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Short Communication

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Management of Colorectal Cancer in Hereditary Syndromes

Bradley A. Krasnick, Matthew F. Kalady*

Division of Colon and Rectal Surgery, Clinical Cancer Genetics Program, The Ohio State University College of Medicine, USA

***Corresponding Author:** Matthew F. Kalady, Professor of Surgery and Chief, Division of Colon and Rectal Surgery, Medical Director, Clinical Cancer Genetics Program, The Ohio State University College of Medicine, N737B Doan Hall, 410 W. 10th Ave, Columbus, OH 43210, USA; E-mail: Matthew.Kalady@osumc.edu

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Abstract

Colorectal cancer (CRC) is the 3rd most common malignancy in the United States. Up to 15% of CRC cases have an associated germline pathogenic variant. It is important for clinicians to be aware of the different syndromes and their clinical management. In this review, we provide an overview of the different CRC hereditary syndromes and discuss management of the more common syndromes, familial adenomatous polyposis and Lynch Syndrome.

Keywords: *Familial adenomatous polyposis; Lynch syndrome; Hereditary non-polyposis colorectal cancer (HNPCC)*

Introduction

Colorectal cancer is the 3rd most common malignancy for both females and males in the United States, and overall, the second leading cause of cancer related death for both genders. Approximately 10-15% of these cases will have a pathogenic germline variant in a cancer susceptibility gene [1-3]. Approximately 5% of CRCs have a defined syndrome caused by some of these germline pathogenic variants. It is important to identify patients who carry these pathogenic variants so that the patient and their families can undergo appropriate screening, surveillance, and treatment to decrease the risk of developing cancer and future cancer-related death. In general, hereditary CRC can be broadly classified into polyposis and non-polyposis conditions. The polyposis syndromes can further be characterized by the types of polyps that are predominant. The adenomatous polyposis syndromes include familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), polymerase proofreading-associated polyposis (PPAP), and NTHL-1 polyposis (NAP). The hamartomotous polyp syndromes include juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS) and PTEN-hamartoma tumor syndrome. Serrated polyposis syndrome (SPS) is characterized by an abundance of serrated colorectal polyps. SPS continues to be defined, but it does carry a higher risk of polyposis and CRC in first-degree relatives, although only a small percentage of patients have a defined pathogenic mutation. Non-polyposis syndromes include Lynch syndrome (LS) and familial colorectal cancer type X (FCC-X). It is important to note that there is phenotypic overlap between these syndromes and patients may have different histologic types of polyps. These syndromes are summarized in Table 1. For the purposes of this review, we will focus on the management of FAP and LS.

Table 1: Overview of hereditary colorectal cancer syndromes.

Hereditary Syndrome	Pathogenic Gene Variant	Inheritance Pattern	Main Polyp Type
Polyposis			
FAP	APC	Autosomal dominant	Adenomas
MAP	MUTYH	Autosomal recessive	Adenomas
PPAP	POLE, POLD1	Autosomal dominant	Adenomas
NAP	NTHL-1	Autosomal recessive	Adenomas
JPS	SMAD4, BMPR1A	Autosomal dominant	Juvenile polyps/Hamartomas

PJS	STK11	Autosomal dominant	Peutz-Jegher polyps/Hamartomas
PHTS	PTEN	Autosomal dominant	Hamartomas
SPS	RNF43*	unknown	Serrated polyps
Hereditary mixed polyposis syndrome	GREM1	Autosomal dominant (Ashkenazi Jews)	Adenomas, serrated polyps, Hamartomas
Non-Polyposis			
LS	MLH1, MSH2, MSH6, PMS2, EPCAM	Autosomal dominant	Adenomas
FCC-X	Unknown	Autosomal dominant	Adenomas

*Mutation in SPS is only identified in a minority of cases.

[FAP: Familial adenomatous polyposis; MAP: MUTYH associated polyposis; PPAP: Polymerase proofreading-associated polyposis; NAP: NTLH1 polyposis; JPS: Juvenile polyposis syndrome; PJS: Peutz-Jeghers syndrome; PHTS: PTEN hamartoma tumor syndrome; SPS: Serrated polyposis syndrome; LC: Lynch Syndrome; FCC-X: Familial colorectal cancer type X].

FAP

FAP is an autosomal dominant condition characterized by a mutation in the APC gene which is located on chromosome 5. Approximately 1 in 4 cases arise sporadically, without a family history [4]. Penetrance approaches 100% by age 40. Common clinical manifestations include diffuse colorectal adenomas, duodenal adenomas, desmoid tumors, osteomas, thyroid cancer and congenital hypertrophy of the retinal pigment epithelium. The clinical presentation and phenotype vary by the location of the pathogenic variant location within the APC gene [5]. Some variants may cause complete loss of APC protein function, while other variants may yield a partially functioning APC protein and thus the polyposis may not be as severe, called attenuated FAP (AFAP). These patients typically have a decreased adenoma burden (20-100 polyps) compared to FAP. The management of FAP, like all hereditary CRC syndromes revolves around diagnosis, surveillance, and treatment.

Diagnosis

As stated above, FAP is diagnosed by a germline pathogenic variant in the APC gene. For people with a known APC variant in their family, genetic testing may be completed for the diagnosis, usually at age 10-12. For families without a known variant, flexible sigmoidoscopy should be done in at-risk family members at age 10, with subsequent management depending on the findings.

Prevention

For people with FAP, a colonoscopy is recommended annually beginning at age 10-12 years [6]. Similar surveillance is recommended for patients with a family history but who have not received or refused genetic testing [7]. In general, polyps larger than 5 mm are removed at the time of colonoscopy if able. Larger polyp size is correlated with advanced dysplasia and cancer. The mere presence of polyps is not an absolute indication for colectomy. Unless there are symptoms, advanced neoplasia, or rapidly growing number or size of polyps, the colon may be safely surveyed until the patient is physically and emotionally mature for prophylactic surgery. A summary of extracolonic surveillance in FAP is given in Table 2.

Table 2: Surveillance recommendation in FAP.

Organ	Cancer Risk	Screening/surveillance Recommendations
Colon and rectum	100%	Annual colonoscopy starting at 10-12 years
Stomach	0.1-7.1%	Evaluated at time of EGD for duodenal lesions
Duodenum/periampullary	1-10%	Upper endoscopy starting at 20-25 years
Desmoid, intra-abdominal	10-24%	No routine recommendations
Thyroid	1.2-12%	Ultrasound as late teenager, repeat 2-5 years if normal
Note: Adapted from Gupta S, et al. (2022) NCCN Guidelines 2.2022: Genetic/Familial High-Risk Assessment: Colorectal Cancer [6].		

Colorectal Treatment

If left untreated, all patients with FAP will develop CRC. With the fact that surgery is inevitable, decisions are then based on balancing cancer risk reduction and quality of life. Thus, the timing of surgery and the extent of surgery are two crucial decision points. The risk of CRC before age 20 is extremely low and deferral of surgery into adulthood is usually safe with the caveats of symptoms and findings on colonoscopy as will be discussed below [8]. The average age of developing CRC in FAP is 39 years. Absolute indications for colectomy or proctocolectomy are the presence of CRC, symptoms of bleeding per anus, and profuse polyposis (>1000 adenomas). Relative indications which should prompt surgery include the presence of multiple adenomas greater than one cm or adenomas with high-grade dysplasia. For patients who do not require surgery, annual colonoscopy should continue with removal of larger polyps with note of the changes in polyps size and burden over time.

Once a decision is made to proceed with surgery, the extent of resection should be discussed. The main resection options include total abdominal colectomy (TAC) with ileorectal anastomosis (IRA), or total proctocolectomy (TPC) with or without reconnection of the gastrointestinal tract. Restoration includes creation of an ileal pouch with anastomosis to the anus – ileal pouch-anal anastomosis (IPAA). For patients who do not wish to have a restorative procedure, or for those who are not candidates due to poor sphincter function or rectal cancer involving the anal sphincters, a TPC with an end ileostomy is performed.

In deciding between TAC or TPC, the colorectal polyp burden is the main determinant of extent of resection, with also consideration regarding quality of life and bowel function. Patients with a moderate colon polyp burden (< 500 - 1000) and a relatively spared rectum (< 20 polyps) can usually be safely treated with a TAC and IRA. When employing the criteria of having less than 20 rectal polyps and subsequently undergoing TAC with IRA, only 1.6% of patients at 12-year follow-up required proctectomy for cancer, and 5.4% underwent proctectomy for non-cancer reasons [9]. For patients who underwent a TAC and IRA who had more than 20 polyps in the rectum, 10.8% of patients developed subsequent rectal cancer. If a TAC is done, annual surveillance of the rectum is mandatory. In addition, patients with high-grade dysplasia or cancer, or multiple large polyps in the rectum should undergo TPC [7].

Cancer treatment and risk reduction should take priority, but quality of life issues should also be considered in balance. Although there is an associated rectal adenoma and cancer risk after a TAC/IRA, there are considerable functional advantages compared to a TPC and IPAA. Pelvic surgery is associated with risk of pelvic nerve damage. Short term bladder dysfunction is common and up to 4% of patients can have long term urinary dysfunction [10]. Sexual dysfunction can also be seen after proctectomy. For males, this can mean retrograde ejaculation and erectile dysfunction. For females, dyspareunia is the most common manifestation of sexual dysfunction. In general, sexual dysfunction is seen in 10-30% of patients after proctectomy for cancer [11]. Risk factors for sexual dysfunction are older age (>65 years), radiation therapy and abdominoperineal resection, and thus outcomes in younger patients undergoing prophylactic proctectomy (as seen in typical FAP patients) are significantly lower. In addition to sexual dysfunction, fecundity may be decreased 54% after TPC with IPAA as compared to TAC with IRA [12]. Lastly, bowel frequency and function are worse after TPC and IPAA compared to TAC. On average, IPAA patients have 6 bowel movements per day, as compared to 4 after IRA, and have more instances of anal seepage and incontinence [13].

There are other considerations when deciding between extent of surgery in FAP patients. The presence of desmoid tumors or risk of desmoid tumor development should also be discussed. Approximately 15-30% of patients with FAP will develop desmoid tumors, with most occurring after surgery. Mesenteric desmoids can have disastrous complications including small bowel obstruction, enterocutaneous fistula, and ureteric obstruction. Therefore, minimizing factors that may contribute to desmoid formation is important. In patients who are at high-risk for desmoid disease, it may be prudent to delay colorectal surgery as long as safely possible. If surgery is needed, the technical approach matters, with less desmoid tumors developing after a minimally invasive approach compared to an open approach. In a retrospective study of 345 patients, only 14.5% of TAC with IRA and 21.5% of laparoscopic cases resulted in future desmoid tumor formation [14]. This is as compared to 43.6% of cases with TPC + IPAA, and 35.7% of open cases. As expected, family history of desmoid tumors and mutation location (highest risk with mutation 3' of codon 1900) also resulted in increased future desmoid tumor risk.

For patients who require TPC and will undergo an IPAA, there are 2 options for dealing with the anal transition zone. The rectal dissection may proceed to about 2 cm above the dentate line and the lower rectum/upper anal canal is stapled across and resected with preservation of the anal transition zone. The ileal pouch is then connected using a stapled anastomosis. This technique generally leaves 1-2 cm of anal transition zone and results in better function, although does leave a small cuff of mucosa that could develop subsequent neoplasia. The other option is to remove all rectal mucosa to the dentate line by performing an anal mucosectomy. This requires a handsewn anastomosis at the dentate line. The advantage of this technique is that there is less subsequent neoplasia risk, but there is worse function. With a mucosectomy and hand sewn anastomosis, anal seepage and

episodes of incontinence are worse [13,15]. Despite this, global quality of life scores is similar. In contrast to the worse functional outcomes, after mucosectomy with IPAA there has been shown to be a decreased future adenoma risk in the anal transition zone (ATZ) [15]. In a retrospective study, 21% of patients undergoing mucosectomy developed an ATZ adenoma, versus 34% of those who had a double-stapled IPAA. At 10 years follow up, 52% of patients in the double-stapled group were found to develop ATZ adenomas [16]. Regardless of which operation is done (TAC or TPC), any residual mucosa is at risk for development of adenomas and advanced neoplasia, and regular surveillance is mandatory.

Non-polyposis and Lynch Syndrome

It is important to apply the appropriate nomenclature for the non-polyposis syndromes. The original description of hereditary non-polyposis colorectal cancer (HNPCC) was based on clinical definitions since the genetic cause was not yet identified. In an effort to identify and study patients and families with this hereditary condition, this syndrome was defined by a series of clinical criteria, initially developed at a conference in Amsterdam and thus named the Amsterdam criteria [17]. The criteria were expanded in 1999 to include more than CRC, but also the extracolonic cancers seen in this syndrome [18]. Briefly, for patients to be considered to have HNPCC, they must fulfil the following Amsterdam II criteria: At least 3 relatives are affected with an HNPCC-associated cancer (CRC, endometrial cancer, small bowel cancer, renal pelvis cancer, ureteral cancer, sebaceous adenocarcinoma); at least one affected member is a first degree relative of the other two with at least two successive generations affected; at least one cancer is diagnosed prior to age 50; and FAP was excluded. After the genetic cause of LS was identified, now only patients with a pathogenic variant are defined as having LS. Importantly, not all patients with LS will meet Amsterdam criteria and not all patients who meet Amsterdam criteria will have LS. Patients with CRC who meet Amsterdam criteria, but have microsatellite stable tumors are said to have Familial Colorectal Cancer Type X (FCC-X) [19]. As each of the syndromes have different risk factor and management recommendations, it is important to understand this distinction [20].

Lynch Syndrome

Diagnosis

Lynch syndrome (LS) is defined by the presence of a germline pathogenic variant in one of the DNA mismatch repair genes MLH1, MSH2, MSH6, or PMS2. Patients with LS have an increased rate of colorectal and multiple extracolonic malignancies with the risks varying according to the variant and gender (Table 3) [21]. MLH1 and MSH2 mutations have a higher incidence of CRC. The exact penetrance of PMS2 variants as a causative factor for cancer remains debated and continues to be defined. Overall, LS accounts for 3% of colorectal cancer cases, and among LS patients, 20-30% will develop rectal cancer [3,16].

Table 3: Colorectal Cancer Incidence by Age and Mutation.

Group	Age	MLH1	MSH2	MSH6
CRC, both genders	40	14%	9%	0%
	70	46%	35%	20%
CRC, males	40	17%	8%	0%
	70	47%	37%	14%
CRC, females	40	11%	11%	0%
	70	45%	33%	26%
Note: CRC = Colorectal cancer, adapted from Moller et. Al., Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Adopted from Moller P, et al. (2018) [21].				

Prevention – Screening

Colonoscopy is recommended for LS patients beginning between ages 20 and 25 years old, or 2-5 years before the youngest family member diagnosed (if <25 years at diagnosis). Polypectomy should be performed for any lesions found. Colonoscopy should be repeated every 1-2 years, favoring the shorter interval if adenomas are found or if there is a family history of CRC at younger ages.

Prevention - Chemoprevention

Aspirin can be considered as a means for chemoprevention against CRC in LS patients. In the CAPP2 trial, patients with MLH1, MSH2 and MSH6-associated LS who received 600 mg daily aspirin had a decreased rate of CRC formation compared to controls. In the study, 24 patients needed to be treated to prevent 1 CRC [22]. A follow-up study, CAPP3 compares the effectiveness

of different dosing: 100 mg, 300 mg, and 600 mg daily. Accrual has completed and follow-up is underway.

Treatment of Colorectal Cancer

Treatment of CRC in LS involves both treatment of the primary tumor as well as extended prophylactic resection to prevent future metachronous CRC. Although each patient should be addressed as an individual, the general recommended treatment for colon cancer in LS in TAC and IRA [7]. Extended colectomy decreases metachronous risk compared to segmental colectomy alone. One study evaluated 296 patients (combination of LS patients and patients meeting Amsterdam criteria) and compared results of extended colectomy to segmental colectomy. At a median of 104 months follow-up, 25% of those undergoing segmental resection developed a second primary colorectal cancer, compared to only 8% in the TAC group [23]. The risk increases over time. In a multiple site international collaborative study, risk of metachronous CRC in patients with LS was estimated to be 62% at 30 years following segmental colectomy [24]. The functional aspects of extended colectomy should be considered. In one study looking at function and quality of life after segmental and extended resections, overall quality of life was found to be excellent for all patients, but was higher for patients that underwent a more limited colonic resection [25].

Surgical management of rectal cancer in LS is more complex than that of colon cancer. Extended prophylactic resection includes TPC which carries more significant functional implications. Another difference with rectal cancer, is the use of neoadjuvant therapy, as preoperative radiation is included in the standard of care for locally advanced rectal cancer. We recommend all rectal cancer cases be presented at a multidisciplinary tumor board to help guide management [26].

The primary goal is to remove the rectal cancer using oncologic principles of total mesorectal excision and high ligation of the inferior mesenteric artery to ensure adequate lymph node harvest. Surgical options include proctectomy (low anterior resection or abdominoperineal resection) or TPC. In regards to risk reduction with extended resection, future cancer risk and quality of life must be balanced. In a 2012 study looking at 50 patients meeting Amsterdam criteria with microsatellite unstable rectal cancer treated with proctectomy, 40% were found to develop high risk adenomas during follow up, and 15% developed a metachronous cancer [27]. This data has been corroborated by other studies [16,28].

Quality of life must also be weighed when deciding between LAR with coloanal anastomosis, versus TPC with IPAA. In general, bowel movements after IPAA are more frequent than after LAR with coloanal anastomosis and patients can have frequency and seepage [29-31]. Patients who undergo neoadjuvant radiation prior to an IPAA tend to have worse function than those with an IPAA who did not get radiation, therefore this must be considered in the decision-making process. As in colon cancer, the treatment decisions for rectal cancer should be made after informed discussions with patients in consideration of both oncologic and functional outcomes. An additional consideration for rectal cancer involves newly published data on immunotherapy for microsatellite-high/mismatch repair deficient rectal cancer. In a recent study in the New England Journal of Medicine, Cercek A, et. al. (2022) reported on 12 patients with MSI-H rectal cancer who achieved clinical complete response at 1 year follow-up after anti PD-1 immunotherapy, with all patients achieving a complete clinical response and none requiring surgery [32]. Enrolment of more patients and longer-term follow-up are needed to more clearly define the role of immunotherapy and what to do after a complete response, but these data provide exciting potential.

Familial Colorectal Cancer Type X

It's worth briefly mentioning the management of FCC-X in contrast to Lynch syndrome. By definition, patients with CRC who meet Amsterdam criteria but have MSS tumors are characterized as FCC-X. These patients do not have an increased risk of synchronous CRC and can be treated with oncologic segmental colectomy. For first-degree relatives, CRC screening should begin at age 40 (or 10 years earlier than the youngest cancer, with subsequent intervals every 3-5 years [33].

Summary

Overall, the management of CRC as part of a hereditary syndrome is a complex topic, and multiple factors need to be included in the decision-making process. One must not only think about treating CRC but also preventing future CRC and extracolonic cancers, while trying to preserve quality of life.

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