Endoscopic and Surgical Management of Hereditary Nonpolyposis Colorectal Cancer

Rebecca B. Baucom, M.D.¹ Paul E. Wise, M.D.¹

¹Section of Surgical Sciences, Vanderbilt University Medical Center, Nashville, Tennessee.

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Address for correspondence and reprint requests Paul E. Wise, M.D., Section of Surgical Sciences, Vanderbilt University Medical Center D5248 Medical Center North, Nashville, TN 37232-2543 (e-mail: paul.e.wise@vanderbilt.edu).

Abstract

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is a disease characterized by autosomal dominant clustering of colorectal cancer (CRC) as well as other cancers. It is critical for clinicians and surgeons caring for patients with HNPCC to be familiar with their management related to CRC. Based on retrospective studies, screening colonoscopy is recommended every 1 to 2 years beginning at age 20 to 25, or 10 years younger than the earliest CRC in the family (whichever is earlier). HNPCC patients with colon cancer should be considered for total abdominal colectomy rather than a more limited segmental colon resection due to the increased risk of metachronous neoplasia associated with the condition. Rectal cancer in HNPCC has not been well studied, but discussions with the patient regarding surgical management should weigh the risks of metachronous CRC with the morbidity and quality of life issues associated with proctocolectomy. Regardless of the procedure, a patient with HNPCC requires close postoperative endoscopic surveillance of any remaining at-risk mucosa. In terms of chemoprevention, aspirin has been shown to be effective in preventing colorectal neoplasia in prospective trials and should be considered in patients who do not have a contraindication to the drug. Trials for other chemopreventative agents in HNPCC are ongoing. As more is learned about particular genotype–phenotype correlations with Lynch syndrome, this will likely affect surgical decision making. Despite all of these efforts in the management of patients with HNPCC or Lynch syndrome, incident CRCs still occur, thus reinforcing the need for further studies to better understand the optimal management of these patients.

Keywords

- ▶ HNPCC
- ▶ hereditary nonpolyposis colorectal cancer
- ▶ Lynch syndrome
- ▶ colon cancer
- ▶ colorectal cancer
- ▶ hereditary cancer syndrome

Objectives: On completion of this article, the reader should be able to: (1) summarize the screening and postoperative colonoscopic/endoscopic surveillance recommendations for colorectal cancer in patients with HNPCC/Lynch syndrome; (2) describe the surgical options and their justification for the treatment of colon cancer in patients with HNPCC/Lynch syndrome; (3) describe the surgical options and their justification for the treatment of rectal cancer in patients with HNPCC/Lynch syndrome; and (4) summarize the chemoprevention options for patients with HNPCC/Lynch syndrome.

Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is the most common form of hereditary colorectal cancer (CRC), accounting for 3 to 5% of all CRCs.^{1,2}

Many affected families have a germline mutation in DNA mismatch repair (MMR) genes including *MLH1*, *MSH2*, *MSH6*, or *PMS2*. As more is learned about the genetics of this syndrome, surveillance and management decisions become more complex. Particular controversy surrounds the role of prophylactic colectomy, time interval between screening colonoscopies, and extent of resection in individuals with colorectal cancer (CRC). This review discusses the management related to CRC in individuals affected with HNPCC or Lynch syndrome, including screening and surveillance recommendations, surgical interventions, and considerations of chemoprevention.

For the purpose of this review, the terms HNPCC and Lynch syndrome will not be used interchangeably. HNPCC will be

defined clinically as an autosomal dominantly inherited disease characterized by early-onset cancers, most commonly CRC, endometrial and ovarian^{2,3} as defined by the Amsterdam, Amsterdam-like, and/or the Bethesda clinical criteria (described earlier in this edition of *Clinics*). Lynch syndrome includes those patients and their family members with a known germline mutation in an MMR gene, or those who meet the HNPCC clinical criteria and have microsatellite unstable tumors but have not had genetic testing for a germline MMR mutation.^{4,5} "Familial colorectal cancer type X" is a term recently used to describe families that meet Amsterdam criteria, but without an MMR gene mutation.^{2,6}

Colorectal Cancer Screening in HNPCC

The CRC that occurs in HNPCC typically develops from adenomas just as CRC does in sporadic cases, however, they pass through the adenoma to carcinoma transformation sequence more quickly than the 8 to 15 years that it takes to occur in sporadic CRC. This leads to a younger age at diagnosis of CRC in HNPCC (mean of 45 years old) and a need for a shortened screening interval.⁷ These CRCs are also more likely to be right-sided (60–70%), and are associated with high risk of synchronous (18%) and metachronous (11–45%) tumors.^{1,2,8,9} Therefore, it is imperative that the entire well-prepped colon is evaluated during screening and that screening colonoscopy begin earlier than in individuals with average CRC risk (i.e., earlier than age 50).

The goal of screening is to detect and remove premalignant lesions and to prevent cancer-related morbidity and mortality. One prospective controlled trial demonstrated a statistically significant 63% decrease in development of CRC from 11.9% to 4.5% ($P = 0.03$) in members of 22 families with HNPCC who underwent surveillance with colonoscopy or barium enema plus sigmoidoscopy every 3 years ($n = 133$) compared with families with HNPCC who underwent no screening ($n = 118$).¹⁰ Mortality differences were not significant in the study (12 control deaths vs 6 case deaths, $P = 0.08$). A 15-year follow-up study of this same patient cohort demonstrated both the 63% decrease in CRC incidence with screening as well as decreased CRC-associated mortality in those patients who underwent screening compared with those who did not.¹¹ In the subset of Lynch syndrome patients in this study, CRC incidence rates also dropped significantly from 41% to 18% ($P = 0.02$), but cancers continued to develop despite their screening regimen. Of note, the CRCs were diagnosed at an earlier stage (and therefore more often amenable to curative operative intervention) in patients undergoing screening as compared with those who were not being screened who were diagnosed with CRC based on symptoms.

Because of the continued CRC incidence in HNPCC despite the 3-year screening, most authors have recommended more frequent screening. Vasen et al demonstrated that in 745 patients with Lynch syndrome who underwent screening at a mean interval of every 16 months during the years between 1995 and 2009, 4.4% developed CRC while under surveillance, with most cases occurring after age 40. The risk of developing

CRC at 10 years was reduced to 6% with this shorter interval when compared with a 10% risk at 10 years with screening every 2 to 3 years. Interestingly, they also looked at screening in patients with familial CRC type X and showed that their risk of developing CRC under surveillance was significantly lower and occurred in older individuals when compared with Lynch syndrome patients. The authors concluded that individuals with Lynch syndrome should undergo screening every 1 to 2 years beginning at 20 to 25 years of age, and that a less intensive colonoscopic surveillance program might be appropriate in patients who meet Amsterdam criteria but do not have a demonstrated MMR mutation.⁶ Alterations in screening intervals between Lynch syndrome patients versus those with HNPCC have not been studied in a prospective fashion, however; therefore, most authors recommend colonoscopy every 1 to 2 years beginning at age 20 to 25, or 10 years younger than the first diagnosis in the family (whichever is first), then yearly after age 40 for patients with either HNPCC or Lynch syndrome.^{2,7,12}

Adjunctive technologies beyond standard colonoscopy may increase the identification of neoplasia during screening of HNPCC patients and may impact CRC mortality rates in these patients. Technologies such as dye-spray or chromoendoscopy,¹³ as well as narrow band imaging have shown promise in better-identifying adenomas when used for screening HNPCC patients.^{14,15} Because these technologies are not yet widely available, they are not considered the standard of care in the screening of those with HNPCC. Even increased magnification and slow withdrawal times during colonoscopy, however, have shown increases in adenoma identification in Lynch syndrome up to 55% over standard colonoscopy. This was equivalent to the improvement in detection rates with chromoendoscopy.^{13,15,16}

Surgical Management of Colorectal Cancer in HNPCC

Colon Cancer in HNPCC

Surgery for HNPCC can be either therapeutic or prophylactic with therapeutic resections for colon cancer being the most common indication for surgery. Once colon cancer is diagnosed, surgical options include segmental resection (removal of just the affected portion of colon such as a right or left hemicolectomy) versus total abdominal colectomy (TAC) with ileorectal anastomosis (removing the entire colon and anastomosing the terminal ileum to the upper rectum or rectosigmoid). A TAC in the setting of colon cancer is both therapeutic and prophylactic because it involves removing the portion of the colon affected by the cancer as well as the remainder of the colon which harbors risk of metachronous neoplasia.² Most authors agree that TAC is the favored option for a patient with Lynch syndrome and colon cancer due to the high risk of metachronous neoplasia in the remaining colon if a segmental resection is performed.^{1,17–19} However, no prospective trials have been done to demonstrate a true survival benefit for TAC versus segmental resection.

In retrospective studies, the risk of developing a metachronous colon cancer after partial colectomy ranges from 11

to 45% over 8 to 13 years (► **Table 1**).^{1,2,8,18} Parry et al assessed the risk of metachronous CRC in 382 Lynch syndrome patients from the Colon Cancer Family Registry who underwent TAC versus segmental resection as treatment for their first CRC. Interestingly, only 50 of the 382 patients studied (13%) underwent the more extensive colon resection for their first colon cancer, while the remaining 332 patients (87%) underwent segmental resection. The incidence of metachronous CRC (i.e., rectal cancer) in those undergoing TAC was zero, whereas 22% (74/332 patients) of those who underwent segmental resection developed a metachronous cancer at a mean follow-up of 9 years. The cumulative risk of metachronous CRC was 16% at 10 years, 41% at 20 years, and 62% at 30 years after segmental resection. Nearly 80% of the patients who developed these lesions were undergoing surveillance colonoscopy every 1 to 2 years. Notably, the greater the extent of the segmental resection for colon cancer, the lower the risk of metachronous cancer development (31% risk reduction for every 10 cm resected). Although most metachronous CRCs after segmental resection were stage I and II, 18% (10/57) were stage III, and over half of those patients diagnosed with stage III disease were undergoing screening endoscopy every 1 to 2 years. There was no survival difference at 5 or 10 years between the patients who had undergone segmental resection versus more extensive resection. At 5 years, 98% of patients from both groups were alive ($P = 0.8$); at 10 years, 98% of those who underwent extensive colectomy and 97% of those who underwent segmental resection were alive ($P = 0.7$).¹⁸

Another retrospective study, published by Natarajan et al, looked at metachronous CRC rates, reoperation rates, and survival in 37 Lynch syndrome patients (*MLH1* and *MSH2* MMR carriers only) who had undergone TAC for their first cancer or as prophylaxis versus 69 age, sex, and MMR gene mutation-matched controls who had undergone segmental resection (or no operation to match as controls versus the prophylactic colectomy cases). A median follow-up of 12 years was achieved, and even with equivalent endoscopic surveillance in both groups, results favored extended operation: The

rate of metachronous cancer was 6% versus 26% ($P < 0.006$), reoperation rate was 16% versus 37% ($P < 0.04$), and death was 7% versus 12% ($P = \text{NS}$), respectively, when comparing TAC versus segmental resection.⁸

Other studies have used retrospective risk data to use mathematical models to aid operative decision making in HNPCC. One such Markov model predicts an increased life expectancy of 2.3 years if a colon cancer diagnosed in a Lynch syndrome patient at the age of 27 years is treated by TAC as compared with performing a segmental colectomy. One important consideration, though, is that the median age of persons with CRC under surveillance programs for HNPCC is around 45 years. Using this model, the estimated increased life expectancy for a 47 year old undergoing total colectomy is only one year.^{18,20} Therefore, some have argued that this recommendation for more extended resection should be reconsidered given the increased morbidity associated with TAC compared with segmental resection.

Although the recommendations have supported TAC with ileorectal anastomosis, still most of the first CRCs in HNPCC are treated by segmental colectomy, even in patients from Amsterdam-criteria positive families and some with known MMR mutations. For example, one study from the Cleveland Clinic looking at operative trends in patients with Lynch syndrome found that only 16 of 33 patients (48%) with HNPCC and CRC at their own institution underwent TAC as their first operation. In other clinics across the United States, however, only 7 of 60 persons (12%) with HNPCC or Lynch syndrome with CRC underwent total colectomy.²¹ The exact reasons for favoring segmental resections in practice, even when acknowledging the high risk of metachronous CRCs, are not known. Some of the patients may have been diagnosed with Lynch syndrome only after their segmental colectomy based on postoperative tumor testing, which underscores the importance of preoperative family history and genetic assessment/counseling (and consideration of preoperative tumor testing, see below). The decision related to extent of resection also likely relates to patient and surgeon concerns over changes in bowel habits and increased surgical risks related

Table 1 Total Colectomy versus Segmental Resection in HNPCC: Metachronous Colorectal Cancer Formation

Study		Segmental Colectomy	Total Colectomy	P Value
Kalady et al ¹	Number of patients	253	43	
	Patients with endoscopic surveillance	221 (87%)	38 (88%)	N/A
	Average time from index surgery to 2 nd CRC, months	69	227	N/A
	Patients with metachronous CRC	55 (25%)	3 (8%)	
Natarajan et al ⁸	Number of patients	69	37	
	Time range from index surgery to 2 nd CRC, months	6–160	16–175	<.006
	Total number of second CRCs	23 (33%)	4 (11%)	N/A
Parry et al ¹⁸	Number of patients	332	50	
	Metachronous CRCs (over 8–9 years of f/u)	74 (22%)	0 (0%)	<.001
	Endoscopic frequency, months (mean)	Q20 months	Q16 months	0.16

CRC, colorectal cancer; f/u, follow-up; N/A, not available/reported.

to TAC/ileorectal anastomosis versus segmental resections, as well as lack of understanding of the metachronous CRC risks related to HNPCC, even when the condition is recognized preoperatively. Of course, segmental resection may be appropriately favored over TAC in those instances where patients may have more significant comorbidities, fecal incontinence, and/or decreased life expectancy (thus minimizing the benefit of preventing a metachronous CRC given that the risk is ~16% at 10 years¹⁸). Unfortunately, with no prospective studies to prove the appropriate extent of resection in HNPCC or Lynch syndrome, most experts would recommend more extended resection in those patients for whom it is a safe operative option.

Proponents of segmental resection argue that the HNPCC patient's quality of life should be given greater consideration, particularly if over the age of 40, given the relatively small predicted increase in life expectancy with more extensive resection.^{20,22} Quality of life after TAC versus segmental colectomy was not evaluated in the study mentioned above by Parry et al, and very little data looking at quality of life exists in the literature. One small study from Cleveland Clinic (abstract only) compared 22 patients who underwent TAC and ileorectal anastomosis with 22 control patients who underwent right or left hemicolectomy. At 2 years, frequency of bowel movements was four per day for patients after TAC and two per day for those who underwent segmental resection. This was not associated with any difference in continence, nor was there a difference in quality of life as measured by the SF-36.^{2,18} Quality of life is an area that needs further study before accurate conclusions can be drawn comparing segmental resection and TAC in HNPCC.

The surveillance required in patients with HNPCC after resection for colon cancer has not been studied, so they are based on the screening recommendations for HNPCC. After TAC, surveillance of the remaining rectum (rigid or flexible proctoscopy) should be performed at least annually, and this can usually be performed after enema preparation and without the need for sedation. After segmental colectomy, any remaining mucosa must be evaluated every 1 to 2 years, which means a standard bowel preparation will be required as well as sedation, leading to time away from work as well as the risk of dehydration or electrolyte abnormalities. It must be underscored that even perfect compliance with surveillance (or screening) recommendations does not prevent a patient from developing metachronous CRC, as supported by the retrospective screening studies as well as the studies assessing the extent of resection mentioned above. Patients and physicians must have an appropriate understanding about screening and surveillance and the benefits of earlier detection as well as decreased, but not zero, incidence of metachronous CRC with screening. Furthermore, surgical decision making should also take into account likely compliance with future surveillance. One study evaluated the screening behavior among individuals at high risk for CRC, and they concluded that at least one in four individuals at high risk will deviate significantly from recommended frequency of screening.²³ If there is any question about compliance, TAC should be favored over segmental colectomy.

In summary, TAC should be considered in patients with HNPCC or Lynch syndrome who develop CRC. This recommendation is based upon the increased risk of metachronous CRC in these patients, which has been repeatedly demonstrated to be quite high in retrospective studies. No studies have demonstrated a statistically significant difference in survival between segmental colectomy and TAC, however. Further studies are needed to more adequately assess possible differences in quality of life, taking into account surveillance as well as bowel function.

Prophylactic Colectomy in HNPCC

Prophylactic colectomy in Lynch syndrome (i.e., in patients who have been found to have an MMR mutation but have not developed CRC) is not currently recommended and is not frequently performed. This is in part due to the incomplete penetrance of the disease phenotype as not all patients with a known gene mutation develop CRC; affected individuals have a 60 to 80% lifetime risk for developing CRC, depending on the MMR mutation.^{2,12} Some authors have suggested that prophylactic colectomy could be considered and offered in Lynch syndrome patients under certain circumstances: in those patients who have a colon that is technically difficult to evaluate with colonoscopy, those who cannot or will not comply with screening recommendations, those with severe psychological distress due to fear of developing CRC, families with early onset or severe penetrance of the CRC phenotype, and females who are already undergoing hysterectomy for uterine cancer.² Based on study subsets of small retrospective studies (e.g., eight patients in the Natarajan et al study who underwent prophylactic colectomy—none of whom developed a metachronous CRC), it appears that prophylactic colectomy may be a safe and effective means to prevent the development of colon cancer. Additionally, no data exists to support prophylactic completion colectomy after segmental colectomy for colon cancer in a patient found later to have Lynch syndrome. In this instance, surveillance is continued every 1 to 2 years, and TAC may be considered if the patient develops a metachronous CRC.

Rectal Cancer in HNPCC

Approximately 15% of those with Lynch syndrome will present with rectal cancer as their index cancer^{2,24}; it is unclear how this should be treated as this has not been well-studied in the setting of HNPCC and Lynch syndrome. In those for whom rectal cancer is their index cancer, surgical options to consider include segmental resection (e.g., low anterior resection [LAR] or abdominoperineal resection [APR]) or more extended resection (i.e., total proctocolectomy with end ileostomy or restorative ileal pouch-anal anastomosis). One retrospective study by Lee et al looked at the incidence of metachronous CRC in 18 patients who either met Amsterdam criteria or had documented MMR mutation and presented with an index rectal cancer. They were treated with segmental proctectomy (without colectomy), and 18% later developed a metachronous lesion at a median of 203 months after their initial surgery.²⁴ Data from Cleveland Clinic from 31 HNPCC patients who had undergone segmental proctectomy

at a median follow-up of 106 months showed that 45% of patients developed significant colonic neoplasia, either carcinoma or high-risk adenoma.² Given these high metachronous colon cancer risks, some experts believe that proctocolectomy should be offered as the initial operation for those presenting with rectal cancer in the setting of HNPCC. If not, the remainder of the colonic mucosa remains at risk which requires strict compliance with an intensive, usually yearly, surveillance program.^{2,24}

Those patients with HNPCC or Lynch syndrome who have undergone segmental resection or TAC, either for CRC or prophylactically, are also at risk for developing a metachronous rectal cancer. One retrospective study by Rodriguez-Bigas found that rectal cancer developed in 11% of 71 patients who had undergone TAC or subtotal colectomy at a median of 158 months after initial surgery. They determined that the risk of developing rectal cancer is around 12% at 12 years after colectomy.⁹ Interestingly, this is the same risk found after TAC in individuals with familial adenomatous polyposis (FAP) which led to the recommendation that individuals affected with FAP undergo total proctocolectomy as the standard of care (with or without ileal pouch anal anastomosis). The difference between Lynch syndrome and FAP lies in the polyp burden and the ability to adequately screen the remaining mucosa. In the Rodriguez-Bigas study mentioned above, all but one patient who developed rectal cancer were being closely followed in surveillance programs. The time from most recent surveillance endoscopy to the development of rectal cancer ranged from 6 to 24 months. The one patient not active in surveillance did present with an advanced stage tumor and died from the disease. The authors concluded that frequency of endoscopic examinations of the rectum in these patients should be no less than annually after 10 years at risk and should be considered as frequently as every 6 months.⁹ Again, surveillance does not prevent the development of cancer, but in patients with Lynch syndrome, endoscopy can decrease the incidence of cancers and detect cancers at an earlier stage. No prospective data exist evaluating surveillance of the rectum or optimal surgical treatment in this patient population.

In all patients with HNPCC who develop rectal cancer, any surgical treatment must take into account the tumor stage and possible need for chemoradiation therapy. If a patient presents with stage III or IV rectal cancer, the risk of death from metastatic disease may be greater than the risk of developing a metachronous cancer, and these patients should be treated with more limited bowel resection (e.g., LAR or APR) in an effort to preserve bowel length and quality of life.² Additionally, if a patient is to undergo creation of a colonic pouch or restorative ileal pouch, any radiation should be performed preoperatively to avoid radiating the pouch and thus adversely impacting its function. As with segmental resections for colon cancer, HNPCC patients with rectal cancer who undergo segmental proctectomy (whether LAR or APR) with or without chemoradiation and/or adjuvant chemotherapy need to have continued close surveillance of the remaining colon as discussed above.

Other Considerations

Genotype–Phenotype Correlations

The specific MMR gene mutations in Lynch syndrome may also play a role in surgical decision making in the future as more studies uncover the genotype–phenotype correlations in this condition. Several studies show that the risk of CRC is significantly higher in families with *MLH1* and *MSH2* mutations when compared with mutations in *PMS2* and *MSH6*, although more data are needed to fully understand and quantify these cancer risks.^{18,25} As more is learned, a patient's specific genotype may aid in counseling the patient to more strongly consider TAC over segmental resection if CRC risk is known to be particularly high for that patient's particular gene mutation. The same may be true for segmental resection if the CRC penetrance of the patient's gene mutation is found to be much lower. Currently, however, this form of personalized medicine cannot be advocated for the management of Lynch syndrome without further supportive data from larger genotype–phenotype studies that are currently ongoing (e.g., the International Mismatch Repair Consortium with over 10,000 gene mutation carriers from 3800 families).

Preoperative Tumor Testing

For those patients who present with CRC and a history suspicious for HNPCC (early age of onset, right-sided cancer, characteristic pathology, family history or personal history of other HNPCC-associated tumors, etc.), the surgeon or endoscopist should have a low threshold for performing microsatellite instability (MSI) testing or immunohistochemistry studies for the protein products of the MMR genes on the tumor itself to allow for subsequent focused genetic testing. Although somewhat controversial, several institutions now reflexively test all CRCs due to the high potential for identifying Lynch syndrome patients even in the absence of these clinical or pathologic high-risk features.²⁶ Ideally, all tumor and genetic testing would occur before surgery, if possible, to guide surgical planning.²⁷ This is especially true in rectal cancer where neoadjuvant chemoradiation can affect the accuracy of any tumor testing strategies, either due to lack of sufficient tissue for testing or radiation-induced tissue alterations diminishing the accuracy of any tumor tests.^{28–30} Unfortunately, the results of MSI testing or MMR gene testing can take weeks to process, often longer than most patients are willing to wait for surgical intervention for a CRC. Therefore, an extensive discussion with a patient whose clinical picture is suspicious for HNPCC is needed to ensure that they fully understand the risks and benefits of segmental or extended resection for colon or rectal cancer. This is especially true if they elect to proceed with their operation prior to completion of preoperative testing.

Chemoprevention

To prevent or delay the development of neoplasia in the colon and rectum in the setting of HNPCC or Lynch syndrome, and hopefully avoid the need for surgical intervention, there has been an attempt to use medical therapy as chemopreventative

agents, much as they have been used in the setting of FAP (see article on FAP in this issue of *Clinics*).⁷ Unlike FAP, however, fewer human trials have been conducted because of the relative infrequency of developing adenomas in HNPCC, the numbers of patients that are required for such trials, and the lack of understanding of the impact of genotype-phenotype correlations on the development of neoplasia based on each patient's MMR gene mutation (assuming they have been gene tested or they are positive for a mutation).¹³ Much like in FAP, however, attempts at developing or identifying chemoprevention agents seem appropriate given the high risk circumstances for HNPCC patients. This allows for more leeway when compared with chemopreventative agents used in average risk individuals when looking at cost of the agents, cost of trials to develop them, as well as safety and efficacy of the agents.¹³

Preclinical studies in cell lines and mouse models have been helpful to direct human chemoprevention trials, but these models do not always mimic the human situation with MMR deficiency.³¹ Most of the agents being studied were identified as chemoprevention candidates based on observational studies of CRC risk in normal populations. These include but are not limited to aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), selective COX-2 inhibitors, and supplements such as calcium/vitamin D. Even vaccines for MSI tumors have been developed, and while in their preclinical infancy, they are being tested in HNPCC models.³¹

Aspirin has been the best-studied drug in the setting of HNPCC. Aspirin is thought to function by increasing MMR protein production in MMR-deficient cells based on preclinical models.³¹ The Colorectal Adenoma/Carcinoma Prevention Program 2 (CAPP2) study of aspirin in Lynch syndrome is the first and largest chemoprevention trial aimed at a genetic condition. The trial recruited 937 Lynch syndrome and HNPCC patients from 1999 to 2005 into a 2 × 2 factorial trial of 600 mg aspirin and aspirin placebo as well as 30 g resistant starch and starch placebo with the primary endpoint being the development of CRC. Initial results showed no difference in the treatments, leading the authors to conclude, "The use of aspirin, resistant starch, or both for up to 4 years has no effect on the incidence of colorectal adenoma or carcinoma among carriers of the Lynch syndrome."³² Interestingly, however, subsequent analyses showed that after a mean followup of 56 months, there was a statistically significant decrease in the development of colorectal neoplasia (HR, 0.41; 95% CI, 0.19–0.86; $P = 0.02$) in the 861 patients from the initial cohort who had been randomized to aspirin or placebo.³³ The authors concluded in the follow-up study that at least 2 years of daily aspirin use by Lynch syndrome patients leads to a significant decrease in the incidence of CRC and polyps (but not other Lynch-associated cancers). They concluded in the follow-up trial that "...aspirin is an effective chemopreventative agent in hereditary cancer with an effect equivalent to that achieved with surveillance colonoscopy. The case for prescription of aspirin to this high-risk group is clear."³³ The follow-up study to CAPP2 will be CAPP3 that has started recruiting patients as of late 2011 (<http://www.capp3.org/>). The aim of the study is to determine the dose effect of aspirin on the development of

neoplasia in Lynch syndrome patients by recruiting 3000 MMR gene mutation carriers into three treatment groups at varying doses of daily aspirin intake: 600 mg, 300 mg, and 75 to 100 mg.

NSAIDs, such as sulindac, have shown great promise in chemoprevention trials in other hereditary syndromes, but NSAIDs have been noted to increase cell proliferation and even tumor development in Lynch syndrome mouse models.³¹ A placebo-controlled, crossover trial of sulindac in 22 patients with HNPCC showed statistically increased cell proliferation in the right colon similar to the mouse model findings; therefore, this agent has fallen out of favor in HNPCC.³⁴ Nitric oxide (NO)-donating NSAIDs for Lynch syndrome have shown promise based on their inhibition of MSI with apparently low toxicity, whereas more selective COX-2 inhibitors (such as celecoxib) have unclear promise as chemoprevention in HNPCC based on mixed expression of COX-2 in Lynch syndrome tumors (as opposed to high expression in some sporadic adenomas).^{7,31,35} Human studies with COX-2 inhibitors in HNPCC are ongoing. Calcium has been considered as a chemopreventative agent as it is thought to bind fatty acids and bile salts thus decreasing colonic irritation and cell proliferation. However, human studies with calcium have shown no change in cell proliferation in the colon and rectum of 30 patients with HNPCC when compared with placebo,^{36,37} so no trials are ongoing looking at calcium and HNPCC.

Currently, in addition to the use of daily aspirin in those HNPCC patients without a contraindication to the drug, the best CRC prevention modality in HNPCC is appropriate endoscopic screening for neoplasia.^{38,39} Other recommendations such as maintaining a healthy lifestyle (e.g., avoiding smoking, maintaining a healthy weight, etc.) seem intuitive, but may have a beneficial effect in HNPCC patients just as it appears to have in patients at risk for sporadic CRC. Chemoprevention agents may allow for increasing the interval for screenings and postoperative surveillance in HNPCC, if not avoiding them altogether, but this will require further confirmatory studies.

Conclusion

In conclusion, there is still much to be learned about the management of patients with HNPCC and Lynch syndrome. As more is learned about particular genotype-phenotype correlations, this will certainly affect surgical management and decision making. Additionally, prospective data are needed to better understand the optimal surgical treatment of patients with Lynch syndrome or HNPCC who are diagnosed with colon or rectal cancer. At this time, screening is recommended every 1 to 2 years beginning at ages 20 to 25 or 10 years younger than the first diagnosis of CRC (whichever comes earlier). Patients who develop CRC should be considered for total abdominal colectomy due to the increased risk of metachronous lesions. Rectal cancer has not been well studied, but discussions with the patient should weigh the risks of future metachronous CRC with the morbidity associated with total proctocolectomy. Finally, it appears that aspirin may be an effective chemopreventative agent in patients with HNPCC,

and should be considered in patients who do not have a contraindication to the drug.

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