Clinical Practice Guidelines for the Surgical Treatment of Patients With Lynch Syndrome

Daniel O. Herzig, M.D. • W. Donald Buie, M.D. • Martin R. Weiser, M.D.
Y. Nancy You, M.D. • Janice F. Rafferty, M.D. • Daniel Feingold, M.D.
Scott R. Steele, M.D.

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The American Society of Colon and Rectal Surgeons is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines 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 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 to dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, healthcare workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines.

It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all of the circumstances presented by the individual patient.

STATEMENT OF THE PROBLEM

The American Society of Colon and Rectal Surgeons participated in development of the 2014 US Multi-Society Task Force on Colorectal Cancer Guidelines[1] for Lynch syndrome, which provide a colorectal cancer risk-assessment tool to screen individuals in the office or endoscopy setting and a strategy for universal screening for Lynch syndrome by tumor testing of patients diagnosed with colorectal cancer, algorithms for genetic evaluation of affected and at-risk family members of pedigrees with Lynch syndrome, and guidelines for screening at-risk and affected persons with Lynch syndrome. These guidelines are summarized in Table 1, and the reader is encouraged to refer to them directly for supplementary content. Additional guidance is given here more specifically for the surgical management of patients with Lynch syndrome.

Colorectal cancer is the third most common cancer in men and women in the United States and the second leading cause of cancer deaths.[2] Approximately 20% to 30% of colorectal cancer cases are associated with a family history of colorectal polyps or cancer, and ≈3% to 5% of cases are associated with an identifiable inherited colorectal cancer syndrome. The most common of these is Lynch syndrome, characterized by a mutation in one of the DNA mismatch repair genes.

The diagnosis of Lynch syndrome was initially based on a set of clinical criteria known as the Amsterdam criteria (Table 2).[3,4] As the molecular understanding of the syndrome improved, microsatellite testing has been used as a screening test for patients with Lynch syndrome. The Bethesda criteria, first published in 1997 and updated in 2004 (Table 3),[5,6] were initially intended to define who should be tested for microsatellite instability and not meant as a way to diagnose Lynch syndrome. With the identification of the specific genes involved, additional screening methods were developed, including immunohistochemical staining of the proteins produced by the genes and germline testing. Germline sequencing of the mismatch repair genes remains the gold standard for confirming the causative gene mutation for Lynch syndrome. An estimated 40% of patients meet Amsterdam criteria but have no mutation identified; because Lynch syndrome is now defined by its genetic basis, this clinical condition, termed *familial colorectal cancer type X*, is now considered separately from Lynch syndrome.[7]

METHODOLOGY

These guidelines are built on the last set of the American Society of Colon and Rectal Surgeons *Practice Parameters*

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TABLE 1. Summary of Multi-Society Task Force guidelines

Variable	*Recommendation*
Screening/testing	
Genetic testing	Universal testing (tumor testing) • Testing for MMR deficiency of newly diagnosed CRC should be performed • This can be done for all CRCs or CRC diagnosed at age ≤70 y and in individuals >70 y who have a family history concerning for LS • Analysis can be done by IHC testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for MSI • Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation • To facilitate surgical planning, tumor testing on suspected CRC should be performed on preoperative biopsy specimens, if possible Traditional testing (germline testing) • Individuals who have a personal history of a Lynch syndrome–related tumor showing evidence of MMR deficiency (without evidence of *MLH1* promoter methylation) • Personal history of uterine cancer diagnosed at age <50 y • A known family MMR gene mutation • Fulfill Amsterdam criteria or revised Bethesda guidelines • Have a personal risk of ≥5% chance of LS based on prediction models
LS management	• Screening for CRC by colonoscopy is recommended in persons at risk (first-degree relatives of known MMR gene mutation carriers who have not had genetic testing) or affected with LS every 1 to 2 y, beginning between ages 20 and 25 y or 2 to 5 y before the youngest age of diagnosis of CRC in the family if diagnosed before age 25 y • For MMR germline mutation–positive patients, consideration should be given to annual colonoscopy • In carriers of deleterious MSH6 and PMS2 mutations, the risk of CRC is lower and age at diagnosis later than in patients with MLH1 and MSH2 mutations; consideration could be given to starting screening at age 30 y in MSH6 and 35 y in PMS2 carriers, unless an early onset cancer exists in a given family
Endometrial cancer	• Screening should be offered to women at risk for or affected with LS by pelvic examination and endometrial sampling annually starting at age 30–35 y
Ovarian cancer	• Screening should be offered to women at risk for or affected with LS by transvaginal ultrasound annually starting at age 30–35 y
Prophylactic hysterectomy and oophorectomy	• Hysterectomy and bilateral salpingo-oophorectomy should be recommended to women with LS who have finished childbearing or at age 40 y • Patient considerations in this decision could include differences in uterine cancer risk, depending on MMR gene mutation; morbidity of surgery; and the risk of menopausal symptoms, osteoporosis, and cardiac disease if hormone replacement therapy is not given
Gastric cancer	• Screening should be considered in persons at risk for or affected with LS by esophagogastroduodenoscopy with gastric biopsy of the antrum at age 30–35 y • Treatment of *Helicobacter pylori* infection should be administered when found • Subsequent, surveillance every 2–3 y can be considered based on individual patient risk factors
Small intestinal cancer	• Routine screening of the small intestine is not recommended
Cancers of urinary tract	• Screening should be considered for persons at risk for or affected with LS, with urinalysis annually starting at age 30–35 y
Pancreatic cancer	• Routine screening of the pancreas is not recommended; the benefit of screening for pancreatic cancer with this magnitude of risk is not established
Breast and prostate cancer	• Routine screening of the prostate and breast cancer is not recommended beyond what is advised for the general population.
Treatment/prevention	
Colectomy	• Colectomy with ileorectal anastomosis is the primary treatment of patients affected with LS with colon cancer or colon neoplasia not removable by endoscopy • Consideration for less-extensive surgery should be given in patients >60–65 y and those with underlying sphincter dysfunction
Aspirin	• Growing but not conclusive evidence exists that use of aspirin is beneficial in preventing cancer in patients with LS • Treatment of an individual patient with aspirin is a consideration after discussion of patient-specific risks, benefits, and uncertainties of treatment is conducted

MSI = microsatellite instability; MMR = mismatch repair; CRC = colorectal cancer; LS = Lynch syndrome; IHC = immunohistochemistry.
Table was adapted from Giardiello et al.[1]

for the Identification and Testing of Patients At Risk for Dominantly Inherited Colorectal Cancer published in 2003.[8] An organized search of MEDLINE (Ovid MEDLINE and Ovid OLDMEDLINE), PubMed, and Cochrane Database of Systematic Reviews was performed through April 2016. Keyword combinations, including *colorectal neoplasm* (limited to genetics subheading and limited to clinical study, clinical trial, comparative study, guideline, journal

TABLE 2. Amsterdam II criteria[3,4]

1. Three or more relatives with an associated cancer (colorectal cancer or cancer of the endometrium, small intestine, ureter, or renal pelvis); 1 should be a first-degree relative of the other 2
2. Two or more successive generations affected
3. One or more relatives diagnosed before the age of 50 y

Familial adenomatous polyposis should be excluded in cases of colorectal carcinoma

Tumors should be verified by pathologic examination whenever possible

article, meta-analysis, multicenter study, or observational study; 546 references); *hereditary nonpolyposis colon cancer* or *Lynch syndrome* (which mapped to the subject heading colon neoplasms, hereditary nonpolyposis, 3344 references); *genetic counseling* and *colon*; and *genetic screening* and *colon* (14 references) were included. Titles were screened and 1688 selected abstract were reviewed, yielding 229 references selected for additional review. After review, 60 references were considered for grading. Directed searches of the embedded references from the primary articles were also performed in selected circumstances. The final grade of recommendation was performed using the Grades of Recommendation, Assessment, Development, and Evaluation system (Table 4).[9]

MANAGEMENT

1. **For individuals with Lynch syndrome who develop a colon cancer, a total colectomy is preferred for cancer risk reduction.** ***Strong recommendation based on moderate-quality evidence. 1B***

TABLE 3. Revised Bethesda criteria[6]

Tumors from individuals should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is <50 y of age
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age[a]
3. Colorectal cancer with the MSI-H[b] histology[c] diagnosed in a patient who is <60 y of age[d]
4. Colorectal cancer diagnosed in 1 or more first-degree relatives with an HNPCC-related tumor, with 1 of the cancers being diagnosed under age 50 y
5. Colorectal cancer diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

[a]Hereditary nonpolyposis colorectal cancer (HNPCC) –related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors; sebaceous gland adenomas; and keratoacanthomas in Muir–Torre syndrome, as well as carcinoma of the small bowel.
[b]Microsatellite instability–high (MSI-H) in tumors refers to changes in 2 or more of the 5 National Cancer Institute–recommended panels of microsatellite markers.
[c]Data include the presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.
[d]There was no consensus among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep <60 y of age in the guidelines.

In contrast to sporadic colon cancer, 3 issues must be evaluated when considering the appropriate surgical treatment for colon cancer in the setting of Lynch syndrome: 1) appropriate treatment of the primary tumor, 2) consideration of risk reduction with prophylactic removal of nonneoplastic colon, and 3) morbidity and quality of life after colectomy. There is no prospective randomized trial comparing extended resection with a limited resection. Three retrospective studies have examined the degree of metachronous cancer risk reduction. Kalady et al[10] examined a cohort of patients meeting Amsterdam criteria with colon cancer. Of the cohort of 296 patients, segmental colectomy was performed in 253 patients (85%) and total colectomy in the remaining 43. There was superior risk reduction in the total colectomy group, with second primary cancers occurring in 25% of the segmental colectomy group versus 8% of the total colectomy group. The difference was seen despite annual endoscopic surveillance in 88% of patients; median follow-up was 104 months. Nearly identical findings were noted from a case–control study of 37 patients with Lynch syndrome who were treated with either segmental or prophylactic total colectomy compared with 69 matched control subjects. The study showed a significant decrease in metachronous cancer with a total abdominal colectomy compared with segmental resections of cancers (6% vs 26%).[11] The largest cohort analysis to date from the Colon Cancer Family Registry examined 382 patients with colon cancer and mismatch repair gene mutations.[12] Most patients (332/382 (87%)) underwent segmental resection. Metachronous cancer occurred in 74 (22%) of 332 patients who had segmental colectomy versus 0 (0%) of 50 patients who had total colectomy. Both groups underwent appropriate endoscopic surveillance, with an average of 1 examination every 20 months in the segmental group and 1 examination every 16 months in the total colectomy group. The cumulative risk of metachronous colorectal cancer in patients in the segmental group was 16% at 10 years, 41% at 20 years, and 62% at 30 years. This rate is at least as high, or higher, than the anticipated risk of a patient with Lynch syndrome developing colorectal cancer without ever having a segmental colectomy, suggesting that there is no risk reduction against metachronous cancer when patients undergo segmental resection. They noted that the risk of metachronous colorectal cancer was reduced by 31% for every 10 cm of bowel removed.

As noted in Table 1, the US Multi-Society Task Force on Colorectal Cancer recommends total colectomy with ileorectal anastomosis for the treatment of colon cancer in the setting of Lynch syndrome.[1] The 2013 Mallorca guidelines, composed of expert opinion from the Mallorca group, recommend that "the option of subtotal colectomy including its pros and cons should be discussed with all Lynch syndrome patients with CRC, especially younger patients."[13]

It should be noted that before available data regarding the benefit of metachronous cancer risk reduction

TABLE 4. The GRADE system: grading recommendations

Number	*Description*	*Benefit vs risk and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low- or very low– quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2C	Weak recommendation, Low- or very low– quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations, other alternatives may be equally reasonable

Table was adapted from Guyatt et al.[1] Grading strength of recommendations and quality of evidence in clinical guidelines are found in a report from the American College of Chest Physicians Task Force.
RCT = randomized controlled trial.

was defined, segmental resection was widely preferred and performed (≈85%–87% of the time, as shown above). In part, this may be secondary to functional issues of a total versus segmental colectomy (see below), although oncologically segmental colectomy does not address the risk of metachronous cancer. This practice may be slow to change given the recent nature of the cited literature. However, based on currently available evidence, there is superior cancer risk reduction with total colectomy for the treatment of colon cancer in the setting of Lynch syndrome, and total abdominal colectomy with ileorectal anastomosis is the preferred treatment for most patients. This may not be applicable to all patients because of the morbidity of the operation or quality-of-life issues.

2. **Patients with Lynch syndrome who develop a colon cancer may consider segmental colectomy despite the inferior cancer risk reduction because of differences in bowel function between segmental and total colectomy.** ***Weak recommendation based on low-quality evidence. 2C***

Despite the benefits of cancer risk reduction from a more extensive colectomy, some patients may still consider segmental resection. Two retrospective surveys have examined functional results and quality of life after more extensive resections.[14,15] Although not limited to patients with Lynch syndrome, You et al[15] examined 201 patients with total colectomy and 321 patients who had a segmental colectomy using the Irritable Bowel Syndrome-Quality of Life instrument. Overall, quality of life scores after segmental resection and ileorectal anastomosis were 98.5 and 91.2. Haanstra et al[14] surveyed patients with Lynch syndrome who had surgical treatment of a colorectal cancer and compared quality-of-life outcomes in 51 patients who had a partial colectomy with 53 patients who had a total colectomy with 3 validated instruments. After total colectomy, there was a detrimental effect on stool frequency, social impact, and problems with defecation. However, none of the 3 instruments demonstrated a negative impact on overall quality of life. In light of these 2 reports, patients should be informed of the functional differences but similar overall quality of life between the 2 operations. Unfortunately, there are no studies that can provide guidance regarding who might be at higher-than-average risk for functional impairment after total colectomy. As noted above, in the absence of data regarding a benefit of reduction of risk for metachronous cancer, segmental resection is widely preferred to total colectomy. Therefore, some patients may choose segmental colectomy for its positive dif-

ference in bowel function despite the superior cancer risk reduction with a total abdominal colectomy.

3. **Annual colonoscopy should be performed after segmental resection of colon cancer in patients with Lynch syndrome.** ***Strong recommendation based on moderate-quality evidence. 1B***

Considerable data exist regarding the screening interval for Lynch syndrome before a diagnosis of cancer. A systematic review of the literature from Lindor et al[16] concluded that endoscopic surveillance should occur every 1 to 2 years starting at age 20 to 25 or 10 years younger than the youngest age of colon cancer in a family member. A recent meta-analysis suggests that the balance of benefits of screening may not outweigh the risks until age 30 years.[17] Conventional colonoscopy at yearly intervals may detect polyps, but there is a high rate of interval cancers even with appropriate screening.[18,19] Enhanced detection techniques, such as chromoendoscopy, prolonged withdrawal time, and narrow-band imaging, may improve the detection of flat lesions.[20–22] It is not clear how much of the data from screening done before a diagnosis of cancer are applicable to determining the endoscopy interval after segmental resection.

Two of the retrospective reviews of segmental versus total colectomy (described earlier) have addressed the effectiveness of postoperative endoscopic surveillance. Kalady et al[10] reported results of endoscopic surveillance in their 253 segmental colectomy patients, 221 (88%) of whom had postoperative surveillance at a medial interval of 25 months between endoscopies. In 74 patients (33%), 256 adenomas were detected, and 55 patients (25%) developed a second colorectal cancer despite surveillance. Only 16 of these 55 cancers were stage I at diagnosis, demonstrating the difficulty in preventing advanced-stage cancer with endoscopic surveillance after segmental colectomy. Parry et al[12] reported the cumulative risk of colon cancer after segmental resection to be 16% after 10 years, and this was despite an average of 1 colonoscopy every 20 months. In those developing a metachronous cancer after total colectomy, 47% were diagnosed as stage I, in contrast to the study by Kalady et al,[10] which showed a higher proportion of advanced-stage disease. Only 1 retrospective review has separately described the risk of rectal neoplasia after resection of a colon cancer in the setting of Lynch syndrome.[23] There are inadequate data to clearly define the role of annual surveillance of the rectum after total colectomy, but an annual examination is recommended, because there is clearly a risk of metachronous rectal cancer.[24]

4. **For patients with Lynch syndrome and rectal cancer, the rectal cancer should be treated based on standard oncologic principles, as in sporadic rectal cancer. The decision for concomitant colectomy may be considered on a selective basis.** ***Weak recommendation based on poor-quality evidence. 2C***

Patient-specific variables need to be considered in developing a treatment plan for patients with a rectal cancer in the setting of Lynch syndrome. Although proctocolectomy with or without IPAA would possibly provide absolute risk reduction, specific concerns about bowel function, urogenital function, and the need for pelvic radiation must be considered. In 2012, Kalady et al[25] reported outcomes of a cohort of 50 patients meeting Amsterdam criteria with rectal cancer treated with proctectomy. Of the 33 patients with long-term follow-up, 5 (15%) developed a metachronous colon cancer after a median of 6 years, only 2 of which were early stage. Despite endoscopic surveillance, 17 (33%) of the cohort developed an advanced adenoma or cancer in the remaining colon. Win et al[26] reported a retrospective review of 79 patients with Lynch syndrome and rectal cancer who were treated with proctectomy. With a median follow-up of 9 years, 27% developed colon cancer. Endoscopic surveillance in this study was more frequent than other reports, with an average of 1 colonoscopy every 1.2 years.

The evidence base of 2 small retrospective cohort studies suggests that the high risk of neoplasia in the remaining colon justifies consideration of proctocolectomy for risk reduction. However, the functional differences from a proctocolectomy compared with a more limited resection would be expected to be more pronounced. Individual characteristics, such as tumor location, need for pelvic radiation, preoperative functional status, and the possibility of sphincter salvage, create a much different set of variables when considering the appropriateness of risk reduction through more extensive resection. The quality-of-life data reviewed in recommendation 2 suggest that, in many cases, the oncologic benefit of a more extensive resection is justified. In most cases, treatment of the rectal cancer should follow standard oncologic principles. The decision to remove the rest of the colon may be performed on an individual basis after discussion with the patient.

5. **Hysterectomy and bilateral salpingo-oophorectomy should be offered to women with Lynch syndrome undergoing colectomy, particularly if they have finished childbearing.** ***Strong recommendation based on moderate-quality evidence. 1B***

The 2014 Lynch syndrome guidelines by the US Multi-Society Task Force on Colorectal Cancer, which were reviewed by the American Society of Colon and Rectal Surgeons, recommended hysterectomy and bilateral salpingo-oophorectomy in all women over age 40 years or who have finished childbearing.[1] The evidence base for this is 1 case–control study of 315 women, all of whom had Lynch syndrome. Sixty-one women who underwent prophylactic hysterectomy and 47 women who underwent bilateral salpingo-oophorectomy were matched with women who

had not had the procedures.[27] The risk reduction was dramatic, preventing 100% of endometrial and 100% of ovarian cancers. For endometrial cancer, there were no cancers in the prophylactic surgery group versus 69 (33%) of 210 in the control group, and for ovarian cancer there were no cancers in the prophylactic surgery group versus 12 (5%) of 223 in the control group. The basis for recommending the procedures in women over age 40 years is from 1 cost-effectiveness analysis, which suggested that prophylactic surgery at age 40 years is the optimal strategy.[28] However, there are major limitations in the assumptions made, and the decision about the proper strategy must also take into account other factors than cost-effectiveness, most notably patient preference. No clear specific age recommendation can be made based on the evidence. Because of the clear benefit of prophylactic surgery independent of colectomy, it is reasonable to offer hysterectomy and bilateral salpingo-oophorectomy to all women who are having a colon resection for Lynch syndrome.

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