Inherited Colon and Rectal Cancer: Surgical Perspectives

Part 2: Hereditary Nonpolyposis Colorectal Cancer: From Diagnosis to Treatment

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The Alphabet Soup of Genetics and Diagnosis Explained

In this four-part series, Part 1 reviewed the basic pathologic and genetic concepts underlying hereditary nonpolyposis colorectal cancer. This second part defines the clinical challenges facing the clinician who is at the forefront of diagnostic and treatment efforts. Parts 3 and 4 will examine familial adenomatous polyposis and related polyposis syndromes.

To Screen: Who, When and How

With steady advances in the understanding of the genetics controlling inherited colorectal cancer, the clinician is now in the position of securing a diagnosis before the disease has transitioned from a simple DNA error to a complex multiorgan disease.

The evaluation of inherited colorectal cancers often begins when a patient presents with a family history suggestive of hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch Syndrome. The diagnosis of HNPCC may also be suggested in the postoperative period on finding a poorly differentiated tumor with mucin, signet ring cells, or tumor-infiltrating lymphocytes. This leads to further investigation. The pathologist and then the geneticist are often the first physicians to diagnose HNPCC. How should screening and evaluation of the patient and family members proceed?

Mass screening of the general population is impractical, and because molecular sampling of all colorectal tumors is likewise unreasonable, much attention has been focused on finding more efficient tools to aid in the initial identification of at-risk populations before or after operative intervention. Screening techniques have used various combinations of family history, tumor pathology, evaluation of tumor microsatellite instability (MSI), immunohistochemistry (IHC) staining, or whole blood gene sequencing. (These genetic tests were discussed in Part 1 of this series.) A coherent screening strategy is needed that is based on current understanding of HNPCC at both the clinical and molecular levels.

Clinical Evaluation

Investigation begins with the construction of a family pedigree. Beginning with the 1990 Amsterdam criteria,1 also known as the “3-2-1” rule, attempts have been made to develop clinical screening criteria to distinguish patients with sporadic colorectal cancer from those patients with inherited colorectal cancer, known as hereditary nonpolyposis colorectal cancer, or Lynch I Syndrome. The criteria evolved into the Amsterdam-2 criteria in 1998. The Amsterdam-2 criteria were created to include patients with Lynch II Syndrome, or inherited colorectal cancer associated with one or more extracolonic neoplasms. In women with Lynch II, there is a 50% to 70% lifetime risk for developing endometrial cancer, with the average age at diagnosis being 46 years.2 Other malignancies associated with Lynch II are ovarian cancer (3%-13%); gastric cancer (2%-13%); transitional cell carcinoma of the ureter and renal pelvis (1%-12%); small bowel cancer occurring most commonly in the duodenum and jejunum (4%-7%); central nervous system tumors, most often glioblastomas (1%-4%); and hepatobiliary cancer (2%).3

The Amsterdam-2 criteria are:

• 3 or more relatives with a Lynch Syndrome–associated cancer;
• 2 or more successive generations affected;
• 1 or more relatives diagnosed before age 50 years;

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One family member should be a first-degree relative of the other 2 members.

Familial adenomatous polyposis should be excluded in cases of colorectal carcinoma; tumors should be verified by pathologic examination.

As the clinical guidelines evolved, so did the understanding of the genetics underlying HNPCC. The Bethesda Guidelines were developed in 1996 to help determine the following:

- Colorectal carcinoma diagnosed in a patient who is less than 50 years old;
- Presence of a synchronous or metachronous colorectal carcinoma or other Lynch Syndrome–associated tumors, regardless of age (a synchronous tumor is discovered at the same time as the original tumor, in the same organ system and of the same pathologic type as the original tumor; a metachronous tumor is of the same pathologic type as the original tumor, in the same organ system and develops more than 12 months after the date of discovery of the original tumor);
- Colorectal carcinoma with high MSI histology (MSI-H) or lack of IHC staining diagnosed in a patient less than 60 years old;
- Colorectal carcinoma diagnosed in one or more first-degree relatives with a Lynch Syndrome–associated tumor, with one of the cancers being diagnosed in a patient less than 50 years old; and
- Colorectal carcinoma diagnosed in 2 or more first- or second-degree relatives with Lynch Syndrome–associated tumors, regardless of age.

The clinician must balance the ideal need to screen and find all individuals affected by HNPCC, whether this is the patient or family member(s), against the psychological and financial costs of testing. Various approaches to the molecular evaluation are based on prescreening the at-risk population using the Amsterdam–2 criteria, the Bethesda Guidelines, or variations of these clinical guidelines combined with some form of genetic evaluation.

The authors use an approach that combines the most relevant features of all available techniques. The approach is based on clinical identification of individuals at risk for an inherited colorectal cancer followed by a genetic evaluation at the molecular level. This strategy may not be available in all institutions. The strategy is separated into a testing scheme for patients with tumor tissue available for analysis (Figure 1) and a strategy for patients from whom tissue is not available for testing (Figure 2, page 38). It is important to note that in patients who are undergoing IHC testing and/or germline analysis, specific genetic information may be uncovered. Patients must give informed consent before undergoing this testing, and genetic counseling must be available. A caveat regarding the use of the algorithm approach: There are other algorithms which do not use MSI testing, but employ IHC as the only initial molecular test.

**Familial Colorectal Cancer**

***Type X*** Colonic surveillance should begin 5 or 10 years earlier than the earliest diagnosed colorectal cancer in the family, and no less often than every 5 years. Aggressive endometrial cancer screening is not necessary and is not supported by data in this group of patients.

Family surveillance is same manner as in patient/proband

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**Figure 1. Evaluation of HNPCC in patients meeting the Bethesda Guidelines or the Amsterdam-2 criteria and in whom tumor tissue is available for analysis.**

- Microsatellite instability (MSI) testing in patient with tumor tissue available for analysis
- MSI-stable (MSI-S), MSI-low (MSI-L)
- MSI-high (MSI-H)
- IHC staining/analysis of MLH1, MSH2, MSH6, PMS2 proteins
- Absent IHC staining (mismatch repair (MMR) gene mutation identified)
- IHC staining is normal (no MMR gene mutation identified)
- Germline analysis (whole blood) of mutant gene identified on IHC
- MMR gene mutation
- No MMR gene mutation
- MLH1 mutation by IHC staining (above)
- Sporadic disease
- Surveillance as described in article text
- Hypermethylation/BRAF analysis
- Hypermethylation found and BRAF mutation present
- Family surveillance as for general population
- Hypermethylation not found and no BRAF mutation
- Family surveillance as if HNPCC
- Non-informative test
- Surveillance as if HNPCC

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*If there is a high index of suspicion of disease in patients not meeting the Bethesda Guidelines or the Amsterdam-2 criteria, proceed with testing or begin surveillance as if disease exists.*

*Further germline testing in patients with MSI-S or MSI-L tumors is unlikely to find a germline mutation.*

*As parts of the diagnostic algorithm involve tests with lower than optimal sensitivities, emphasis has been placed on screening and surveillance as if the patient or family member has a Lynch tumor or is an HNPCC carrier, so as not to miss disease in the patient under study.*
Colorectal Cancer

Germline analysis of all MMR genes

Clinical Review

evaluation before germline analysis. This approach has the advantages of being easier to perform than MSI testing and may be more widely available for clinical use. However, IHC testing has the disadvantage of being unable to distinguish Familial Colorectal Cancer Type X from a non-informative test result. Surveillance for each of these entities is different.

The initial step in the evaluation is to determine whether the patient or family member meets the Amsterdam-2 criteria, the Bethesda Guidelines, or has a suspicious history which does not meet the strict clinical screening criteria.

When Tumor Tissue Is Available

If tumor tissue is available, it is first tested for MSI (Figure 1). This test is highly sensitive at 98%, and any patient who is MSI-stable (MSI-S) or MSI-low (MSI-L), most likely does not have HNPCC. Further molecular testing of this group is unhelpful, yielding little new information. However, this group of patients carries a diagnosis of Familial Colorectal Cancer Type X, which has an inherited etiology as the origin of the tumor, caused by an unknown genetic mutation. Patients in this group appear to have a lower overall incidence of colorectal cancer and a lower risk for non-colorectal cancers than families with documented HNPCC.7 The colorectal cancers seem to occur at a later age as well. Surveillance in this group of patients is different from that in patients with a diagnosis of HNPCC. It is started five or 10 years earlier than the earliest diagnosed colorectal cancer in the family, and conducted no less often than every five years. Aggressive endometrial cancer screening is not necessary and is not supported by data in this group of patients. Tumors that are MSI-H are subjected to IHC staining, searching for the identification of the mutant gene. If IHC staining is normal, with normal protein expression of the known MMR genes, the test is considered non-informative. However, both the patient and family members are followed as if they carried a diagnosis of HNPCC. Even though the test is non-informative, emphasis is placed on intensive surveillance so as not to miss any patients in this group who might have HNPCC. The major disadvantage of this approach is that patients who, in fact, do not have HNPCC may undergo screening and continued intensive surveillance as if they were carriers of the mutation. This has obvious psychological and financial costs as well as the downside of any morbidity associated with the surveillance procedures.

Patients or family members without tumor protein staining by IHC undergo germline sequencing of the newly discovered mutant MMR gene. If germline testing confirms the mutation, this patient or family member is identified as having HNPCC and undergoes surveillance as described below. Finding a mutation in a known MMR gene is the sine qua non for diagnosing true HNPCC.

A patient who has previously undergone a segmental colon resection for what was thought to be sporadic disease now carries an additional diagnosis of HNPCC. Consideration must be given to continued intensive lifetime colorectal surveillance, or to a repeat operation with resection of the remaining colorectal tissue. Surveillance of other organ systems is indicated and is detailed below.

As MLH1 hypermethylation accounts for 20% of all sporadic colorectal cancers, tumors demonstrating high MSI and absent MLH1 staining on IHC, and in whom no MMR gene mutation is found on germline analysis, will undergo testing looking for sporadic, non-inherited disease, or an epigenetic mutation. Attention is paid to continued intensive surveillance as if disease exists.

Family surveillance as if HNPCC gene carrierb (See article text.)

Figure 2. Diagnostic algorithm for the evaluation of patients and/or family members meeting the Bethesda Guidelines or the Amsterdam-2 criteria, in whom no tissue is available for analysis:a

Patient/family member with no tissue available for analysis

Germline analysis (whole blood sample)

Patient/family member with a relative having a known mutation in a known mismatch repair (MMR) gene

Germline testing for known mutant gene

Patient/family member with unknown family genetic information

Germline analysis of all MMR genes

No MMR gene mutation

MMR gene mutation

Normal germline. Surveillance as for general population

HNPPC. Surveillance as described in article text

Family members undergo germline testing. If positive, family member is a carrier requiring same surveillance as for HNPCC. If family member tests negative, no disease or carrier state is present. Surveillance as for general population

Non-informative test. Surveillance as if HNPCC gene carrierb (See article text.)

Family surveillance as if HNPCC gene carrierb (See article text.)

*a* If there is a high index of suspicion of disease in patients not meeting the Bethesda Guidelines or the Amsterdam-2 criteria, proceed with testing or begin surveillance as if disease exists.

*b* As parts of the diagnostic algorithm involve tests with lower than optimal sensitivities, emphasis has been placed on screening and surveillance as if the patient or family member has a Lynch tumor or is an HNPCC carrier, so as not to miss disease in the patient under study.
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is focused on MLH1 because, with few exceptions, it is the methylated gene commonly associated with sporadic colorectal cancer. An epigenetic mutation is one in which the underlying DNA sequence is normal and a change, such as nucleotide hypermethylation, has occurred on top of this normal DNA sequence. This change, although affecting gene function, is not considered to be inherited. The βRAF gene is involved in cell signaling. When the βRAF gene mutates, cell growth and function are affected. Patients without protein staining for MLH1 who test positive on both of these tests are considered to have sporadic, non-inheritable disease. Surveillance for this group and family members is the same as for the general population.

If the hypermethylation and βRAF tests are negative, the genetic test results are considered to be non-informative and further surveillance is the same as for patients with HNPCC.

When Tumor Tissue Is Not Available

In patients who meet the clinical screening criteria or guidelines, without tissue for study (the patient has previously undergone a tumor resection and the tissue is not available, or in family members of patients with known HNPCC), germline MMR gene analysis is the first and only molecular evaluation performed (Figure 2).

If there is a family history of a known specific genetic mutation, this gene is sequenced in the patient. Testing for an already known mutant gene avoids having to laboriously analyze all MMR genes. If a mutation is confirmed, a diagnosis of HNPCC is made and surveillance proceeds appropriately. If the patient’s family has no clinical findings of disease, this patient is considered to be a carrier of the HNPCC mutation. Surveillance proceeds as for patients with HNPCC. Descendants of this patient must be screened as if a diagnosis of HNPCC has been confirmed. The patient undergoes surveillance as if an HNPCC mutation exists.

Importantly, if there is a high index of suspicion of inherited colorectal cancer in patients not meeting the Bethesda Guidelines or the Amsterdam-2 criteria, testing is begun as if malignant disease exists.

Because the genetics of all inherited colorectal cancers are not completely understood, parts of the diagnostic algorithm involve tests with lower than optimal sensitivities. Emphasis has been placed on screening and surveillance as if the patient or family member has a Lynch tumor or is an HNPCC carrier, so as not to miss disease in the patient under study.

Understanding Surgical Options

Intensive Watchful Waiting or Surgical Prophylaxis In Patients Without Evidence of Disease?

After using clinical screening guidelines to direct evaluation and molecular testing, patients without detectable disease who have an HNPCC-associated mutation or who are to undergo surveillance as if they were known HNPCC mutation carriers should begin full colon surveillance every one to 2 years beginning at age 20, or 10 years earlier than the youngest age of onset of colorectal cancer in the family, whichever is earlier. This should continue to age 40, at which time surveillance should be conducted annually. Accelerated carcinogenesis occurs in HNPCC and a tiny colon adenoma may emerge as a carcinoma within 2 to 3 years, as opposed to the 8 to 10 years this process may take in the general population. It is for this reason that annual colonoscopic surveillance should begin at the age of 40. The entire colon must be evaluated, as tumors tend to occur in the more proximal colon.8

Because endometrial cancer is the most common extracolonic malignancy, women at risk for HNPCC should have an annual transvaginal ultrasound with consideration given to regular endometrial biopsies and evaluation of CA-125 levels after age 25. Female patients should be made aware of the value of prophylactic hysterectomy and oophorectomy, especially after the child-bearing years are completed.

Upper gastrointestinal endoscopy should be performed regularly. Families having a predilection for genitourinary tumors should undergo ultrasound and urine cytology screening every 2 years beginning at age 25. However, prophylactic intervention is not recommended.

The risk–benefit ratio for prophylactic colectomy versus lifetime endoscopic surveillance in carriers of the HNPCC mutation is equivocal. Not all carriers will develop disease and operative intervention carries morbidity. Therefore, recommendations for surgical intervention in asymptomatic patients are complex. In the most straightforward case, a prophylactic resection is indicated in those patients with an MMR mutation in whom surveillance is not technically possible, in noncompliant patients, or in those with a personal preference for prophylactic operative intervention.9 The goal of a prophylactic resection is to remove as much at-risk tissue as possible while retaining normal colorectal functioning. Even with a prophylactic resection, patients remain at risk for the development of extracolonic neoplasms, and continued surveillance is necessary.

Understanding Surgical Options

The Surgeon

In patients with an HNPCC-associated MMR mutation and a dysplastic adenoma or a colorectal cancer, a choice exists between a segmental resection, a proctocolectomy with a permanent ileostomy, a total abdominal colectomy with an ileorectal anastomosis, or a proctocolectomy with an ileal pouch–anal anastomosis (IPAA). There are advantages and disadvantages with each option.

First, a thorough evaluation should be undertaken to locate any sites of extracolonic disease that could be removed concomitantly during a colonic resection, or which would suggest widespread, late-stage disease precluding a colonic resection for cure. In patients whose tumors are MSI-H and/or lacking IHC staining for MLH1, and in whom germline analysis does not reveal an MMR gene mutation, hypermethylation testing and βRAF mutation testing should be performed to rule out sporadic colorectal cancer. A standard oncologic segmental resection would be the obvious operative choice in patients with sporadic disease.

The ideal operative approach attempts to balance the need for removing as much at-risk tissue as possible against the side effects associated with a more radical extirpation. The functional results are generally considered to be better with a greater amount of colon or rectum left intact. Conversely, not removing all of the colorectal mucosa exposes the patient to a 45% increased risk for a metachronous lesion.

Four Choices

In patients with an HNPCC lesion, a proctocolectomy with an end ileostomy will remove all at-risk tissue and will prevent the development of a metachronous colorectal lesion. However, this will leave the patient with a permanent stoma and is not a popular choice among young patients. This operative approach is not without morbidity.

A total abdominal colectomy with an ileorectal anastomosis removes most of the colonic tissue while attempting to preserve normal rectal reservoir function. The remaining rectum is at risk for the development of a second cancer and will require frequent surveillance for the lifetime of the patient, as there is a 12% incidence of the development of a rectal cancer at 10 years postoperatively.10,11

A proctocolectomy with an IPAA removes almost all colorectal tissue. However, microscopic islands of mucosa may remain and are subject to malignant transformation. Lifetime proctoscopic examinations are necessary. Frequent daytime and nocturnal bowel movements can strongly impact the postoperative quality of life. Sexual function may be affected with extended resections, and immediate postoperative morbidity is higher as well. Pouch failure requiring excision of the pouch may occur and is more common after local sepsis in the postoperative period.

What about the possibility of performing a more limited, segmental resection? It has been shown that a segmental resection is associated with a higher rate of development of a second colorectal cancer, a shorter period of time to the development of the colorectal cancer, and a similarly shorter period of time to a second operative resection compared with a primary operative procedure of a total abdominal colectomy with an ileorectal reconstruction or a proctocolectomy with an IPAA. These results are not surprising, as leaving in place a greater amount of colorectal tissue with a segmental resection exposes the remaining at-risk tissue to the same genetic forces that caused the original cancer.12

However, this is not the entire story, as an extended resection is associated with a higher postoperative morbidity rate. This rate increases in older patients undergoing a more radical procedure.

Segmental Resection and Extended Resection: Postoperative Quality of Life And Life Expectancy

When evaluating quality-of-life results in patients undergoing a total abdominal colectomy with an ileorectal anastomosis, subjects were found to have a good postoperative quality of life, but also had three to four formed stools per day, a slightly increased incidence of fecal urgency and occasionally required anti diarrheal medication. There was a suggestion that postoperative problems were more severe in patients who had undergone an ileo-rectal anastomosis (mid-rectal was defined as an anastomosis 10 cm proximal to the anal canal).13 These “manageable” results and low incidence of postoperative problems were contrasted with the
need for more invasive, intensive lifetime surveillance in patients undergoing a more limited, segmental resection.

Life expectancy after an extensive resection was compared with that after a limited resection. The gain in life expectancy after a proctocolectomy with an IPAA compared with a segmental resection was 3.2 years if the initial operation was performed at age 27. With operative intervention at age 47, the gain was 1.3 years, and the gain was 0.3 year with operative intervention at age 67. The gain in life expectancy after a total abdominal colectomy with an ileorectal anastomosis compared with a segmental resection was 2.3 years if the initial operation was performed at age 27. With operative intervention at age 47, the gain was one year, and the gain was 0.3 year with operative intervention at age 67. It was noted that older patients had significantly more difficulty with postoperative bowel control and increased potential for developing an anal stenosis and additional life expectancy after either type of extended resection.11

The same study evaluated the differences in life expectancy after each type of operative intervention in patients with HNPCC when stratified by the Dukes classification of tumor stage at the time of diagnosis and treatment. The study found that the earlier the stage at which an MMR gene for colorectal cancer was detected and the younger the patient at the time of detection, the greater was the benefit in years of life expectancy gained using the more extensive operations. A proctocolectomy with an IPAA compared with a segmental colectomy or hemicolecotomy yielded an average gain in life expectancy of 4.7 years in Dukes A tumors, 2.4 years in Dukes B tumors, and 9 months in Dukes C tumors. The gain was 3.4 years after a total abdominal colectomy with an ileorectal anastomosis in Dukes A lesions. These differences decreased drastically with advancing age to the point at which the type of operation made no difference in years of life expectancy at age 67, irrespective of the Dukes tumor stage. Stated another way, older age was associated with a negligible gain in life expectancy after a more extensive, radical operation, irrespective of tumor stage. (The data appeared to indicate that “older age” was between 50 and 60 years, although the authors stated only that it was “less than 60 years of age.”) The authors did point out that the results may have been influenced by a bias in the choice of operative treatment, as the study was performed retrospectively before the knowledge of the tumor stage.13

The authors underscored the statistically significant gain in years of life expectancy in relation to regular, intensive surveillance beginning at a young age, to detect tumors at an early stage.12 It is recommended that in younger patients with a known diagnosis of a Lynch I or Lynch II colorectal tumor, an extended resection should be performed. The type of extended resection is an individual decision balancing the expected increase in postoperative life expectancy and the postoperative long-term morbidity. A total abdominal colectomy with an ileorectal anastomosis and annual proctoscopic surveillance is a reasonable option in younger patients. As HNPCC tumors tend to occur in the proximal colon, leaving the rectum intact to obtain a better functional result achieves a reasonable balance between cure, prevention and morbidity.

In older patients, especially in those with abnormal sphincter function, there is minimal gain in life expectancy after a more radical resection compared with increased morbidity. A segmental resection and annual surveillance colonoscopy may be preferable.

In patients with a colorectal tumor who meet the Amsterdam-2 criteria or the Bethesda Guidelines and who have an MSI-H tumor or absent IHC protein staining, and no discoverable germline mutation (a non-informative test), a segmental resection with lifetime annual colonoscopic surveillance may be offered. The risk for developing colorectal cancer or extracolonic neoplasia is lower than in HNPCC, and the age at diagnosis of colon cancer is older than in HNPCC.7 Depending on the age of the patient and any other mitigating features, an extended resection with annual proctoscopy may be performed. Genetic counseling may assist in the decision-making process in these cases.14

Although the data are less clear with regard to a prophylactic resection in HNPCC-associated mutation carriers who do not have a colorectal malignancy, an extended resection remains the procedure of choice, because there is less remaining colorectal tissue at risk for metachronous disease. This is especially true in younger patients, but again, the patient must be aware of the increased morbidity accompanying an extended resection.

Rectal Cancer: Operative Options

In patients harboring a rectal cancer, a low anterior resection with sparing of the colon may be offered. Patients may have better bowel function after this but will require regular, lifetime surveillance of all remaining colonic tissue. However, the rate of development of a metachronous cancer in the remaining colon after a limited resection may be as high as 45%,15,16 Alternatively, a proctocolectomy with an IPAA may be performed. The potential for developing a metachronous colon cancer using the limited resection would seem to favor performing the more extensive resection. Patient age, sphincter function, and genetic counseling may be the vital criteria used in decision making.

Prophylaxis for Women

Finally, in women with HNPCC who are undergoing a colon resection or other abdominal operations or who have completed childbearing, a prophylactic hysterectomy and bilateral salpingo-oophorectomy may be offered. This recommendation is emphasized for women with a specific family history of endometrial or ovarian cancer in addition to the MMR mutation.3,16

New Knowledge, Improved Survival

HNPCC is associated with a 30% incidence of nodal metastases compared with an incidence as high as 65% in the more advanced stages of sporadic colorectal cancer.17 There is also a 9% incidence of peritumoral lymphocytic invasion in HNPCC tumors, signaling a possible enhanced immune response. When matched for age of onset and tumor stage, HNPCC colorectal cancers are associated with a significantly better survival rate than sporadic colorectal tumors.18,19

Ultimately, treatment decisions should be discussed with the patient after consultations with all relevant specialists.

As new knowledge becomes available and light is shed on the genetic underpinnings of inherited colorectal cancers, the uncertainties in diagnosis and treatment will recede into the past history of our experience. Treatment and treatment algorithms will improve. But for now, a thorough understanding of the genetics of HNPCC will aid the physician in diagnosing and managing a complex problem in its early stages rather than later.

Parts 3 and 4 will examine familial adenomatous polyposis and other inheritable polyposis syndromes.

References

11. Rodriguez-Bigas MA, Vasaen HF, Pecka-McKlein J, et al. Rectal cancer risk in hereditary nonpolyposis colorectal cancer after extended colectomy and limited resection with sparing of the colon may be offered. The potential for developing a metachronous colon cancer using the limited resection would seem to favor performing the more extensive resection. Patient age, sphincter function, and genetic counseling may be the vital criteria used in decision making.