up colonoscopy, advanced polyp histology, adequate endoscopic resection for malignant polyps, metastatic colorectal cancer, or complications between the two groups ($P>0.05$ for all outcomes).

Conclusions A longer wait time for EMR of colorectal polyps, increasing from a median of 92 to 191 days, was not associated with worse outcomes.

Introduction

Colorectal cancer is the fourth leading cause of cancer in the United Kingdom (UK), responsible for over 42,000 new diagnosis each year [1]. The majority of colorectal cancers arise from precancerous polyps and their removal has been shown to reduce the risk of colon cancer [2,3]. Because the progression from adenoma to adenocarcinoma is believed to generally occur over a number of years, most polyps encountered during colonoscopy are benign [4]. However, complex polyps, which are usually larger in size and may be sessile, flat, laterally spreading, or depressed, carry a higher risk of being malignant, defined as invasion into the submucosa but not the muscularis

propria [5, 6]. These malignant polyps represent the earliest form of colon cancer [7].

Over the past decade, there has been a paradigm shift in the management of complex polyps from surgical resection to endoscopic mucosal resection (EMR), usually by an advanced endoscopist [7–10]. Currently, there is clinical equipoise regarding how long a delay is appropriate between detection of the complex polyp by a general endoscopist and EMR by an advanced endoscopist. The British Society of Gastroenterology (BSG) recommends a target of <4 weeks from complex polyp detection until referral to an advanced endoscopist and a target of < 8 weeks from receipt of the referral to the EMR procedure. However, the BSG concedes there was no evidence upon which this recommendation was based and instead, extrapolated from the general timeline recommended by the United Kingdom National Health Service (NHS) for suspected cancers. Since then, both the US Multi-Society Task Force on Colorectal Cancer and the European Society of Gastrointestinal Endoscopy have released guidelines addressing EMR, although neither address suitable wait times [7, 9].

An unintended consequence of the COVID-19 pandemic in 2020 was the unique opportunity to examine the impact of a prolonged wait time for EMR on the risk of adverse outcomes. This was due to the closure of many endoscopy units around the world during the early stages of the pandemic to slow transmission as well as to conserve healthcare resources and personal protective equipment [11, 12]. In this bidirectional cohort study, we compared the outcomes of EMRs impacted by COVID-19 related prolonged delays with EMRs performed prior to the pandemic.

Patients and methods

Study design

A bidirectional cohort study was conducted to evaluate the effect of a prolonged delay for EMR on adverse outcomes. Between April 1, 2020 and June 1, 2020, all EMR procedures were suspended due to a government-mandated reduction in endoscopy services in the province of Ontario, Canada, in an effort to limit transmission of COVID-19 and to conserve healthcare resources. All EMR procedures delayed by the service reduction were considered the "exposed" group and were compared to the "unexposed" group, which comprised all EMR cases performed during a 15-month period before the government mandate. All procedures were performed at the London Health Sciences Centre or St. Joseph's Hospital, both tertiary care centers affiliated with Western University with a referral population of 1.6 million inhabitants. Exclusion criteria included: 1) individuals younger than 18 years old; 2) EMRs performed for polyps <10 mm in size; and 3) EMRs performed at the index colonoscopy by the advanced endoscopists. This last exclusion criterion was necessary because it encompassed cases in which a complex polyp was detected by an advanced endoscopist and removed during the same session. Because these cases do not have a wait time, they would not be considered "at risk" for wait time-related adverse outcomes. Patients were followed until their first follow-up colonoscopy to assess for recurrence, typically 6 to 9 months post EMR. However, due to the pandemic, we followed the COVID-delayed group up to 18 months to ensure we captured all follow-up colonoscopies. Approval was obtained by the Western University Health Sciences Research Ethics Board and the study was reported according to STROBE guidelines [13].

Exposure definition

EMR procedures performed in the colon or rectum after June 1, 2020 but with an index colonoscopy detecting the polyp prior to April 1, 2020 were subject to a minimum of 2 months of additional delay and defined as the "exposed" group. The "unexposed" group was not affected by the government-imposed delay and were defined as EMR procedures performed in the colon or rectum between January 1, 2019 and March 30, 2020. The wait time was defined as the number of days between the index colonoscopy when the complex polyp was detected and the EMR procedure.

Outcomes

The primary outcome was the incidence of malignant polyps, defined histologically as submucosal invasion not reaching the muscularis propria. Secondary outcomes included technical success, defined as removing all endoscopically visible polyp tissue; polyp recurrence on follow-up colonoscopy; advanced polyp histology, defined as any villous component, high-grade dysplasia, or sessile serrated polyps with any dysplasia; probability of meeting criteria for an adequate endoscopic resection for malignant polyps, defined as en bloc resection with negative margins >2 mm, well to moderately differentiated, lack of lymphovascular invasion, lack of tumor budding, and invasion < 1000 µm [7]; metastatic colorectal cancer among the malignant polyps; and complications.

Statistical analysis

The baseline characteristics of patient, procedure, and polyp were described using median and interquartile range (IQR) for continuous variables, and frequencies and percentages for categorical variables. The difference in baseline characteristics between the pre-COVID-19 and delayed COVID-19 EMR periods was compared using Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for categorical variables. For the primary outcomes, Fisher's exact test was performed to assess the difference between baseline and delayed COVID-19 EMR periods because more than 20 % of cells had expected frequencies <5. For the secondary outcomes, the Fisher's exact test was performed except for advanced polyp histology, which was assessed using the Chi-square test as no cells had expected values <5. The proportion of metastatic colorectal cancer was compared using the one sample proportion test. All statistical analysis was performed using the statistical software Rstudio (ver 2022.02.3 Build 492). All tests were two-sided with a significance level of $P<0.05$. A formal sample size calculation, either a priori or post-hoc, was not performed due to the use of a fixed available sample, in keeping with recommendations from the STROBE guidelines [13].

Results

Patient and polyp characteristics in exposed and unexposed groups

During the study observation period, a total of 321 EMR procedures were performed in the colon or rectum, of which 45 were performed at the index colonoscopy and eight were < 1 cm in size, leaving 268 EMRs eligible for the study. Overall, 60 EMR cases (22.4 %) cases were delayed due to the COVID-19 pandemic whereas 208 EMR cases (77.6 %) cases were performed prior to the service reduction and served as the control group (▶ **Table 1**). The median (IQR) age was 72 (13.0), 58.8 % were men, and there with no significant differences between the COVID-19-delayed and control group ($P > 0.05$ for all variables). Polyps in the COVID-19-delayed group were on average slightly smaller (median (IQR) 30 (15) vs. 30 (15) mm, $P = 0.002$) although the distribution of polyp location and Paris classification subtypes were not significantly different between the two groups ($P > 0.05$). The median (IQR) wait time from the index colonoscopy when the polyp was detected until the EMR procedure was 191 days (127.8) in the COVID-19-delayed group whereas the control group was 92 days (87.8) ($P < 0.001$).

Polyp-related outcomes in the exposed and unexposed groups

There were a total of 14 malignant polyps (5.2 %) detected in the cohort, of which four (6.7 %) and 10 (4.8 %) were in the COVID-19-delayed and control groups, respectively (P = 0.52) (▶ **Table 2**). There were no significant differences in the probability of technical success for polyp removal (86.7 % vs. 91.4%, $P = 0.46$), polyp recurrence at follow-up colonoscopy (8.3 % vs. 6.7 %, $P = 0.19$), advanced polyp histology (46.7 % vs. 53.4 %, $P = 0.42$), probability of achieving an adequate resection for malignant polyps (3.3 % vs. 0.5 %, $P = 0.18$) or metastatic colon cancer (0 % vs. 0 %, $P = 0.18$) between the delayed group vs. the control group, respectively. There were 16 intraprocedure bleeding events (6 %), all of which were managed endoscopically with no significant differences between the two groups, one delayed microperforation, and one delayed bleed, both of which were in the control group and were managed with observation, neither requiring surgery or another colonoscopy.

Discussion

The unprecedented COVID-19 pandemic created a unique opportunity to study the effect of delayed endoscopic removal of complex polyps on health outcomes. Historically, this has been a challenging area to study, reflected by the lack of evidence supporting suitable wait time targets in prior guidelines addressing EMRs and the management of complex polyps [7, 9, 10]. Randomized controlled trials (RCTs) are typically considered the "gold standard" for answering clinical questions but that methodology was not well suited for this scenario. For one, it may not be ethically acceptable to randomize patients to an intentional delay in the interest of science, even if clinical equipoise exists due to the potential for harm. More pragmatically, recruitment for such a clinical trial would likely be extraordinarily difficult because patients would have to consent to the possibility of being randomized to an intentionally delayed arm with no foreseeable benefits. Similarly, observational studies are not suitable due to confounding by indication. This is a frequent form of bias in observational studies because the allocation between the "exposed" and "unexposed" groups is not random, instead being based on clinical need or indication [14]. In this scenario, an observational study examining the association between wait times for EMR and adverse outcomes may find that those with the shortest wait times are at the highest risk for a poor outcome. In this example, this finding would likely be the result of confounding by indication, whereby the endoscopist triages the highest acuity cases, such as polyps with depression, to the shortest wait times. As such, the cause of the worse outcomes in the shorter wait time group is not the wait time itself, but the higher-acuity cases that were rightly performed first.

The COVID-19 pandemic provided an unintended opportunity to address, in part, the problem of confounding by indication by applying an across-the-board delay in all EMR cases of 2 months in our cohort. Thus, all EMR cases, regardless of acuity, were delayed equally. This was reflected in our median wait time for EMR, which increased significantly from a median of 92 days at baseline to 191 days during the pandemic. However, despite this substantial increase, there were no significant differences in clinically meaningful outcomes, such as the probability of having a malignant polyp, technical success of the procedure itself, polyp recurrence at follow-up colonoscopy, advanced polyp histology, probability of endoscopic cure for malignant polyps, metastatic colorectal cancer, or complications.

To our knowledge, there have been no prior studies of this nature. The most similar report we could find was by Samani et al., who recently shared their experiences with complex polyps during COVID-19 at two large NHS hospitals in the UK in a letter to the editor in the journal Gut [15]. In that report, they compared COVID-19-delayed colorectal EMR cases (n = 35) with a baseline group 1 year before the pandemic (n = 76). Not surprisingly, the COVID-19-impacted group had longer median wait times (16 weeks vs. 8 weeks, $P = 0.001$). As the primary outcome, they compared the median size increases from the index colonoscopy until the EMR between the two groups. The COVID-19-delayed group had a greater median size increase from 20 to 40 mm ($P = 0.03$) compared with the baseline group, which increased from a median size of 25 mm to 30 mm ($P = 0.06$). This report is difficult to reconcile with our findings due to the limited data available in the publication (e. g. lack of information describing baseline patient and polyp characteristics between the two groups and whether outcome assessors were blinded to exposure status). Furthermore, their primary outcome, polyp size, may be problematic as it is highly subjective and prior studies have shown that polyp size estimation by endoscopists is frequently inaccurate [16, 17]. Finally, it was surprising to see that the median polyp size had doubled from the time of the index colonoscopy to the EMR procedure in the COVID-19-delayed group, despite the median wait time being only 16 weeks. Given that polyps typically take years to pro-

▶ **Table 1** Baseline patient and polyp characteristics.

	Baseline EMRs	COVID-19-delayed EMRs	Total	*P* value
	(N = 208)	(N = 60)	(N = 274)	
Sex				0.054
▪ Female	92 (44.23 %)	18 (30.00 %)	113 (41.24 %)	
▪ Male	116 (55.77 %)	42 (70.00 %)	161 (58.76 %)	
Age (years)				0.735
Median [IQR]	72 [13.25]	72 [8.75]	72 [13.0]	
Bowel preparation				0.305
▪ Very good	170 (81.73 %)	48 (80.00 %)	224 (81.75 %)	
▪ Fair	38 (18.27 %)	10 (16.67 %)	48 (17.52 %)	
▪ Poor	0 (0.00 %)	1 (1.67 %)	1 (0.36 %)	
Location of polyp referred for EMR/ESD				0.278
▪ Cecum	55 (26.44 %)	10 (16.67 %)	66 (24.09 %)	
▪ Ascending	59 (28.37 %)	14 (23.33 %)	76 (27.74 %)	
▪ Hepatic flexure	23 (11.06 %)	11 (18.33 %)	34 (12.41 %)	
▪ Transverse	24 (11.54 %)	11 (18.33 %)	36 (13.14 %)	
▪ Splenic flexure	5 (2.40 %)	0 (0.00 %)	5 (1.82 %)	
▪ Descending	4 (1.92 %)	2 (3.33 %)	6 (2.19 %)	
▪ Sigmoid	17 (8.17 %)	7 (11.67 %)	25 (9.12 %)	
▪ Rectum	20 (9.62 %)	5 (8.33 %)	25 (9.12 %)	
No. days between index colonoscopy and EMR				
Median [IQR]	92 [87.85]	191 [127.8]	107 [104.5]	< 0.001
EMR polyp size (mm)				
Median [IQR]	30 [15]	30 [15]	30 [20]	0.002
Paris Classification				0.167
▪ IIa	104 (50.00 %)	23 (38.33 %)	127 (46.35 %)	
▪ IIa + IIb	2 (0.96 %)	0 (0.00 %)	2 (0.73 %)	
▪ IIa + IIc	2 (0.96 %)	1 (1.67 %)	3 (1.09 %)	
▪ IIa + Is	3 (1.44 %)	1 (1.67 %)	4 (1.46 %)	
▪ IIb	6 (2.88 %)	1 (1.67 %)	7 (2.55 %)	
▪ IIc	2 (0.96 %)	1 (1.67 %)	3 (1.09 %)	
▪ Ip	10 (4.81 %)	3 (5.00 %)	13 (4.74 %)	
▪ Ip + Is	2 (0.96 %)	2 (3.33 %)	4 (1.46 %)	
▪ Is	32 (15.38 %)	21 (35.00 %)	55 (20.07 %)	
▪ Is + IIa	2 (0.96 %)	0 (0.00 %)	2 (0.73 %)	
▪ Is + IIc	2 (0.96 %)	0 (0.00 %)	2 (0.73 %)	
▪ Is + Ip	2 (0.96 %)	0 (0.00 %)	2 (0.73 %)	

EMR, endoscopic mucosal resection; IQR, interquartile range; ESD, endoscopic submucosal dissection.

▶ **Table 2** Study outcomes.

	Baseline EMRs (N = 208)	COVID-19 delayed EMRs (N = 60)	*P* value
Malignant polyp			
▪ No	198 (95.19 %)	56 (93.33 %)	0.52
▪ Yes	10 (4.81 %)	4 (6.67 %)	
Technical success			
▪ No	14 (6.73 %)	6 (10.00 %)	0.46
▪ Yes	190 (91.35 %)	52 (86.67 %)	
▪ Removal not attempted	4 (1.92 %)	2 (3.33 %)	
Polyp recurrence on follow-up colonoscopy			
▪ No	127 (61.06 %)	29 (48.33 %)	0.19
▪ Yes	14 (6.73 %)	5 (8.33 %)	
▪ No follow-up colonoscopy required[1]	66 (31.73 %)	26 (43.33 %)	
Advanced polyp histology			
▪ No	96 (46.15 %)	32 (53.33 %)	0.42
▪ Yes	111 (53.37 %)	28 (46.67 %)	
Adequate endoscopic resection for malignant polyps			
▪ No	9 (4.33 %)	2 (3.33 %)	0.18
▪ Yes	1 (0.48 %)	2 (3.33 %)	
Metastatic CRC found for malignant polyps			
▪ No	10 (4.81 %)	4 (6.67 %)	0.18
▪ Yes	0 (0.00 %)	0 (0.00 %)	
Complications			
▪ None	188 (90.38 %)	55 (91.67 %)	0.73
▪ Intraoperative bleeding	11 (5.29 %)	5 (8.33 %)	
▪ Other[2]	2 (0.96 %)	0 (0.00 %)	

EMR, endoscopic mucosal resection; CRC, colorectal cancer.
[1] No follow-up colonoscopy required either due to having surgery for a malignant or unresectable polyp or having an en bloc EMR with negative margins.
[2] Other complications include intraoperative perforation, delayed perforation, and delayed bleeding.

gress from adenomas to colon cancer, and based on our collective experiences with complex polyps, it is possible that this may be a spurious finding owing to a small sample size or perhaps affected by unconscious bias, given the subjective nature of this outcome and the possible lack of blinding of outcome assessors.

There are two limitations of our study that should be addressed. First, we did not examine shorter or longer wait times. The baseline median wait time in our study was 92 days and the COVID-19-delayed wait time was 191 days. It is plausible that future comparisons using shorter wait times, such as less than 30 days, or longer wait times, such as > 6 months, may produce different results. Ultimately, these studies will likely never be completed due to the difficulty in conducting RCTs or observational studies related to wait times as explained above. The second limitation relates to the risk of confounding. Adjustments by means of regression were not possible due to the low event rate for malignant polyps. However, because adenocarcinomas generally affect only 0.2 % to 5 % of polyps [7, 10], a study would require an unfeasible sample size 10 times larger, or 2,600 EMRs, to have adequate events to permit multivariable regression. Nonetheless, it is reassuring that the baseline patient and polyp characteristics were comparable, with no significant differences between the two groups with the exception of polyp size. However, given that the median (IQR) was the same between the two groups and taking into consideration the known inaccuracies of polyp size estimation by endoscopists [16, 17], we felt the small differences in polyp size was likely not clinically significant and would not have meaningfully influenced our results.

Conclusions

The purpose of this study was not to advocate for longer wait times, but rather, to provide some reassurance to patients who experience delays in the performance of EMR. This is because some patients with complex polyps referred for EMR likely already harbor a small malignancy at the time of detection, and as such, should undergo resection and possibly surgery as soon as possible. Instead, the intent of our study was to examine whether longer wait times, when necessary due to resource constraints or other factors, were associated with negative outcomes. Fortunately, this was not the case. Thus, we conclude that there was no increased harm associated with an increase in median wait times for colorectal EMRs from 92 to 191 days.

Competing interests

The authors declare that they have no conflict of interest.

References

[1] Bromham N, Kallioinen M, Hoskin P et al. Colorectal cancer: summary of NICE guidance. BMJ 2020; 368: m461

[2] Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977–1981

[3] Zauber AG, Winawer SJ, O'Brien MJ. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012; 366: 687–696

[4] Rex DK, Dekker E. How we resect colorectal polyps < 20 mm in size. Gastrointest Endosc 2019; 89: 449–452

[5] Puig I, Lopez-Ceron M, Arnau A et al. Accuracy of the narrow-band imaging international colorectal endoscopic classification system in identification of deep invasion in colorectal polyps. Gastroenterology 2019; 156: 75–87

[6] Burgess NG, Hourigan LF, Zanati SA et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. Gastroenterology 2017; 153: 732–742 e731

[7] Shaukat A, Kaltenbach T, Dominitz JA et al. Endoscopic Recognition and Management Strategies for Malignant Colorectal Polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2020; 159: 1916–1934

[8] Zwager LW, Bastiaansen BAJ, Dekker E et al. Setting up a regional expert panel for complex colorectal polyps. Gastrointest Endosc 2022; 96: 84–91 e82

[9] Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017; 49: 270–297

[10] Rutter MD, Chattree A, Barbour JA et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut 2015; 64: 1847–1873

[11] Soetikno R, Teoh AYB, Kaltenbach T et al. Considerations in performing endoscopy during the COVID-19 pandemic. Gastrointest Endosc 2020; 92: 176–183

[12] Gralnek IM, Hassan C, Beilenhoff U et al. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic. Endoscopy 2020; 52: 483–490

[13] Vandenbroucke JP, von Elm E, Altman DG et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007; 18: 805–835

[14] Signorello LB, McLaughlin JK, Lipworth L et al. Confounding by indication in epidemiologic studies of commonly used analgesics. Am J Therap 2002; 9: 199–205

[15] Samani S, Mir N, Naumann DN et al. COVID-19 and endoscopic services: the impact of delays in therapeutic colonoscopies on patients. Gut 2021; 70: 2019–2020

[16] Chaptini L, Chaaya A, Depalma F et al. Variation in polyp size estimation among endoscopists and impact on surveillance intervals. Gastrointestinal endoscopy 2014; 80: 652–659

[17] Anderson BW, Smyrk TC, Anderson KS et al. Endoscopic overestimation of colorectal polyp size. Gastrointest Endosc 2016; 83: 201–208