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New strategies in diagnosing and managing colic polyposis syndromes

E. Urso, M. Agostini, I. Mammi, S. Pucciarelli, D. Nitti

Centro di Prevenzione dei Tumori del Colon, Clinica Chirurgica 2^ (Direttore: Prof. D. Nitti)
Dipartimento di Scienze Oncologiche e Chirurgiche, Azienda Ospedaliera-Università di Padova

Name and Address of the corresponding Author:
Emanuele Urso
Clinica Chirurgica II
Policlinico Universitario, 6^ piano
via Giustiniani 2
35128-Padova
Tel. 0498212055 (segreteria)
Tel. 049-8212075 (studio)
Fax: 049-651891
e.mail: edl.urso@unipd.it

Introduction

Colorectal cancer is one of the most common type of cancers worldwide. It represents about 11% of all newly diagnosed cancers in the USA, and is responsible for 10% of cancer-related deaths.[1] In Europe, about 217 000 new cases of colorectal cancer are diagnosed yearly with an estimated incidence of 58 cases per 100 000 individuals. Since about 50% of the colorectal cancer patients could be cured, mortality for this cancer is about half the incidence.[2]

The prognosis of colorectal cancer patients is strongly related to the degree of tumor penetration through the bowel and to the presence of nodal and distant metastases (tumor stage) [3]. Diagnosis at an early stage of disease is associated with a better prognosis and consequently several screening programs, based on different diagnostic techniques, have taken place worldwide with the aim of increasing early diagnosis of adenomas and colorectal cancer [4]. The most known risk factors for the development of colorectal cancer are: age (> 50 years), gender (male>female), diet (total energy intake, intake of animal and saturated fat, low consumption of fiber, fruits and vegetable) [5] and family history of the same tumor [6]. Individuals at high risk of developing colorectal cancer have the greatest benefit of screening and surveillance. Almost 25% of cases of colorectal cancer occur in individuals with family history of colorectal cancer or adenomas and a small percentage of cases (5%) occur in association with inherited colorectal cancer syndromes[7]. Inherited syndromes with increased risk of colorectal cancer could be divided into two groups: the polyposis syndromes and the non-polyposis syndromes. In the non-polyposis syndrome, colonic polyps could be present, but the polyp's number doesn't characterize the phenotype. Polyposis syndromes could be divided in other subgroups: the adenomatous polyposis and the non-adenomatous polyposis syndromes. The famous (even if very rare) non adenomatous polyposis syndromes are Peutz-Jeghers syndrome and Juvenile polyposis syndrome.

Peutz -Jeghers syndrome is characterized by amartomatous polyps of colon and upper digestive tract and typical peri-oral pigmentation; Juvenile polyposis syndrome is characterized by amartomas with typical cystic structure, mucus and infiltration of lymphoid, neutrophil and eosinophil cells. Both these syndrome will not be further discussed in this article.

The adenomatous polyposis syndromes are: familial adenomatous polyposis syndrome (FAP), its attenuated subtype (A-FAP) and the polyposis related to mutation of MYH gene (MAP). The non polyposis syndromes are the hereditary non polyposis colorectal cancer syndrome (HNPCC or Lynch syndrome) and its subtypes: the Muir Torre syndrome (association with sebaceus tumors) and the Turcot syndrome (presence also of brain tumors). The inherited non polyposis

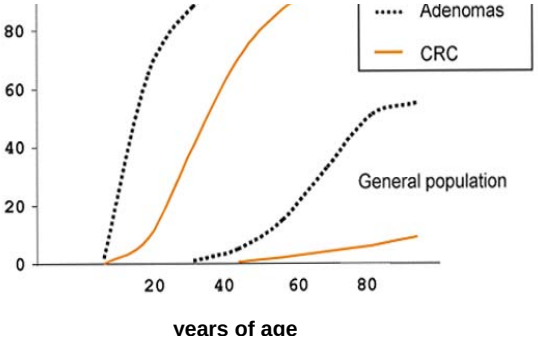
syndromes would be object of a next article on this web site.
Polyposis and non-polyposis colorectal cancer syndromes show important differences in age of onset, tumor distribution, and the natural history: so screening guidelines and management of these two different high risk groups vary.

The colonic polyposis syndromes

Familial adenomatous polyposis syndrome (FAP).
FAP is a genetic disorder inherited through an autosomal dominant manner and with complete penetrance. The germline mutation responsible of the disease is on the APC gene.
APC is a tumor suppressor gene located on 5q21 involved in the Wnt signaling pathway, which regulates the breakdown of β-catenin, a protein involved in cell proliferation, differentiation, migration and apoptosis[8, 9]. APC gene in also involved in controlling the cell cycle and in stabilizing microtubules for chromosomal stability. [8, 9]
Even if the disease is known as *Familial* Adenomatomatous Polyposis, some 1/3 of the newly diagnosed cases have no family history of polyposis coli: in these cases *de novo* mutations are probable.
The birth frequency of FAP is 1/13000-1/18000 live births in North Europe[10] (no data is available for the Italian population) and FAP accounts for less than 1% of all CRCs.[11]

Colonic phenotype.
The hallmark of FAP is the presence of more than 100 adenomas throughout the colon and rectum[7].
Polyps development begin at young age (14-20 years of age) from rectum to the proximal colon; malignant transformation of one or more of the colonic adenomas is very rare before 20 years of age, whereas colorectal cancer occurs in the majority of those patient who did not undergo colectomy within 40 years of age (figure 1).[7]

Figure 1: Incidence of adenomas and colorectal cancer in relation to age



Other clinical manifestation of FAP could be: polyps of the upper gastrointestinal tract; desmoid tumor of the abdominal and the retroperitoneum walls; thyroid cancer, hepatoblastomas and osteomas, fibromas, sebaceous cistys, congenital hypertrophy of the retinal pigment epithelium.

Polyps of the upper gastrointestinal tract
Upper gastrointestinal polyps are present in quite 90% of patients with FAP and the percentage of stomach and duodenal adenomas increases with age[12].
The most common type of gastric polyps is fundic gland polyps. Fundic gland polyps are often benignant lesions, but in FAP patients they could harbor *foci* of dysplasia and rare cases of gastric carcinoma associated with diffuse fundic gastric polyps are reported.[13]
The most dangerous lesions are duodenal adenomas: 2/3 of them occur close to the Vater papilla. Small bowel cancer related to duodenal adenomas represents the third cause of death (following metastatic disease and desmoid tumors) in FAP patients who underwent colectomy [14].
The severity of duodenal polyposis could be classified according to the Spiegelman classification (table 1), which could also be used to plan adequate endoscopic surveillance[15].

Desmoid tumors. [16, 17]
Desmoid tumors are aggressive and locally invasive fibromatosis. Desmoids are rare in the general population, but occur in about 15% of FAP patients. Desmoids are the second cause of death in FAP patients who underwent colectomy [14]: they occur especially in the small bowel mesentery or in the abdominal wall. Risk factors for desmoid developments are APC mutations between codons 1310 and 2011, and previous abdominal surgery. Desmoids can be asymptomatic or cause pain, bowel obstruction and perforation or hydronephrosis. The presence of desmoids in the bowel mesentery may preclude the construction of the ileal-pouch anal anastomosis, especially when rectal resection follows an initial ileo rectal anastomosis. The

surgical excision of the desmoid(s) often needs small bowel resection. Local recurrence of the disease is common and sometimes more aggressive.

Thyroid cancer [18, 19, 20]
Thyroid cancer occurs in some 1-2% of FAP patients; the mean age at diagnosis is the third decade of life. The most common histotype is the papillary cancer with cribriform pattern.

Hepatoblastoma [21, 22]
Hepatoblastoma is a pediatric embryonal tumor of the liver which affects patients with FAP under 3 years of age. This malignancy is rare in FAP (1/235 FAP patients) even if it is much more frequent than in the general population (1/100000 new born).

Brain tumors [23]
Brain tumors may be associated to polyposis. The most frequent histotype is medulloblastoma; ependimomas and astrocitomas are also described to be in association with APC germline mutations. Brain tumors, namely glioblastomas, are also associated to colorectal cancer related to mismatch repair genes dysfunction (Lynch syndrome). The association of polyposis or colorectal cancer and brain tumors is known as the **Turcot syndrome** (irrespective of if germline mutation is found in APC or in one of the mismatch repair genes).

Osteomas
Osteomas are benignant lesions that occur most frequently in the jaw bone; other localizations could be skull and ribs.

Dental abnormalities and excessive number of teeth could occur in some 20% of FAP patient.

Epidermal cystis, lipomas, fibromas, leiomyomas are other frequent lesions that can be present in the face, limbs scalp and other sites of the FAP patients, more often at young age. The association of polyposis coli and osteomas and skin tumors (fibromas, lipomas, and cystis) has been historically known as **Gardner syndrome**.

Congenital hypertrophy of the retinal pigmented epithelium (CHRPE) [24, 25]
CHRPE is a pigmented lesion of the fundus that is present in about 80% of the FAP patients and it is usually present at birth; these lesions are asymptomatic and before the genetic test for FAP, CHRPE usually used for the pre-symptomatic diagnosis in relatives of patients affected by FAP.

Some genotype/phenotype correlations have been observed:
- aggressive disease (more colorectal polyps, younger age at CRC development): mutation at codon 1309; [26]
- attenuated disease (attenuated polyposis): mutations in the extreme proximal and distal portion of the APC gene [27]
- increased risk of duodenal adenomas: mutations from codons 976 to 1067 [28]
- increased risk of desmoid tumors: mutations between codons 1445 and 1580 [29]

Genetic counseling
Patients with FAP have to be informed on their disease, and consequently on the surveillance program and treatments proposed.
Surveillance and timely colectomy have reduced the incidence of colorectal cancer in FAP patients and have improved their survival [30]. Both clinical surveillance and genetic testing are needed for adequate care of FAP families.
The finding of a mutation in the APC gene is helpful for the pre-clinical diagnosis in the first degree relatives of affected individuals. Counseling has to be planned not before 12-14 years of age.
Subjects, who do not carry the APC mutation found in one relative with polyposis, are not affected by FAP and they do not need surveillance for this disease.
Relatives of FAP patients who carry the same mutation of an affected family member have to be surveyed and timely treated.

Surveillance

Yearly rectosigmoidoscopy have to be planned for affected individuals at puberty; when polyposis has been diagnosed, full colonoscopy can be planned and upper gastrointestinal tract surveillance can be started.

The interval time between two esophagus-gastro-duodenoscopies (EGDSs) depends on the number, dimension, and grade of dysplasia of the adenomas eventually found (see Spiegelman's classifications[15] on table 1); interval time more than two years is however

not recommend. For sons of affected individuals yearly hepatic ultrasound is also advisable for surveillance of hepatoblastoma.
Periodic clinical examination of the thyroid is recommend; the use of ultrasound screening is under debate due to the rarity and the good prognosis of these malignancy in FAP patients.[18] Desmoids and other tumors have not been noticed in asymptomatic FAP patients.

Table 1. Classification of duodenal polyposis severity (Spiegelman classification) [15]

Score	1	2	3
Polyp Count	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histologic type	Tubular	Tubulo villous	Villous
Dysplasia	Low grade	Intermediate	High grade

Stage 0: 0 Point, **Stage I**: 1-4 Points, **Stage II**: 5-6 Points, **Stage III**: 7-8 Points, and **Stage IV**: 9-12 Points.

Treatment

Pharmacologic treatment.
There are no data to support pharmacologic treatment in FAP patients as an alternative to colorectal and upper gastrointestinal surgery.
Non steroidal anti inflammatory drugs (NSAID) like sulindac, and more recently celecoxib and rofecoxib, [30, 31, 32] have been used to reduce the number of polyps, especially in the rectal stump after colectomy or in the duodenum. NSAID have given good results in these indications even if long term benefits are inconsistent.
Moreover recent reports on the potential cardiovascular adverse effects of celecoxib have to be taken into consideration.
For both abdominal wall and retroperitoneal desmoids, tamoxifen is an option to slow the growth of mildly symptomatic lesions [34].
For more aggressive desmoid, chemotherapy can be considered: both combination of vinblastine and methotexate, and doxorubicine and dacarbazine have been used with good result. [35, 36]
Radiotherapy can have a role in palliative treatment.
The relevant side effects caused by the small bowel irradiation have to be considered.

Surgery
Colo-rectal surgery
Almost all FAP patients will develop colorectal cancer at young age if they do not undergo surgery (figure 2), so prophylactic colectomy is recommended. The best timing for surgery is usually at the end of the second decade of life [37], since risk of cancer is low before 20 years of age. Major concern remains on how to manage the rectum. There are 3 surgical options for FAP patients [37]:

a) **total proctocolectomy with definitive ileostomy (TPC).** Nowadays this option is applied only if there is a rectal cancer involving the sphincter or if there are fibrosis or large desmoids of the small bowel mesentery in which ileo-rectum (or ileo-anal anastomosis) is not feasible.

b) **subtotal colectomy with ileo-rectum anastomosis (IRA).** Indications for this intervention are: small number of polyps in the rectum (less than 20) without high grade dysplasia; refusal of a temporary stoma (a covering stoma is often constructed after ileo-anal anastomosis); compliance with frequent controls of the spared rectum. The major advantage of this type of surgery for FAP is a better defecatory function [38] and a low rate of complications (namely low percentage of sexual morbidity) if compared to the proctocolectomy.
If ileo-rectum anastomosis is preferred, patients have to be advised that adenocarcinoma can occur in the spared rectum even if adequate endoscopic controls are planned and that a second intervention for rectal resection can be necessary in the following years: some 4-8% and 26-32% of FAP patients with IRA require re-intervention in uncontrollable rectal polyposis or rectal cancer, respectively after 10 and 25 years after the first resection. [28, 39]

c) **proctocolectomy with ileo-anal anastomosis (IPAA).** With this operation the whole colon and rectum is removed and the anastomosis is made after the construction of an ileal pouch (figure 1),

because it has been demonstrated that defecatory function and the quality of life of a patient with ileo-anal anastomosis can be improved with the use of a 10-12 cm J pouch. Using this surgical option the risk of cancer is low. Risk of cancer on the cylindrical epithelium eventually retained after resection depends also on if the anastomosis is hand sewn or stapled, and if mucosectomy of the transitional zone (some 2 cm of cilindric epithelium left after resection) was performed. Risk of cancer after stapled anastomosis is reported to be 28 to 31% during follow up; risk of malignancy is lower after hand sewn anastomosis and mucosectomy: 10-14%. Polyps can re-occur in the ileal J-pouch with not negligible percentage (quite 40% at 10 years after colectomy). These issues explain why periodic endoscopic follow up of the ileo-pouch anal anastomosis is also strictly suggested after IPAA. [40, 41] It has to be noted that even if some authors report more surgical complications and worse bowel function after IPAA, other studies do not confirm significant differences in functional results and in quality of life of FAP patients who underwent IRA or IPAA. [42, 43]

Figure 2. Extension of colorectal resection and ileal J-pouch with low rectum or anus anastomosis in case of proctocolectomy respectively with preservation of the low rectum (a) or complete rectal excision (b).

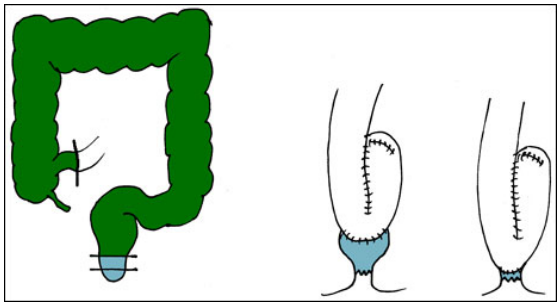


Figure from: www.tumoriereditari.info (with permission)

Upper gastrointestinal surgery

Management of gastric and especially duodenal polyps is a major concern in FAP patients, since duodenal cancer represents the second cause of death in patients who underwent prophylactic colectomy [14]. In the presence of histological diagnosis of gastric cancer, gastrectomy is obviously recommended. Gastrectomy is also a prophylactic option of cure in the case of repeated diagnosis of high grade dysplasia, especially if the diagnosis is made on random biopsies of polyps with benignant endoscopic features. When gastrectomy is planned in a FAP patient it has to be kept in mind that the duodenum needs to be followed-up. Reconstruction of digestive tract with Roux technique is not recommended in FAP patients: an alternative surgical technique is an esophageal-jejunum-duodenum anastomosis, using a segment of 50 cm of jejunum to limit the biliary reflux.

The management of high grade duodenal dysplasia depends on the number of polyps at risk of cancer. If the number of large and dysplastic polyps is low, endoscopic procedures are the best choice[44]. They include: endoscopic mucosal resection, polypectomy, and snare ampullectomy and laser ablation. On this regard one needs to keep in mind that high risk polyps often are localized close to the Vater papilla in FAP patients: endoscopic procedures at this site can be complicated with pancreatitis. Transduodenal excision is a surgical option when localized, large, dysplastic adenomas are not controllable with endoscopic techniques. Adenoma recurrence is frequent and difficult to treat with this procedure because the scars preclude anatomical dissection especially close to the papilla.

Pancreas-sparing duodenectomy (PSD) is a good option of cure when the number of adenomas or repeated recurrences preclude endoscopic or transduodenal approaches. PSD can be an alternative to prophylactic pancreatico-duodenectomy and it can be performed, in the absence of an invasive cancer**,** with acceptable morbidity rate in specialized surgical units. [45] In case of invasive duodenal cancer pancreatico-duodenectomy is the only curative procedure recommended.

Attenuated familial adenomatous polyposis (A-FAP)

A major concern on diagnosis, genetic testing and clinical management of patients with multiple colonic polyps regards patients with less than 100 adenomas of the colon and rectum. These patients do not fulfill the definition of FAP and their disease often has other characteristics not typical of the FAP. These cases are known as attenuated polyposis coli: A-FAP.

Nowadays the criteria for the diagnosis of A-FAP in not generally accepted, but most authors agree to the fact that a patient with more than 10 but less than 100 polyps has an A-FAP. A-FAP is different from FAP not only of the polyps number, but also of age at onset and the distribution of polyposis through the

colon. The diagnosis of A-FAP is often made at an age older than 45 years and polyps show predominance in the proximal colon. In A-FAP, colorectal cancer risk is also high and it is estimated of about 80% lifelong, unless colectomy is performed.[46, 47]
About one third of cases of A-FAP can be explained by a mutation in the following two genes: APC and MYH; the genetic bases of the rest of cases of A-FAP is still unknown. Polyposis coli with demonstrated biallelic mutation on MYH are known as MYH associated polyposis: MAP.
The colonic phenotype of the APC or MYH associated attenuated polyposis is often undistinguishable. It has to noted that MYH associated polyposis can also present hundreds adenomas, but the age at diagnosis is always delayed compared to the classical FAP.
Risk of extracolonic tumors in A-FAP with APC mutation are the same as the classical FAP.
In MAP, the risk of gastric adenomas and of desmoids is not higher. Duodenal polyposis has been found in 6 out of 33 MAP patients [48], so it is possible that the risk of duodenal adenomas is increased in this syndrome.
Since family history of colorectal cancer or polyposis coli is often negative, most MAP patients are detected by symptoms, and probably for this reason, approximately 50% of patients already present CRC.[48]

Genetic testing.
APC germline mutations are detected in 20-30% of cases of attenuated polyposis and biallelic MYH mutations can be identified in 10-20% of patients with polyposis without germline mutation identified on APC [48, 49]
In A-FAP, APC mutations are usually located at the proximal or distal parts or in exon 9 of the APC gene. The pattern of inheritance is autosomic and dominant, like for FAP. The pattern of inheritance of MAP is autosomal and recessive, as demonstrated by the absence of vertical transmission from parent to offspring.
MYH encodes a protein which is involved in the base excision repair (BER) pathway.
The BER pathway repairs free radical damaged purine and pyrimidine bases, abasic sites and single strand breaks, and it is essential for maintaining genome stability. Biallelic germline mutations in the *MYH* gene were shown to cause multiple colorectal adenomas and carcinomas because loss of *MYH* function results in increased frequency of G:C>T:A somatic mutations in APC and other genes.[50,51]There are two mutations most frequent found on MYH in the Caucasian population: Y165C and G382D.
The role of the monoallelic mutation on MYH is still unclear: most likely monoallelic MYH mutation carriers have a mildly increased risk of colon cancer if compared to the general population. MYH germline mutation testing is indicated in patients with 10 or more adenomas after exclusion of an APC mutation, especially in cases lacking an autosomal dominant means of inheritance. Genetic testing is simplified by the presence of two "hot spot" mutations representing 80% of all mutations (Y165C and G382D).[52, 53, 54]

Surveillance and treatment
A-FAP
Surveillance of the family member at risk can start a little later than classical FAP.
Because of the proximal location of polyps, complete colonoscopy is necessary.
The first colonoscopy can be performed at the age of 15 and if no polyps are found biannual colonoscopy can follow.
Upper GI polyposis and other features of FAP occur in similar frequencies compared to typical FAP: recommendation for surveillance of the extracolonic tumors are the same for FAP.
When endoscopic procedures are not sufficient to safely control the polyposis, colectomy should be performed. Because diffused rectal polyposis in not frequent in A-FAP, rarely, proctocolectomy, with ileo-pouch-anal anastomosis (IPAA) is necessary.
MYH-associated polyposis (MAP)
There are no generally accepted guidelines for the surveillance of MAP patients and for their family members at risk.
If biallelic germline mutation on an MAP patient is identified, the same can be used to screen at risk and not at risk family members (especially siblings). At risk family members are those with biallelic MYH mutation, or siblings of MAP patients who refuse genetic testing.
For sons of an affected subject, genetic testing can be performed at the end of the second decade of life.
For individuals at risk, biannual colonoscopy starting at the age of 20 can be recommended. Since duodenal polyposis may occur, periodical upper GI endoscope can be proposed; interval time between two examinations depends on each endoscopic findings.

Report of the serie of FAP and A-FAP of the Centro di Prevenzione dei Tumori del Colon, Clinica Chirurgica II^, Azienda Ospedaliera, Università di Padova

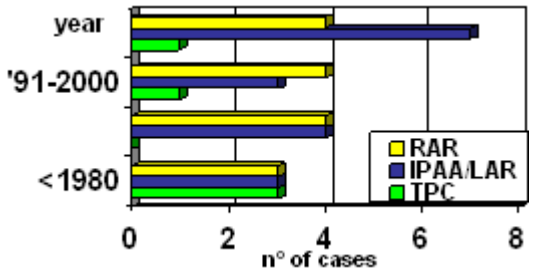
Patients and Methods

The enrolment concerns patients who had counseling at Centro per i Tumori Ereditari del Colon of Padova from January 2003 to September 2007.
Personal and family history and clinical records were achieved and a dedicated database was taken.
After genetic counseling and informed consent, direct sequencing of APC gene was carried out. In patients with non informative APC test, MHY gene was sequenced.

Familial Adenomatous Polyposis Coli

Inclusion criteria are: more than 100 polyps diagnosed at endoscopic examination and less than 60 years at diagnosis.
Twenty two FAP families and 85 family members were accrued at Centro di Prevenzione dei Tumori del Colon of Azienda Ospedaliera di Padova. After genetic testing and endoscopic examinations, 47 subjects (25 male and 22 female) were diagnosed as affected by FAP. Median age at diagnosis was 25 year (range11-53). Mutation on APC was found in 14 families; in one family genetic study was not informative; in 7 families genetic tests are ongoing.
Invasive colorectal adenocarcinoma was present in 12 cases at diagnosis (25%): median age of these patients was 35 years (versus 24 years of FAP patients without invasive tumor). Thirty seven 37 patients underwent colorectal surgery: 7 coloproctectomies with ileo-J pouch-anal anastomosis (IPAA), 10 colectomy with ileo-J pouch- low rectal anastomosis (Low-IRA), 15 colectomy with ileorectal anastomosis (IRA) and 5 total proctocolectomy with definitive ileostomy (TPC) were performed. Ten patients are on waiting list for surgery (median age 20 years; range: 12-28 years): all but 3 of these patients are younger than twenty years of age. Three patients, all female, of 24, 26 and 28 years, refused colectomy: they are followed yearly with endoscopic control. Colectomy with sphyncter preservation was the procedure most performed (Figure 3). The main indication for sphincters amputation was the presence of rectal cancer: four out twelve FAP patients with rectal cancer at diagnosis had coloproctectomy with definitive ileostomy, whereas only one (operated in 1976) out of 31 FAP patients without rectal adenocarcinoma at diagnosis had permanent ileostomy as primary intervention. Four out of twelve patients with colorectal carcinoma at diagnosis developed metastatic disease during follow up.
Four out the fifteen patients with IRA (26.6%) underwent re-operation for uncontrollable polyposis (3 cases) or for cancer (1 case) on the rectal stump: CAA was performed in 3 patients and in one case permanent ileostomy was constructed. The median interval time before the primary colectomy and the re-intervention on the rectal stump was 12, 5 years (range2-23 years). None of the patients with CAA or low LAR as primary surgery required re-intervention: endoscopic procedures were often performed to remove polyps ≥ 0.5 cm or more.
One patient (2%) with *de novo* mutation had duodenal peri-ampullary adenocarcinoma synchronous to a rectal cancer at diagnosis of FAP, when he was 35 years old.
Duodenal adenomas were present in 7 patients (15%): all these patients were managed with endoscopic procedures. One female patient has severe duodenal polyposis (Spiegelman classification stage IV) 12 years after colectomy: she refuses a major surgery and is been followed up closely.
Two patients had gastrectomy: one for gastric adenocarcinoma and one due to repeated diagnosis of severe dysplasia on gastric adenomas of innocent endoscopic appearance.
Five patients (11%) suffered from desmoid (3 of the retroperitoneum and 2 of the abdominal wall). Only one desmoid of the abdominal wall, symptomatic for pain, underwent surgical excision and relapsed a few months after surgery.
Two patients suffered cancers apparently not related to FAP: kidney and cervix carcinomas.

Figure 3: Surgery for FAP in past years: patients accrued at the Centro per i Tumori Ereditari del Colon of Padova.



Attenuated polyposis coli.

Inclusion criteria are: >10 colonic synchronous adenomas, <100 colonic polyps at any age or >100 polyps and age >60 years at diagnosis of polyposis.

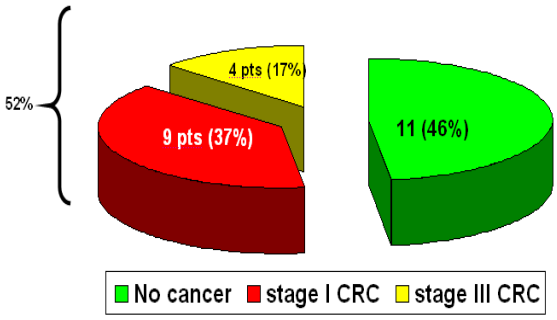
Twenty four patients [mean age: 50 yrs (32-74) M/F=18/6] were enrolled. Patients with first degree relatives and second degree relatives with adenoma(s) or colorectal cancer were 13 (54%) and 5 (22%) respectively. Median number of polyps, adenomas and hyperplasic polyps was 42 (10-90), 35 (3-90) and 7 (0-15) respectively. Adenomas and hyperplasic polyps coexist in 13 patients (54%). In 3 patients the number of colonic polyps has not been clearly stated. Colon cancer was present in 13 (54%) patients: AJCC stage I in 9 cases and stage III in 4 cases (Figure 3). Treatment was: subtotal colectomy, segmental resection, trans-anal excision and multiple endoscopic polypectomy in 12 (50%), 5 (21%), 1(4%) and 6 (25%) cases respectively.

Eight patients (33%) had one metachronous cancer (cancer of esophagus, thyroid, pancreas, CNS, two cases of kidney cancer and two cases of lymphomas) and 1 patient (4%) had two metachronous tumors (breast and lung cancer).

In the 16 cases of which genetic study was been concluded, four biallelic mutation on MYH, one monoallelic mutation on MYH and one APC Ashkenazy mutation were found; in 10 patients APC and MYH test was not informative and in 8 patients the genetic test is ongoing. All patients enrolled are alive and cancer free at the moment.

Data of our series of attenuated polyposis coli…..the follow: adenomas and hyperplasic polyps often coexist in A-FAP; subtotal colectomy has been chosen as the best treatment in more than half of cases of A-FAP registered at our Centro di Prevenzione; colon cancer has been diagnosed in more than half of patients, but at the first AJCC stage in most of cases (Figure 4); the association with non colonic metachronous tumors seems remarkable in A-FAP; even if, at the moment, genetic study has been completed in only half of these cases, biallelic MYH mutation seems to be a frequent cause of A-FAP.

Figure 4: Prevalence of ColoRectal Cancer (CRC) in 24 patients with A-FAP



References

1. American Cancer Society. Cancer Facts and Figs. 2003. Atlanta, GA: American Cancer Society, 2003
http://www.cancer.org/docroot/STT/stt0.asp.

2. EUCAN-Cancer Incidence, Mortality and Prevalence in the European Union-1998 Estimates.
www-dep.iarc.fr/eucan/eucan.htm.

3. Green FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (eds). AJCC Cancer Staging Manual (6th edn). New York: Springer: 113, 2002.

4. Chorost MI, Datta R, Santiago RC, Lee B, Bollman J, Leitman IM, Ghosh BC. ‘‘Colon cancer screening: where have we come from and where do we go?’’ J. Surg. Oncol. 85 :7-13, 2004.

5. Shike M. Diet and lifestyle in the prevention of colorectal cancer: an overview. Am J Med. 25;106(1A):11S-15S, 1999.

6. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med. 331:1669-7, 1994.

7. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 348 :919-32, 2003.

8. Nathke I. APC at a glance. J Cell Sci 117:4873–5, 2004.

9. Goss KH, Groden J. Biology of the adenomatous polyposis coli tumor suppressor. J Clin Oncol 18:1967–79, 2000.

10. Bisgaard ML, Fenger K, Bulow S et al. Familial adenomatous polyposis (FAP), frequency penetrance and mutation rate. Hum Mut 3: 121-5, 1994.

11. Burt RW, Bishop DT, Lynch HT, et al. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. BullWorld Health Organ 68:655–65, 1990.

12. Bulow S, Bj¨ork J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. The DAF Study Group. Gut 53:381–6, 2004.

13. Hofgartner WT, Thorp M, Ramus MW, et al. Gastric adenocarcinoma associated with fundic gland polyps in a patient with attenuated familial adenomatous polyposis. Am J Gastroenterol 94:2276–81, 1999.

14. Arvanitis ML, Jagelman DG, Fazio VW, et al. Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 33:639–42. 30, 1990.

15. Spigelman AD, Williams CB, Talbot IC et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 2: 783-785, 1989.

16. Clark SK, Neale KF, Landgrebe JC et al. Desmoids tumors complicating familial adenomatous polyposis. Br J Surg 86:1185-1189, 1999.

17. Soravia C, Berk T, McLeod RS et al Desmoid disease in patients with familial adenomatous polyposis. Dis Colon Rectum 43:363-369, 2000

18. Bulow C, Bulow S, Leeds Castle Polyposis Group. Is screening for thyroid carcinoma indicated in familial adenomatous polyposis? Int J Colorectal Dis 12:240–2, 1997.

19. Truta B, Allen BA, Conrad PG, et al. Genotype and phenotype of patients with both familial adenomatous polyposis and thyroid carcinoma. Fam Cancer 2:95–9, 2003.

20. Perrier ND, Van Heerden JA, Goellner JR, et al. Thyroid cancer in patients with familial adenomatous polyposis. World J Surg 22:738–42, 1998.

21. Giardiello FM, Petersen GM, Brensinger JD, et al. Hepatoblastoma and APC gene mutation in familial adenomatous polyposis. Gut 39:867–9, 1996.

22. Hughes LJ, Michels VV. Risk of hepatoblastoma in familial adenomatous polyposis. Am J Med Genet 43:1023–5, 1992.

23. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot’s syndrome. N Engl J Med 332:839–47, 1995.

24. Ruhswurm I, Zehetmayer M, Dejaco C, et al. Ophthalmic and genetic screening in pedigrees with familial adenomatous polyposis. Am J Ophthalmol 125:680–6, 1998.

25. Traboulsi EI, Krush AJ, Gardner EJ, et al. Prevalence and importance of pigmented ocular fundus lesions in Gardner's syndrome. N Engl J Med 316:661–7, 1987.

26. Friedl W, Caspari R, Sengteller M, et al. Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. Gut 48:515–21, 2001.

27. Friedl W, Caspari R, Sengteller et al. Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. Gut 48: 515-521, 2001.

28. Bertario L, Russo A, Sala P, et al. Multiple approach to the exploration of genotype-phenotype correlations in familial adenomatous polyposis. J Clin Oncol 21:1698–707, 2003.

29. Eccles DM, van der Luijt R, Breukel C et al. Hereditary desmoid disease due to a frameshift mutation at codon 1924 of the APC gene. Am J Hum Genet 59: 1193-1201, 1996.

30. Heiskanen I, Luostarinen T, J¨arvinen HJ. Impact of screening examinations on survival in familial adenomatous polyposis. Scand J Gastroenterol 35:1284–7, 2000.

31. Giardiello FM, Hamilton SR, Krush AJ, et al: Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 328:1313-1316, 1993.

32. Steinbach G, Lynch PM, Phillips RK, et al: The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 342:1946-1952, 2000

33. Higuchi T, Iwama T, Yoshinaga K, et al: A randomized, double-blind, placebo-controlled trial of the effects of rofecoxib, a selective cyclooxygenase-2 inhibitor, on rectal polyps in familial adenomatous polyposis patients. Clin Cancer Res 9:4756-4760, 2003

34. Bus PJ, Verspaget HW, van Krieken JH, et al:Treatment of mesenteric desmoid tumours with the anti-oestrogenic agent toremifene: Case histories and an overview of the literature. Eur J Gastroenterol Hepatol 11:1179-1183, 1999

35. Azzarelli A, Gronchi A, Bertulli R, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer 92:1259-1264, 2001

36. Lynch HT, Fitzgibbons R Jr, Chong S, et al. Use of doxorubicin and dacarbazine for the management of unresectable intra-abdominal desmoid tumors in Gardner's syndrome. Dis Colon Rectum 37:260-267, 1994

37. Guillem JC, Wood WC, Moley JF, Berchuck A, Karlan BY, Mutch DG, et al. ASCO/SSO Review of Current Role of Risk-Reducing Surgery in Common Hereditary Cancer Syndromes J Clin Oncol 24:4642-4660.

38. Aziz O, Athanasiou T, Fazio VW, Nicholls RJ, Darzi AW, Church J, Phillips RK, Tekkis PP. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 93:407-17, 2006.

39. Vasen HF, van der Luijt RB, Slors JF et al Molecular genetic test as a guide to surgical management of familial adenomatous polyposis. Lancet 348:433-435,1996

40. Van Duijvendijk P, Vasen HF, Bertario L et al Cumulative risk of developing polyps or malignancy at the ileal pouch anal anastomosis in patients with familial adenomatous polyposis. J Gastrointestinal Surg 3; 325-330,1999.

41. Remzi FH Church JM, Bast J et al Mucosectomy versus stapled anastomosis in patients with familial adenomatous polyposis: functional outcome and neoplasia control. Dis Colon Rectum 44; 1590-96, 2001.

42. Kartheuser AH, Parc R, Penna CP et al. Ileal pouch anastomosis as the firs choice in patients with familial adenomatous polyposis: a ten years experience. Surgery 119: 615-623,1996.

43. Hassan I, Chua HK, Wolff BG et al Quality of life after ileal pouch anal anastomosis and ileorectal anastomosis in patient with familial adenomatous polyposis. Dis Colon Rectum 48: 2032-2037, 2005.

44. Norton ID, Geller A, Petersen BT, et al. Endoscopic surveillance and ablative therapy for periampullary adenomas. Am J Gastroenterol 96: 101-106, 2001

45. Sarmiento JM, Thomson GB, Nagorney, MD, Donohue JH, Farnell MB Pancreas sparing duodenectomy for duodenal polyposis Arch Surg 137:557-63, 2002

46. Knudsen AL, Bisgaard ML & Bulow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Fam Cancer 2: 43-55, 2003.

47. Burt RW, Leppert MF, Slattery ML et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 127: 444-451, 2004.

48. Aretz S, Uhlhaas S, Goergens H et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer 119: 807-814, 2006.

49. Spirio L, Olschwang S, Groden J et al. Alleles of the APC gene: an attenuated form of familial polyposis. Cell 75: 951-957, 1993.

50. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, Hodges AK, Davies DR, David SS, Sampson JR, Cheadle JP. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet 30:227-32, 2002.

51. Lipton L, Halford SE, Johnson V, Novelli MR, Jones A, Cummings C, Barclay E, Sieber O, Sadat A, Bisgaard ML, Hodgson SV, Aaltonen LA, et al. Carcinogenesis in MYH associated polyposis follows a distinct genetic pathway. Cancer Res 63:7595-9, 2003.

52. Jenkins MA, Croitoru ME, Monga N, Cleary SP, Cotterchio M, Hopper JL, Gallinger S. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers 15:312-4, 2006.

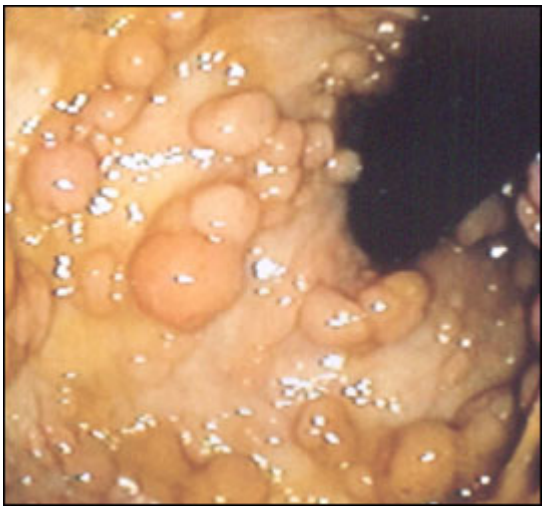
53. Croitoru ME, Cleary SP, Di Nicola N, Manno M, Selander T, Aronson M, Redston M, Cotterchio M, Knight J, Gryfe R, Gallinger S. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. J Natl Cancer Inst 96:1631-4, 2004.

54. Farrington SM, Tenesa A, Barnetson R, Wiltshire A, Prendergast J, Porteous M, Campbell H, Dunlop MG. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 77:112-9, 2005.

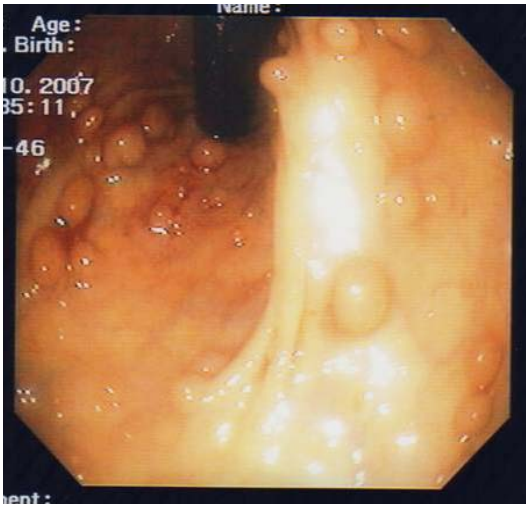
Pictures collection

Endoscopic vision of the rectal ampulla in FAP patients (a,b)

(a)

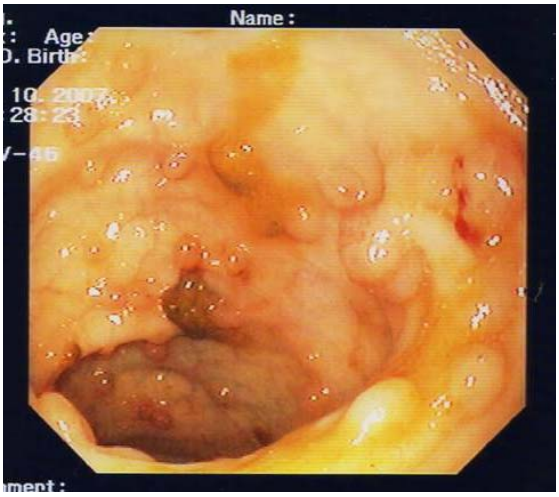


(b)

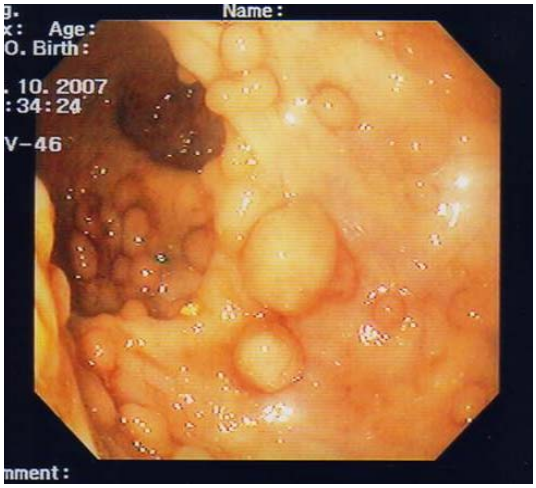


Endoscopic vision of sigmoid colon in young FAP patient.

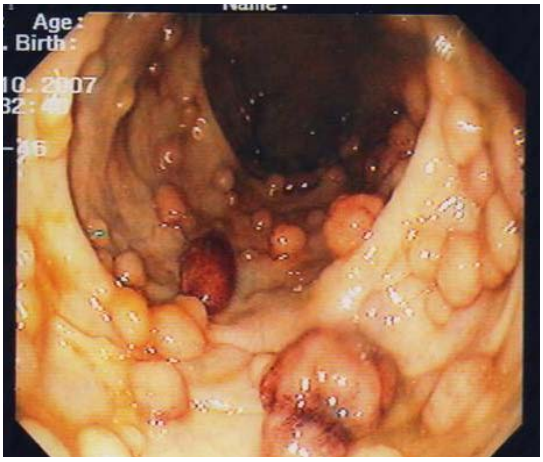
(a)



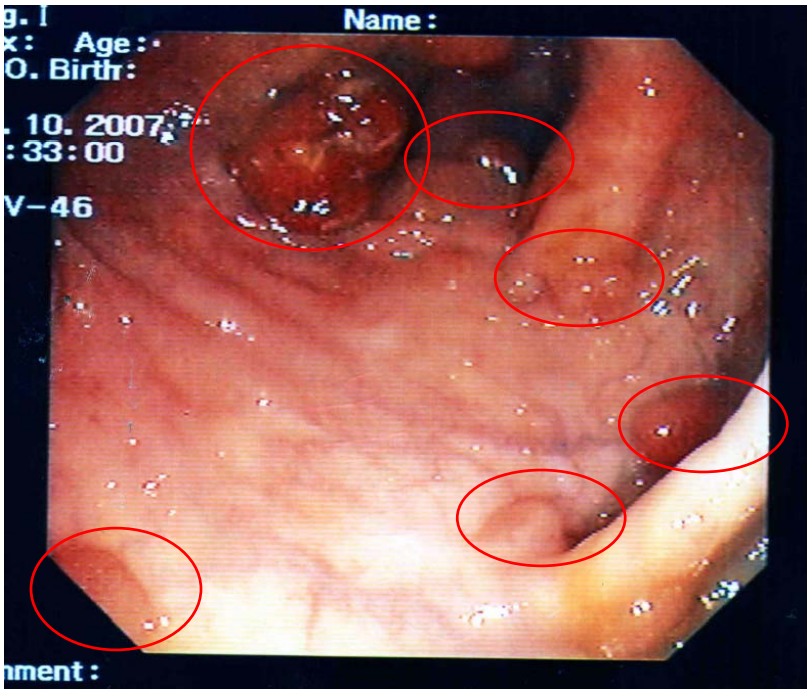
(b)



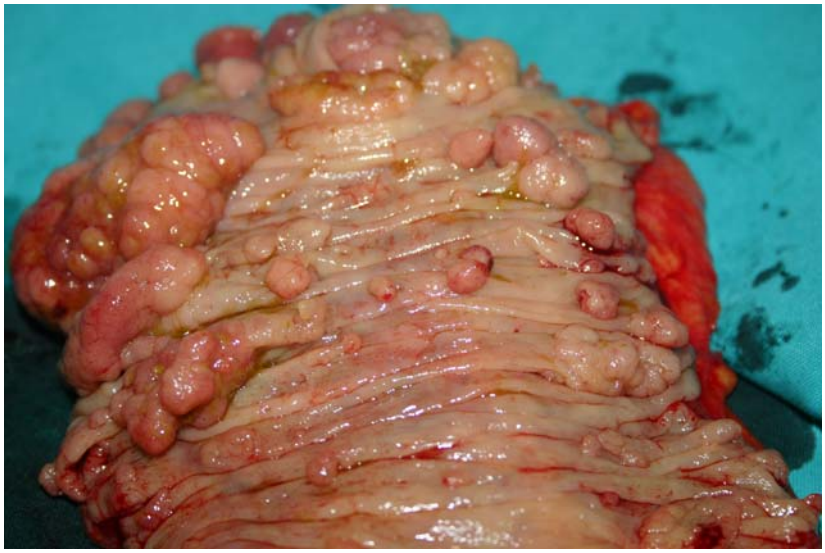
(c)



Endoscopic vision of attenuated polyposis of the colon (A-FAP)

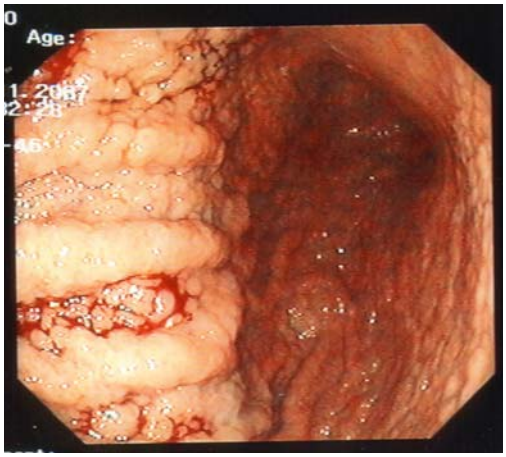


Colectomy for Polyposis Coli (the colon is open). The genetic test revealed biallelic MYH mutation in this patient.



Endoscopic vision of carpet of gastric polyps (a) and stage IV duodenal polyps in a FAP patient (b)

(a)



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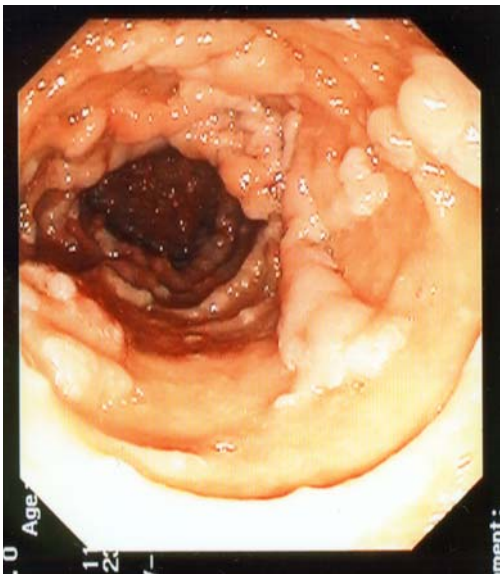

Gastrectomy in FAP for repeated findings of high grade dysplasia in polyps with innocent endoscopic feature.