

Practice Parameters For The Treatment Of Patients With Dominantly Inherited Colorectal Cancer

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PRACTICE PARAMETERS FOR THE TREATMENT OF PATIENTS WITH DOMINANTLY INHERITED COLORECTAL CANCER (Familial Adenomatous Polyposis and Hereditary Nonpolyposis Colorectal Cancer)

Prepared by The Standards Task Force The American Society of Colon and Rectal Surgeons

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The American Society of Colon and Rectal Surgeons is dedicated to assuring high quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The standards committee is composed of Society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This Committee was created in order to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus. This is accompanied by developing Clinical Practice Guidelines based on the best available evidence. These guidelines are inclusive, and not prescriptive. Their purpose is to provide information on which decisions can be made, rather than dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, health care workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines.

Practice Parameters for the Treatment of Patients With Dominantly Inherited Colorectal Cancer

Inherited colorectal cancer includes two main syndromes in which predisposition to the disease is based on a germline mutation that may be transmitted from parent to child. Familial adenomatous polyposis (FAP) is associated with a germline mutation of *APC*, a prominent tumor suppressor gene active in the Wnt/Wingless signaling pathway.(1) Hereditary nonpolyposis colorectal cancer (HNPCC) is due to a germline mutation in one of the DNA mismatch repair genes, typically *hMLH1*, *hMSH2* or *hMSH6*.(2,3) The lifetime risk of colorectal cancer is close to 100 percent in FAP and approaches 80 percent in HNPCC. Patients are prone to synchronous and metachronous colorectal neoplasms, neoplasia starting at an early age, and both benign and malignant extracolonic tumors in several different organs. The first step in management of these syndromes is to identify them. Guidelines for the identification and testing of families affected with these syndromes have recently been presented.(4) In this

article we propose practice parameters for the treatment of affected individuals. They are grouped into two sections: those concerning FAP and those concerning HNPCC. This manuscript was reviewed by the members of the Standards Committee of The American Society of Colon and Rectal Surgeons, by the Executive Committee of the Collaborative Group of the Americas on Inherited Colorectal Cancer, and was approved by the Executive Council of The American Society of Colon and Rectal Surgeons

A MEDLINE search of the English language literature was performed to determine the prevailing attitudes and favored treatments of several common but difficult clinical scenarios. These include choice and timing of surgery, management of extracolonic tumors and the role of preoperative counseling. Eight guidelines for familial adenomatous polyposis and four for hereditary nonpolyposis colorectal cancer are outlined, along with supporting evidence. Levels of evidence used are defined in an appendix to this article.

Many of the parameters to be discussed concern the choice and timing of surgery, topics for which no prospective, randomized studies are available. Similarly, there are no randomized studies dealing with desmoid tumors or the role of counseling in these syndromes. With the exception of some chemoprevention studies, the majority of parameters are therefore supported by level III evidence, derived from retrospective case-controlled studies (see Appendix).

SECTION 1. Familial Adenomatous Polyposis

Guideline 1: Treatment Must Be Preceded by Thorough Counseling About the Nature of the Syndrome, Its Natural History, Its Extracolonic Manifestations, and the Need for Compliance With Recommendations for Management and Surveillance

Level of Evidence: III Dominantly inherited colorectal cancer syndromes show a striking pattern of cancer in affected families. This is because of the high penetrance (penetrance = percent of patients with the mutation who have the disease) and often-severe expression (expression = clinical consequences of the mutation) of the mutations involved. FAP has a penetrance of close to 100 percent, colorectal cancer occurs at an average age of 39 years, and every affected patient is guaranteed at least one major abdominal surgery.(5-7) Despite these calamitous prospects, families with FAP adapt well to their disease. Most patients are compliant with recommended treatments, take a keen interest in the syndrome, and play an active role in encouraging relatives to undergo screening. However, when a relative has a bad outcome, either because of severe disease or complications of treatment, family psychology may be affected. Noncompliance, denial, or a refusal to accept recommendations may ensue. The best way of avoiding both bad outcomes and an unfortunate response to them is to provide comprehensive, integrated counseling, support, and clinical services. These sorts of services are best provided through a department, registry, or center with personnel who have experience in managing patients and families with these syndromes.(8)

Guideline 2: Prophylactic Colectomy or Proctocolectomy Is Routine. The Timing and Type of Surgery Depend on the Severity of the Polyposis Phenotype and to a Lesser Extent on the Genotype, Age, and Clinical and Social Circumstances of the Patient

Level of Evidence: III The recommendation for prophylactic colectomy or proctocolectomy in FAP is based on the very high rates of colorectal cancer seen in patients who are not screened.(9,10) In unscreened patients the incidence of cancer is over 60 percent. Appropriate screening and timely surgery(9,10) can minimize this. The risk of cancer is not uniform, however, and is related to the severity of the colonic polyposis. Debinski *et al.*(11) showed the rate of cancer for patients with >1,000 colonic polyps was twice that of patients with <1,000 colonic polyps. In its turn, the severity of the colorectal polyposis is often related to the site of the *APC* mutation in a family. The "hot spot" mutation at codon 1309 is in an area of the gene where mutations always cause severe disease.(12-15) Mutations in codons 3 and 4 are classically associated with attenuated FAP while mutations in the part of codon 15 that is 3' of codon 1450 are usually associated with mild colorectal disease.(16) Mutations in exons 5 to 15E have a variable colorectal phenotype, where some family members have relatively mild disease and others severe. The important aspects of surgery to consider are its timing, its type, and the technical options to be used.

Timing of Surgery. Even in patients with severe disease, cancer is rare under the age of twenty.(17) At-risk family members start screening (either genetic or with flexible sigmoidoscopy) at around puberty. If there is a positive genotype or an adenoma is seen on sigmoidoscopy, colonoscopy is recommended. The risk of cancer of any individual patient can be estimated from the size and number of the adenomas seen on colonoscopy and surgery planned accordingly. For patients with mild disease and low cancer risk, surgery can be done in mid teen years (15-18 years). Where there is severe disease, or if the patient is symptomatic, surgery is done as soon as convenient after diagnosis.

Type of Surgery. There are three main surgical options: colectomy and ileorectal anastomosis (IRA), proctocolectomy with ileostomy (TPC), and proctocolectomy with ileal pouch-anal anastomosis (IPAA).(18-20) For any of these options there are choices of technique. The ileal pouch-anal anastomosis can be stapled, leaving 1 to 2 cm of anal transitional epithelium and low rectal mucosa, or it can be handsewn after a complete anal mucosectomy. The operation can be done conventionally (*i.e.*, open), laparoscopically, or laparoscopically assisted. The ileostomy may be a regular end stoma or one of the varieties of continent ileostomy (K or T).(21,22)

Choice of Procedure. TPC is almost never done as a first operation except when a proctocolectomy is required and there is a contraindication to a pouch-anal anastomosis (*e.g.*, a mesenteric desmoid tumor prevents the pouch from reaching the pelvic floor, a low rectal cancer invades the pelvic floor, or poor sphincters mean inability to control stool).

There is debate among authorities on which of the other two options should be

preferred. Some recommend IPAA for all or almost all FAP patients, basing their recommendation on the risk of rectal cancer after IRA and equivalent quality of life after the two operations.(23-25) Others have shown better functional outcomes after IRA and recommend it for patients with mild colorectal polyposis.(26-28) However, the risk estimates of rectal cancer that are an overriding concern for the proponents of universal IPAA are based on data collected before restorative proctocolectomy was an option and may well be overestimates, especially when applied to patients with mild disease.(29) The risk of rectal cancer after IRA is strongly related to the severity of colorectal polyposis at presentation, and IRA is a reasonable option in mildly affected patients (<20 rectal adenomas, <1,000 colonic adenomas). Retrospective data show that such patients have a very low risk of rectal cancer and include all those with attenuated FAP.(30) Bowel function is usually good after IRA, the operation is simple, and complication rates are relatively low.(26-28) Bowel function after a stapled IPAA is almost as good as with an IRA, and the anastomosis is usually safe enough to allow consideration of the option of avoiding a temporary ileostomy.(31,32)

There is no argument that patients with severe rectal (>20 adenomas) or colonic (>1,000 adenomas), or those with a severely dysplastic rectal adenoma, a cancer anywhere in the large bowel, or a large (>3 cm) rectal adenoma should have a primary IPAA.(30) A stapled IPAA is associated with a risk of anal transitional neoplasia in 30 percent of patients, although if serious neoplasia occurs (high-grade dysplasia or carpeting of the mucosa), the transitional zone can usually be stripped transanally and the pouch advanced to the dentate line.(33-35) Even mucosectomy and handsewn IPAA is associated with anal neoplasia, although at a lower rate.(33,34) The disadvantage of anal mucosectomy is worse function and increased complication rates.(31,32) Both IRA and IPAA require lifelong surveillance of the rectum or pouch, because both are at risk of developing adenomas.(36-38)

Choice of Technique. Mobilization of the colon using minimally invasive techniques such as laparoscopy or a Pfannenstiel incision is ideal for performing colectomy in children, because it minimizes the trauma of the surgery and the pain of the incisions. Its cosmetic result is appealing and it allows an early return to full activities.(38) Whether minimally invasive techniques lower the risk of postoperative intra-abdominal desmoid tumors is unknown, but the concept is attractive.(39) A preoperative erect abdominal x-ray will usually show the position of the flexures and indicate whether use of a Pfannenstiel incision for mobilizing the colon is feasible.

Guideline 3: Lifetime Follow-Up of the Rectum (After IRA), Pouch (After IPAA), and Ileostomy (After TPC) Is Required; Increasing Neoplasia in the Rectum Is an Indication for Proctectomy

Level of Evidence: III The combination of a germline *APC* mutation, stasis of stool, and glandular epithelium is potent at producing epithelial neoplasia. Adenomas and carcinomas have been described in the rectum,(40) the ileostomy,(41-44) and the ileal pouch itself,(45,46) with the risk and severity of

neoplasia increasing with time. The risk of severe neoplasia is mainly determined by the position of the mutation in the gene, as reflected by the severity of the polyposis.(12) Severely affected patients have such a high risk of rectal cancer after IRA that subsequent proctectomy is almost routine and initial IPAA is to be preferred. Yearly endoscopic surveillance of the bowel after the index surgery for FAP is standard. Two thirds of patients undergo spontaneous regression of rectal polyps after IRA, an effect that lasts three to four years.(47) Subsequent surveillance will give a picture of the stability of the rectal mucosa. Small (<5 mm) adenomas can be watched, although random biopsies are done to exclude severe dysplasia. Increasing number and size of adenomas are indications for more frequent surveillance, and adenomas >5 mm should be removed cleanly with a snare. Repeated fulguration of rectal polyps over many years can cause dense scarring that makes cancers flat and hard to see, and rectal dissection during proctectomy can be very difficult. Chronic rectal scarring makes rectal biopsy difficult, because the forceps tend to "bounce off" the scarred mucosa. Furthermore, scarring leads to reduced rectal compliance, increased stool frequency, and a tendency to seepage and incontinence. Severe dysplasia, or villous adenomas >1 cm, are indications for proctectomy. Proctoscopy is best done with a video endoscope, because comfort is enhanced and the view is better. Excellent preparation and a good view are essential to pick up early cancers that can be flat and subtle.

Sulindac (Clinoril®; Merck & Co., Inc., West Point, PA), either by mouth or by suppository, is effective in making polyps disappear.(48-52) Celecoxib reduces polyp load,(53) as does the sulindac metabolite exisulind.(54) However, cancers have been reported in cases where sulindac had been effective in minimizing rectal polyps in the rectum of FAP patients who had had IRA,(52,55) and these anecdotal cases make the long-term use of chemoprevention for rectal polyposis suspect. If it is used in patients who cannot tolerate rectal polypectomy, or who are unwilling or unable to have a proctectomy, close surveillance (every 6 months) with random biopsies to look for severe dysplasia is needed.

There have been at least three recent reports describing adenomas in ileal pouches,(36-38) with a frequency and severity that depend on time from the initial surgery. Two prospective studies have independently calculated the rate of pouch polyposis as 42 percent at seven years.(36,37) There have been anecdotal reports of large adenomas and over 100 adenomas in an ileal pouch. In general these have been treated successfully by oral sulindac, in a dose of 150 to 200 mg twice daily. The full impact of pouch polyposis will not be obvious until the cadre of FAP patients with ileal reservoirs reaches a mean follow-up of 20 years. This is the time to most ileostomy cancers,(41-44) and to the highest rates of rectal cancers after IRA.(40)

Guideline 4: Use of Chemoprevention as Primary Therapy for Colorectal Polyposis Is Not Proven and Is Not Recommended

Level of Evidence: I to II Sulindac, celecoxib, and exisulind are nonsteroidal anti-inflammatory drugs that have been shown to reduce the number and size of colorectal adenomas in patients with FAP.(48-54) While many studies are short-

term, two show effectiveness of sulindac maintained over four years.(48,52) These studies were in patients who had undergone colectomy and IRA. A recent randomized, placebo-controlled, double-blind study of sulindac in genotype-positive, phenotype-negative FAP patients failed to show any effect of sulindac on polyp progression.(56) Furthermore, there have been case reports of cancers occurring in patients with sulindac-mediated ablation of polyps,(52,55) and the only report of a permanent, complete resolution of rectal polyposis comes from Winde *et al.*,(48) who used sulindac suppositories. The effect on polyps is dependent on continued compliance,(48) and there are significant side effects with each medication.(48-54) These medications should not be used as an alternative to surgery, except in patients with pouch polyposis or in selected patients with rectal polyposis after IRA in whom surgery is risky or unwanted by the patient. In these groups of patients, close surveillance (proctoscopy or pouchoscopy every 6 months) is indicated.

Guideline 5: Treatment of Duodenal Adenomas Depends on Adenoma Size and the Presence of Severe Dysplasia. Small Tubular Adenomas With Mild Dysplasia Can Be Kept Under Surveillance, But Adenomas With Severe Dysplasia Must Be Removed

Level of Evidence: II to III The incidence of duodenal adenomas in FAP patients is in the range of 80 to 90 percent.(57-59) All FAP patients therefore undergo screening esophagogastroduodenoscopy starting at age 20 years. The risk of invasive cancer developing in a duodenal adenoma, or in the duodenal papilla, is considerably higher than that for the average population, but in absolute terms it is still low.(60) The aim of endoscopy is not to eradicate all neoplasia but to make sure that there is no severe dysplasia. Studies of the natural history of duodenal neoplasia in FAP show that rapid progression of dysplasia is uncommon, occurring in only 11 percent of cases over a mean follow-up of seven years.(61) Prospective, randomized studies have shown that treatment with nonsteroidal anti-inflammatory drugs is ineffective in treating duodenal adenomas,(62-64) although a recent report indicates that celecoxib may have some effect.(65) If they are not medically treated, low-risk adenomas (small, tubular, low grade dysplasia) may be biopsied and left alone. High-risk adenomas (>1 cm, villous) are treated. Adenomas with confirmed high-grade dysplasia must be removed. As endoscopic or even transduodenal excision or destruction is ineffective in the long term; duodenectomy has to be considered for duodenal adenomas with high-grade dysplasia after the diagnosis has been confirmed on review by an experienced gastrointestinal pathologist.(66,67)

Guideline 6: Duodenectomy or Pancreaticoduodenectomy Is Recommended for Patients With Persistent or Recurrent Severe Dysplasia in the Papilla or Duodenal Adenomas

Level of Evidence: III A review of literature reporting treatment of advanced duodenal adenomas shows that recurrence is almost guaranteed unless the duodenum is removed.(66-68) Transduodenal polypectomy or endoscopic polypectomy may be temporarily effective, but does not offer a permanent cure. The results of pancreas-preserving duodenectomy(69,70) or

pancreaticoduodenectomy(71,72) for benign or early malignant disease are good, with low recurrence and acceptable morbidity. The outcome of surgery for established cancer is not good with recurrence and death the usual outcome.(60) Although the risk of duodenal/periampullary cancer is relatively low in patients with FAP, patients with persistent high-grade dysplasia in the duodenum or papilla are a high-risk group. Careful surveillance is needed, and conservative surgery or endoscopic therapy may be tried. If the severe dysplasia returns or persists, consideration must be given to duodenectomy.

Guideline 7: Surgery for Intra-Abdominal Desmoid Tumors Should Be Reserved for Small, Well-Defined Tumors With a Clear Margin; Abdominal Wall Desmoid Tumors Should Be Excised Whenever Possible

Level of Evidence: III Desmoid tumors are histologically benign overgrowths of fibroaponeurotic tissue occurring rarely in the general population but in 12 to 17 percent of patients with FAP. In the general population desmoids are usually found in limbs or limb girdles; in FAP desmoids are usually (80 percent) intra-abdominal(73-75) and often (80 percent) present within two to three years of an abdominal surgery. Intra-abdominal desmoid tumors usually involve the mesentery of the small bowel, where they are intimately involved with the mesenteric vessels. They tend to infiltrate diffusely, kink adjacent bowel loops, and may obstruct the ureters. Attempts at excision are often unsuccessful, involve removal of a variable length of small intestine, and are associated with a high morbidity and a high recurrence.(76,77)

Intra-abdominal desmoid tumors may affect prophylactic colorectal surgery by limiting the length of the small bowel mesentery. This will sometimes prevent an ileal pouch-anal anastomosis.(78-80) The most common scenario in which this occurs is in patients with Gardner's variant of FAP who need proctectomy after a previous ileorectal anastomosis. Patients need to be warned about this possibility and the likelihood of ileostomy before undergoing the surgery. The second most common site for desmoids in FAP is in the abdominal wall. Abdominal wall desmoid tumors are easier to excise than intra-abdominal tumors, recurrence rates are lower, and the morbidity associated with excision is less. They should be excised with a 1-cm margin. It is often necessary to use mesh to cover the defect in the abdominal wall.

Guideline 8: Intra-Abdominal Desmoid Tumors Involving the Small Bowel Mesentery Are Treated According to Their Rate of Growth and Their Presentation. Clinically Inert Tumors Should Be Treated With Sulindac or Not Treated at All. Slowly Growing or Mildly Symptomatic Tumors May Be Treated With Less Toxic Regimens Such as Sulindac and Tamoxifen or Vinblastine and Methotrexate. Rapidly Growing Tumors Need Aggressive Therapy With Either Very High-Dose Tamoxifen or Antisarcoma-Type Chemotherapy. Radiation Is an Option if Collateral Damage Is Not a Big Concern

Level of Evidence: III Intra-abdominal desmoid tumors vary in their clinical behavior from aggressive, relentless growth to indolent, asymptomatic coexistence. There is no single, predictably effective way of managing intra-

abdominal desmoids. Evidence suggests that sulindac is partially effective but that a response to this nonsteroidal anti-inflammatory agent may not be noticeable for up to two years.(81) The role of high-dose antiestrogens is uncertain, with one report describing good results in aggressive desmoids with tamoxifen in a dose of 120 mg/day.(82) Toremifene, a more potent antiestrogen than tamoxifen, has some effect on desmoid tumors but seems to work better in non-FAP desmoids than FAP.(83,84) A pilot study of the antifibrosis agent pirfenidone resulted in some modest responses (in a conversation with N. Lindor, October 2000). Most aggressive desmoids receive chemotherapy, and there are two regimens reported. The combination of vinblastine and methotrexate has low toxicity and produces some responses.(85,86) Non-FAP desmoids seem more likely to respond to this combination, although no prospective studies have been done. Antisarcoma therapy such as doxorubicin and dacarbazine is much more toxic but seems to be more effective for rapidly growing intra-abdominal desmoid tumors associated with FAP.(87-89) Radiation is effective in destroying tumors but its effect on the small bowel can be disastrous, causing fistulas and necrosis.

Intra-abdominal desmoids that are not growing may be treated by sulindac alone. If they are growing slowly or causing symptoms it is reasonable to add tamoxifen in a dose range of 80 to 120 mg/day. The dose should be gradually escalated to these levels over a few weeks. If the tumor continues to grow, chemotherapy is appropriate. Really rapid growth is an indication for antisarcoma therapy, while a slower growth rate means vinblastine/methotrexate can be tried. A recent report of successful intestinal transplantation after resection of abdominal desmoids(90) reinforces the extent of the surgery needed to remove them, but also offers some hope for tumors that fail to respond to anything else.

SECTION II: HNPCC

Guideline 1: Treatment Must Be Preceded by Thorough Counseling About the Nature of the Syndrome, Its Natural History, Its Extracolonic Manifestations, and the Need for Compliance With All Recommendations for Management and Surveillance

Level of Evidence: III Hereditary nonpolyposis colorectal cancer is a dominantly inherited syndrome due to an inactivating mutation in one of the human DNA mismatch repair genes. The syndrome is more complex than FAP because more genes are involved, penetrance is less complete, and expression is more varied. Furthermore, the clinical criteria defining HNPCC are arbitrary and not particularly accurate,(4) and the yield of testing for germline mutations is lower than for FAP. HNPCC has a penetrance of at least 80 percent, and colorectal cancer occurs at a mean age of 46 years.(6,7) Affected patients usually have at least one surgery and are committed to lifelong surveillance of several organs. Careful counseling is necessary to allow patients and their families to understand the implications of these complexities.

Guideline 2: When Patients With HNPCC as Defined by Genotype or Compliance With Amsterdam I Criteria Are Diagnosed With More Than One Advanced Adenoma or a Colon Cancer, They Should Be Offered the Options of Prophylactic Total Colectomy and Ileorectal Anastomosis (IRA) or

Hemicolectomy Plus Yearly Colonoscopy. The Choice of IRA Assumes the Anal Sphincter and Rectum Function Normally

Level of Evidence: III When patients known to be affected with HNPCC are diagnosed with advanced neoplasia, they can be offered a choice of conventional partial colectomy with surveillance of the remaining large bowel or total colectomy with rectal surveillance. Surveillance involves colonoscopy or proctoscopy (after IRA) every one to two years for life. There is evidence that cancers can occur in HNPCC within two years of a negative colonoscopy,(91) but that cancers found on screening exams performed with a three-year interval can be cured.(92) The risk of metachronous cancer after conventional treatment of an index cancer is 45 percent in patients with HNPCC,(93) high enough to make prophylactic colectomy a reasonable option. The downside of colectomy and IRA lies in its effect on bowel function and quality of life. In a study of patients having IRA for FAP, quality of life was maintained, although stool frequency increased.(26) These patients were younger than typical HNPCC patients having surgery, but even older patients can do well after IRA provided their anal sphincters and rectums are normal. The outcome of partial colectomy and effective surveillance can be similar to that of colectomy and IRA(94) in terms of minimizing metachronous cancers. Likely patient compliance, the anticipated quality and frequency of colonoscopy, and the relative costs and reimbursement of the two options therefore influence the choice. Even after IRA, the risk of rectal cancer is 12 percent in 12 years,(95) so continuing surveillance of the rectum is mandatory.

HNPCC patients diagnosed by genotype with a normal colon are also candidates for prophylactic colectomy. If penetrance of the mutation in the family approaches 100 percent, this should be strongly considered.(96,97) There have been two attempts to discern the relative benefits of surgery vs. surveillance using decision analysis methods. Syngal *et al.*(98) showed that prophylactic colectomy/proctocolectomy performed at the time of diagnosis led to a greater benefit in years of life expectancy gained than surveillance, but that this benefit decreased the longer surgery was delayed. Furthermore, if prophylactic surgery is performed at the time of diagnosis of a cancer, the gain in life expectancy is only four days for colectomy/IRA and six days for proctocolectomy. The advantage of surgery is further reduced if the gain in years is discounted. When the outcome of the analysis was quality-adjusted life years, surveillance was the most effective strategy, with a gain of 14 quality adjusted life years (QALYs) compared with no surveillance, 3.2 QALYs compared with prophylactic proctocolectomy at diagnosis of HNPCC, and 0.3 QALYs compared with colectomy. A similar phenomenon was seen when comparing colectomy with proctocolectomy. Use of QALYs improved the relative value of the lesser operation. In the decision analysis published by Vasen *et al.*,(99) prophylactic colectomy at age 40 conferred an increase in life expectancy over surveillance of 8 to 18 months. In the same scenario, Syngal *et al.* calculated a benefit for surgery of 9.6 months. These analyses do not take costs into account, however, and they assume a level of compliance and quality of endoscopy that may not be realistic. In the absence of a randomized comparison of surveillance and surgery,

both options must be explained to the patient and individual circumstances, such as comorbidity, gastrointestinal physiology, likely compliance and ease of colonoscopy, taken into account.

Guideline 3: Patients With HNPCC Who Have a Rectal Cancer Should Be Offered the Options of Total Proctocolectomy and IPAA or Anterior Proctosigmoidectomy, Assuming That the Sphincters Can Be Saved

Level of Evidence: III Rectal cancer is an uncommon index cancer in patients with HNPCC. Surgical options, assuming the sphincters can be saved, are restorative proctocolectomy (with ileal pouch-anal anastomosis) and anterior resection. There are substantial differences in bowel function after these two procedures, but the risk of metachronous colon cancer after a primary rectal cancer is not known. The decision to preserve the proximal colon and commit to a program of intensive surveillance is therefore based on likely compliance of the patient with surveillance and the likely impact of the surgery on quality of life.

Guideline 4: Female Patients With HNPCC and Uterine Cancer in Their Family May Be Offered Prophylactic Hysterectomy Once Their Family Is Complete or When Undergoing Surgery for Other Intra-Abdominal Conditions

Level of Evidence: III The lifetime risk of uterine cancer in HNPCC is 42 percent,(100) and although it is most common in families with *hMSH6* mutations,(101,102) it is also associated with *hMSH2* and *hMLH1* mutations.(103) Screening for endometrial cancer in females with HNPCC has been shown in at least one study to be ineffective in detecting cancer,(104) and so where uterine cancer is a feature in families, affected females should be offered prophylactic hysterectomy.(105) Oophorectomy should be done at the same time, because the risk for ovarian cancer associated with HNPCC is high and in a multi-institution review of HNPCC-associated ovarian cancer, synchronous endometrial cancer was present in 21.5 percent of 80 patients.(106)

Brown *et al.*(107) have shown that an increased risk for gynecologic cancer begins by age 25 years. Although the mean age at gynecologic cancer in their series of 67 affected females (43 uterine, 24 ovarian) was 49.3 years, five gynecologic cancers were diagnosed before age 35. The timing of prophylactic hysterectomy and oophorectomy is therefore debatable. It is tempting to offer surveillance during the childbearing years and delay surgery until the patient has had a chance to have her family. Until more data are available, this is the best option. Surgery can be done at the time of another abdominal surgery, or as a separate operation once the patient's family is complete.

Appendix A

Level of evidence(108):

Level I

Evidence from properly conducted randomized, controlled trials.

Level II

Evidence from controlled trials without randomization. or Cohort or case-control

studies. or Multiple times series, dramatic uncontrolled experiments.

Level III

Descriptive case series, opinions of expert panels.

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