ORIGINAL CONTRIBUTION

Rectum-Sparing Surgery May be Appropriate for Biallelic MutYH-Associated Polyposis

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PURPOSE: The risk of cancer or severe polyposis of the rectal stump after total colectomy for MutYH-associated polyposis is scarcely defined. To evaluate this risk, we describe the findings of endoscopic surveillance of the rectal stump in a series of patients with biallelic MutYH mutations and polyposis.

METHODS: This is a retrospective, observational, multicenter case series derived from 2 familial cancer registries. Biallelic, germ-line MutYH mutations were found in 14 patients with no adenomatous polyposis coli gene mutations. Eleven of them underwent total colectomy with ileorectal anastomosis and yearly proctoscopic surveillance thereafter. Phenotype and histology of rectal polyps were recorded at diagnosis and during follow-up. Development of adenomas and carcinomas during endoscopic surveillance of the rectal stump was observed.

RESULTS: At diagnosis, 6 patients had attenuated polyposis (10–100 adenomas), 5 patients had classical polyposis, 8 patients had colon carcinoma, and no patient had rectal carcinoma. The mean number of rectal polyps at diagnosis was 2.64 ± 2.11 (range, 0–6). No patients had rectal cancer. The most frequent MutYH mutations were Y165C/Y165C and G382D/G382D in 6 and 2 patients, respectively. During surveillance of the rectal stump after surgery (median duration, 5 y; range, 2–23 y), no patient developed rectal cancer. The mean number of adenomas per proctoscopy was 1.23 ± 2.19 (range, 0–10 adenomas per proctoscopy). This study was limited by the small size and retrospective nature of the case series.

CONCLUSION: Total colectomy with ileorectal anastomosis may be appropriate for patients with MutYH-associated polyposis, provided that they have no rectal cancer or severe rectal polyposis at presentation and that they undergo yearly endoscopic surveillance thereafter.

KEY WORDS: MYH-associated polyposis; Total colectomy; Endoscopic surveillance.

MutYH (or MYH)-associated polyposis (MAP) is an autosomal recessive disorder characterized by multiple colorectal adenomas, and an up to 100% lifetime risk for colorectal cancer.[1]

Because most subjects have an attenuated phenotype, both colectomy or endoscopic removal of polyps might be adequate for disease control.[2,3] Nonetheless, surgery is mandatory in many patients because colon cancer or an excessive number of polyps are present at the time of diagnosis.[4] For patients without cancer or severe polyposis of the rectum, total colectomy with ileorectal anastomosis is considered the appropriate treatment.[5] To date, however, the evidence on the subsequent risk of cancer or severe polyposis of the rectal stump is scarce.

The present study aimed to evaluate the adenoma and carcinoma burden in the rectal stump of MAP patients undergoing total colectomy and ileorectal anastomosis.

MATERIALS AND METHODS

This study had an observational and retrospective design. All data were obtained from the records of Brescia and Padua Polyposis and Hereditary Colorectal Cancer Registries after approval of the institutional review boards. All

Financial Disclosure: None reported.

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Dis Colon Rectum 2010; 53: 1670–1675
DOI: 10.1007/DCR.0b013e3181ee3d6b

patients had consented to the anonymous use of their data when they were registered originally.

Inclusion criteria were the following: 1) biallelic mutation of MutYH gene, and 2) total colectomy with ileorectal anastomosis for colorectal polyposis with or without colon carcinoma.

Fourteen patients with MutYH biallelic mutation were identified. All of them were unrelated and were adenomatous polyposis coli-mutation negative. Eleven patients underwent a total colectomy with ileorectal anastomosis between 1980 and 2008, and were therefore included in the study. The remaining 3 patients (21.4%) were excluded because they underwent proctocolectomy at the time of diagnosis because of rectal carcinoma (2 cases) or extensive polyposis (1 case: more than 10 rectal adenomas). Nonetheless, a brief description of these cases has been made available to provide a comprehensive overview of rectal pathology (see below).

Proctoscopy with removal of all visible polyps of the rectal stump was performed within 2 months after surgery; thus all patients had a polyp-free rectum after surgery. Screening of extraintestinal manifestations was performed at diagnosis in every patient by means of upper gastrointestinal endoscopy, abdominal ultrasonography, ophthalmoscopy, and skull and dental x-rays. After surgery, all patients were enrolled in a surveillance program with proctoscopy and an outpatient visit every year. Beside standard 5-year follow-up for patients with colon cancer, further surveillance included upper gastrointestinal endoscopy and abdominal ultrasound every second year. No chemoprevention protocol was adopted.

The primary end point of the study was the observation of the number of adenomas of the rectum stump developing during endoscopic surveillance after surgery. The secondary end point was the analysis of preoperative clinicopathological predictors of the mean number of adenomas per year during surveillance after surgery. To attain these end points the following variables were examined: age at diagnosis, gender, colorectal polyp count and distribution at diagnosis, the number of rectal adenomas at diagnosis, presence and multiplicity of colon carcinomas at diagnosis, presence and type of extracolonic manifestations at diagnosis and during surveillance.

The number and distribution of colonic polyps at diagnosis were obtained from the pathologic report on the surgical specimen, whereas the number of rectal polyps was obtained from the perioperative endoscopic report. The cumulative and mean number of rectal polyps developed during surveillance was obtained from the endoscopic records.

Genetic Analysis

Genomic DNA was extracted from 200 μL of EDTA-anticoagulated blood with use of the QIAamp DNA Blood Mini Kit and according to the manufacture's instructions (QIAGEN, Milan, Italy). The primers for polymerase chain reaction (PCR) amplifications of MutYH exons are shown on Table 1.

PCR reactions were performed in a 50-μL volume with 100 ng of template genomic DNA, 200 μM each of the deoxynucleotide triphosphates, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 2 mM $MgCl_2$, 1.5 U of AmpliTaq Gold (Applera Italia, Monza, Italy), and 25 pmol of each primer.

Denaturing High-Performance Liquid Chromatography Analysis

Heteroduplexes were obtained by denaturing the PCR products at 94°C for 10 minutes and cooling at 56°C for 60 minutes. Mutation analysis was performed according to a previously described method[6,7] on a Transgenomic WAVE System (Transgenomic Inc., Omaha, NE) equipped with a

TABLE 1. Primers for PCR amplifications of MutYH exons

Exon	*Forward*	*Reverse*
1	5′-GAA GCT GCG GGA GCT GAA A-3′	5′-ATC CCC GAC TGC CTG AAC C-3′
2	5′-CTG CTT TGG CTG GGT CTT T-3′	5′-CGC ACC TGG CCC TTA GTA AG-3′
3	5′-AGC CTG TGC AGG GAT GAT TG-3′	5′-CAA CCC CAG ATG AGG AGT TAG G-3′
4	5′-CTC ATC TGG GGT TGC ATT GA-3′	5′-GGG TTG GCA TGA GGA CAC TG-3′
5	5′-GGG CAG GTC AGC AGT GTC-3′	5′-TAC ACC CAC CCC AAA GTA GA-3′
6	5′-TAC TTT GGG GTG GGT GTA GA-3′	5′-AAG AGA TCA CCC GTC AGT CC-3′
7	5′-GGG ACT GAC GGG TGA TCT CT-3′	5′-TTG GAG TGC AAG ACT CAA GAT T-3′
8	5′-CCA GGA GTC TTG GGT GTC TT-3′	5′-AGA GGG GCC AAA GAG TTA GC-3′
9	5′-AAC TCT TTG GCC CCT CTG TG-3′	5′-GAA GGG AAC ACT GCT GTG AAG-3′
10	5′-GTG CTT CAG GGG TGT CTG C-3′	5′-TGT CAT AGG GCA GAG TCA CTC C-3′
11	5′-TAA GGA GTG ACT CTG CCC TAT G–3′	5′-GCC AAG AGG GCT TTA GG-3′
12	5′-AGC CCT CTT GGC TTG AGT A-3′	5′-TGC CGA TTC CCT CCA TTC T-3′
13	5′-AGG GCA GTG GCA TGA GTA AC-3′	5′-GGC TAT TCC GCT GCT CAC TT-3′
14	5′-TTG GCT TTT GAG GCT ATA TCC-3′	5′-CAT GTA GGA AAC ACA AGG AAG TA-3′
15	5′-TGA AGT TAA GGG CAG AAC ACC-3′	5′-GTT CAC CCA GAC ATT CGT TAG T-3′
16	5′-AGG ACA AGG AGA GGA TTC TCT G-3′	5′-GGA ATG GGG GCT TTC AGA-3′

PCR = polymerase chain reaction.

preheated C18 reversed-phase column based on nonporous poly(styrene/divinylbenzene) particles (DNASep; Transgenomic Inc., Omaha, NE). We injected 8 μL of the PCR mixture into the column, and the heteroduplexes and homoduplexes were eluted with a linear gradient formed by mixing buffer A (0.1 mol/L triethylamine acetate, pH 7.0) and buffer B (0.1 mol/L triethylamine acetate, pH 7.0, containing 250 mL/L acetonitrile) at a constant flow rate of 0.9 mL/min. DNA was detected by monitoring the absorbance at 260 nm. For each fragment, the initial and final concentrations of buffer B were adjusted to obtain a retention time between 3 and 5 minutes. The column was then washed with 100% buffer B for 30 seconds and equilibrated at starting conditions for 1 minute. The melting characteristics of the DNA fragments were predicted by use of the Wavemaker software (Transgenomic Ltd., Glasgow, UK).

Denaturing High-Performance Liquid Chromatography (dHPLC) does not recognize mutant homozygous in a single run because the altered profile is attributable to the differential melting of heteroduplexes. Therefore, to detect homozygous mutations, the normal amplicons must be mixed with an equal amount of wild-type DNA, denatured, reannealed, and analyzed for heteroduplexes. For the identification of homozygotes, the patient amplicons were mixed with normal amplicons from healthy subjects. An abnormal profile indicated the presence of a homozygous sample. Direct sequencing confirmed the findings from the dHPLC analysis. MYH variants with altered elution profiles in dHPLC were sequenced directly in both directions with the appropriate primers.

Statistical Analysis

Data are expressed as means ± SD, unless indicated otherwise. Normal distribution of data was assessed using graphical methods and the Kolmogorov-Smirnov test. The association of the mean number of adenomas per year developing during surveillance with categorical variables was assessed by applying Mann-Whitney and Kruskal-Wallis tests, whereas linear regression analysis was applied for continuous variables.

$P < .050$ was considered significant, and 95% confidence intervals were determined. All analyses were conducted using Stata statistical software version 7.0 for Windows (Stata Corporation, College Station, TX) and SPSS version 13.0 for Windows (SPSS, Chicago, IL).

RESULTS

Phenotype and Genotype at Presentation

MutYH mutation and phenotype of each subject are summarized in Table 2. There were 7 males and 4 females with a mean age at diagnosis of 50.27 years (median, 50; range, 40–69 y).

A classical polyposis (>100 polyps) was diagnosed endoscopically in 5 patients (45.5%), whereas the remaining

TABLE 2. Characteristics of MAP patients and surveillance

Patient	*Sex*	*MutYH mutations*	*Age at diagnosis of FAP (y)*	*No. of colorectal polyps*	*No. of rectal polyps at diagnosis*	*Colon cancer*	*Age at diagnosis of MAP (y)*	*Length of follow-up after colectomy (y)*	*Cumulative polyp count after surgery*	*Mean polyp no./y after surgery*	*Extracolonic manifestations*
1	M	R231H/1103delC	52	100–200	6	Yes	76	23	33	1.4	Pancreatic cancer
2	F	Y165C/Y165C	51	10–50	6	Yes, multiple	71	23	17	0.7	–
3	F	Y165C/Y165C	43	500–1000	4	Yes	60	20	54	2.7	–
4	F	Y165C/Y165C	48	50–100	1	Yes	65	19	4	0.2	Duodenal adenomas
5	M	Y165C/Y165C, G382D	57	100–200	3	Yes	64	10	8	0.9	Gastric cancer, duodenal adenomas
6	M	G382D/G382D	69	10–50	0	No	71	5	0	0	–
7	M	Y165C/Y165C	50	100–200	1	Yes, multiple	52	5	1	0.2	–
8	M	Y165C/Y165C	45	10–50	1	Yes, multiple	47	3	30	10	–
9	M	IVS10+3A>C/IVS10+3A>C	48	10–50	1	No	50	3	0	0	–
10	M	G382D/G382D	50	100–200	2	Yes	51	2	1	0.5	–
11	F	Y165C/1103delC	40	10–50	4	No	40	2	0	0	–

MAP = MutYH (or MYH)-associated polyposis; FAP = familial adenomatous polyposis.

patients had an attenuated polyposis (between 10 and 99 polyps). In 5 cases (45.5%) more than 75% of polyps were sited in the right colon or in the left colon and rectum, whereas the remaining patients had a diffuse distribution of polyps. There was no significant association between type of polyposis and distribution of polyps at diagnosis ($P = .870$).

Eight patients (72.7%) had at least one colon carcinoma at the time of diagnosis. Three of 8 (27.3%) patients had 2 synchronous carcinomas. Cumulatively there were 11 colon carcinomas, 7 of which were in the right colon and 4 in the left colon. None of the patients had distant metastases, but 3 patients had metastatic lymph nodes and underwent adjuvant 5-fluorouracil-based treatment after surgery. None of the patients had local recurrence or distant metastases during follow-up.

The mean number of rectal polyps at diagnosis was 2.64 ± 2.11 (median, 2.0; range, 0–6); all polyps were adenomas with low-grade dysplasia. None of the patients included in the study had rectal carcinoma.

The number of rectal adenomas at diagnosis was not significantly correlated with patient gender ($P = .783$), age at diagnosis ($P = .297$), MutYH mutation ($P = .717$), or type of colonic polyposis (classical or attenuated) ($P = .386$). Patients with diffuse or mainly left-sided polyposis were associated with an higher number of rectal adenomas at diagnosis ($P = .022$).

At diagnosis, none of the patients showed the extracolonic manifestations of familial adenomatous polyposis. One patient had a history of renal carcinoma diagnosed and treated 4 years before the diagnosis of polyposis. The vast majority of patients (81.8%) had no family history of colorectal cancer. Two patients reported a family history of colorectal adenomas and cancer involving his own generation only in one subject, involving 2 generations with vertical transmission in the other one.

The most frequent MutYH variants were Y165C/Y165C, which was found in 6 patients (54.5%), and G382D/G382D, which was found in 2 patients (18.2%). The 5 MutYH variants in the study group (Y165C, G382D, R231H, 1103delC, IVS10+3A>C) and their functional and carcinogenic effects have been previously reported.[3,8,9]

The main clinical and genetic characteristics of the 3 patients who underwent proctocolectomy at the time of diagnosis and were consequently excluded from the present analysis are as follows: Patient A was a 47-year-old female when, in 1987, she was given a diagnosis of familial adenomatous polyposis (50–100 colonic adenomas, 14 rectal adenomas) with 3 synchronous carcinomas (transverse and sigmoid colon, rectum); the biallelic MutYH variant was Q324S/Q324S. Patient B was a 74-year-old male when, in 2003, he had a diagnosis of adenomatous polyposis (50–100 colonic adenomas, 1 rectal adenoma) with 3 synchronous carcinomas (ascending and transverse colon, rectum); his biallelic MutYH variant was G382D/G382D. Patient C was a 39-year-old male when, in 2007, he had a diagnosis of familial adenomatous polyposis (100–200 colonic adenomas, 18 rectal adenomas) with a MutYH biallelic 379delC/IVS10+3A>C variant.

Rectal Stump Adenomas and Extrarectal Evolution after Colectomy

Cumulatively, the 11 patients were followed up for 114 years after surgery. The median surveillance time was 5 years (mean, 10.36 ± 8.91; range, 2–23 y). Four patients have been followed-up for more than 15 years. Up to the present time, none of the patients has been lost to follow-up. A total of 118 surveillance proctoscopies were performed, for an average 10.73 ± 9.26 proctoscopies per patient (range, 2–24). All patients still living underwent a proctoscopy during 2009.

Up to the present time, no patient has developed rectal cancer. A total of 148 macroscopic adenomas were found in the rectal stump. The mean number of adenomas per proctoscopy was 1.23 ± 2.19 (median, 0.33) ranging from 0 to 10 adenomas per proctoscopy. More than 3 adenomas at a single examination were found in 27 surveillance proctoscopies (22.9%). The mean number of adenomas per year per patient was 1.52 ± 2.93 (median, 0.50).

No adenoma of the rectal stump was found in 3 patients (median surveillance, 3 y; range, 2–5 y). Of 148 adenomas found in the remaining 8 patients, 147 were at low-grade dysplasia, and one only (0.7%) was at high-grade dysplasia; 5 adenomas (3.4%) had a 1- to 2-cm diameter, 64 adenomas (43.2%) had a 0.5- to 1-cm diameter; and the remaining 79 adenomas (53.4%) had a <0.5-cm diameter. A tubular or a tubulovillous architecture was found in 89 (60.1%) and in 59 (39.9%) adenomas, respectively.

One patient developed duodenal polyposis (Spiegelmann I) 8 years after colectomy at the age of 66 years and a gastric adenoma 1 year later; another patient developed duodenal polyposis (Spiegelmann I) 20 years after colectomy at the age of 68 years. One male patient died of pancreatic cancer 24 years after colectomy at the age of 76 years.

To date, none of the 11 patients has received chemoprevention, including continuous nonsteroidal anti-inflammatory drug treatment.

Predictors of the Number of Adenomas in the Rectal Stump

In the present series, the mean number of rectal adenomas per year was not significantly associated with patient gender ($P = .924$), age at diagnosis ($P = .531$), MutYH mutation (Y165C/Y165C vs other variants, $P = .096$), presence of family history of polyposis or colon cancer ($P = .095$), type of colonic polyposis (classical vs attenuated) ($P = .406$), site distribution of polyposis (right vs left colon vs diffuse, $P = .241$), or number of rectal adenomas at diagnosis ($P = .735$).

The mean number of adenomas per year found during endoscopic surveillance of the rectal stump in patients with colon cancer at diagnosis was higher (2.08 ± 3.30) than in those patients without colon cancer, in whom no rectal adenomas were found after surgery ($P = .012$). The presence of multiple synchronous colon carcinomas at diagnosis was not associated with the mean number of rectal adenomas per year ($P = .368$).

DISCUSSION

Most MAP patients undergo intestinal surgery at the time of first diagnosis. The proportion of those requiring colectomy at presentation because of colorectal cancer ranges from 50% to 79%.[2,3,10,11] Moreover, further patients have extensive polyposis and also require surgery.

Among surgical patients, those having rectal cancer or severe polyposis of the rectum should undergo a proctocolectomy, whether restorative or not. Although a minor involvement may be predicted, the size of this subgroup has scarcely been defined. Aretz et al[3] found a rectal carcinoma in 15 of 71 patients with biallelic MutYH mutations (21%) at the time of diagnosis, whereas Nielsen et al[2] found a rectal cancer in 6 of 40(15%) MAP patients. In our smaller series, 2 patients with biallelic MutYH mutation had a rectal cancer at the time of diagnosis (14%), but, because they were undergoing proctocolectomy, they were excluded from the study cohort.

Whether to preserve or to remove the rectum in those cases having less severe rectal disease (from previous figures, they should be the majority of surgical MAP patients) remains a debated issue. The recent guidelines from the Mallorca Workshop[5] state that: "If surgery is required, an ileorectal anastomosis will be sufficient in most cases to eliminate the cancer risk"; however, little evidence on the long-term safety of such an approach is available from specific follow-up studies. In particular, Valanzano and coworkers,[12] for 41 to 201 months, followed up 3 patients with biallelic MutYH mutation who underwent total colectomy without finding cancer of the rectal stump. Proctoscopic surveillance with polypectomy was conducted every 6 to 12 months in all patients. Leite and coworkers[13] described a MAP patient who developed rectal cancer 18 years after total colectomy, whereas no rectal cancer was found during follow-up in 5 other patients undergoing total colectomy. Unfortunately, no information is available on the type and timing of rectal stump surveillance conducted by these authors.

The 11 patients in the present series have been monitored for up to 23 years since total colectomy, and, to the best of our knowledge, this is the first study looking specifically at the follow-up of MAP patients undergoing total colectomy. Up to the present time, endoscopic surveillance has provided adequate control on adenoma burden in the rectal stump, because no patient has developed rectal cancer.

In our opinion, the key elements for a safe rectum-preserving approach have been the stringent rules for preoperative selection of patients and for postoperative rectal surveillance. Only those patients having fewer than 10 adenomas with no high-grade dysplasia and no carcinoma were offered a total colectomy with rectum preservation. Moreover, extensive counseling has been provided to the patients to evaluate compliance and expectations of each subject and to obtain optimal adherence to the surveillance protocol.

The rate and characteristics of adenomas that developed after total colectomy in our series indicate that widening proctoscopy intervals beyond 12 months may carry a substantial risk. Unfortunately, the small numbers of cases included in the present and previous studies[12,13] hampers a proper statistical evaluation of preoperative risk factors for developing rectal cancer after surgery. Similarly, it is also difficult to define what "severe rectal polyposis" actually means (5 adenomas? 10 adenomas? 20 adenomas? etc). Further follow-up studies on larger series are clearly mandatory, and more comprehensive surveillance protocols need to be validated on the basis of a spectrum of disease severity that might be wider than previously expected.[14]

CONCLUSION

Our observational study confirms that total colectomy with ileorectal anastomosis may be appropriate with MAP, provided that patients have no rectal cancer or severe rectal polyposis at presentation and that they undergo yearly endoscopic surveillance thereafter.

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