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Missed Adenomas During Colonoscopic Surveillance in Individuals with Lynch Syndrome (HNPCC)

Elena M. Stoffel, MD, MPH[1], **D. Kim Turgeon, MD**[2], **David H. Stockwell, MD, MPH**[1], **Lili Zhao, PhD**[6], **Daniel P. Normolle, PhD**[7], **Missy K. Tuck, MS**[2], **Robert S. Bresalier, MD**[5], **Norman E. Marcon, MD**[3], **John A. Baron, MD**[4], **Mack T. Ruffin, MD, MPH**[2], **Dean E. Brenner, MD**[2], and **Sapna Syngal, MD, MPH**[1]

Great-Lakes New-England Clinical Epidemiology and Validation Center of the Early Detection Research Network (GLNE-EDRN)

[1] Brigham and Women's Hospital/ Dana-Farber Harvard Cancer Institute, Boston, MA

[2] University of Michigan Medical Center, Ann Arbor MI

[3] The Wellesley Site-Saint Michael's Hospital, Toronto, Ontario

[4] Dartmouth Medical School, Lebanon, NH

[5] MD Anderson Cancer Center, Houston, TX

[6] Biostatistics Unit, University of Michigan Comprehensive Cancer Center

[7] Department of Radiation Oncology, University of Michigan Medical School

Abstract

Background & Aims—Lynch syndrome (also known as hereditary nonpolyposis colon cancer, HNPCC) is associated with an increased risk for colorectal cancer, which can arise despite frequent colonoscopic exams. We evaluated the adenoma miss rate of conventional colonoscopy in patients with Lynch syndrome, and compared the sensitivity of chromoendoscopy *versus* intensive inspection for detecting polyps missed by conventional colonoscopy.

Methods—Fifty four subjects with Lynch Syndrome underwent tandem colonoscopies at four centers of the Great-Lakes New England Clinical Epidemiology and Validation Center (GLNE) of the Early Detection Research Network (EDRN). All participants first had a conventional colonoscopy with removal of all visualized polyps. The second endoscopy was randomly assigned as either pan-colonic indigocarmine chromoendoscopy or standard colonoscopy with intensive inspection lasting ≥20 minutes. Size, histology, and numbers of polyps detected on each exam were recorded.

Results—After undergoing standard colonoscopy, twenty-eight individuals were randomized to a second exam with chromoendoscopy and 26 underwent intensive inspection. The mean interval since last colonoscopy was 17.5 months. Seventeen polyps (10 adenomas and 7 hyperplastic polyps) were identified on the first standard colonoscopies. Twenty-three additional polyps (12 adenomas and 11 hyperplastic polyps) were found on the second exams, yielding an adenoma miss rate of 55%. Fifteen polyps (5 adenomas and 10 hyperplastic polyps) were found in subjects who had chromoendoscopy and 8 polyps (7 adenomas and 1 hyperplastic polyp) in those who had intensive inspection. Chromoendoscopy was associated with more normal tissue biopsies (11 vs. 5) and longer procedure times compared with intensive inspection (29.8 ±9.5 mins vs. 25.3±5.8 mins; p=0.04). Controlling for age, number of previous colonoscopies, procedure time, and prior colonic resection,

Corresponding Author: Elena M. Stoffel, MD, MPH, Division of Gastroenterology, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, 617-632-5335, Fax 617-632-4088, estoffel@partners.org.

chromoendoscopy detected more polyps (p=0.04), but adenoma detection was not significantly different compared with intensive inspection (p=0.27).

Conclusions—Small adenomas are frequently missed in Lynch Syndrome patients. Although chromoendoscopy did not detect more missed adenomas than intensive inspection in this pilot study, larger trials are needed to determine optimal surveillance techniques in this high risk population.

Introduction

Lynch Syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common hereditary colorectal cancer syndrome and is estimated to account for 3–5% of colorectal cancer (CRC) cases.(1) Lynch Syndrome is caused by inherited mutations in genes involved in DNA mismatch repair (MMR), which predispose to cancers of the gastrointestinal, female reproductive and urinary tracts, as well as other extracolonic tumors.(2) MMR mutation carriers have a lifetime risk for developing CRC of 70–80% in the absence of colonoscopic screening, with a mean age of CRC diagnosis of 44 years.(2) Despite the term “non-polyposis colorectal cancer”, there is evidence that most CRCs in Lynch Syndrome patients arise from adenomatous polyps, many of which have been described as small and/or flat with a higher degree of dysplasia compared with sporadic adenomas.(3) Although colonoscopy has been found to be effective in reducing CRC-related mortality in families with Lynch Syndrome, reports of tumors developing in the interval between colonoscopic exams are not infrequent. (4,5) Consequently, current CRC screening recommendations for individuals at risk for Lynch Syndrome include colonoscopy every 1–2 years beginning at age 20–25.(6)

Conventional white-light colonoscopy is considered the gold standard for detecting adenomatous polyps; however studies in average and moderate risk individuals have documented adenoma miss rates of 6–27%. (7) (8,9) Chromoendoscopy, performed by spraying dye on the colorectal mucosa during colonoscopy, has been reported to improve visualization of mucosal lesions. (10–12) Previous randomized trials examining chromoendoscopy for adenoma detection in average and moderate-risk individuals have reached different conclusions about the utility of spraying dye since most of the additional lesions found during chromoendoscopy are small. (13–15) Although recent reports demonstrate that advanced histology may be present in 10% of small (5–10mm) colorectal adenomas(16), the clinical significance of missing these small lesions is not known. Since carcinogenesis may be accelerated in Lynch Syndrome, improved detection of small lesions may be especially important in this patient population.

We conducted a randomized multi-center study to 1) determine the prevalence of missed lesions following a standard colonoscopy in patients with Lynch Syndrome and 2) compare chromoendoscopy vs intensive inspection for detection of missed lesions in this population at high risk for developing CRC.

Materials and Methods

Study subjects were enrolled at four collaborating study centers (University of Michigan, Dana-Farber/Brigham and Women’s Hospital, MD Anderson Cancer Center, University of Toronto) associated with the Great-Lakes New England Clinical Epidemiology and Validation Center of the Early Detection Research Network (EDRN). In order to be eligible for the study, subjects had to have a clinical diagnosis of Lynch Syndrome/HNPCC, defined as 1) documented history of a pathogenic mismatch repair gene mutation in one of the mismatch repair genes *MLH1, MSH2, or MSH6* or 2) personal history of a Lynch-associated cancer and family history meeting Amsterdam I or II criteria.(17) Individuals under 18 years of age, with poor performance status, receiving active treatment for cancer, or using anticoagulant medications were ineligible for

the study. This study was approved by the Institutional Review Board or ethics board at each institution.

Study Procedure

All subjects underwent back-to-back colonoscopy exams, with a conventional colonoscopy followed immediately by a second endoscopy performed with either chromoendoscopy or intensive colonoscopy. Subjects were randomized after the cecum (or ileocolonic anastomosis) was reached during the second exam and randomization was performed in blocks sizes of two, stratified by study site. The endoscopist, study coordinator and endoscopy nurse were not made aware which randomization arm had been assigned until the cecum/ileocolonic anastomosis was reached during the second colonoscopy and the randomization envelope was opened.

Subjects provided informed consent and completed demographic and medical history questionnaires prior to colonoscopy. Subjects took a standardized preparation on the day prior to colonoscopy (magnesium citrate (12 oz) followed by either large volume (4 liter) polyethylene glycol colonic lavage, 1.5 oz of oral phosphosoda followed by 24 oz water (2 doses), or Visicol ™ tablet prep).

The first exam for all subjects was a standard colonoscopy with removal of all visualized polyps. On completion of the first colonoscopy, subjects were considered eligible to undergo the second exam if all of the following criteria were satisfied: the preparation was considered excellent, the first standard colonoscopy was completed in less than 30 minutes, the endoscopist considered the exam to be technically easy, and the endoscopist, study coordinator, and endoscopy nurse all agreed that the subject was comfortable and clinically able to immediately undergo a second procedure. Study participants were contacted 24 to 72 hours after their procedures to determine if they had experienced any adverse effects.

All 7 endoscopists participating in this study underwent training in chromoendoscopy technique and recognition of polyp morphology. Standard non-magnifying Olympus-160 or Pentax -160 colonoscopes were used for all study procedures.

Study coordinators recorded duration of the endoscopic procedures (including time from endoscope insertion to visualization of cecal landmarks, withdrawing from cecum to anal verge, and performing polypectomy) and assessed the location and size of each polyp as measured by placing an open standardized biopsy forceps (Bard 00823 C diameter 9.6mm inner dimension) adjacent to the polyp. Endoscopists classified polyp morphology as polypoid or flat, with flat polyps defined as having height less than half of the diameter of the lesion. (13,14,18) All polyps were numbered and photographed before they were fully removed with standardized biopsy forceps or snares, according to standard clinical practice.

For subjects randomized to chromoendoscopy as their second exam, the entire colon was sprayed during withdrawal of the colonoscope with 0.2% indigo carmine solution with a standardized (Olympus pw-5v-1) spraying catheter and the mucosa was inspected in 10 cm segments. Each 20 ml of indigo carmine solution contained 1 ml of simethicone as an antifoaming agent. An average of 100 ml of solution was used per patient.

Subjects randomized to intensive inspection received a thorough examination of the colon without indigocarmine dye. Endoscopists were instructed to spend at least 20 minutes visualizing the colonic mucosa during withdrawal from the cecum, exclusive of time spent performing polypectomy.

All polyps or areas suspicious for neoplasia identified on withdrawal of the endoscope during each of the two colonoscopic examinations were removed, fixed in 10% buffered formalin,

and examined by the pathologist at each of the four collaborating institutions as per routine practice. Lesions were categorized as adenomatous polyps, hyperplastic polyps, normal tissue or "other."

Statistical Methods

The primary objective of this study was to compare the adenoma detection rates of chromoendoscopy and intensive inspection colonoscopy without dye spraying peformed after a standard colonoscopic examination. The study was designed as a multicenter randomized trial with 50 subjects, and was subsequently extended to 54 subjects. Polyp and biopsy counts were analyzed by means of generalized linear models (SAS PROC GENMOD, SAS Institute, Cary, NC), which assume that the number of lesions of any particular type identified in a given patient follows a Poisson distribution, with different means in each of the two study groups. Linear mixed models (SAS PROC MIXED) were used to compare the size of lesions between the treatment groups. Predictors in both patient-level and polyp-level models included clinical site, age, sex, race, smoking status, drinking status, total number of previous colonoscopies, number of months since most recent colonoscopy, history of previous surgical resection of the colon, and identified gene mutation. Descriptive statistics are reported as mean ± standard deviation.

Results

Subject Demographics

A total of 54 subjects completed the study. Mean age of subjects was 43.1 years (19–68). Forty six (85%) individuals carried pathogenic mutations in a mismatch repair gene, and 25 (46%) had a prior diagnosis of CRC. After the first routine colonoscopy was completed and the cecum (or ileocolonic anastomosis) was reached during the second exam, 28 subjects were randomized to undergo chromoendoscopy and 26 subjects to intensive inspection colonoscopy without dye spraying. The baseline characteristics of subjects are shown in Table 1. There were no statistically significant differences between the two arms with respect to baseline subject characteristics.

First Colonoscopy (Conventional Exam)—Prior to randomization, all subjects underwent an initial conventional colonoscopy. The average procedure time (from insertion of colonoscope to removal, minus time spent in removal of polyps) was 18.2 minutes and lesions were removed from 13/54 (24%) subjects. Of the 22 lesions biopsied, 10 (45%) were adenomatous polyps, 7 (32%) were hyperplastic polyps, 5 (23%) were normal tissue. The characteristics of the first colonoscopy procedures are presented in Table 2 . There were no significant differences in the total number of adenomas detected (6 vs 4) or in number of subjects with adenomas (5 vs 3) between those subsequently randomized to intensive inspection vs chromoendoscopy, respectively. Additional characteristics of polyps found on the first exam are presented in Table 3. There was no statistically significant variation by arm in location or distribution of adenomas, hyperplastic polyps and normal biopsies (p=0.40). Mean size of adenomas was 6.50 ±6.95 mm compared with 4.53 ±3.79 mm in subjects subsequently randomized to intensive inspection vs chromoendoscopy, respectively. This difference was not statistically significant (p=0.62) and resulted from one large (20mm) adenoma in one subject in the intensive inspection arm. Four of 10 (40%) of the adenomas found on first exams were considered flat. There was no association between procedure time of the first colonoscopy and number of adenomas detected.

Intensive Inspection Colonoscopy—Twenty-six subjects were randomized to intensive inspection without dye spraying for their second colonoscopy, with a mean procedure time of

25.3 ± 5.8 minutes (range 15–39 minutes) and lesions were biopsied from 9/26 (35%) subjects. Five subjects had polyps and each of these had one or more adenomas (Table 2). Of the total of 13 lesions biopsied, 7 (53.8%) were adenomas, 1 (7.7%) was a hyperplastic polyp, and 5 (38.5%) were normal tissue (Table 3).

The adenomas detected on the intensive inspection exams were not significantly smaller than those removed during the first colonoscopy (1.86 ±0.38mm vs 6.50 ±6.95mm; p=0.1) and all 7 (100%) were classified as flat (Table 3). There was no association between procedure time and the numbers of polyps and adenomas identified. Of 8 subjects randomized to intensive inspection who had adenomas discovered at either colonoscopy, 3 (38%) had adenomas found only on the second exam.

Chromoendoscopy—Twenty-eight subjects were randomized to chromoendoscopy, with an average procedure time of 29.8±9.5 minutes (range 8–43 minutes) and lesions were biopsied from 15/28 (54%) subjects. Ten subjects had polyps and 3 had adenomas (Table 2). Of the total of 26 lesions biopsied, 5 (19.2%) were adenomas, 10 (38.5%) were hyperplastic polyps and 11 (42.3%) were normal tissue (Table 3). The adenomas found during chromoendoscopy exams were not significantly smaller than those found on the first exam (mean size 3.80±1.92mm vs. 4.50±3.79mm; p=0.73) and 3 of 5 (60%) were classified as flat (Table 3). There was no association between procedure time and the numbers of polyps and adenomas identified during the exam. Of 5 subjects randomized to chromoendoscopy who had adenomas discovered at either colonoscopy, 2 (40%) had adenomas found only during the second exam.

Intensive Inspection Colonoscopy versus Chromoendoscopy—
Chromoendoscopy took significantly longer than intensive inspection, with an average procedure time of 29.8±9.5 minutes versus 25.3±5.8 minutes, respectively (p=0.04). Chromoendoscopy exams yielded significantly more hyperplastic polyps (10 vs 1 for intensive inspection exams, p=0.01). Although subjects who underwent chromoendoscopy had more biopsies (0.9 ±1.1 biopsies/subject compared with 0.5 ±0.8 for intensive inspection), chromoendoscopy exams identified fewer total adenomas (5 vs 7 for intensive inspection); however these differences did not achieve statistical significance (p=0.1 and 0.77, respectively) (Tables 2 and 3). The percentages of biopsies that were normal tissue were 5/22 (23%), 5/13 (38%) and 11/26 (42%) in the standard colonoscopy, intensive inspection and chromoendoscopy examinations respectively. There were no adverse events reported for any of the 54 subjects.

Three of 28 (11%) subjects in the chromoendoscopy arm and 5 of 26 (19%) in the intensive inspection arm had additional adenomas found during the second colonoscopy (Table 2). Overall, 12 of 22 (55%) total adenomas were found on second exams. The adenomas detected on the second exams were not significantly smaller than those removed during the first colonoscopy (2.67±1.56mm vs. 5.7±5.72mm; p=0.09) (Table 3). There was no difference in adenoma detection rates between subjects with MMR gene mutations and those with cancer histories that met Amsterdam Criteria without MMR gene mutations.

In multivariate analysis controlling for subjects' age, number of previous colonoscopies, procedure time, and prior history of surgical resection of the colon, chromoendoscopy was associated with finding more overall polyps compared with intensive inspection (p=0.04); however, there was no significant difference in adenoma detection between the two techniques (p=0.27).

Discussion

We designed this randomized trial of back-to-back colonoscopies to 1) determine the miss rate of adenomas during conventional colonoscopy in patients with Lynch Syndrome and 2) test whether chromoendoscopy is better than intensive inspection without dye spraying for detecting adenomatous polyps missed by routine exams. We found that the second colonoscopy exams more than doubled the adenoma yield after the standard colonoscopy exams; however there was no statistical difference between the use of chromoendoscopy and intensive inspection in detection of additional adenomas.

Only two previous studies have examined the use of chromoendoscopy for screening and surveillance of patients with Lynch Syndrome. Comparing back-to-back exams in which a standard colonoscopy was followed by a second chromoendoscopy exam, Hurlstone *et a*l (19) and Lecomte *et al* (20) found that the number of adenomas detected in individuals with Lynch Syndrome more than doubled with the second exam. In examining the yield of a second colonoscopy using narrow band imaging (NBI) technology (which uses optical filters to provide an “electronic chromoendoscopy”), East *et al* (21) also found that the second exam nearly doubled the number of adenomas detected in patients with Lynch Syndrome. These studies all concluded that the enhanced endoscopic technique (chromoendoscopy or narrow band imaging (NBI)) significantly improved adenoma detection in patients with Lynch Syndrome. However, none of these studies of back-to-back colonoscopies compared the enhanced endoscopy technique of the second exam to a second standard colonoscopy “control” and, consequently, it is impossible to determine whether the increase in adenoma yield with the second exam is a result of the enhanced endoscopic technique or simply a careful “second look.”

Our study of back-to-back colonoscopies in 54 individuals with Lynch Syndrome is unique in that subjects were randomized to a second exam which used either chromoendoscopy or intensive inspection. While we also found that adenoma yield doubled after the second exams and chromoendoscopy exams detected more polyps overall; they did not identify more adenomas than the intensive standard white light colonoscopy exams. Interestingly, these results differ from those of our randomized trial comparing chromoendoscopy to intensive inspection in subjects with prior history of CRC and/or adenomas. In that trial, which used the same study design and endoscopists (conducted simultaneously with the present study, *manuscript in press*), we found that chromoendoscopy significantly improved adenoma yield compared with intensive inspection alone. In comparing the two studies, it is evident that the overall prevalence of adenomas was very different between the two populations: only 22 adenomas in total were detected in 13 of 54 (24%) Lynch Syndrome subjects, compared with 64 adenomas in 27 of 50 (54%) subjects in the sporadic cohort. In addition to being significantly younger, the subjects with Lynch Syndrome reported more frequent colonoscopic screening, which likely contributed to the lower prevalence of adenomas. The small number of adenomas in our study population did not afford adequate statistical power to detect clinically meaningful differences in adenoma detection rates between the study arms. Thus, our finding that there is no difference in adenoma detection between chromoendoscopy and intensive inspection exams in Lynch Syndrome patients may be real, or may be the result of a type II statistical error.

We recognize our study has other limitations. This was a small study and despite blinded randomization, there were differences between subjects by study arm, although none of these were statistically significant. While endoscopists could not be blinded to procedure type, they were not aware of which randomization arm had been assigned until after the first colonoscopy was completed, and there were no differences in procedure characteristics of the first colonoscopy by randomization arm (procedure time, number of biopsies) to suggest differential bias in adenoma detection. We performed all of the exams using standard colonoscopes, rather

than high definition or magnification colonoscopes, since we believed this technique would be more exportable to other clinical practice settings; however there are data showing HD/ magnification endoscopes increase sensitivity of chromoendoscopy, so our results may underestimate the efficacy of chromoendoscopy.

Our results have several important implications. Twelve of the 22 (55%) adenomas in the individuals with Lynch Syndrome were found on the second exams, so half of the adenomas present in these high risk patients may be missed by standard colonoscopy exams. Furthermore 10/12 (83%) of the missed adenomas were flat. A recent large study demonstrated that 15% of individuals (who did not have Lynch Syndrome) had small nonpolypoid colorectal neoplasms seen with chromoendoscopy and these “flat” lesions were 10 times more likely to contain advanced dysplasia than polypoid lesions(22). Since small, flat adenomas may be more prevalent in patients with Lynch Syndrome, further studies are needed to determine the biologic significance of these missed lesions.

Ours is the first multicenter North American trial to examine the utility of chromoendoscopy for adenoma detection in Lynch Syndrome patients and it is unique in its use of randomized tandem colonoscopies comparing chromoendoscopy to a time- intensive conventional colonoscopy control. Although our study was unable to detect a difference in adenoma detection between chromoendoscopy and intensive inspection exams, our findings suggest that larger studies are needed to be able to compare the adenoma yield of one colonoscopic imaging modality to another in these patients who undergo frequent endoscopic screenings. Lynch Syndrome is the most common hereditary colorectal cancer syndrome; however these patients are still quite rare. Larger randomized trials, organized through multicenter collaborations, are necessary to provide sufficient statistical power to test the effectiveness of new endoscopic techniques to improve cancer prevention for these individuals at highest risk for developing CRC.

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Table 1

Characteristics of the study participants by randomization arm

	Chromoendoscopy	Intensive Colonoscopy
Number of Patients	28	26
Mean Age (years)	40.6	45.7
Female	15 (53.6%)	14 (53.9%)
Non-White	0	3
Personal History of CRC Family History of CRC	14 (50%) 27 (96.4%)	11 (42.3%) 25 (96.2%)
Number of Polyps on Previous Colonoscopies:		
1–2	22 (81.5)	16 (66.7%)
3–5	4 (14.8%)	5 (20.8%)
> 5	1 (3.7%)	3 (12.5%)
Number of Previous Colonoscopies:		
1	7 (25%)	4 (5.4%)
2	3 (10.7%)	3 (11.5%)
3+	14 (50%)	18 (69.2%)
Mean Time Since Last Colonoscopy (months):	19.7	15.2
Range	0.7–65.4	0–31.1
History of Partial Colon Resection	10 (35.7%)	6 (23.1%)
History of ever Smoking Current Smoking	8 (28.6%) 1 (3.6%)	6 (23.1%) 2 (7.7%)
Average number of alcoholic drinks/wk – (range)	4.36 (0–28)	3.96 (0–28)
Gene Mutation for subjects who had genetic testing		
MLH1	6 (23.1%)	9 (36%)
MSH2	17 (65.4%)	12 (48%)
MSH6	0	2 (8%)
Other	1 (3.9%)	0
No mutation identified	2 (7.7%)	2 (8%)

(There were no statistically significant ($p<0.05$) differences between arms in any of the listed variables.)

Table 2

Characteristics of Procedures (time, # of biopsies) by randomization arm

	1st Standard Colonoscopy	2nd colonoscopy= Intensive Inspection	2nd colonoscopy= Chromoendoscopy
# Subjects	54	26	28
Ave. procedure time (min)	18.2±8.0	25.3±5.8	29.8±9.5
# Subjects with biopsies	15	9	15
# Subjects with polyps	13	5	10
# Subjects with adenomas	8	5	3
# Biopsies per subject	0.4±0.8	0.5±0.8	0.9±1.1
# Polyps per subject	0.3±0.6	0.3±0.7	0.5±0.8
# Adenomas per subject	0.2±0.5	0.3±0.6	0.2±0.5

Table 3

Characteristics of polyps (mean sizes, counts) found at first and second colonoscopy by randomization arm

	First Colonoscopy Mean polyp size ±sd in mm (counts)		Second Colonoscopy Mean polyp size ±sd in mm (counts)	
	Intensive Inspection Arm Subjects=26	**Chromo-endoscopy Arm Subjects=28**	**Intensive Inspection *Arm* Subjects=26**	**Chromo- endoscopy Arm Subjects=28**
All Polyps	5.44±5.77 (9)	3.75±2.76 (8)	1.88±0.35 (8)	2.67±1.50 (15)
Adenomatous Polyps	6.50±6.95 (6)	4.5±3.79 (4)	1.86±0.38 (7)	3.80±1.92 (5)
Morphology				
Flat	8.33±10.12 (3)	4.00±NC (1)	1.86±0.38 (7)	3.33±0.58 (3)
Polypoid	4.67±2.89 (3)	4.67±4.62 (3)	(0)	4.5±3.54 (2)
Location				
Right-Sided	2.50±0.71 (2)	4.00±NC (1)	(0)	(0)
Left-Sided	11.5± 12.02 (2)	2.00±0 (2)	1.80± 0.45 (5)	4.25± 1.89 (4)
Rectal	5.50±3.54 (2)	10.00±NC (1)	2.00±0.00 (2)	2.00±NC (1)
Hyperplastic Polyps	3.33±1.53 (3)	3.00±1.41 (4)	2.00±NC (1)	2.10±0.88 (10)
Morphology				
Flat	3.33±1.53 (3)	2.50±2.12 (2)	2.00± NC (1)	2.13±0.99 (8)
Polypoid	(0)	3.50±0.71 (2)	(0)	2.00±0 (2)
Location				
Right-Sided	(0)	4.00± NC (1)	(0)	4.00±NC (1)
Left-Sided	5.00± NC (1)	4.00± NC (1)	2.00± NC (1)	1.00± NC (1)
Rectal	2.50±0.71 (2)	2.00±1.41 (2)	(0)	2.00±0.53 (8)
Normal Samples	6.00±2.83 (4)	2.00±NC (1)	4.20±2.95 (5)	3.55±2.46 (11)
Location				
Right-Sided	(0)	(0)	5.50±4.95 (2)	1.00±NC (1)
Left-Sided	6.00±3.46 (3)	(0)	5.00±NC (1)	6.5±2.12 (2)
Rectal	6.00±NC (1)	2.00±NC (1)	2.50±0.71 (2)	3.13±2.1 (8)

Mean±standard deviation (number of specimens); NC (not calculable)