Follow-up after surgical treatment of patients with familial adenomatous polyposis: Results in a Southern Spanish population

C. Cordero Fernández, A. Pizarro Moreno, M. Garzón Benavides, R. García Lozano, O. Belda Laguna, S. Sobrino, J. M. Bozada and T. Zulueta Dorado

Services of Digestive Diseases, ‘Immunology and ‘Pathological Anatomy. Virgen del Rocío University Hospital. Sevilla, Spain

INTRODUCTION

Familial adenomatous polyposis (FAP) is a hereditary disease that is transmitted as an autosomal dominant trait, caused by a germline mutation in the adenomatous polyposis coli (APC) gene, located on chromosome 5q21 (1). FAP is classically characterized by the presence of more than 100 polyps in the colon and rectum, the natural evolution of which is inevitably toward carcinoma around the fourth decade of life.

To prevent the development of cancer, it would be necessary to extirpate the entire colonic and rectal mucosa. At the present time there is no single procedure to achieve this objective, and the disease, which has other extracolonic neoplastic manifestations, in no case is cured.
Since patients with FAP are generally young and asymptomatic when diagnosed, they usually refuse to undergo total proctocolectomy with permanent ileostomy as preventive treatment. The two existing surgical alternatives are subtotal colectomy with ileorectal anastomosis (IRA), and proctocolectomy with ileal pouch-anal anastomosis (IPAA). The functional results with IRA are good and complications are rare. However, after 25 years of follow-up, the cumulative risk of developing cancer in the rectal stump is 15%, and around 40% of patients undergoing this procedure may eventually require a secondary proctectomy or conversion to IPAA to treat uncontrollable polyps (2). IPAA preserves anal continence, avoids the need for ileostomy, and reduces the risk of rectal cancer. The disadvantages of this surgical procedure are its greater complexity and the risk –although lower than that associated with IRA– of developing adenomatous polyps or cancer within the pouch itself or in the remaining rectal mucosa (3-5).

In the present study we describe the changes occurred in the rectal mucosa and ileal pouch in FAP patients treated with IRA or IPAA in our center, and evaluate the appropriateness of follow-up and treatment as recommend, as well as complications.

PATIENTS AND METHODS

 Patients

Between 1976 and 2004, 45 patients from 15 families with FAP were identified and attended at the Gastroenterology Department, “Virgen del Rocio” Hospital, Seville, Spain –a hospital with an assigned population of 596,468. The number of patients recruited corresponds to the expected prevalence of FAP in our population. All patients were included in a departmental database.

Thirty-two of these patients diagnosed with FAP were treated surgically in our hospital, the rest are still on the wait list because of age criteria. Of all 32 patients, 15 were proband patients and 17 were family members diagnosed by means of genetic testing and/or colonoscopy. Seven patients had no previous family history of cancer or FAP, and therefore were considered to have first mutations.

Surgical procedure for the polyposis treatment

The procedures were performed by different surgeons in Gastrointestinal Surgery Department. Surgically-treated patients were studied prior to the procedure, and followed afterwards by a single member of our Gastroenterology Department who is devoted to colon cancer prevention.

The procedures were either subtotal colectomy with IRA, total proctocolectomy with IPAA, or proctocolectomy with permanent ileostomy, depending on a number of factors and involving the gastroenterologist, the surgeon, and the patient in the decision.

Each patient was previously informed about the risk and benefits of each option.

Treatment protocol

After surgery all patients were followed prospectively according to a structured protocol where we recorded: patient age at the time of diagnosis with polyposis, number of polyps in the rectal ampulla before surgery, type of procedure performed, and postoperative rectal and oral endoscopic findings. These included: number of adenomas, location, size, treatment employed (polypectomy, argon plasma, or surgery), histological findings in resected polyps, and course for those that were not resected. The patients were grouped together according to whether they had less than 10 polyps, between 10 and 20, or more than 20, and polyps were classified according to size: less than 5 mm, between 5 and 10 mm, and more than 10 mm. Histological grade was defined as high or low on the basis of dysplasia, and carcinoma was characterized according to its intramucosal or invasive nature. Polyps measuring more than 10 mm, villous polyps, and those presenting with a high degree of dysplasia were considered to be high-risk lesions.

At each follow-up visit a thorough endoscopic examination of the rectal mucosa, pouch, and anorectal junction was requested. The anorectal junction was examined using always retrograde vision. Endoscopies were performed with a flexible colonoscope that was either fiberoptic or videoscopic. The interval between follow-up endoscopies was 6 months for patients with IRA and 12 months for those with IPAA.

Treatment during the follow-up

All polyps measuring more than 3 mm in size were removed by endoscopic polypectomy, and surgery was indicated for those that could not be resected by this technique. Since the introduction or argon plasma coagulation in our Endoscopy Unit in 1998 incipient polyps were treated with argon plasma. The follow-up interval was reduced when high-risk polyps were detected, and endoscopic therapy continued until they were completely removed.

Twenty FAP patients underwent IRA, eight underwent IPAA, and four underwent total proctocolectomy with permanent ileostomy, three of them because they already had cancer at the rectosigmoid junction at the time of the procedures, and the fourth was a particular indication of the surgeon in charge.

IPAA was introduced in our hospital in 1993. Before this date patients had no other option than IRA. Since its introduction IPAA was recommended to patients with more than 20 polyps in the rectal ampulla. We established
in 20 the limit for controlling rectal polyps by endoscopic excision. This was a decision made in accordance with our endoscopists’ opinions. Rectal polyps were endoscopically excised when possible before surgery. The mean follow-up of patients with IRA was 7.47 years (range: 0.72 to 16.75 years), and that of patients with IPAA was 4.05 years (range: 1.48 to 7.34 years).

Three of the patients who had undergone IRA required proctocolectomy: one who developed a high-risk polyp in the anorectal junction, which could not be removed endoscopically, and two who developed rectal carcinoma. One of these patients had refused conversion from IRA to IPAA, which was recommended two years before the diagnosis of carcinoma after the detection of numerous polyps in the rectal ampulla for which endoscopic resection was difficult. Two patients were receiving nonsteroidal anti-inflammatory drugs (NSAIDs) to treat gastric and duodenal adenomatous polyps related with PAF.

RESULTS

The study group consisted of 19 men and 12 women with a mean age of 28.6 years. The mean age of patients with IRA was 30.15 years (range: 13 to 55 years), and that of patients with IPAA was 20.8 years (range: 12 to 30 years). Of the 20 patients who underwent IRA, 11 (55%) had 10 or less adenomas in the rectal ampulla before surgical treatment, one patient (5%) had between 10 and 20 adenomas, and eight (40%) had more than 20 adenomas. These eight patients had been treated surgically between 1976 and 1993, before the introduction of IPAA in our hospital.

The eight patients who were treated with IPAA had more than 20 adenomas in the rectal ampulla before surgery, and six of them (75%) had between 30 and 100 adenomas.

Course of patients who underwent IRA

IRA was performed in 20 FAP patients. At the time of the first follow-up endoscopic examination five of these patients (25%) were free from adenomas. Of the remaining 15 patients (75%) three (20%) had less than 10 adenomas, six (40%) had between 10 and 20, and 6 (40%) had more than 20. The adenomas measured less than 5 mm in 11 patients (74%), between 5 mm and 10 mm in two (14%), and more than 10 mm in the remaining two (14%) patients. The histological study revealed the presence of tubular adenomas with mild dysplasia in 100% of cases. During the follow-up period the number, size, and degree of dysplasia of adenomas observed remained the same or decreased in 14 patients (74%), while they increased in 5 (26%); it was possible to treat all but one of these five patients by means of endoscopic polypectomy. In one patient the follow-up period was too short to evaluate these parameters. The treatment of adenomas detected in follow-up visits consisted of endoscopic polypectomy in 12 patients (67%), polypectomy plus coagulation with argon plasma in four (22%), polypectomy plus anti-COX2 in one (6%), and anti-COX2 therapy in another (6%). One of the latter two patients received anti-COX2 to treat multiple duodenal polyps, and the other to treat hyperplastic polyps in the gastric fundus.

Eleven years after surgery one female patient developed a flat villous adenoma measuring 10 mm in diameter and with a high degree of dysplasia in the anorectal junction. As the lesion recurred twice after two attempts at endoscopic polypectomy, a proctectomy with permanent ileostomy was indicated. However, the presence of intense, highly vascularized pelvic fibrosis impeded resection of the rectal ampulla. The decision was to perform a permanent ileostomy with closure of the rectal stump. The polypoid lesion recurred two more times following two attempts of transanal resection, although the degree of dysplasia was reduced. Finally, the patient developed a stenosis of the rectal ampulla that precluded endoscopic follow-up. Seven years after the detection of this stenosis she is asymptomatic and there is no evidence of lesions in follow-up monitoring involving pelvic computed tomography and magnetic resonance imaging. Another patient had attenuated familial adenomatous polyposis (AFAP), diagnosed after the detection of hypertrophy of the retinal pigment epithelium, more than 100 hyperplastic polyps in the gastric fundus, around 20 minimal polyps in the right colon, and absence of rectal polyps. Before any surgical intervention had been indicated, he developed a tubular adenoma measuring 10 x 6 mm and with a low degree of dysplasia in the anorectal junction. The polyp, diagnosed on retrograde endoscopy, was totally removed. His condition was normal in subsequent examinations. After eight years of follow-up he underwent IRA. At the time of the operation he had around 50 polyps all throughout the colon, all of them measuring less than 10 mm in size. There were no polyps in the rectal ampulla, and after 3 years of postoperative follow-up no polyps have been detected at that level.

Rectal carcinoma was diagnosed in two patients (11%) at 16 and 17 years after the operation. Both of them had discontinued follow-up 21 and 31 months before the diagnosis of cancer because of family and personal problems, and thus had failed to undergo 3 and 6 examinations, respectively. One of them had developed more than 30 polyps measuring less than 5 mm in the rectal ampulla since the surgical intervention, despite repeated polypectomies. For that reason a conversion from IRA to IPAA was recommended, a suggestion that he refused one year before discontinuing follow-up. The first examination he was subjected after withdrawing from follow-up revealed the presence of a 2.5-cm adenomatous polyp containing invasive carcinoma in T2N0M0 stage. It was treated by abdomino-perineal resection. The patient died several years later because of another cause. The other patient
developed a 3-cm adenocarcinoma, T3N0M0 stage. Moreover, he had also 25 more polyps measuring less than 5 mm in the rectal ampulla. He underwent radiotherapy and abdomino-perineal resection, and died 24 months later because of local recurrence.

Course of FAP patients who underwent IPAA

IPAA was performed in eight patients, none of whom underwent total mucosectomy; in all patients a cuff or rectal mucosa measuring a 3 cm on average was left (range: 1 to 5 cm). In the first postoperative follow-up endoscopy, adenomas were observed in the remaining rectal mucosa in two of the eight patients (25%). In both cases, there were less than 10 adenomas, all of which were tubular and measured less than 5 mm in diameter. In the second endoscopic examination adenomas appeared in two further patients; they were similar in number, histological type, and size to those found in the first two patients. In subsequent examinations the number of adenomas decreased in one patient (14%), whereas their number and characteristics were unchanged in the other three. Treatment consisted of endoscopic polypectomy in every case. No patient developed adenocarcinoma or high-risk polyps. Two patients in our series developed complications as a consequence of polypectomies. One of them had von Willebrand’s disease, and on several occasions had mild hemorrhages following polypectomy, which resolved spontaneously. The other patient developed an untreatable stenosis of the rectal ampulla after undergoing repeated polypectomies and rectal mucosal stripping.

DISCUSSION

At present the treatment most widely accepted by patients with FAP is surgical intervention involving IRA or IPAA with subsequent endoscopic follow-up. The latter is necessary to prevent cancer, which may develop in the remaining rectal mucosa or in the pouch with a variable incidence depending on the procedure carried out and other factors. The risk of rectal mucosa carcinoma during follow-up varies widely depending on the year of publication of the various series. For example, in 1971 it was 59% after 23 years of follow-up (6), and 10 years later it was 32%, whereas 20 years later (7) and in more recent series risks of 13% after 25 years (8) and 12% after 20 years of follow-up (9) have been reported. Since IPAA was introduced, the decision to perform IRA can be made much more selectively, and therefore the risk of developing cancer in the rectal stump should probably be quite reduced, as demonstrated in the series recently published by the Cleveland Clinic group (29).

Before undergoing surgery 40% of patients treated with IRA in our series had more than 20 adenomas in the rectal ampulla, all of them were operated before 1993 when IPAA was not available in our center. Of these 75% had polyps in the first follow-up endoscopic examination performed six months after the operation. While the majority of these polyps were small, in two cases they measured more than 10 mm in size, a circumstance that did not impede their treatment by endoscopic polypectomy. Nevertheless, none of the patients who complied with the proposed follow-up and treatment developed cancer during the follow-up period.

Only two patients in our series (11.7%) developed cancer in the rectal ampulla. Both had discontinued endoscopic follow-up, and cancer diagnosis was established in the first endoscopy, performed at 21 and 36 months, respectively, after the interruption of follow-up. While both patients had had numerous rectal polyps prior to surgery, and more than 15 years had elapsed since the operation, the fact that they correspond to the only two cancer cases in our series, and are the only patients who failed to comply with the follow-up protocol out of all 20 subjects studied here, leads us to consider that cancer development is associated with noncompliance with postoperative examinations. None of the other patients in our series who had large numbers of rectal polyps prior to surgery, or those who had the other risk factors mentioned in the literature (6,10-13), developed cancer.

The finding in two patients of flat polyps in the anorectal junction, one of them with a high degree of dysplasia, is of interest. They were only detectable in retrograde view, and it is very probable that their early treatment prevented the development of carcinoma. The results in our series appear to indicate the efficacy of our follow-up protocol, with meticulous examination of the anorectal junction at six-month intervals by means of retrograde endoscopy and endoscopic treatment of lesions. The possibility that the relatively short follow-up period may have influenced our results cannot be completely ruled out, but we consider it significant that, in our series, noncompliance with the protocol was the only factor associated with the development of rectal cancer.

Two patients in the series received NSAIDs, one for the control of duodenal polyps and the other, a patient with attenuated FAP, in an attempt to control polyps in the gastric fundus (14). The use of sulindac in the treatment of rectal polyps has been questioned in the literature with the publication of four cases of rectal cancer in patients with IRA treated with this agent, whose polyps, according to previous examinations (15-20), had apparently disappeared. This fact, and the changes observed in the polyps after said treatment, which makes them hard to recognize and treat, has led us to refrain from using NSAIDs in the control of rectal polyps in our patients.

IPAA, which is still a relatively recent technique, is universally accepted since the risk of rectal cancer is significantly lower than that observed with IRA. However, it is associated with an overall complication rate of 24%, including obstruction of the small intestine, pelvic sepsis,
male and female sexual dysfunction, pouch failure and pouchitis (21-29), and risk of developing neoplastic polyps and cancer in the pouch or in the remaining rectal mucosa, findings that have been reported in recent publications (9,30-38), and which should not be disregarded.

The seriousness of these neoplastic lesions appears to be related to the time elapsed since the operation, with a mean interval between surgery and the development of adenomas of 4.7 years (range: 0.15 to 12 years) (31). Their importance is yet to be determined.

In our series, with a mean follow-up period of 4.05 years (range: 1.8 to 7.5 years), we have observed no cases of cancer in the ileo-anal anastomosis or the remaining rectal mucosa. Fifty percent of patients developed polyps in the mucosal cuff left after the intervention, but the risk associated with these lesions was always low and they were susceptible to endoscopic treatment. We have found no polyps in the pouch at the end of the study period, although we have recently begun to stain the pouch with vital dyes, a practice that has revealed the presence of multiple small polyps that had not been visible prior to staining.

The efficacy of follow-up examinations will probably improve with the use of magnifying endoscopes and vital dyes, which will make it possible to identify small neoplastic lesions, and examine all of the zones of the anal canal, and the intestinal metaplasia that cannot be viewed with conventional endoscopes.

CONCLUSIONS

The main aim of the surgical treatment of FAP patients is the prevention of colorectal cancer. The choice of a type of intervention should take into consideration the risk factors of each patient, as well as his or her personal characteristics and understanding of the disease. IRA continues to be a good therapeutic option for young, low-risk patients, provided they undergo the recommended periodical examinations. These include a careful examination of the rectal stump every six months in patients with IRA, and of the pouch and ileoanal anastomosis in those who underwent IPAA, as well as the systematic study of the anorectal junction by means of retrograde endoscopy.

In our experience, none of the patients who have complied with the established follow-up examinations have developed cancer in the rectal mucosa or pouch. It is highly important that the patient understand the absolute necessity of periodical checkups.

Polypectomy was the treatment most frequently employed during periodical examinations, and in the majority of patients has resulted in a reduction in the number and size of polyps, and a lower histological grade.

There have only been two complications attributed to this therapeutic approach: one case of mild hemorrhage that, while it occurred twice following polypectomy, resolved with no need of treatment, and a case of untreated stenosis with consequences to be determined in the future.

REFERENCES


