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Recurrent Polyps in the Ileo-anal Pouch or Rectum in Familial Adenomatous Polyposis

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Most small bowel polyps in familial adenomatous polyposis (FAP) occur in the peri-ampullary region, and distal small bowel adenomas and carcinomas are comparatively less common. As standard therapy in FAP consists of proctocolectomy with ileal pouch anal anastomosis, or ileorectal anastomosis, it is essential to be aware of the potential for adenomatous polyp formation in the terminal ileum and rectum. Ileal adenomas are found in 9–20% of patients with FAP, and new polyps may develop after colectomy. Ileal lymphoid hyperplasia and polyps are 2–4 times more common than adenomas, may be indistinguishable from adenomas on examination (requiring biopsy for diagnosis), and tend to regress after colectomy. Adenomas may arise in pouches, usually after an interval of several years, and have been documented to occur in the terminal ileum up to 25 years after colectomy. At pouch construction, rectal mucosectomy may theoretically fail to remove all mucosa at risk. Small islets of rectal mucosa may remain after this technically difficult operation, and the late development of cancer, up to 20 years postoperation has been noted. A stapled anastomosis may arguably have a better physiological result, but a greater amount of residual rectal mucosa may increase late cancer risk. Annual endoscopic follow-up of pouches is recommended. All polyps or suspicious lesions should be biopsied, excised or destroyed, preserving a sample for histology. After ileorectal anastomosis, cancer risk in the rectal stump increases with chronological age, with risk ranging from 5–10% at age 50 years, to 14–29% at age 60 years. Surveillance of the rectal stump in FAP is recommended every 4–6 months. There may be a role for prostaglandin synthesis inhibitors in some patients.

Key words: familial adenomatous polyposis (FAP), ileal pouch, ileorectal anastomosis, ileal polyps, small bowel polyps, colonic cancer

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INTRODUCTION

THERE IS A marked predilection for small bowel polyps in familial adenomatous polyposis (FAP) to occur in the peri-ampullary region, suggesting that the presence of bile is a cofactor in the genesis of these polyps. Less information is available on the prevalence of polyps in the more distal small bowel, which is more difficult to image accurately.

In most FAP patients, adenomas are present in hundreds all over the large bowel, with a higher density in the rectum, sigmoid, and descending colon. Adenomas on the left side of the colon tend to be larger than on the right colon. There is almost always a sharp demarcation at the ileocaecal valve. Polyps more proximal in the distal ileum are less common, and are more often lymphoid rather than adenomatous.

As standard therapy in FAP consists of proctocolectomy with ileal pouch anal anastomosis or in selected cases ileorectal anastomosis, it is essential that the gastroenterologist is aware of the potential for adenomatous polyp formation in the terminal ileum and rectum. Preservation of the rectum is only possible when the rectum is not studded with polyps, when the few adenomas present can be easily removed, and when proper postoperative endoscopic surveillance is present with destruction of all recurrent polyps by fulguration or Nd:YAG laser photocoagulation.

Arguments in favour of ileorectal anastomosis are the relative simplicity of the operation, the low morbidity, and the gratifying functional results [1] with no risk of urinary or sexual dysfunction.

PREVALENCE OF ADENOMAS IN THE SMALL BOWEL

Literature information on the prevalence of adenomas is scant. Iida and associates [2] found small bowel adenomatous polyps in 12 of 20 patients who underwent systematic intra-operative endoscopy at the time of colectomy. Most polyps were in the proximal jejunum. In this same group of patients, 4 of 20 patients had adenomatous polyps in the last 60 cm of ileum. Seventy per cent had ileal lymphoid polyps, which were indistinguishable in appearance from the adenomas. Burt and associates [3] found ileal adenomatous polyps in 6 of 9 patients examined. All belonged to the same kindred, possibly accounting for the high proportion of polyps. Tonelli and colleagues [4] examined the distal 60 cm of ileum in 24 patients with FAP at a mean time of 55 months following colectomy. 10 patients had from 4 to 50 polyps 1–3 mm in diameter. 5 patients had adenomatous polyps confirmed at histology, and the remainder

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had lymphoid polyps. Nakahara and associates [5] noted multiple ileal adenomas in 2 patients at 5 and 7 years after ileostomy construction. These 2 patients apparently had very small (less than 2 mm) adenomas detected by intra-operative endoscopy at the time of colectomy. These polyps were felt to have increased in size and number postcolectomy. Hamilton and colleagues [6] published a multicentre report on 9 patients with FAP who developed ileal adenomas from 23 months to 25 years postcolectomy.

Nugent and associates [7] retrospectively reviewed 203 operative specimens from patients who came to colectomy and recorded 42 (21%) as having lymphoid hyperplasia, and 18 (9%) as having ileal adenomas. Several reports note lymphoid polyps as being more common than adenomas in the ileum in FAP. In a Japanese series [2], some 80% of patients had lymphoid polyps.

Ileal polyps may be present at the time of diagnosis of colonic polyps. They may occur postresection with a latent period of several years, with Nugent and colleagues [7] noting a trend for this to occur in patients who had ileal adenomas prior to operation. Lymphoid hyperplasia or polyps generally tend to regress following colectomy, as found by Nugent's group.

Small bowel carcinomas, presumed or found to arise from precursor adenomas, may be found in the jejunum after colectomy with ileorectal anastomosis [8], may occur in an ileostomy [9, 10] or following ileo-anal anastomosis [11]. These neoplasms occur rarely in FAP, and may present from 2–19 years following operation. Unlike the situation in ileo-anal pouches, colonic metaplasia does not seem to be an associated finding, and these neoplasms probably represent part of the spectrum of small bowel adenomas/carcinomas found in FAP.

POLYPS IN ILEAL RESERVOIRS

Polyps may be present or may develop in ileal pouches (Figure 1). Whether they are adenomatous or lymphoid can only be ascertained with histology (Figure 2). Nugent and colleagues [7] prospectively evaluated 38 patients who had restorative proctocolectomy with ileal reservoir construction. Four mildly dysplastic adenomas arose in ileal mucosa, at a median of 4 years after pouch construction. Shepherd and associates [12] found two mildly dysplastic tubular adenomas in ileal reservoirs from 12 patients with FAP at 1 year postoperation. Both patients had histologically normal ileal mucosa at the time of colectomy. Beart and colleagues [13] noted innumerable ileal tubulovillous adenomas 6 years after a Kock pouch was formed. Stryker and associates [14] documented over 50 ileal tubulovillous adenomas 12 years after Kock pouch formation, with no polyps found at an examination 4 years prior to that. The Shepherd study noted that 16 of 32 patients examined had mucosa producing colonic mucin present in the pouch, but none of the other studies mention the presence of colonic metaplasia.

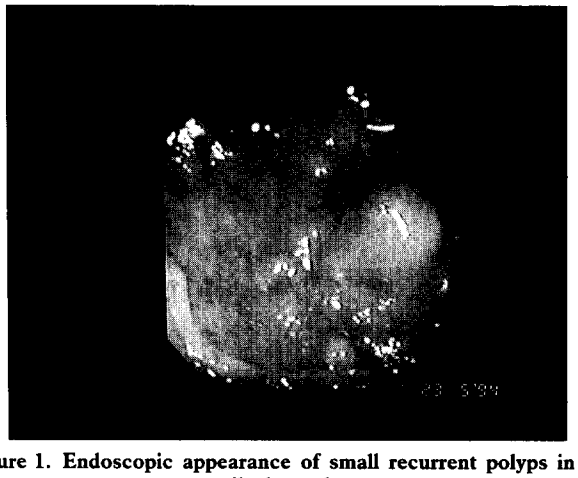

Figure 1. Endoscopic appearance of small recurrent polyps in an ileal pouch.

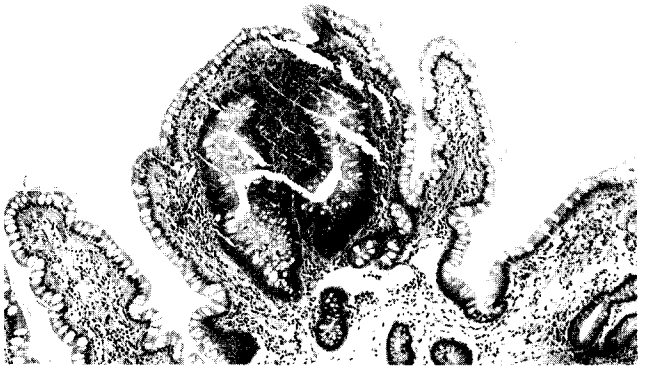

Figure 2. Histological confirmation of the adenomatous nature of the polyp shown in Figure 1.

CANCER RISK IN THE RECTAL STUMP

Thomson [15] noted the cumulative risk of rectal cancer in the St Mark's Hospital, U.K. experience with FAP to be approximately 10% at 25 years, with a cumulative mortality of approximately 5%. Bess and associates [16] found that 32% of the patients followed at the Mayo Clinic, U.S.A. developed cancer over a median follow-up of 20 years. Statistically significant risk factors for cancer included a greater number of rectal polyps present pre-operatively, and cancer resected at or before colectomy. Feinberg and colleagues [17] from the Cleveland Clinic, U.S.A. found a 15% risk of rectal cancer at 15 years. 3 of 7 patients who developed rectal cancer were not compliant with the recommended annual proctoscopy and developed advanced cancers (1 Dukes' B, 2 Dukes' C). In contrast, 4 of the 7 patients who were compliant with the surveillance programme developed Dukes stage A cancer.

Nugent and Phillips [18] from St Mark's Hospital, U.K. reviewed the risk of rectal cancer in 224 patients using life table analysis, with the mean age of cancer occurrence at 48 years. Cancer risk appeared to be related to chronological age; with a risk of 10% until age 50, increasing to 29% at age 60. The risk did not appear to be related to age at original operation or length of time postileorectal anastomosis.

De Cosse and colleagues [19] reviewed the experience of the Scandinavian FAP registries with 297 patients at risk accumulated over a 40-year period. The cumulative risk of carcinoma in the rectal stump was 4.5% at 10 years, and 13% at 25 years. The risk also increased with age, being 5.2% at age 50 years, increasing to 14.1% at age 60 years. The interval from the most recent endoscopy to detection of cancer was less than 6 months in 24 of the 50 who developed rectal cancer. All 4 patients who had cancer diagnosed more than 2 years after the last endoscopy had a Dukes' C lesion. In 18 of 33 patients who had accurate measurements taken, the tumour occurred in the most cephalad third of the rectum; none occurred in the distal 4 cm of rectum.

Iwama and associates [20] tabulated the results of a Japanese registry following 1050 FAP patients. The risk of developing rectal cancer in the retained rectum following ileorectal anastomosis was 13% at 10 years, rising to 37% at 20 years.

Matsumoto and colleagues [21] found one non-polypoid cancer in the rectal remnant of 2 patients with FAP at 17 and 27 years following colectomy. It is unclear whether these lesions represent part of the spectrum of flat adenomas/carcinomas that seem to have been reported more commonly in the Japanese literature. There is one similar case report in the American literature [21].

Currently recognised risks for the development of rectal cancer are the presence of many or large rectal polyps precolectomy, cancer resection at or before colectomy, the presence of confluent "carpet-like" polyps, poor or inadequate follow-up, and in two studies [18, 19], increasing chronological age of the patient. Surveillance, polyp destruction, and polyp regression are discussed below.

CANCER RISK AFTER PROCTOCOLECTOMY AND ILEAL POUCH ANAL ANASTOMOSIS

In FAP, both colonic and rectal mucosa are believed to have malignant potential, and on a theoretical basis, postcolectomy removal of all rectal mucosa by proctectomy and distal rectal mucosectomy would eliminate future cancer risk. Restoration of intestinal continuity after this operation is with construction of an ileal pouch or straight ileo-anal anastomosis.

Mucosectomy requires technical skill, and even in skilled hands, incomplete removal of anorectal mucosa may leave residual mucosa at risk of disease or neoplasia. O'Connell and associates [22] found islets of residual rectal mucosa between the denuded rectal cuff and the ileal pull-through in 4 of 29 patients who had excision of the ileal pouch at a mean of 17 months after construction. Rectal mucosa was found at the ileal pouch anal anastomosis in 2 patients.

Tsunoda and colleagues [23] studied mucosectomy specimens taken from the anorectal stump during restorative proctocolectomy. Dysplasia was present in mucosa from 12 of the 14 FAP patients evaluated, with severe dysplasia in 3 and moderate dysplasia in 1. 2 patients had small adenomas present.

Anastomosis construction with the stapling device, faster and technically easier since it avoids the submucosal dissection of mucosectomy, is preferred by some authors. Controversy remains as to whether this operation has a better functional and physiological result than mucosectomy. There is believed to be less risk of sphincter damage [24], better preservation of continence and autonomic nerve function, and less risk of anastomotic leakage resulting in pelvic sepsis. These potential advantages must be balanced against the long term risks associated with residual colorectal mucosa.

An early study demonstrated lower resting anal sphincter pressures in patients postileo-anal anastomosis compared to controls, but near normal pressures on contraction [25]. Other studies noted significantly better anal sensation and discrimination function with preservation of the anal mucosa compared with mucosectomy [26]. Sagar and associates [27] corroborated these findings, noting lower resting anal pressures, absent recto-anal inhibitory reflex, and complaints of incontinence in 17 of 36 (47%) patients who had a mucosectomy; 8–10% of a comparable stapled group had incontinence.

The optimal level of transection with a stapling device is controversial. Even with a low stapling technique, there is an unavoidable and substantial risk of rectal mucosa being retained. Rectal mucosa was found in at least one biopsy in 7 of the 15 patients surveyed by Slors and associates [28]. Sagar and colleagues [29] found no advantage to everting the rectal mucosa before stapling.

The anal transition zone (ATZ) is derived from the cloaca, constitutes the approximately 1 cm of mucosa proximal to the dentate line, and is cuboidal mucosa. This transitional mucosa is felt by some to be an important contributor to normal discrimination of slatus and faeces, aiding preservation of normal function. It may be at lesser risk of inflammation in ulcerative colitis, and perhaps at less risk in FAP. Proponents suggest that anastomosis at this level may provide a compromise between mucosectomy and stapling [26], forming the basis of the ileal pouch–distal rectal anastomosis [30]. However, it can be difficult to locate landmarks precisely at operation. Even if the anastomosis is precisely located at the proximal cuboid epithelium, rectal mucosa may be retained due to bilateral "dog ear" formation, as demonstrated by Slors and colleagues [28]. Ambroze and associates [31] found that columnar rectal epithelium extended through the ATZ at some point in the circumference of the anal canal in 90% of 50 ulcerative colitis proctocolectomy specimens examined. Preservation of the ATZ may leave the patient with a small and variable amount of residual rectal mucosa; dysplasia and cancer can occur in the ATZ (Figure 3).

Colonic metaplasia and putative "regeneration" of rectal mucosa are other factors to be considered. In 2 related patients, Wolfstein and colleagues [32] found regeneration of rectal mucosa for a distance of 8 and 12 cm above the ileo-anal anastomosis, constructed 1 cm above the dentate line. This occurred within 3 years postoperation, with many adenomas found in the neorectal mucosa. The mucosa of pouches is almost always noted to have chronic low-grade inflammation, possibly related to changes in bacterial ecology and stasis. Patchy colonic metaplasia has been found in several studies [12, 33], which tends to increase with time. This is accompanied by changes from small intestinal to colonic mucin, but such small bowel mucosal functions, such as B12 absorption, still remain. If the colonic mucosa in FAP has malignant potential, the risk of cancer in these areas of colonic metaplasia remains to be determined in careful prospective studies.

Adenomas have been found to develop in the terminal ileum

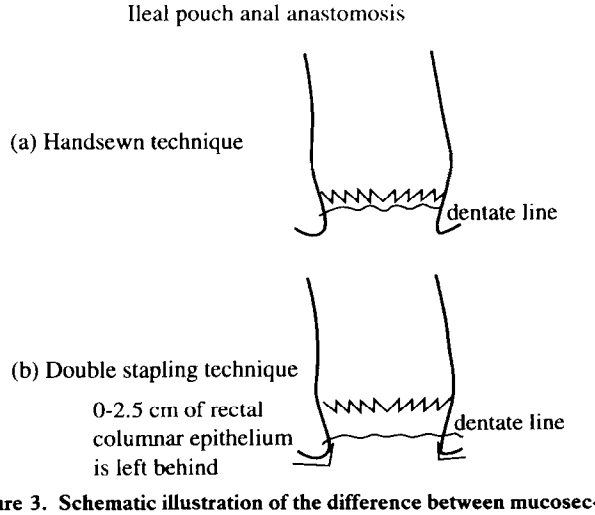

Figure 3. Schematic illustration of the difference between mucosectomy, a handsewn anastomosis and a stapled anastomosis.

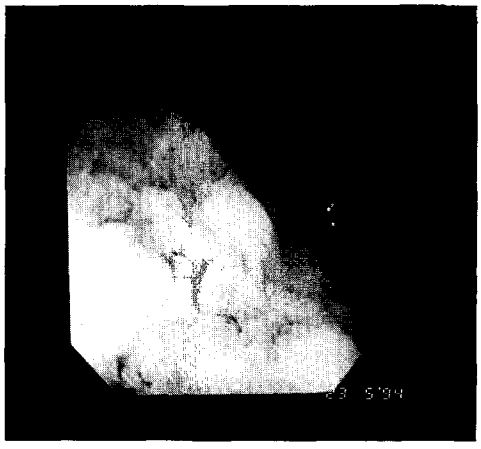

Figure 4. Recurring adenomatous growth of the level of the anastomosis in a stapled ileal pouch and anastomosis.

after a latent period of 25 years following rectal mucosectomy to the dentate line and straight ileo-anal anastomosis [34]. In the same patient, adenomas at the anastomotic line had earlier developed. Kock pouches may also develop adenomas, with Beart and colleagues [13] and Stryker and colleagues [14] reporting a patient who had multiple adenomas 6 years after pouch construction. Ojerskog and colleagues [35] did not find dysplastic changes after 16–20 years in their series of Kock pouches, however.

The fate of residual retained rectal mucosa must be determined at careful, prospective long term follow-up. One of 4 patients [28], after a low stapled anastomosis, developed adenomatous polyps in the proximal anal canal which were removed endoscopically at 28 months (Figures 4 and 5). Hoehner and Metcalf [11] found a carcinoma in a patient who had mucosal protectomy and ileo-anal anastomosis 20 years previously. The patient's follow-up was sporadic, with the last examination some 2.5 years before discovery of the neoplasm. Ross and Mara [10] described a proctectomy specimen with "cobblestoning" of polyps down to the columns of Morgagni, and King and associates [36] described a case where adenocarcinoma extended to the dentate line in a patient with ulcerative colitis. These cases further illustrate that there may be a long-term risk from residual rectal mucosa in what is topographically thought to be the ATZ.

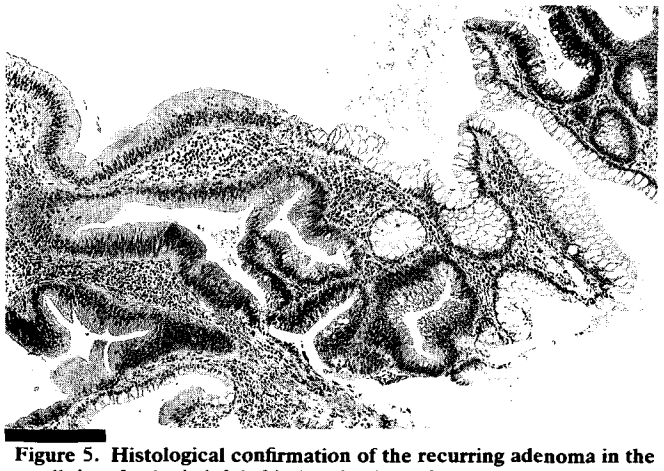

Figure 5. Histological confirmation of the recurring adenoma in the small rim of colonic left behind at the time of surgery, corresponding to Figure 4.

The various procedures, ranging from ileorectal anastomosis with stumps of varying lengths to the ileal pouch–distal rectal anastomosis, leave different amounts of rectal mucosa. It is unclear whether the magnitude of the cancer risk varies with the amount of residual mucosa. If so, the cumulative risk of neoplasia with a short segment of residual rectal mucosa may be small, and cancer may not become apparent until after many years of follow-up. Metaplastic colonic epithelium in ileal pouches may also represent a small but real neoplastic risk, that may become evident only upon long-term assessment. Various dye staining techniques may help the endoscopist identify areas of colonic or rectal mucosa more accurately, enhancing targeted biopsies of abnormal areas, and deserves study.

MANAGEMENT AND SURVEILLANCE OF THE RECTAL STUMP

Residual rectal mucosa is still at risk for malignancy, and proper and adequate surveillance is mandatory. Two studies report regression of rectal polyps after ileorectal anastomosis. Feinberg and colleagues [17] found that 56 of 88 patients at the Cleveland Clinic had a downstaging in the number of their rectal polyps at 1 year follow-up. 33 had complete regression of the polyps in 1 year, and 15 did not develop more polyps over a mean follow-up of 2.1 years. The other 18 were found to have *de novo* polyp formation at a mean follow-up of 6.8 years, suggesting that longer follow-up would be reflected in a higher percentage of patients with recurrent polyps. 7 patients developed rectal cancer at an average of 14.7 years after operation. 2 of these 7 had previous complete regression of polyps, and 3 others had occasional polyp-free examinations. Patients who presented for regular follow-up had cancers detected, if they occurred, at an earlier pathological stage. Nicholls and colleagues [37] found a decrease in mean polyp number from 50 to 22 in 14 patients with ileorectal anastomosis followed for a mean period of 10 months.

The reasons for polyp regression are unclear, but the Cleveland Clinic data show that regression is found in a subset of patients, and many of the polyps which initially regress will reform if the patient is followed for a sufficient period of time. Farmer and Phillips [38] found a decrease in labelling index in a group of patients with FAP following ileorectal anastomosis compared with another group of FAP patients precolectomy. Watne and colleagues [39] correlated decrease in polyps in the rectal stump in one patient with a decrease in coprostanol and increase in primary bile acids; polyp formation was accompanied by a reversal of these biochemical changes.

Sulindac has been found, in a prospective randomised clinical trial, to result in a decrease in the number of rectosigmoid polyps in unoperated patients [40]. This was also found in several smaller studies of patients pre- and postcolectomy. Nugent and associates [41] documented a decrease in the mucosal labelling index. The mechanism of action is unclear, but elevated prostaglandin levels have been found in FAP colonic mucosa, and inhibition of prostaglandin formation with a non-steroidal agent may be the mechanism. Further support comes from Hirata and colleagues [42] who found indomethacin suppositories efficacious in rectal polyp regression.

The frequency of surveillance has varied in several studies, but Nugent and colleagues [18] found a median time from sigmoidoscope examination to rectal cancer development to be 6 months. They suggested a change in policy from a previous time

period of every 6 months, to sigmoidoscopy every 4 months in patients over the age of 45 years, or more frequently if large polyps are present. Flexible endoscopy is considered to give much better visualisation of the mucosa, with an enema 30 min prior to preparation. Video recording of the examination can aid follow-up. It may be difficult to differentiate adenomas from lymphoid hyperplasia or polyps by visual inspection, especially at or proximal to the anastomosis, thus biopsy or destruction of suspicious lesions is required. In patients with many polyps, the institutional policy may vary from selective destruction of suspicious or large lesions [43] to fulguration of any polyps seen at follow-up [44]. Because of the malignant potential of colorectal epithelium in FAP, and to a lesser extent the small bowel epithelium, it would seem that lifelong follow-up of FAP patients will be required. Polyp histology is essential to stratify patients into risk groups. Polyps may be removed with snare cautery, or destroyed by a variety of fulguration methods or by Nd:YAG laser.

DISCUSSION

Polyps can be difficult to detect. The detection rate is higher with endoscopy than with barium examination. Most of the small bowel is inaccessible to endoscopes, and visualisation of mucosal lesions may be affected by the presence of chyme, mucus, secretions, and such variables as the amount of air insufflated. Intra-operative endoscopy offers a much more complete view of the small bowel. Newer model sonde enteroscopes [45] hold promise in evaluating the small bowel, although examination is time-consuming and uncomfortable for the patient.

There are no large, systematic, prospective surveillance studies available to clarify the exact prevalence of small bowel polyps in FAP. Several small studies suggest an increase in the number and size of ileal polyps following colectomy. This probably reflects a longer period of observation. The time of formation of these polyps and their possible relation to colonic and duodenal polyposis is unclear, although there is a clinical impression that some patients have a tendency toward diffuse polyposis affecting the entire gut. Published reports often do not specify the histology of surrounding mucosa, but colonic metaplasia seems to be an uncommon associated finding.

With the available data, it is difficult to make firm recommendations for surveillance of the ileum and ileal pouch in FAP. Prospective studies will certainly be of use to clarify the exact magnitude of risk, but distal small bowel cancer does not seem to be a common occurrence in FAP. The greater cancer risk with increasing chronological age, and the late occurrence of cancer after many years of follow-up, suggest that lifelong periodic surveillance of FAP patients is required. Given available data, it is reasonable to suggest that patients with ileorectal anastomosis should be followed-up every 4 months. This would consist of digital examination, and flexible endoscopy after enema preparation, preferably with video documentation. Those with ileo-anal pouches may be followed up at 3 and 6 months postoperatively, then annually. Patients with stapled anastomoses, who have more residual mucosa than those who have had rectal mucosectomy may require closer follow-up than the mucosectomy group. Polyps, when found, should be biopsied, since lymphoid and adenomatous polyps can be indistinguishable on examination. Patients with biopsy-proven adenomas, dysplasia, or those with a tendency for polyp formation should be followed more regularly. There may be a role for prostaglandin synthesis inhibitors in selected patients.

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