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Original article

Colorectal cancer in familial adenomatous polyposis: Are there clinical predictive factors?☆

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ARTICLE INFORMATION

Article history:
Received March 9, 2010
Accepted May 9, 2010

Keywords:
Adenomatous polyposis coli
Adenomatous polyps
Cancer
Colorectal neoplasms/surgery
Mortality

A B S T R A C T

Background: Familial Adenomatous Polyposis (FAP) is a hereditary disorder with multiple colorectal polyps that exhibit an almost inevitable risk of colorectal cancer (CRC) in untreated patients.
Goals: To evaluate clinical features related to CRC risk at diagnosis.
Material and methods: Charts from 88 patients were reviewed to collect information regarding age, family history, symptoms, polyposis severity and association with CRC.
Results: 41 men (46.6%) and 47 women (53.4%) were assisted. CRC was detected in 53 patients (60.2%), with a frequency of 9.1% under 20 years, 58% between 21-40 and 85% over 41 years of age. Average age of patients without CRC was lower at treatment (29.5 vs 40.0 years; *P*=.001). Family history was reported by 58 patients (65.9%), whose average age did not differ from those who didn't report it (33.4 vs 34.4; P=.17). Asymptomatic patients comprised 10.2% of the total; in this group, CRC incidence was much lower when compared to those presenting symptoms (1.1% vs 65.8%; P=.001). Patients without CRC presented a shorter length of symptoms (15.2 vs 26.4 months; P=.03) and less frequent weight loss (11.4% vs 33.9%; *P*=.01). At colonoscopy, polyposis was classified as attenuated in 12 patients (14.3%), who presented greater average age (48.2 vs 33.3 years; *P*=.02) and equal CRC incidence (58.3% vs 58.3%; P=.6) when compared to those with classic polyposis.
Conclusions: The risk of CRC in FAP patients 1) increases significantly after the second decade; 2) is associated with higher age, weight loss, presence and duration of simptomatology; 3) is similar in patients with attenuated or classic phenotype.

☆Part of the present work has been presented in the 2009 Brazilian Congress of Coloproctology (September 7-9 in São Paulo, Brazil).
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El cáncer colorrectal en la poliposis adenomatosa familiar: ¿existen factores clínicos de predicción?

Palabras clave:
Poliposis adenomatosa coli
Pólipos adenomatosos
Cáncer
Neoplasias/cirugía colorrectal
Mortalidad

RESUMEN

Antecedentes: La poliposis adenomatosa familiar (PAF) es un trastorno hereditario caracterizado por pólipos colorrectales múltiples que presenta un riesgo casi inevitable de cáncer colorrectal (CCR) en los pacientes sin tratar.

Objetivos: Evaluar las características clínicas relacionadas con el riesgo de CCR en el momento del diagnóstico.

Material y métodos: Se examinaron los expedientes clínicos de 88 pacientes para recopilar información sobre la edad, la historia familiar, los síntomas, la gravedad de la poliposis y la asociación con el CCR.

Resultados: Se atendió a 41 hombres (46,6%) y 47 mujeres (53,4%). Se detectó CCR en 53 pacientes (60,2%), con una frecuencia del 9,1% entre aquellos menores de 20 años, 58% entre 21 y 40 años y 85% entre los mayores de 41 años. En el momento del tratamiento, la edad media de los pacientes sin CCR era inferior (29,5 años frente a 40,0 años; p = 0,001). Un total de 58 pacientes (65,9%) notificó la existencia de antecedentes familiares, y la edad media de estos no era diferente de los que no notificaron dicha condición (33,4 frente a 34,4 años; p = 0,17). Los pacientes asintomáticos representaban el 10,2% del total; en este grupo, la incidencia de CCR fue mucho menor comparada con la que presentaban síntomas (1,1% frente al 65,8%; p = 0,001). En los pacientes sin CCR la duración de los síntomas era más corta (15,2 frente a 26,4 meses; p = 0,03), y la pérdida de peso menos frecuente (11,4% frente al 33,9%; p = 0,01). En la colonoscopia, la poliposis se clasificó como atenuada en 12 pacientes (14,3%), que presentaban una edad promedio superior (48,2 frente a 33,3 años; p = 0,02) y una incidencia de CCR idéntica (58,3% frente a 58,3%; p = 0,6), comparados con aquellos con poliposis clásica.

Conclusiones: El riesgo de CCR en los pacientes con PAF 1) aumenta de forma significativa después de los 20 años de edad; 2) se asocia con una edad mayor así como una pérdida de peso, presencia y duración de la sintomatología superiores, y 3) es similar en los pacientes con fenotipo atenuado y clásico.

Introduction

Familial Adenomatous Polyposis (FAP) is a genetic disease with dominant character caused by an APC gene mutation (*"adenomatous polyposis coli"*)[1] predisposing to the development of numerous adenomatous colorectal polyps. According to national registries data, this disorder comprises less than 1% of colorectal cancer cases (CRC), affecting both sex equally in one case for every 6 to 22 thousand newborns.[2-4] Although highly penetrant, up to one third of patients may reveal no family history, including those with *de novo* mutation.[5,6]

The adenomatous nature and the great number of polyps are responsible for the risk of malignancy in non-treated patients, when colorectal cancer (CRC) may develop 10 to 15 years after the polyps appear (around 35years) and cause death at the beginning of the fourth decade.[7,8] For this reason, patients should be managed with prophylactic colectomy to avoid the development of CRC, which is the main cause of death in this group.

During the initial years, clinical symptoms are mild or even absent. Diagnosis of classical FAP is based on the identification of more than 100 small adenomatous colorectal polyps appearing during puberty.[9] However, patients with the attenuated form of the disease present a smaller number of lesions, which are usually flat and located within proximal segments of the colon. In this group, CRC develops later, around 50 years of age.[10-12] Recently, another gene (MUTYH) associated with an attenuated form of polyposis has been described.[13-15]

Besides the large bowel, PAF is nowadays considered a systemic disease that may involve the three germinative layers causing different extraintestinal manifestations in the ectoderm (skin cysts, retinal lesions, endocrine tumors, central nervous tumors), endoderm (hepatic tumor, gastric, small bowel and biliary adenomas and adenocarcinomas) and mesoderm (dental abnormalities, desmoids tumors and osteomas).[16,17]

During the last decades, we have tried to collect clinical, operative, endoscopic and histological data about FAP at the University Colorectal Surgery Unit, in an attempt to add information to the previously published papers among us.[16,18-24] and to document the disease features in our country.

Thus, the aim of the present work was to evaluate the main clinical features in FAP patients that could be associated with the CRC risk at diagnosis.

Material and methods

This study was ethically approved by the Ethics Committee of our hospital.

Patient features and data

The population consisted of FAP patients operated at the Colorectal Unit (University of São Paulo) from 1977 to 2006. Data from patient's charts were retrospectively collected, retrieving clinical (sex, age, familial history, symptoms, physical exam), endoscopic (adenoma distribution, polyposis severity, presence of CRC, topographic localization, synchronous tumors), operative and histological data (association with CRC).

Polyposis severity was estimated in accordance to the colonoscopist impression regarding the number and distribution of lesions throughout the colon and rectum. Is was classified as severe or intense (when the endoscopist used words such as "numerous", "thousands" or "carpet mucosa") or as mild or attenuated (when the description included terms such as "few", "sparse", "rare" or when there was less than 100 adenomas throughout the colon and rectum).

Statistical analysis

Much of the retrieved information was used to compare patients with and without CRC. Statistical analysis employed parametric (Student t test) and non-parametric tests (Chi-square and Mann-Whitney), adopting $P<.05$ to express significant results.

Results

Age, sex, symptoms and family history

Clinical data from 88 patients were evaluated, comprising 41 men (46.6%) and 47 women (53.4%). Average age was 33.0 years (13 to 80) at the beginning of symptoms and 33.7 years (10 to 80) at diagnosis (Table 1). During surgical treatment,

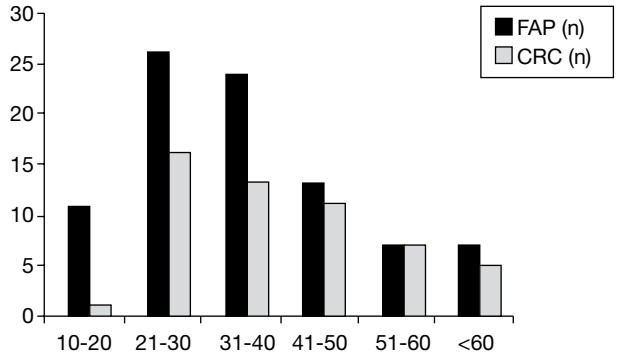
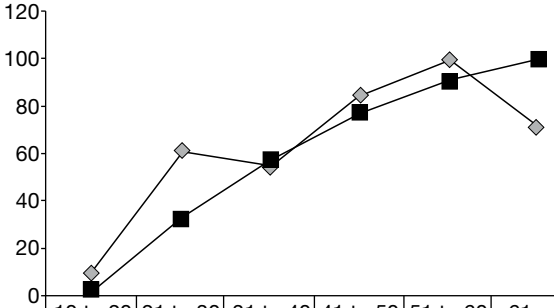


Figure 1 – Distribution of FAP and CRC cases in ten years age level. CRC indicates colorectal câncer; FAP, familial adenomatous polyposis.



	10 to 20	21 to 30	31 to 40	41 to 50	51 to 60	<61 years
◇CRC%	9.1	61.5	54.1	84.6	100	71.4
■CI%	1.9	32.1	56.7	77.4	90.6	100

Figure 2 – Crude and cumulative incidences of colorectal cancer in each decade. CI% indicates cumulative incidence of colorectal cancer cases; CRC%, percentage of colorectal cancer/FAP cases in each decade.

Table 1 – Patient's age at surgery and at beginning of symptoms

Age	At surgery	At beginning of symptoms	Probability (T test)
Average variation	35.9	33.0	P<.001
	15 to 82	13 to 80	
With câncer	40.0 (18-82) *S	35.6 (13-80) *S	P=.014
Without cancer	29.5 (15-68) *S	27.8 (15-66) *S	

*S indicates statistically significant.

Table 2 – Distribution of FAP cases and incidence of CRC by age

Age	Before 20 years	21-40 years	>41 years	P value (Chi-square)
No. (%)	11 (12.5)	50 (56.8)	27 (30.7)	P<.001
CRC (%)	01 (9.1)	29 (58.0)	23 (85.0)	P<.001

CRC, colorectal cancer; FAP, familial adenomatous polyposis; No., number.

average age was 35.9 years (15 to 82), being smaller in patients without CRC [29.5 years (15 to 68)] when compared to those with CRC [40.0 years (18 to 82)] (P<.001).

Table 3 – Clinical signs and symptoms in 79 symptomatic patients

Symptoms	Number	Per cent
Bleeding	54	61.4%
Diarrheia	38	43.2%
Abdominal pain	36	40.9%
Weight loss	22	25%
Anaemia	17	19.3%
Mucus in feces	15	17.0%
Intestinal obstruction	6	6.8%
Constipation	5	5.7%
Nausea and vomiting	3	3.4%
Intestinal perforation	1	1.1%
Others	11	12.5%
Symptomatic	79	89.7%
Asymptomatic	9	10.2%

Age	Asymptomatic		Symptomatic	
	No.	%	No.	%
<20 years (11)	4	36.4	7	63.6
>20 years (77)	5	6.5	72	93.5

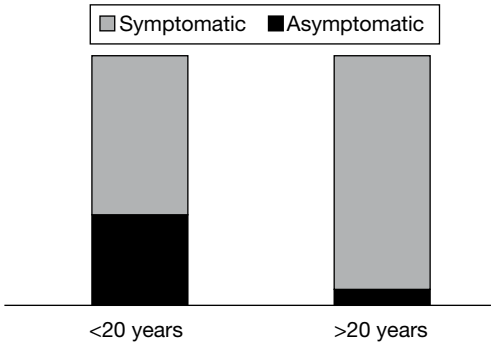


Figure 3 – Number of asymptomatic and symptomatic patients before and after 20 years of age.

Table 2 shows distribution of FAP patients by age. Disease incidences before 20 years, from 21 to 40 years and after 40 years were 12.5%, 56.8%, and 30.7%, respectively. Seven patients (7.9%) were older than 60 years. CRC incidence increased from 9.1% before 20 years to 58% from 21 to 40 and 85% after 41 years of age (P<.001). Figures 1 and 2 show that the CRC crude and cumulative incidences increase significantly after the second decade of life.

Familiar history of FAP was reported by 58 patients (65.9%), but only 21 (23.8%) were diagnosed due to affected relatives. Other 67 patients (76.1%) were diagnosed on the basis of symptoms related to the polyposis. Groups with or without familiar history presented no statistical difference regarding age (median 33.4 vs 34.4 years) or incidence of CRC (32/58; 55.2% vs 21/30; 70%) [P=.17].

At diagnosis, 53 patients (60.2%) already had CRC associated with the polyposis and only 9 (10.2%) revealed no clinical complaints. The most common symptoms (Table 3) were intestinal bleeding (61.4%), diarrhea (43.2%), abdominal pain (40.9%) and weight loss (25.0%).

Figure 3 reveals that the percentage of asymptomatic patients falls significantly from 36.4% to 6.5% after 20 years of age. Table 4 shows that CRC was significantly less frequently

Table 5 – Topographic distribution of 53 colorectal carcinomas in Familial Adenomatous Polyposis patients

	Number	Per cent
Isolated carcinomas		
Cecum	1	1.9
Ascendent colon	2	3.8
Transverse colon	4	7.5
Descendent colon	1	1.9
Sigmoid colon	11	20.8
Rectum	14	26.4
Total	33	62.2
Double carcinomas		
Sigmoid–rectum	6	11.3
Ascendent colon–rectum	1	1.9
Hepatic flexure–rectum	3	5.7
Transverse colon–rectum	1	1.9
Left colon–sigmoid	1	1.9
Total	13	24.5
Multiple carcinomas (3)	07	13.2

Table 4 – Clinical symptoms in patients with and without colorectal cancer (CRC). Values are compared with Chi-Square and Mann-Whitney tests

	Without CRC (35)		With CRC (53)		P value
	No.	%	No.	%	
Asymptomatic (9)	8	88.8	1	1.1	<.001 *S
Symptomatic (79)	27	34.1	52	65.8	<.001 *S
Weight loss	4	11.4	18	33.9	.017 *S
Bleeding	22	62.8	32	60.4	.815 *NS*
Symptoms, months	15.2 (0 to 60)		26.4 (1 to 120)		.030 *S

CRC indicates colorectal cancer; NS, not significant; *S, statistically significant.

Table 6 – Clinical features of attenuated and classical forms of polyposis

FAP	Male/female ratio	Average age and variation	CRC incidence	Diagnosis by symptoms
Classical (72)	34 M/38 F=0.9	33.3 (17-67)	42 (58.3%)	53 (73.6%)
Attenuated (12)	6 M/6 F=1.0	48.2 (26-82)	7 (58.3%)	10 (83.3%)
T Student test	P=.8 NS	P=.02 *S	P=.6NS	P=.7 NS

CRC, colorectal cancer; F, female; FAP, familial adenomatous polyposis; M, male; NS, not significant; *S, statistically significant.

detected among asymptomatic patients (n=1; 1.1%) when compared to those presenting symptoms (n=52; 65.8%) (P<.001). Average length of symptoms was smaller among patients without cancer (15.2 vs 26.4 months; P=.03). Weight loss was referred by 18 patients (33.9%) with CRC and only 4 patients (11.4%) without CRC (P=.017). Intestinal bleeding was equally reported by patients with (n=32/53; 60.4%) or without CRC (n=22/35; 62.8%) (P=.8).

Association with carcinoma and features of colorectal polyposis

Colonoscopy and specimen pathology detected the presence of CRC in 53 patients (60.2%). There were found one tumor, two or more than three in 33 (62.2%), 13 (24.5%) and seven patients (13.2%), respectively. Isolated lesions were mostly found in the rectum (14) and sigmoid colon (11) [Table 5].

Characterization of the polyposis severity by colonoscopy was possible in 84 patients. An attenuated pattern was observed in 12 patients (14.3%), the rest been considered classical or severe polyposis (n=72; 85.7%). Table 6 exhibits a comparison regarding clinical data of PAF and PAFA. When compared to patients with classical features, average age in attenuated polyposis was greater (48.2 vs 33.3 years) and CRC incidence was similar (58.3% vs 58.3%). The diagnosis of polyposis in both groups was established on the basis of symptoms for the majority of patients (83.3% and 73.6%, P=.7). Two patients with attenuated phenotype developed metachronous rectal cancer after ileorectal anastomosis.

Discussion

Classical FAP is characterized by development of hundreds to thousands of adenomas during puberty, although the disease does not usually manifest until late childhood or early adult life. But wide limits concerning the initial age of clinical manifestations have been reported.[2,5] Its most important clinical feature lies on the possibility of CRC development at a young age. In this context, age at diagnosis turns into a predictive risk parameter for CRC and must be taken into account to choose the best moment for surgery.

In the present series, the average age was 33 years when symptoms began and 35.9 years at surgical treatment, similarly to others that found mean ages of 33[25] and 34 years.[26] Age distribution revealed 12.5% before 20 years, 56.8% from 21 to 40 years and 30.7% with more than 41 years. Incidences of 15%, 53%, and 32% were reported in the study of Croner et al[26] for the same ages.

Today it is well recognized that familiar screening is the best way to achieve early diagnosis and treatment. This fact is evidenced by the lower average age among patients without associated CRC [29.5 years (15 to 68)] when compared to those with CRC (40.0 years, 18 to 82).

As shown in Figure 2, we have also found that the crude incidences of CRC increased from 9.1% in patients before 20 years to 58% from 21 to 40 years and 85% over 41 years. Similar findings have been reported by Croner et al[26] in a series of 143 patients, with no patients with CRC with age below 20 years and incidences of 30.2% (23/76) and 65% (30/46) in the groups between 20-40 years old and older than 40 years, respectively.

An analysis of a great number of FAP families from 1970 to 1980[27] showed that the CRC risk before 20 years is very low. Similar data from the *Leeds Castle Polyposis Group*[28] showed only one patient younger than 15 years. A recent review[29] showed that the proportion of FAP-patients with CRC diagnosed before 20 years of age in 1073 patients from five European Registries was 1.6%. In our series (Figure 2), we found a cumulative incidence of 1.9% and 32.1% in patients under 20 and 30 years, respectively. Altogether, this data suggest that surgical indication for classical FAP may be delayed till the beginning of the third decade unless any suspicious lesion is detected.

Furthermore, this information gives support to the so called “staged ileoanal anastomosis” (performance of ileorectal anastomosis and proctectomy with pouch after a 10-15-year period) when planning the surgical strategy and timing for surgery for young FAP patients. The rationale for this approach is based on the fact that some patients can avoid functional, reproductive and stoma complications associated with restorative proctocolectomy,[30,31] along with minimization of desmoids disease in at risk patients.[32]

The incidence of CRC in patients diagnosed out of screening programs may be greater than 60%.[33] We diagnosed associated CRC in 60.2% because the majority of our patients were diagnosed on the basis of clinical symptoms rather than familiar screening. In the literature, most studies show a greater incidence of CRC (50% to 70%) in symptomatic patients than in those identified in screening programs (3% to 10%).[7,27,34-36]

We diagnosed FAP on the basis of family history in only 24% of the patients, and clinical diagnosis was established throughout symptoms in the great majority (76%), similarly to Croner et al[26] who detected FAP on the basis of symptoms in 84%. Both groups didn`t have statistical difference regarding age or CRC incidence, although there was a small trend

toward a greater proportion of CRC among those without family history (70% vs 55%, *P*=.1).

Although a family history led to the diagnosis of the syndrome in about one fourth of the patients, this fact didn't influence their decision to enter a screening program that could help them establish an early diagnosis. Consequently, mean age of both groups was not significantly different at diagnosis, and this feature probably had a major impact on the incidence of CRC despite being conscious of a family history. If a greater proportion of patients with positive family history had entered an active screening at an adequate age (at most during the second decade of life), it would be possible to appreciate the influence of family information leading to a reduced association with CRC.

Despite the presence of polyps, clinical symptoms may be vague or even absent during the early stages of the disease. For this reason, genetic testing or endoscopic screening should start at puberty, before symptoms and colorectal cancer occur. Fecal bleeding is usually the initial manifestation, turning more frequent and intense over time. As the disease progresses, polyps may increase in number and size, and patients may experience diarrhea, mucous discharge, crampy abdominal pain, anemia, weight loss and constipation. However, these symptoms may not occur until the condition has become cancerous. Diarrhea, blood and mucus are considered an alert for the development of cancer.[9]

In our series, average length of symptoms was smaller (15.2 vs 26.4 months) in patients without cancer when compared to those with cancer. Furthermore, we found a significant smaller cancer incidence among asymptomatic patients (1.1% vs 65.8%). Similarly, Bulow[37] reported CRC in 67% of probands (diagnosed on the basis of symptoms, without knowing the hereditary disease) against 3% detected by familiar screening in Denmark. In other countries, data from National Polyposis Registries showed similar results in Netherlands (47% vs 4%),[36] Finland (65,5% vs 6,6%),[38] Australia (75% vs 6%),[39] and Italy (80% vs 3,3%).[40] These numbers clearly demonstrate the value of screening on CRC incidence associated with the syndrome.

Besides age, the presence of clinical symptoms, complaint of weight loss and the length of symptoms were also associated with a greater risk of CRC. We observed that 18 (33.9%) from 53 patients with CRC reported weight loss, while only 4 (11.4%) individuals without CRC did it (*P*=.01). On the other side, intestinal bleeding was similarly referred by patients with (n=32/53; 60.4%) and without CRC (n=22/35; 62.8%).

Thirty-three of our patients presented only one tumor (62.2%), mainly located in the rectum (14) and sigmoid (11). And it is worthy to note that a significant number of patients had two (24.5%) or more tumors (13.2%). This fact has important therapeutic and prognostic implications, as it raises the need for an oncologic resection of all segments during prophylactic colectomy. Other series[26] found a predominance of colon (59.5%) over rectal cancers (40.5%), similar to our findings in patients with one lesion in the specimen (57.6% and 42.4%, respectively).

The opportunity to indicate surgical treatment in the absence of CRC depends on factors such as age, genomic features and also on polyposis severity. It is well recognized that the presence of more than 1000 polyps duplicates the risk of CRC,[41] and this phenomena is related to the mutation locus where some regions (*hotspots*) such as codon 1309 lead to severe disease[42-47] and early beginning of symptoms.[10,27,28,34] When not treated, mortality of patients with CRC and mutation in codon 1309 occurs in average 10 years earlier.[34]

Previously named hereditary flat-adenoma syndrome,[48] the attenuated familial adenomatous polyposis (AFAP) is caused by specific mutations and its frequency is not yet defined. These patients develop CRC around 10 to 15 years later than classical FAP,[12] but earlier than patients with sporadic CRC.[49,50]

Among our patients, the characterization of polyposis severity by colonoscopy was obtained in 84 patients, defining 12 (14.3%) as attenuated and 72 (85.7%) as classical form. Comparison of the two groups revealed a greater average age among patients with AFAP (48.2 vs 33.3 years) and similar incidence of associated CRC (58.3% vs 58.3%). Otherwise, it is important to note that in both groups the diagnosis was established on the basis of symptoms rather than familial history (83.3% and 73.6%, respectively; *P*=.7). Thus, this result raises again the value of symptoms length even in those patients with milder disease.

During follow-up, it was possible to detect rectal cancer in six patients (16.6%) after ileorectal anastomosis. As two of them had been previously diagnosed for attenuated disease at 47 and 56 years of age, it becomes evident that even AFAP patients are not free from the risk of metachronous rectal cancer mainly when related to advanced age.[51]

All the data discussed here raises attention to the greater CRC incidence in patients diagnosed out of screening programs. It is also suggested that age is a crucial indicative factor for the risk of CRC, thus becoming a natural guide to define the best moment for surgical treatment. Our results suggest that the risk of CRC in FAP patient's increases significantly after the second decade of life, and it is associated with other clinical features such as weight loss and duration of symptoms.

FAP is a rare and complex disease that exhibits multiple clinical expressions. Thus, one management scheme does not fit all the patient`s demands, turning FAP treatment an issue for specialists. The decision of how and when to operate may become especially difficult when dealing with young female patients that must be convinced to undergo a prophylactic colectomy that eventually may alter body image, fertility and evacuation functions.

Assuming this difficult scenario, the proper discussion of all the problems by a specialist may facilitate the understanding of risks and details involved in the surgical decision. The option for the surgical procedure must be primarily based on disease severity. Thus, while most patients with few rectal adenomas, mild colonic phenotype, no colorectal carcinoma, family history of a mild phenotype, and those with attenuated forms (AFAP and MAP-MUTYH associated polyposis) do well with an ileorectal anastomosis, patients with profuse polyposis will need a restorative proctocolectomy.[20,51]

Secondly, the decision must be individualized in respect to age, health status and personal wishes.[33,52] Even in cases with severe polyposis, IRA is still a good option for young women aiming for childbirth, although it should be emphasized the need of a close surveillance and the risk of an eventual proctectomy with ileoanal anastomosis when necessary.[52]

When available, the aid of genetic information may influence the final decision. A recent research has showed that mutation analysis may predict the need for a secondary proctectomy.[53] Nonetheless, the evaluation of clinical and endoscopic data must help the surgeon to decide when and how to operate patients with different characteristics.

The risk of CRC in FAP patients 1) increases significantly after the second decade; 2) is associated with higher age, weight loss, presence and duration of simptomatology; 3) is similar in patients with attenuated or classic phenotype.

Conflict of interest

There are no conflict of interest and no funding sources to declare.

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