Adenomatous Polyposis Syndromes: Diagnosis and Management

Jonathan B. Mitchem, MD[1] Jason F. Hall, MD, MPH, FACS, FASCRS[1]

[1] Department of Colon and Rectal Surgery, Lahey Hospital and Medical Center, Burlington, Massachusetts

Clin Colon Rectal Surg 2016;29:321–329.

Address for correspondence Jason F. Hall, MD, MPH, FACS, FASCRS, Section of Colon and Rectal Surgery, Department of Surgery, Boston Medical Center, FGH Building, Room #5017, 820 Harrison Avenue, Boston, MA 02118 (e-mail: jason.hall@bmc.org).

Abstract

Familial adenomatous polyposis (FAP) syndromes make up fewer than 1% of patients diagnosed with colorectal cancer each year. Patients with familial polyposis syndromes including FAP, attenuated FAP, and MYH-associated polyposis (MAP), are an important group often cared for by colorectal surgeons. Registry and screening programs have been shown to improve survival in patients with adenomatous polyposis, as it allows patients to undergo surgical intervention prior to the development of colorectal cancer. There are several surgical options for the treatment of colorectal polyps in patients with adenomatous polyposis, so it is important to choose the appropriate procedure for each patient after discussing the risk of cancer in the rectal remnant, as well as bowel and sexual function in a predominantly young patient group. Regardless of procedure choice, long-term follow-up is important with yearly endoscopic evaluation of the pouch or remnant rectum, as well as appropriate screening for extracolonic malignancy. Adenomatous polyposis patients require an intense care regimen, but can have a normal lifespan with good quality when cared for appropriately.

Keywords

- polyposis
- familial adenomatous polyposis
- colorectal cancer

Family history is an important risk factor in the development of colorectal cancer (CRC); however, hereditary adenomatous polyposis syndromes make up a relatively small proportion of CRCs diagnosed annually (<1%). The best estimates of familial adenomatous polyposis (FAP) prevalence come from national health data with a prevalence of around 40 cases per million people[1] and an incidence of approximately 1 in 8,000 to 18,000 births.[2–4] The gene responsible for FAP, as discussed in the first article in this issue, is the *adenomatous polyposis coli* (*APC*) gene in the majority of cases.[5–7] The *APC* gene is a tumor suppressor gene in the 5q21 chromosomal region impacting the *wnt* signaling pathway involved in cellular growth. Genetic defects associated with FAP are inherited in an autosomal dominant fashion. As studies of family registers developed, groups of families with less than 100 polyps were noted and subsequently termed *attenuated* FAP (AFAP). These patients were found to have defects in the APC gene at the 5′ and 3′ ends.[8] This condition is rarer than FAP, but the true prevalence of AFAP is not well established. In a study of the Danish polyposis registry, 8% of patients qualified as AFAP (<100 polyps).[8] In 20 to 30% of patients who have a clinical diagnosis of FAP or AFAP without a mutation in the *APC* gene, a mutation in the *MUTYH* gene has been found. These patients have been given the diagnosis of *MUTYH*-associated polyposis (MAP). [9,10] The *MUTYH* gene is involved in base-excision repair and may play some role in *β-catenin* signaling, a member of the *wnt* signaling cascade, which may explain the overlap with FAP. Clinically evident MAP requires a biallelic defect and therefore demonstrates an autosomal recessive pattern of inheritance. The genetic basis of these diseases will be further discussed elsewhere in this issue. In this article, we will discuss the diagnosis and treatment of hereditary polyposis syndromes.

Diagnosis

The diagnosis of a hereditary adenomatous polyposis syndrome is primarily clinical and made on endoscopy or via screening. Classical FAP is diagnosed on the basis of more than 100 adenomatous polyps in the colon seen during

Issue Theme Colorectal Polyps and Polyposis Syndromes; Guest Editor: Paul E. Wise, MD, FACS, FASCRS

DOI http://dx.doi.org/10.1055/s-0036-1584089.
ISSN 1531-0043.

endoscopic evaluation. On pathologic examination, grossly there is a "carpeting" effect of polyposis with the expected microscopic appearance of adenomas. It is important to remember that despite robust screening and registry, approximately 20% of patients present without a family history of CRC[11] and 20% of patients with FAP will not be found to have an *APC* gene mutation. In studies of large polyp registries, typically 40 to 50% of patients in the registry were diagnosed based on symptomatic presentation with hematochezia or bowel habit changes.[4,8,12–14] Patients who present with symptoms are typically diagnosed in their late 30s or early 40s and are significantly more likely to have CRC than those patients who are identified during screening based on a family history or other risk factors for FAP who are typically diagnosed in the range of 18 to 25 years old.[4,12–15] Attenuated FAP patients generally present at a later age but with similar symptoms, and an average number of 25 to 30 polyps, predominantly occurring in the proximal colon.[8,16] Often, patients with more than 10 adenomatous polyps (certainly those with >20) throughout their lifetime are considered to have attenuated polyposis. MAP may present with either an attenuated (<100 polyps) or classic polyposis syndrome and should be considered in any kindred with an autosomal recessive inheritance pattern and/or is negative for an *APC* gene mutation.[9,10]

Screening

Screening in adenomatous polyposis kindreds has dramatically changed the incidence of CRC in these patients. The first familial polyposis registry was established at St. Mark's Hospital in the United Kingdom in 1925 by Dr. Mummery-Lockhart.[17] This was established long before the genes associated with FAP had been identified. Today, many countries have established polyposis registries and implemented screening programs for identified kindreds. Screening has led to a dramatic decrease in the incidence of CRC in patients with early-diagnosed hereditary polyposis syndromes. This is largely related to early surgical intervention in at-risk individuals as patients with conventional polyposis have a near 100% lifetime penetrance of CRC, typically by the fifth decade of life. This risk is lower in patients with aFAP. In the United Kingdom, a decrease in the incidence of CRC from 43.5 to 3.8% with a decrease in mortality from 56 to 5.9% was shown with the implementation of a screening and registry program in patients with polyposis.[15] Groups from North America, Denmark, Sweden, and Japan have all presented similar results highlighting the importance of the development of registry programs.[4,12,13,18] A recent systematic review regarding the implementation of screening and registry programs, including more than 8,000 patients in 33 published studies, all 33 showed a significant mortality benefit and decrease in the risk of CRC development.[19]

Screening recommendations for patients with adenomatous polyposis syndromes have been addressed by several groups. The American College of Gastroenterology (ACG) recommends that patients with a known family history of polyposis begin screening via flexible sigmoidoscopy at the onset of puberty.[20] The rationale for this recommendation is that the average onset of polyp formation is in the late teenage years with the development of CRC before the age of 15 being exceedingly rare.[21] The American Society of Gastrointestinal Endoscopists published similar recommendations,[22] as did a 31-member expert panel from multiple European nations.[23] Within these guidelines, there is the understanding that patients who are symptomatic should be evaluated at the time of onset of symptoms if earlier than the initial screening age. Polyps noted on sigmoidoscopy should prompt full colonoscopic evaluation. Patients who present at a later age for screening should also undergo full colonoscopy. At the time of colonoscopy, all polyps should be counted and biopsies obtained, in addition to removal of all larger polyps (>5 mm), if possible. The ACG additionally recommends that patients in whom surgery is delayed more than 1 year after first polyp diagnosis should have yearly colonoscopic exams until surgical intervention is planned. The interval and length of continued surveillance is a matter of some debate. Patients in a kindred without a known genetic mutation are recommended to undergo yearly or biyearly screening for life as the incidence of CRC in these patients reaches nearly 100% by the age of 40 to 50 years. Surgical intervention is recommended in patients who are diagnosed with polyps given the high risk for the development of CRC.

Screening in patients with aFAP can begin at a later age, as the onset of polyp development and CRC occurs later in this group. Based on data from European polyposis registries, the aFAP study group recommended initiating screening in the late teens or early 20s, as the mean onset of CRC was in their 50s with only two cases reported occurring in patients younger than 30 years.[16] In aFAP patients, however, full colonoscopic evaluation is recommended, as there is a high prevalence of right-sided polyps and proximal colon cancers.[8,16] It is reasonable to manage patients with aFAP with yearly or biyearly colonoscopy as long as polyps can be managed endoscopically[20]; however, if patients develop advanced polyps (>1 cm, villous architecture, high-grade dysplasia, etc.), it is recommended that patients undergo surgical intervention, as cohort studies have indicated a risk for the development of CRC of 69% by age 80.[8]

The risk of cancer development in patients with MAP is approximately 30 times that of the normal population, with a risk of 20% by age 60 and a mean age of cancer diagnosis in the late 40s to 50s based on large population-based studies.[24,25] The phenotype of MAP is somewhat variable based on the mutation, and there are reports of patients who have developed CRC without evidence of polyposis.[25] Based on these results, the recommendation for screening in these patients is similar to that in patients with aFAP.[20] As more is learned about MAP, the more likely screening will be tailored to an individual's specific genotype.[24,25]

Genetic Testing

Genetic testing and referral to genetic counselor is recommended in any patient presenting with a clinical syndrome consistent with FAP, aFAP, or MAP, and will be discussed in greater detail in this issue. If a mutation is discovered, the

patient's family should be tested for that mutation accordingly. Genetic screening in patients born into a hereditary adenomatous polyposis syndrome kindred is recommended to begin around puberty, prior to the initiation of endoscopic screening. Patients without the genetic mutation in a family with a known mutation can forgo endoscopic screening. Testing prior to this time point is unlikely to alter therapy.[20] It is important to remember that 20% of patients with FAP and less than 50% of patients with aFAP will not have an identifiable mutation in the *APC* gene.[2,7,16]

Based on historical data, the phenotypic penetrance of FAP is 100% in affected individuals with the incidence of CRC of nearly 100% by the age of 50 years.[2] The likelihood of the development of CRC is lower in patients with aFAP. Based on European population-based registries, the incidence of CRC is 69% at the age of 80 years[8]; however, other studies have reported a lower risk in aFAP kindreds.[16] The incidence of CRC in patients with MAP may be even lower than that of aFAP. A recent study from the group in the United Kingdom estimated the penetrance of CRC to be 43% in patients with a biallelic *MUTYH* mutation at age 60 years.[24] There was no increased risk of CRC in patients with monoallelic *MUTYH* mutations (i.e., carriers) in MAP families.[24] It is important to understand the risk of CRC development when discussing surgical options in patients with the different adenomatous polyposis syndromes.

Surgical Intervention

The cornerstone of therapy for patients with FAP is surgical extirpation of the colon given that the development of CRC is nearly 100% by age 50.[2,21] The timing of surgery, however, is not well defined. It is generally recommended that patients undergo prophylactic surgery once polyps are first diagnosed and generally by age 20 or 25.[20,22,23] Patients who are symptomatic and have severe polyposis, dysplasia, and/or cancer should undergo colectomy or proctocolectomy at that time. In those patients who are asymptomatic, have a low polyp burden, and are reliable for close endoscopic follow-up, prophylactic colectomy can be scheduled around some life events as long as patients understand the risks of this strategy.[20,22,23] As mentioned earlier, patients with aFAP and MAP may be approached with an aggressive screening and polypectomy regimen. However, once the polyp burden is too great for endoscopic management or dysplasia and/or cancer is diagnosed in these patients, surgical options are similar to those offered to patients with FAP.

Options for surgical intervention include both nonrestorative and restorative procedures, as well as rectal sparing and non–rectal sparing procedures. Patients with a high number of rectal polyps and/or rectal polyps with dysplasia or cancer should be counseled against a rectal sparing operation. Nonrestorative options include total proctocolectomy (TPC) or total abdominal colectomy (TAC) with end ileostomy. In some situations, patients may desire or need a nonrestorative procedure (e.g., familial experience and incontinence). Restorative options include TPC with ileal pouch anal anastomosis (IPAA) or TAC with ileorectal anastomosis (IRA). IPAA and IRA are by far the most common operations for patients with adenomatous polyposis undergoing surgery. It is important to tailor therapy to the appropriate clinical situation and have an open discussion about the risks and benefits with patients prior to embarking on a complex path of surgical therapy.

IPAA versus IRA

Restorative proctocolectomy (TPC with IPAA) is currently the most common operation performed for polyposis. Prior to the advent of IPAA in the 1980s, TAC with IRA was the most common procedure performed in patients with polyposis. Unfortunately, there was a high rate of cancer in the remnant rectum and patients often needed completion proctectomy.[26] In a recent, large meta-analysis of studies comparing IPAA and IRA including 535 patients who underwent IPAA and 455 patients who underwent IRA for FAP with a median follow-up of at least 36 months, 30day postoperative outcomes including wound infection, bowel obstruction, hemorrhage, sepsis, and leak were all the same.[27] There was an increased rate of 30-day reoperation in patients undergoing IPAA (11.6 vs. 23.4%). The reason for this was not clearly evident in the data, but perhaps relates to a difference in the severity of complications, or the numbers in the study were too small to detect these differences. On long-term follow-up, however, patients undergoing IRA were much more likely to undergo repeat operative intervention on the rectum or anastomosis (27.7 vs. 3.1%), including secondary IPAA or proctectomy with end ileostomy. While IPAA appears to be an oncologically superior operation, functional outcomes are generally not as good as IRA. Patients undergoing IPAA had an average of 3.8 to 8 bowel movements per day, 44% of patients experienced night-time defecation, 15% wore a pad for 5 of 24 hours in the day, and 50.5% experienced incontinence during a 24-hour period. These results were all significantly worse than IRA, with IRA patients having two to six bowel movements per day, 8.2% of patients experiencing night-time defecation, 5% wearing a pad, and 29.9% experiencing incontinence. Patients undergoing IPAA did have lower rates of fecal urgency (14.2%) than patients undergoing IRA (39.1%). There were two studies included in this meta-analysis which looked specifically at social restrictions, which found a significantly higher rate of social restriction in patients undergoing the IPAA procedure. In spite of this, there was no difference in sexual function or need for dietary restriction for either procedure. In a study from the group at the Cleveland Clinic, patients who had underwent IPAA for FAP had high overall quality of life (QOL) scores (median: 9 out of 10) on the Cleveland Global Quality of Life Scale at up to 10 years postprocedure.[28] Another study looking at sexual dysfunction in patients undergoing IPAA, IRA or TPC, and ileostomy for the management of FAP in the Netherlands showed no difference between groups.[29]

IPAA: Mucosectomy versus Double-Stapled Anastomosis

Following TPC, IPAA may be performed by two different methods. The most common method of pouch construction is the "J-pouch," and is constructed in the same manner whether doing a hand-sewn or stapled anastomosis (►**Fig. 1**). Historically, IPAA was performed using the

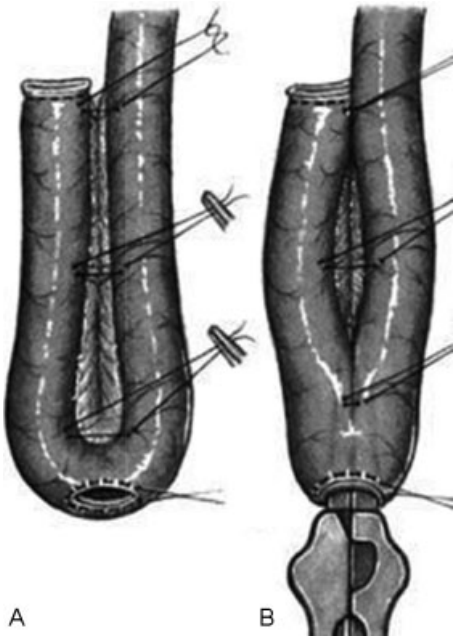

Fig. 1 (**A, B**) Typical J-pouch configuration of the ileal pouch anal anastomosis (IPAA). The J-pouch is formed using the distal 30–40 cm of the terminal ileum and a common enterotomy is created using a GIA stapler. (Adapted with permission from Beck DE, Roberts PL, Saclarides TJ, Senagore AJ, Stamos MJ, Wexner SD, eds. ASCRS Textbook, 2nd ed. New York, NY: Springer; 2011:487.)

technique of rectal mucosectomy and hand-sewn ileoanal anastomosis (►**Fig. 2**). The alternative technique is to perform a double-stapled anastomosis (►**Fig. 3**). In both procedures, it is the authors' practice to protect the anastomosis with a diverting loop ileostomy. In a meta-analysis comparing hand-sewn with stapled anastomosis, the rate of anal transition zone (ATZ) dysplasia increased from 7.8 to 18%, with the only occurrence of rectal cancer in a patient with a stapled pouch anastomosis.[30] One study included in this analysis had rates of ATZ adenomas of 14 and 28% in the hand-sewn and stapled groups, respectively. However, all of these ATZ adenomas were able to be managed with transanal or endoscopic excision and only one patient underwent pouch excision for rectal cancer.[31] While mucosectomy provides the most oncologically complete operation, this is done at some cost. Patients with a double-stapled anastomosis are less likely to experience complications and usually have improved functional outcomes including decreased rates of incontinence, seepage, and pad usage as compared with the hand-sewn technique.[31] Mucosectomy should be considered in patients with a low rectal cancer (who do not require an abdominoperineal resection), high-grade dysplasia at the ATZ, or heavy ATZ polyp burden such that a clear stapled margin may not be achieved.

TPC with End Ileostomy versus IPAA

While many patients undergoing a TPC for adenomatous polyposis desire restoration of continuity with an IPAA, not all patients will be candidates for sphincter sparing procedures, and some patients may be more comfortable with an ostomy. The two most important considerations are functional QOL and adequacy of oncologic operation. Patients with poor sphincter function prior to TPC (or TAC due to continued rectal mucus production and leakage) are unlikely to be as satisfied with their outcome with a restorative procedure. Additionally, patients who have a low rectal cancer or dysplasia, where an inadequate distal margin can be achieved, should not be considered for a sphincter preserving procedure. The comparison between the two main modes of operative therapy for patients with adenomatous polyposis undergoing surgery has not been directly assessed. In patients with ulcerative colitis, QOL was similar between patients treated with TPC and either ileostomy or IPAA. Patients with TPC and ileostomy did have a lower overall body image and were less likely to participate in sports, but they were equally satisfied with their choice when compared with patients who underwent IPAA.[32] Men were

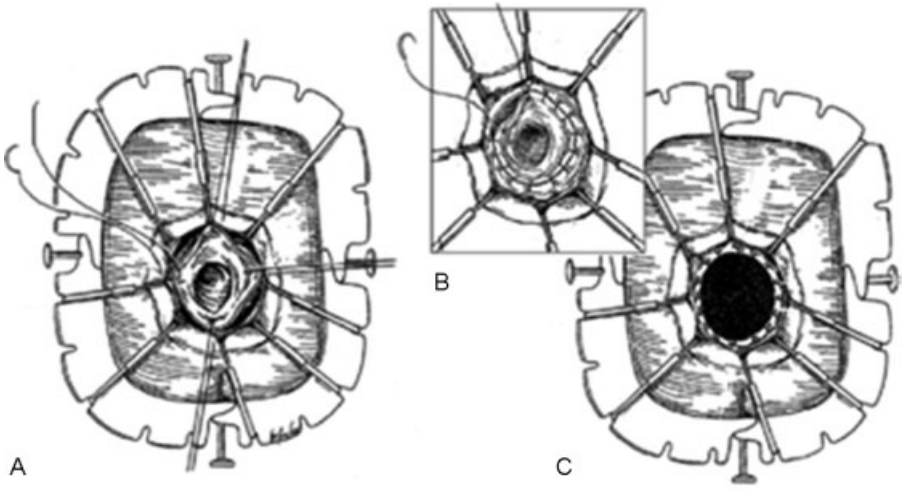

Fig. 2 Technique used for hand-sewn ileal pouch anal anastomosis (IPAA). After mucosectomy is performed, the J-pouch is delivered in the pelvis and the enterotomy which is used to create the common channel is affixed to the anal canal starting with four quadrants (**A**) and sutures can then be run (**B**) or interrupted to affix the pouch fully to the anal canal (**C**). (Adapted with permission from Beck DE, Roberts PL, Saclarides TJ, Senagore AJ, Stamos MJ, Wexner SD, eds. ASCRS Textbook, 2nd ed. New York, NY: Springer; 2011: 488.)

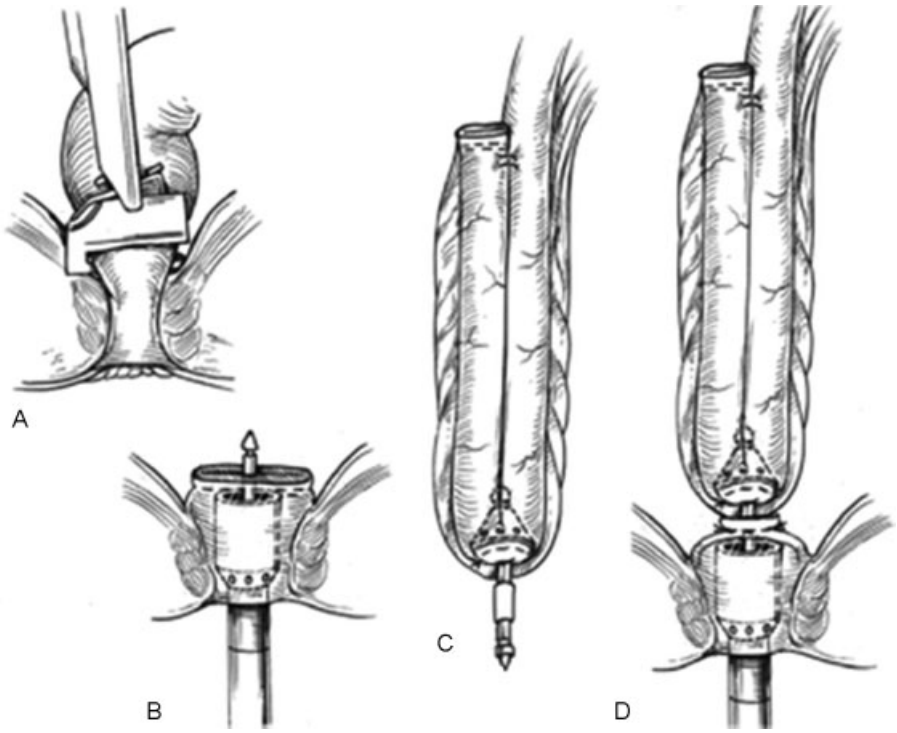

Fig. 3 Double-stapled ileal pouch anal anastomosis (IPAA) technique. The rectum is transected immediately proximal to the anal canal leaving as little remnant rectum as possible using a stapler (**A**). The end-to-end anastomosis (EEA) stapler is introduced via the anal canal (**B**) and the anvil is sutured in the pouch enterotomy using a purse-string technique (**C**). The stapler and anvil are connected, tightened, and the stapler is fired creating the circular anal anastomosis (**D**).

less affected by body image than women. A recent survey of patients with FAP from the Netherlands studied infertility in female patients undergoing TPC with ileostomy, TAC with IRA, or TPC with IPAA and found no differences in fecundity related to procedure, but the risk for decreased fertility was much higher in women who underwent surgery at a younger age.[29] This is in conflict with an earlier study from Denmark, Sweden, and Finland which stated that patients undergoing TAC with IRA had significantly fewer issues with becoming pregnant than patients undergoing TPC with or without IPAA.[33]

Laparoscopic versus Open Approaches

The choice of approach in adenomatous polyposis patients has been studied by numerous groups, but no specific approach has been proven to be superior. The Cochrane group performed a review in 2009 of all available data at that time and found that patients undergoing laparoscopic procedures had an early improvement in cosmetic scores, but there was no difference in terms of postoperative recovery, 30-day mortality, or complications.[34] This is in accordance with a later case-matched study comparing open and laparoscopic IPAA which showed no difference in long-term pouch complications, incisional hernia, or admission for small bowel obstruction after a median follow-up of longer than 8 years.[35] Additionally, outcomes for the hand-assisted and conventional laparoscopic approaches are the same, with decreased operative times in patients undergoing hand-assisted operations and a trend toward decreased conversion rate.[36] The laparoscopic approach to TPC in patients with adenomatous polyposis is safe and feasible but has not been shown to be superior to the open technique. As technology continues to advance, including the application of robotic technology, it is important that we continually reassess the usefulness and utility of these new techniques.

The choice of surgical intervention in patients with adenomatous polyposis syndromes is quite complicated (►**Table 1**). It is important to have an earnest informed consent discussion with patients about the pros and cons of each approach, potential lifestyle changes, need for further screening and surveillance, and the future possibility of cancer prior to embarking on any course of operative therapy. Patients with aFAP or MAP and rectal sparing can likely undergo IRA with continued rectal surveillance with a low risk of the development of rectal cancer. Patients with classic FAP are significantly more likely to develop a rectal cancer and therefore should be counseled based on balancing the risk of cancer in the retained rectum and long-term lifestyle changes including future desire of fertility. Patients with a large burden of rectal polyps (>10–20 polyps) or with rectal dysplasia or cancer are not candidates for a rectal sparing operation. Rectal sparing might also be best avoided in those patients with a strong family history of rectal cancer or with genotypes that are more "aggressive" in terms of their extent of polyposis. As more is learned about the genetic aspects of these diseases, we may be better able to predict which patients are more likely to develop pouch adenomas or cancer in the remnant rectum based on genetic mutation. These data combined with family history should also be used when deciding which patients should be considered as candidates for IRA.[37–39]

Table 1 Comparison of benefits and risks of total abdominal colectomy with ileorectal anastomosis versus total proctocolectomy with ileal pouch anal anastomosis

Procedure	Total proctocolectomy with ileal pouch anal anastomosis	Total abdominal colectomy with ileorectal anastomosis
Patient selection	• Patients with >20 rectal polyps • Patients with >1,000 colon polyps • High-risk genotype • > 3 cm rectal adenoma	• Patients with <20 rectal polyps • Attenuated FAP • MUTYH-polyposis
Bowel function	• Decreased fecal urgency	• Reduced night-time defecation • Fewer bowel movements • Less fecal incontinence • Lower risk of social restriction
Sexual function/fertility	• No difference between techniques in sexual function/satisfaction • May have higher risk of infertility in women	• No difference between techniques in sexual function/satisfaction • May have less infertility in women
Operative outcome	• Increased postoperative morbidity	• ~30% long-term risk of proctectomy
Risk of rectal cancer	• < 2% risk of rectal cancer with surveillance	• < 5% in appropriately selected patients with surveillance
Desmoid formation	• No difference between techniques	• No difference between techniques

Abbreviation: FAP, familial adenomatous polyposis.

Surveillance

The risk of cancer and adenoma development after IPAA or IRA is not completely understood. Much of the long-term data surrounding this issue come from a time prior to the advent of IPAA.[38] The risk of rectal cancer and polyposis in the retained rectum of patients in a well-selected patient group remains low but is not zero.[26,40] The current recommendation is that patients who have undergone an IRA procedure continue with yearly surveillance proctoscopy that may be lengthened out to 2 years if the patient goes for multiple years of screening without the development of polyps.[38] Development of ATZ adenomas has been reported as high as 76% in patients undergoing stapled IPAA after 14 years, but with appropriate screening, the risk of cancer is less than 2%.[41–44] There is no set guideline regarding IPAA surveillance, but it is the authors' practice to perform annual pouchoscopy in patients after IPAA for adenomatous polyposis syndromes.

Extracolonic Malignancy

Patients with mutations in the *APC* gene are at risk for the development of extracolonic malignancies as well as CRC (►**Table 2**). The most important of these are malignancies of the proximal small bowel and stomach. The lifetime risk of duodenal cancer is approximately 3 to 5%, and cancer of the duodenum is one of the leading causes of death in patients who have undergone prophylactic colectomy.[20] The ACG currently recommends initiation of screening via upper endoscopy with side-viewing endoscope at age 25 to 30 years with the frequency of screening based on the Spigelman classification which classifies the risk of duodenal cancer based on the number and size of polyps, histology, and evidence of dysplasia (►**Tables 3** and **4**).[20,45] The risk of duodenal cancer is felt to be similar in patients with FAP, aFAP, and MAP, so the recommendations regarding screening are the same for each group.

Gastric fundic gland polyps are also commonly encountered in patients with adenomatous polyposis syndromes.[20] Pathologically, these polyps are considered hamartomas. Endoscopically, they appear similar to gastric mucosa and are sessile in nature. As with other hamartomatous polyps, there is a very low risk for the development of cancer, but biopsy is recommended as malignant transformation has been reported, as well as to rule out adenomatous polyps because approximately 10% of patients with polyposis will develop gastric adenomatous polyps.[20]

The other commonly encountered type of cancer affecting patients with adenomatous polyposis is papillary thyroid cancer. In some reports, the incidence of papillary thyroid

Table 2 Rates of extracolonic malignancy in patients with familial adenomatous polyposis

Malignancy	Rate of presentation (%)
Papillary thyroid cancer	7–12
Duodenal cancer	3–5
Brain tumors (medulloblastoma, astrocytoma, ependymoma)	1–2
Hepatoblastoma	1–2
Gastric cancer	<1
Pancreatic and biliary malignancy	<1

Table 3 Spigelman classification of duodenal polyps and risk of duodenal cancer[20]

Polyps	1 point	2 points	3 points
Number	<4	5–20	>20
Size	0–4 mm	5–10 mm	>10 mm
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Table 4 Spigelman stage and screening recommendations from the ACG and NCCN[20]

Stage	Points	Screening/surveillance
0	0	Every 4 y
I	<4	Every 2–3 y
II	5–6	Every 1–3 y
III	7–8	Every 6–12 mo
IV	9–12	Expert surveillance every 3–6 mo and surgical consultation

Abbreviations: ACG, American College of Gastroenterology; NCCN, National Comprehensive Cancer Network.

cancer is 7% with more than 70% of FAP patients having nodular thyroid disease.[46,47] Owing to a high incidence of thyroid disease, patients with FAP are recommended to undergo yearly screening ultrasound by the ACG.[20]

Extraintestinal Manifestations

Desmoid tumors are one of the leading causes of death in patients with FAP who are part of a familial registry, and desmoids are reported to affect up to 30% of patients with FAP (►**Fig.4A, B**).[39,48] Desmoid tumors are formed by thick sheets of fibrous tissue. Histologically, they are benign, but they can behave quite aggressively and can be a significant source of morbidity and mortality (e.g., bowel obstructions and fistulas). The true prevalence of desmoids tumors in patients with FAP is unknown as there is no screening process for asymptomatic desmoid tumors. Patients with mutations anywhere in the *APC* gene are susceptible to desmoid growth, but patients with a mutation 3′ of codon 1400 have a much higher risk.[39,49] In addition to the location of the mutation, family history is associated with an increased risk of desmoid development.[39,48] Previous surgery increases the risk of intra-abdominal desmoid, but it is unclear if surgery increases the overall risk of desmoid growth, as these studies have a high risk of selection bias.[39,48] The natural history of desmoid growth is one of periodic growth, recession, and in 10% of patients, resolution.[50,51] Patients who develop abdominal wall desmoids should be considered for resection if abdominal wall integrity is not compromised. Surgical treatment of intra-abdominal desmoid tumors, however, is challenging with a high risk of recurrence. It is often difficult to resect these tumors as they commonly involve the base of the mesentery, and therefore nonoperative therapy, including observation or

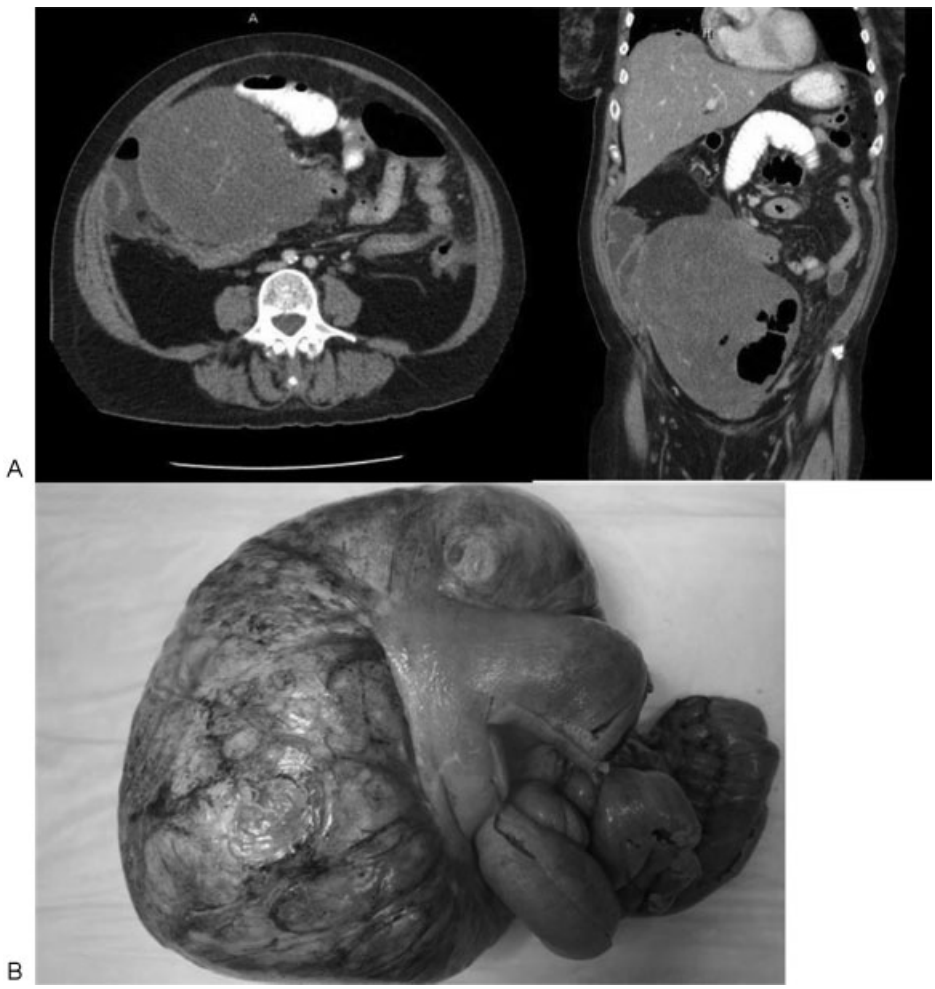

Fig. 4 Example of computed tomographic images (**A**) and surgical resection (**B**) of a patient with a large desmoid causing obstruction with fistula to the small bowel.

systemic therapy, should be considered.[52] Several different therapeutic modalities have been employed including nonsteroidal anti-inflammatory agents (e.g., sulindac), selective estrogen inhibitors, chemotherapy, and/or targeted biologic therapy with varying results.[53] Most recently, imatinib has been shown to positively impact progression-free survival in patients with advanced desmoids, although this group of patients was not exclusively FAP patients.[54] In the care of patients with advanced or advancing desmoid tumors, it is important to involve an oncologist well versed in the treatment of these patients to maximize long-term outcomes.

Mutations in the *APC* gene are associated with several other extraintestinal manifestations, some of which are included as a part of named syndromes including Turcot and Gardner syndromes (the latter more a term of historical note). It is important to recognize that these presentations are simply different phenotypic presentations of various FAP mutations and do not represent a different disease. The most common nonmalignant lesions include congenital hypertrophy of the retinal pigment epithelium (60%), desmoids as mentioned earlier (20–30%), osteomas (~20%), and dental abnormalities (17%).[55] Many patients with FAP may also have cutaneous lesions such as lipomas, epidermoid cysts, and fibromas. It is important to remember these other signs, as they may lead to an obvious diagnosis in young patients presenting with adenomatous polyps or without known polyps but with skin, ophthalmologic, or skeletal/dental findings concerning for FAP. Patients with aFAP may also express these extraintestinal manifestations, but the penetrance in patients with MAP is unknown.

Conclusion

Patients with adenomatous polyposis syndromes present a challenging patient group who manifest phenotypically with 10 to more than 100 adenomatous polyps in the colon and rectum. The importance of screening and registry programs cannot be overstated, as early surgical intervention prevents the development of CRC and improves survival in these patients. As more is learned about the genetic basis of adenomatous polyposis, individualized/personalized therapy based on the genotype may improve survival and QOL in these patients. Practitioners caring for polyposis patients should be fully aware of the implications and consequences of the screening modalities and operative options to treat the various phenotypes of these conditions, including TAC with IRA and TPC with or without IPAA. Finally, the extraintestinal manifestations of the various adenomatous polyposes can facilitate their diagnosis as well as impact patient care, and thus require obligatory understanding of these conditions for those surgeons who care for patients with adenomatous polyposis syndromes.

References

1 Varesco L. Familial adenomatous polyposis: genetics and epidemiology. Tech Coloproctol 2004;8(Suppl 2):s305–s308
2 Bisgaard ML, Fenger K, Bülow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 1994;3(2):121–125
3 Reed TE, Neel JV. A genetic study of multiple polyposis of the colon with an appendix deriving a method of estimating relative fitness. Am J Hum Genet 1955;7(3):236–263
4 Björk J, Akerbrant H, Iselius L, Alm T, Hultcrantz R. Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. Scand J Gastroenterol 1999;34(12):1230–1235
5 Joslyn G, Carlson M, Thliveris A, et al. Identification of deletion mutations and three new genes at the familial polyposis locus. Cell 1991;66(3):601–613
6 Groden J, Thliveris A, Samowitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. Cell 1991;66(3):589–600
7 Powell SM, Petersen GM, Krush AJ, et al. Molecular diagnosis of familial adenomatous polyposis. N Engl J Med 1993;329(27): 1982–1987
8 Burt RW, Leppert MF, Slattery ML, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 2004;127(2):444–451
9 Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003;348(9):791–799
10 Nielsen M, Franken PF, Reinards TH, et al. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). J Med Genet 2005;42(9):e54–e54
11 Ripa R, Bisgaard ML, Bülow S, Nielsen FC. De novo mutations in familial adenomatous polyposis (FAP). Eur J Hum Genet 2002; 10(10):631–637
12 Bülow S. Results of national registration of familial adenomatous polyposis. Gut 2003;52(5):742–746
13 Iwama T, Tamura K, Morita T, et al; Japanese Society for Cancer of the Colon and Rectum. A clinical overview of familial adenomatous polyposis derived from the database of the Polyposis Registry of Japan. Int J Clin Oncol 2004;9(4):308–316
14 Ho JWC, Chu KM, Tse CW, Yuen ST. Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the Hereditary Gastrointestinal Cancer Registry. Hong Kong Med J 2002;8(5):342–347
15 Mallinson EKL, Newton KF, Bowen J, et al. The impact of screening and genetic registration on mortality and colorectal cancer incidence in familial adenomatous polyposis. Gut 2010;59(10):1378–1382
16 Knudsen AL, Bülow S, Tomlinson I, Möslein G, Heinimann K, Christensen IJ; AFAP Study Group. Attenuated familial adenomatous polyposis: results from an international collaborative study. Colorectal Dis 2010;12(10 Online):e243–e249
17 Lockhartmummery P. Cancer and heredity. Lancet 1925; 205(5296):427–429
18 Berk T, Cohen Z, McLeod RS, Cullen JB. Surveillance in relatives of patients with adenomatous polyposis. Semin Surg Oncol 1987; 3(2):105–108
19 Barrow P, Khan M, Lalloo F, Evans DG, Hill J. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. Br J Surg 2013;100(13):1719–1731
20 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110(2):223–262, quiz 263
21 Petersen GM, Slack J, Nakamura Y. Screening guidelines and premorbid diagnosis of familial adenomatous polyposis using linkage. Gastroenterology 1991;100(6):1658–1664
22 Davila RE, Rajan E, Baron TH, et al; Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc 2006;63(4):546–557
23 Vasen HFA, Möslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008; 57(5):704–713

24 Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol 2009;27(24):3975–3980

25 Nielsen M, Joerink-van de Beld MC, Jones N, et al. Analysis of MUTYH genotypes and colorectal phenotypes in patients With MUTYH-associated polyposis. Gastroenterology 2009;136(2): 471–476

26 Church J, Burke C, McGannon E, Pastean O, Clark B. Risk of rectal cancer in patients after colectomy and ileorectal anastomosis for familial adenomatous polyposis: a function of available surgical options. Dis Colon Rectum 2003;46(9):1175–1181

27 Aziz O, Athanasiou T, Fazio VW, et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 2006;93(4): 407–417

28 Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg 2013;257(4):679–685

29 Nieuwenhuis MH, Douma KF, Bleiker EM, Bemelman WA, Aaronson NK, Vasen HF. Female fertility after colorectal surgery for familial adenomatous polyposis: a nationwide cross-sectional study. Ann Surg 2010;252(2):341–344

30 Church J. Ileoanal pouch neoplasia in familial adenomatous polyposis: an underestimated threat. Dis Colon Rectum 2005;48(9): 1708–1713

31 Remzi FH, Church JM, Bast J, et al. Mucosectomy vs. stapled ileal pouch-anal anastomosis in patients with familial adenomatous polyposis: functional outcome and neoplasia control. Dis Colon Rectum 2001;44(11):1590–1596

32 Murphy PB, Khot Z, Vogt KN, Ott M, Dubois L. Quality of life after total proctocolectomy with ileostomy or IPAA: a systematic review. Dis Colon Rectum 2015;58(9):899–908

33 Olsen KØ, Juul S, Bülow S, et al. Female fecundity before and after operation for familial adenomatous polyposis. Br J Surg 2003; 90(2):227–231

34 Ahmed Ali U, Keus F, Heikens JT, et al. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. Cochrane Database Syst Rev 2009;(1):CD006267

35 Benlice C, Stocchi L, Costedio M, et al. Laparoscopic IPAA is not associated with decreased rates of incisional hernia and small-bowel obstruction when compared with open technique: long-term follow-up of a case-matched study. Dis Colon Rectum 2015; 58(3):314–320

36 Marcello PW, Fleshman JW, Milsom JW, et al. Hand-assisted laparoscopic vs. laparoscopic colorectal surgery: a multicenter, prospective, randomized trial. Dis Colon Rectum 2008;51(6): 818–826, discussion 826–828

37 Wu JS, Paul P, McGannon EA, Church JM. APC genotype, polyp number, and surgical options in familial adenomatous polyposis. Ann Surg 1998;227(1):57–62

38 Church J. In which patients do I perform IRA, and why? Fam Cancer 2006;5(3):237–240, discussion 262–2

39 Nieuwenhuis MH, Lefevre JH, Bülow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. Dis Colon Rectum 2011;54(10):1229–1234

40 Bülow S, Bülow C, Vasen H, Järvinen H, Björk J, Christensen IJ. Colectomy and ileorectal anastomosis is still an option for selected patients with familial adenomatous polyposis. Dis Colon Rectum 2008;51(9):1318–1323

41 Wasmuth HH, Tranø G, Myrvold HE, Aabakken L, Bakka A. Adenoma formation and malignancy after restorative proctocolectomy with or without mucosectomy in patients with familial adenomatous polyposis. Dis Colon Rectum 2013;56(3):288–294

42 Tajika M, Niwa Y, Bhatia V, Tanaka T, Ishihara M, Yamao K. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. World J Gastroenterol 2013;19(40):6774–6783

43 Tonelli F, Ficari F, Bargellini T, Valanzano R. Ileal pouch adenomas and carcinomas after restorative proctocolectomy for familial adenomatous polyposis. Dis Colon Rectum 2012;55(3):322–329

44 Ozdemir Y, Kalady MF, Aytac E, et al. Anal transitional zone neoplasia in patients with familial adenomatous polyposis after restorative proctocolectomy and IPAA: incidence, management, and oncologic and functional outcomes. Dis Colon Rectum 2013; 56(7):808–814

45 Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2(8666):783–785

46 Herraiz M, Barbesino G, Faquin W, et al. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. Clin Gastroenterol Hepatol 2007;5(3):367–373

47 Steinhagen E, Guillem JG, Chang G, et al. The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized. Clin Colorectal Cancer 2012;11(4):304–308

48 Sinha A, Tekkis PP, Gibbons DC, Phillips RK, Clark SK. Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis. Colorectal Dis 2011;13(11): 1222–1229

49 Church J, Xhaja X, LaGuardia L, O'Malley M, Burke C, Kalady M. Desmoids and genotype in familial adenomatous polyposis. Dis Colon Rectum 2015;58(4):444–448

50 Church, McGannon, Ozuner. The clinical course of intra-abdominal desmoid tumours in patients with familial adenomatous polyposis. Colorectal Dis 1999;1(3):168–173

51 Campos FG, Martinez CAR, Novaes M, Nahas SC, Cecconello I. Desmoid tumors: clinical features and outcome of an unpredictable and challenging manifestation of familial adenomatous polyposis. Fam Cancer 2015;14(2):211–219

52 Lev D, Kotilingam D, Wei C, et al. Optimizing treatment of desmoid tumors. J Clin Oncol 2007;25(13):1785–1791

53 Yao X, Corbett T, Gupta AA, et al. A systematic review of active treatment options in patients with desmoid tumours. Curr Oncol 2014;21(4):e613–e629

54 Chugh R, Wathen JK, Patel SR, et al; Sarcoma Alliance for Research through Collaboration (SARC). Efficacy of imatinib in aggressive fibromatosis: Results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. Clin Cancer Res 2010; 16(19):4884–4891

55 Groen EJ, Roos A, Muntinghe FL, et al. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol 2008; 15(9):2439–2450