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PREVENTION AND EARLY DETECTION (R BENAMOUZIG, SECTION EDITOR)

Colorectal Surgery in Lynch Syndrome Patients: When and How?

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Abstract Lynch syndrome is the most common inherited colorectal cancer susceptibility syndrome and accounts for approximately 3 % of all colorectal cancers. Clinical assessment and a detailed family history are crucial in identifying patients who need further evaluation via genetic counseling and testing. Discovery of the underlying causative germline mutations in DNA mismatch repair genes has allowed more accurate colorectal and extracolonic cancer risk assignment. Once diagnosed, intensive surveillance via colonoscopy and timely interventions such as polypectomy reduce colorectal cancer development and mortality from it. If colorectal cancer develops within a Lynch syndrome patient, extended surgical resection is recommended based on high metachronous colorectal cancer risk. Extended resections can be achieved without significant decreases in quality of life. Heightened clinical awareness is needed to promote appropriate diagnosis and management.

Keywords Lynch syndrome · Hereditary nonpolyposis colorectal cancer · Colorectal cancer · Microsatellite instability · Mismatch repair genes · Hereditary cancer · Colorectal surgery

Introduction

Lynch syndrome is a genetic predisposition to developing colorectal and extracolonic cancers due to an underlying germline mutation in a mismatch repair (MMR) gene [1]. It is the most common cause of hereditary colorectal cancer (CRC), accounting for approximately 3 % of all colorectal malignancies. Lynch syndrome is characterized by early onset CRC and relatively frequent synchronous and metachronous neoplasia [2]. Individuals may have up to an 80 % risk of developing CRC in their lifetime [3]. It is an autosomal dominant condition, which means all first-degree relatives of an affected patient have a 50 % chance of also carrying the mutation. Therefore, identification of individuals who potentially have Lynch syndrome has serious implications for both the patient and their extended families. As our understanding of the genetics underlying Lynch syndrome has evolved, there has been more accurate assignment of cancer risk. Surveillance and interventions such as polypectomy or colectomy allow opportunities to manage that risk. Surgical decision-making is based on an understanding of cancer risk, the natural history of disease, risks of surgery, and resultant quality of life. Physicians caring for Lynch syndrome patients must be knowledgeable regarding these aspects of care and be able to discuss these with patients. This article presents current data and opinion with respect to each of these aspects, with an emphasis on surgical management of the colon and rectum.

Lynch Syndrome Nomenclature and Terminology

There has been an evolution in the nomenclature of the hereditary constellation. It is relevant to understand the disease within this context. Warthin described a family with numerous cases of endometrial cancer and CRC in the absence of polyposis in 1913 [4]. This was followed by a description of two other families with similar features by Henry Lynch et al. in 1966 [5]. In 1985, after studying a large number of similar families, Lynch introduced the term hereditary nonpolyposis colorectal cancer (HNPCC) to describe a syndrome

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characterized by autosomal dominant inheritance, early onset of cancers, multiplicity of colon cancers, and extracolonic cancers [6]. In 1991, to facilitate clinical research and communication between familial cancer registries, the Amsterdam I criteria were proposed to define families that were considered to have HNPCC [7]. These criteria were revised in 1999 (Amsterdam II) in an effort to improve sensitivity and include extracolonic cancers [8]. The Amsterdam criteria are summarized in Table 1. The Bethesda guidelines were later developed to incorporate some of the histologic characteristics of Lynch syndrome cancers and to help guide which tumors should be tested for microsatellite instability (MSI) [9]. Bethesda guidelines are outlined in Table 2. The shift from clinical diagnosis to genetic diagnosis started when the underlying genetics and molecular mechanisms responsible for Lynch syndrome were first described in 1993 as heritable mutations in the MMR genes [1, 10, 11]. An underlying mutation in one of the MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or a mutation in the *EPCAM* gene causes Lynch syndrome. Loss of MMR function through one of these mechanisms results in an accumulation of uncorrected mismatches and alterations in DNA microsatellite regions and eventual tumorigenesis. It is now evident that cancer risk is correlated with an underlying germline mutation and not necessarily clinical criteria. Thus, Lynch syndrome is defined by the presence of a germline mutation in one of the MMR or *EPCAM* genes.

Studies evaluating the accuracy of the Amsterdam II criteria in predicting patients with MMR mutations have demonstrated that these clinical criteria have a sensitivity of approximately 80 % and a specificity that varies from 46 to 68 % [12]. The molecular hallmark of Lynch syndrome cancers is microsatellite instability, which is present in approximately 93 % of tumors [13]. Occasionally, patients with suspicion of Lynch syndrome based on family history will have a MSI-high (MSI-H) tumor without a germline mutation identified. Although these patients are technically not Lynch syndrome, they may be treated clinically as if they have the disease, as we have not identified all causative mutations [14]. Patients diagnosed with HNPCC by satisfying the Amsterdam criteria but have microsatellite-stable tumors are said to have familial colorectal cancer type X (FCC X) [15]. In summary, while the Amsterdam criteria serve as important clinical markers to establish a working diagnosis of HNPCC and warrant further testing, the diagnosis of Lynch syndrome is established when a pathogenic MMR mutation is demonstrated. When discussing Lynch syndrome, it is important to maintain the correct definitions to allow for the proper classifications of the different phenotypes and genotypes [16].

Colorectal Cancer Risk and Natural History of the Disease

The average lifetime risk of developing colorectal cancer in the USA is 5–6 % for the general population [17] and increased for people with a personal or family history of colorectal neoplasia. The overwhelming majority of colorectal cancers develop sporadically, i.e., due to genetic changes caused by environmental or dietary influences. However, approximately 30 % of colorectal cancer cases have some hereditary predisposition [18]. Lynch syndrome accounts for approximately 3 % of all CRC, and among patients with Lynch syndrome, the risk of developing CRC is 53–69 % in men and 33–52 % in females [19, 20]. CRCs within Lynch patients are characterized by young age onset (mean age is 44–61 years [19, 21]), right-sided location, and mismatch repair deficiency [22]. As the entire colorectum is at risk for developing cancer due to the germline defect, patients with Lynch syndrome also have a higher rate of both synchronous and metachronous CRC [23]. *MSH6* mutation carriers have been reported to carry a higher risk of endometrial cancer than those harboring mutations in the other MMR genes [24, 25•]. There are significant extracolonic cancer risks associated with Lynch syndrome including endometrial (40–60 %) [3, 19, 21], gastric (7 to 19 %), ovarian (9 to 13 %), urinary epithelial (4–5 %), hepatopancreaticobiliary (2 to 7 %), small bowel (1 to 4 %), and central nervous system cancers (1–3 %). These extracolonic cancers and their surveillance and surgical management are beyond the scope of this manuscript and are discussed elsewhere [21, 26, 27].

Table 1 Amsterdam criteria

Amsterdam I (7)

- 3 or more family members affected, one of whom is a first-degree relative of the other two, with colorectal cancer
- 2 successive affected generations
- 1 or more of the cancers diagnosed before age 50 years
- Familial adenomatous polyposis is excluded

Amsterdam II (8)

- As above, but the definition of cancer is broadened from colorectal cancer to include other HNPCC-related cancers:

3 or more family members affected, one of whom is a first-degree relative of the other two, with HNPCC-related cancers[a]

[a] HNPCC-related cancers: colorectal, endometrial, stomach, small bowel, hepatobiliary, renal pelvis, urothelial and pancreatic

Table 2 Revised Bethesda criteria (9)

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

[a] Colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas, and small bowel

[b] Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern

CRC Risk Management/Risk Reduction

Surveillance Colonoscopy and Polypectomy

The purpose of surveillance in patients with Lynch syndrome is to detect and remove premalignant polyps before they develop into cancer. Colonoscopy and polypectomy in Lynch syndrome patients clearly reduce the incidence and death from CRC [28, 29, 30••]. The efficacy of surveillance was evaluated in a trial including 22 families with HNPCC extending over a 15-year period. The study showed that screening for CRC at 3-year intervals reduces the CRC risk by 62 %, prevents CRC deaths, and decreases the overall mortality rate by about 65 % in such families [28]. As this study was conducted before the recognition and genetic definition of Lynch syndrome, it is likely that these estimates are low given that the risk of developing cancer was diluted by the population that were not truly Lynch syndrome.

Carcinogenesis is accelerated in Lynch syndrome when compared to sporadic CRC. Progression from a small colonic adenoma to a carcinoma occurs in 2 to 3 years, as opposed to the 8 to 10 years this process may take in the general population [30••, 31]. Furthermore, the precursor lesions in Lynch syndrome tend to be flat and are commonly located in the right colon, making them harder to find during colonoscopy [32]. These facts tend to lead to the development of interval cancers—i.e., cancers that develop between scheduled colonoscopies—even with strict surveillance regimens [30••]. Therefore, most guidelines recommend surveillance colonoscopy every 1–2 years [33–36]. The mean age at initial colon cancer diagnosis in patients with Lynch syndrome is 44–61 years [19, 21]. Cancer before the age of 20 years is extremely rare, and therefore, the first colonoscopy is recommended at age 20–25 years of age or 10 years younger than the earliest cancer in the family (whichever comes first) [36]. We generally recommend colonoscopy every 2 years until age 40, then yearly after that. However, the interval is moved to 1 year starting at 10 years earlier than the first CRC in the family or if adenomas are detected on a previous examination. Surveillance colonoscopy in these patients must be uncompromising and requires an excellent bowel preparation to allow for meticulous inspection of the mucosa.

Chemoprevention

Building on findings from observational studies, the ongoing Concerted Action Polyp Prevention (CAPP) trials examined the effect of aspirin as chemoprevention in patients with familial adenomatous polyposis syndrome (CAPP1) and Lynch syndrome (CAPP2 and CAPP3). The CAPP2 trial was a large multicentered, double-blinded, randomized study comparing the effect of 600 mg aspirin daily vs. placebo on the development of CRC in patients with Lynch syndrome [37]. The updated results based on a mean follow-up of nearly 56 months for 861 participants with Lynch syndrome were published in 2011 and showed that among participants who took aspirin for at least 2 years (n=258), CRC incidence fell nearly 60 % compared to participants who took a placebo for the same length of time. At least 2 years of aspirin use was also associated with a 55 % reduction in other cancers associated with Lynch syndrome. The authors concluded that these results provide a basis for the recommendation of aspirin chemoprevention in Lynch syndrome as standard of care. It is noteworthy that the utilized dose of aspirin is not a standard formulation nor routinely used in the USA. Also, side effects need to be considered when selecting patients for chemoprevention. Further study is needed to sort this out, and indeed, the ongoing CAPP3 trial aims to establish the optimum effective dose and duration of aspirin treatment in Lynch patients.

Colorectal Surgical Management of Lynch Syndrome—Prophylactic Colectomy

Prophylactic colectomy (i.e., removal of the colon without any identifiable pathology) could be done to prevent development of colon cancer. Although this would be effective, it is not a routine practice based on the ability to prevent cancer with colonoscopy and polypectomy, and balancing risks and benefits of surgery. There are no prospective clinical studies evaluating the potential survival benefit of prophylactic colectomy in Lynch syndrome. A study utilizing a decision analysis-based statistical model suggests a survival benefit of 1.8 years for patients undergoing a subtotal colectomy at 25 years of age when compared with surveillance by colonoscopy. This

survival benefit is decreased when surgery is performed at an older age. Furthermore, when health-related quality of life was considered, endoscopic surveillance led to the greatest quality-adjusted life expectancy benefit when compared to colectomy [38].

There are rare circumstances when prophylactic colectomy may be considered, and this can be discussed between the surgeon and the patient. Examples include patients who have a colon that is technically difficult to examine endoscopically, those with poor compliance with screening recommendations, and those who have severe psychological fear of developing colorectal cancer. Prophylactic surgery may also be considered for patients in families with severe penetrance of disease or early-age onset of colorectal cancer. Again, this would be considered on a case-by-case basis after informed discussion.

Another scenario in which a prophylactic colectomy may be questioned is in patients who underwent a standard segmental colectomy for colon cancer and are then found to have Lynch syndrome postoperatively. The increasing prevalence of tumor testing (for microsatellite instability by PCR and MMR protein expression by immunohistochemistry) as a screen for Lynch syndrome is likely to make this a more frequently encountered scenario. Genetic counseling for these patients and their families is essential. Prophylactic colectomy of the residual colon in the postoperative patient is an option to spare the patient the need for annual colonoscopy. However, similar to the patient without a personal history of colon cancer, this purely prophylactic surgery is not generally recommended. In the authors' opinion, prophylactic colectomy without the presence of CRC should only be offered in special circumstances [39].

Treatment of Colon Cancer in Lynch Syndrome Patients

Preoperative Diagnosis of Lynch Syndrome

In patients with Lynch syndrome, the entire colonic mucosa is unstable and at risk for developing dysplasia and cancer, and there is a high incidence of synchronous and metachronous lesions [23]. Therefore, the optimal surgical management of CRC in patients with an established diagnosis of Lynch syndrome usually calls for a more extended approach than in patients with sporadic cancers. It is therefore essential to preoperatively identify patients with Lynch syndrome when presenting with newly diagnosed CRC. The most important factors favoring a diagnosis of Lynch syndrome are the patient's age and family history. A suspicion of Lynch syndrome should be raised when a CRC occurs in a young person, when there is family history of CRC, or when a person develops multiple primary Lynch syndrome-related cancers. National guidelines including the earlier-mentioned Bethesda guidelines were created to help direct CRC tumor testing to screen for potential cases of Lynch syndrome. The revised Bethesda criteria have historically been the most frequently used guidelines, with the major indication for tumor testing being CRC diagnosis before age 50 years [9]. However, it has been shown that limiting tumor analysis only to patients who fulfill the Bethesda criteria would fail to identify 28 % of the cases of LS [40]. Therefore, many institutions now reflexively test all CRCs due to the high potential for identifying Lynch syndrome patients even in the absence of clinical high-risk features [41]. In an effort to improve on the accuracy of the Bethesda criteria, several clinical prediction models have recently been developed and validated to determine an individual's risk for Lynch syndrome including the MMRpro, MMRpredict, and PREMM models [42]. These models do not replace taking a comprehensive family history. Current guidelines recommend testing for MMR deficiency of all newly diagnosed CRC, or CRC diagnosed at age 70 and younger, and in patients older than 70 years who have a family history concerning for Lynch syndrome [36].

Extent of Resection

When Lynch syndrome is found in patients with newly diagnosed CRC, the decision-making in the surgical management is multifactorial. A detailed discussion about the indications, risks, benefits, and expected functional and oncologic outcomes is mandatory. The final decision depends on the family history, the patient's individual situation, the patient's feelings on risk aversion, other medical comorbidities, and life expectancy. The surgical options include a segmental resection (removal of only the affected segment of the colon) or a total abdominal colectomy with ileorectal anastomosis (TAC-IRA), which consists of removing the entire colon with reconnection of the terminal ileum to the rectum. The latter option provides the patient with the therapeutic treatment of the established colon cancer and the prophylactic removal of the remaining colon at risk of developing metachronous CRC. TAC-IRA is the recommended surgical option in Lynch syndrome patients diagnosed with CRC [33, 43, 44•]. However, preoperative decision-making needs to balance the oncologic benefit of eliminating the risk for metachronous colon cancer with the risk for perioperative morbidity and long-term functional outcomes associated with a TAC-IRA.

Metachronous Colorectal Cancer Risk

While there are no prospective trials showing a survival benefit for TAC-IRA compared with segmental colectomy, the metachronous cancer risk in the remaining colon and mathematical decision models favor the extended approach. A

Markov decision model demonstrated that if a CRC is treated with TAC-IRA, it leads to an increased life expectancy of 2.3 years compared with segmental colectomy at 27 years of age. Comparison of life expectancy gained by performing TAC vs. segmental resection in Lynch syndrome patients at ages 47 and 67 years by Markov modeling was 1 and 0.3 years [45]. Retrospective trials examining the risk of developing a metachronous colon cancer after segmental colectomy have reported risks between 11 and 45 %, with a moderate follow-up of 8 to 13 years [39, 46–49, 50•]. The risk for metachronous cancers has been estimated to be as high as 72 % at 40 years [46]. In one study, 33 % of Amsterdam criteria patients were found to have high-risk adenomas that were removed during surveillance colonoscopies after segmental colectomy [48], indicating that the true cancer risk may be higher than reported, as the high-risk lesions that were removed should be considered as premalignant polyps. While TAC-IRA removes most mucosa at risk for cancer, the remaining rectum still requires yearly surveillance, which in most patients can be done in the office setting after enema preparation without the need for sedation. The risk of metachronous rectal cancer after IRA has been reported between 3 and 12 % at 10–12 years, underlining the importance of meticulous rectal surveillance [29, 48, 51].

Functional Outcomes and Quality of Life

One of the concerns of TAC-IRA instead of a segmental resection for colon cancer patients with Lynch syndrome is the functional outcome after these extended resections. After removing the entire colon, a patient can be expected to have more frequent and looser bowel movements than after a right colectomy or sigmoid colectomy. There is little data on how the quality of life after a TAC-IRA compares to that after a more limited segmental resection. A recent study from the Netherlands specifically looking at this issue compared the quality of life of 53 Lynch syndrome patients who underwent a TAC-IRA with that of 51 Lynch syndrome patients who were treated with a segmental colectomy, utilizing quality of life and colorectal function questionnaires [52]. Quality of life as measured by the Short Form-36 survey showed no significant difference. Analysis of the Colorectal Functional Outcome questionnaire revealed that, after subtotal colectomy, patients have a significantly higher stool frequency ($p<0.01$) and a significantly higher score on stool-related aspects ($p=0.06$) and social impact ($p=0.03$). The authors concluded that although functional outcomes are worse after subtotal colectomy than after partial colectomy, generic quality of life does not differ after the two different surgeries in Lynch syndrome. Similar results were also found in a smaller study from the Cleveland Clinic showing that bowel frequency was greater for patients undergoing total colectomy (four vs. two bowel motions daily), but this was not associated with any difference in continence or overall quality of life [39].

Perioperative and Postoperative Morbidity

In terms of perioperative morbidity and mortality, TAC-IRA has been shown to be a safe procedure with acceptable outcomes even in the elderly population [53–56]. A study comparing perioperative morbidity and mortality of segmental resections with extended resections with IRA or ileo-sigmoid anastomosis found that mortality and serious complications (grade II/III) did not differ significantly between the groups. However, the incidence of postoperative ileus was higher in patients undergoing extended resections, contributing to a significantly longer median length of stay in those patients [56]. Laparoscopy for colon cancer has now been studied by several prospective trials and has shown to offer significant short-term benefits while preserving oncologic outcomes [57–59]. The laparoscopic approach results in smaller incisions, less postoperative pain, shorter hospital stay, and quicker return to normal activity compared with an open procedure. These benefits can help make the concept of the radical TAC-IRA psychologically more acceptable to patients and referring physicians [39]. Laparoscopy is the authors' preferred approach in managing these patients.

To summarize the surgical management philosophy, TAC-IRA should be considered in medically fit patients with Lynch syndrome who develop CRC [36]. This recommendation is based on retrospective studies and mathematical models demonstrating the high risk of metachronous CRC in these patients. Despite these widely accepted recommendations, most Lynch syndrome CRCs in the USA are still treated by segmental colectomy [48, 60]. This discrepancy is mainly due to the lack of a preoperative diagnosis of Lynch syndrome (or HNPCC).

Technical Considerations of Surgery

As in all colorectal surgery for malignancy, the approach to colon cancer in Lynch syndrome patients demands meticulous adherence to oncologic surgical principles. Regardless if the surgery is done open or laparoscopically, a thorough exploration for any metastatic disease involving the peritoneum, omentum, liver, pelvis, and ovaries should be done at the beginning of the procedure. General oncologic principles to be followed include a "no touch" technique; high ligation of the vascular pedicle supplying the lesion; obtaining adequate proximal, distal, and mesenteric margins; and en bloc resection of any involved adjacent organs. A minimum of 12 evaluated lymph nodes is broadly considered to be a quality

indicator for colon cancer surgery [61]. When performing an IRA, there is no data supporting one method of anastomosis (stapled vs. handsewn, end to end or end to side) over another and the method should be determined at the time of the surgery based on anatomic considerations and surgeon preference.

Rectal Cancer in Lynch Syndrome

Despite the relative preponderance of proximal colonic lesions in Lynch syndrome, rectal cancer is common. Approximately 20 to 30 % of patients with Lynch syndrome will develop rectal cancer, including 15 to 24 % with rectal cancer as their index cancer [62, 63, 64•, 65]. A first-degree family history of rectal cancer was associated with an increased risk of rectal cancer [65]. The optimal treatment of rectal cancer in Lynch syndrome is controversial. Surgical options include a segmental proctectomy in the form of a low anterior resection (LAR) or abdominoperineal resection (APR)—depending on sphincter involvement—or an extended resection, removing all of the colonic mucosa at risk in the form of a total proctocolectomy (TPC) with end ileostomy or restorative ileal pouch-anal anastomosis (IPAA or J pouch). Proctectomy alone with colorectal anastomosis yields less frequent bowel movements and more normal function (less incontinence and seepage) than after an IPAA [66]. Furthermore, a TPC with IPAA is a technically challenging procedure requiring specialized surgical training and expertise, and can be associated with significant perioperative morbidity. However, proctectomy alone leaves an entire colon at risk for the development of metachronous colon cancer and leads to the need for fastidious annual surveillance. Retrospective studies have demonstrated that in Lynch syndrome or HNPCC, metachronous colon cancer after proctectomy occurs in 15 to 54 % of patients [62, 63, 64•, 65, 67•]. In a study from the Cleveland Clinic, 33 patients with HNPCC and a primary diagnosis of rectal cancer were treated with a proctectomy and followed with colonoscopic surveillance [64•]. Five patients (15.2 %) developed metachronous adenocarcinoma at a median of 6 years (range 3.5–16) after proctectomy, including three at advanced stage. Furthermore, another 36 % of patients developed high-risk adenomas that were found during screening. Data from the Colon Cancer Family Registries showed an increased risk over time, with the risk of developing metachronous colon cancer being 19 % at 10 years, 47 % at 20 years, and 69 % at 30 years after proctectomy [67•]. Given the high risk of metachronous neoplasia after a segmental proctectomy, a TPC with IPAA should be discussed with all Lynch syndrome patients presenting with rectal cancer. Extended resection for rectal cancer in Lynch syndrome is a controversial topic, and multiple factors including the patient's age, medical comorbidities, rectal cancer stage, preoperative sphincter function, and patient's compliance with rigorous surveillance regimens should be considered.

Decision-Making without a Diagnosis of Lynch Syndrome

Increasing knowledge of the underlying genetic causes of Lynch syndrome and our ability to detect these mutations have revolutionized our treatment of Lynch syndrome. It has helped us define risks and provide more personalized recommendations. However, despite the advances, there are still multiple situations in which we cannot make a definitive diagnosis of Lynch syndrome. In these circumstances, the surgeon and patient are left to make a decision based on clinical acumen.

HNPCC with MSS Tumor: Familial Colorectal Cancer Type X

Approximately 50 % of patients satisfying the Amsterdam criteria do not have an inherited MMR mutation and are termed to have familial colorectal cancer type X (FCC X). These patients have an approximately two-fold increased risk of CRC when compared to the general population but not as high as in the patient with germline MMR mutations [15]. FCC X is thought to encompass a group with a heterogeneous mixture of yet genetically undefined etiologies. Since the average age of CRC onset is 61 years in this population, screening is recommended to start at age 45 or 10 years younger than the earliest CRC in a relative [15, 35]. Since the risk of metachronous CRC is not well defined in this group, these cancers are generally treated surgically like sporadic cancers while considering patient preferences and comorbidities [39]. However, a TAC-IRA should be discussed if there is an extensive family history of metachronous CRC.

HNPCC with MSI-H but Patient Refuses to be Tested

It is not uncommon for patients to forego genetic testing for various reasons including concerns of insurance discrimination, lack of insurance to pay for the test, the desire not to know if there is a genetic syndrome, or genetic counseling or testing is not available. In these situations, the clinician must make a judgment regarding the perceived likelihood of that patient and family having Lynch syndrome. It has been our practice to manage suspected patients as if they have Lynch in terms of screening and surveillance. At-risk family members are offered the same screening and surveillance, recognizing that these tests may be excessive, and even in the presence of confirmed Lynch syndrome, only 50 % of first-degree relatives will be affected. However, based on information at hand for that particular family, we favor more screening than less as the implications of missing a cancer far outweigh the former option.

MSI-H Tumor with IHC Loss but no Identifiable Germline Mutation

As more centers are moving toward universal screening, this subgroup of patients will become more common. For example, a patient with colon cancer undergoes resection and the tumor is reflex tested for mismatch repair deficiency. It is found to be MSI-H and/or lack expression of one of the mismatch repair proteins by immunohistochemistry, thus having the molecular features of Lynch syndrome tumors. However, when that patient is tested for the germline mutation in the specific MMR protein that is lost, no identifiable mutation is found. This group of patients has been termed Tumor Lynch, or Lynch-like; however, no specific nomenclature captures the essence of the true etiology of this condition. Possible reasons for these findings include a true lack of the disease, a different—still unknown—gene causing the clinical phenotype, gene expression is controlled through a different mechanism, or the inability to detect the mutation with current technology. Recent studies have revealed that approximately 50 % of these cases can be attributed to biallelic acquired somatic mutations or genetic mosaicism in about 50 % of cases [68, 69••]. Tumor testing (which is not routinely available at the time of this writing) can be pursued to eliminate Lynch syndrome as a diagnosis in about half of these patients. If possible, the cause should be sought. If Lynch syndrome cannot be eliminated from the diagnosis, we would still favor managing these patients as if they have Lynch, especially in the setting of a suggestive family history. This remains to be further defined.

Conclusions

In summary, Lynch syndrome is an autosomal dominant disorder caused by mutations in MMR genes and represents the most common cause of hereditary CRC. A detailed family history and high index of suspicion are necessary to identify patients and families affected. The Amsterdam and Bethesda criteria help identify patients at risk who should be referred for genetic counseling and testing to make the diagnosis of Lynch syndrome. In patients with Lynch syndrome, regular colonoscopies every 1–2 years starting at age 20–25 have shown to be effective in reducing the incidence of CRC. If CRC is diagnosed in a patient with Lynch syndrome, an extended resection in the form of a TPC-IRA is recommended to decrease the risk of metachronous cancers. Rectal cancer in Lynch syndrome patients requires an individualized approach, but in medically fit patients, a restorative proctocolectomy with an ileal J pouch should be considered. Lynch syndrome patients treated with anything less extensive than a total proctocolectomy warrant meticulous annual endoscopic surveillance of the remaining at-risk colorectal mucosa. Further studies are necessary to better understand the natural history and optimal management of patients clinically suspicious for Lynch syndrome and MSI-H tumors but without an identifiable genetic mutation.

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Compliance with Ethics Guidelines

Conflict of Interest David Liska declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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