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REVIEW

Lynch Syndrome: Current management In 2019

Syndrome de Lynch. Quelle prise en charge en 2019?

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HIGHLIGHTS

- Lynch Syndrome (LS) is linked to a constitutional mutation in one of the genes of the MMR system involved in the repair of DNA replication errors: MLH1, MSH2, MSH6, PMS2 or an 3′ deletion of the EPCAM gene leading to the inactivation of MSH2.
- Clinical diagnosis of LS is based on the Amsterdam I and II Criteria and on the revised Bethesda Criteria.
- Colorectal cancers developed on LS are poorly responsive to 5 fluorouracile but this can be reversed by adjunction of oxaliplatin, particulalrly in stages IIIa.
- Early and regular endoscopic screening of colorectal cancer is recommended, and should be performed every one to two years from the age of 25 onward and then annually from age 40, or starting 10 years before the age of appearance of CRC in the youngest patient in the family.
- There are no formal indications for primary prophylactic colorectal surgery in LS.

KEYWORDS
Colorectal;
Cancer;
Lynch syndrome;
Management;
Surgical indications

Summary Nearly 5% of colorectal cancers are related to constitutional genetic abnormalities. In Lynch Syndrome (LS), the abnormality is a mutation of the deoxyribonucleic acid (DNA) repair system. The goal of this update is to update indications and surgical strategies for patients with LS. Different spectra of disease are associated with LS. The narrow spectrum includes cancers with a high relative risk: colorectal cancer (CRC), endometrial cancer, urinary tract cancers and small intestinal cancer. The broader spectrum includes ovarian tumors, glioblastoma, cutaneous tumors (keratoacanthomas and sebaceous tumors), biliary duct tumors, and gastric tumors. The clinical diagnosis of LS was initially based on the Amsterdam I and II Criteria published in the 1990s and subsequently on the revised Bethesda Criteria, which expanded the criteria and identified patients who should be screened for LS. For patients with LS, learned societies recommend early and regular endoscopic screening because of the high incidence of CRC, i.e., every one to two years from the age of 25 and then annually from the age of 40 or starting 10 years before the age of appearance of the youngest case of CRC in the family. Professional recommendations

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on prophylactic surgery to prevent cancers in patients with genetic predisposition were published in 2009 under the auspices of the French National Cancer Institute and are still current. There is no formal indication for prophylactic colectomy in LS. Numerous advances have been made in the understanding of LS, allowing a better knowledge of the prevalence of CRCs and associated cancers, with better endoscopic monitoring and a decrease in the prevalence and mortality of CRC.

Introduction

While colorectal cancer (CRC) remains a public health problem, many advances have been made over the past two decades, to better appreciate and understand the carcinogenesis pathways of both hereditary and sporadic forms of Lynch Syndrome (LS) (chromosomal instability, microsatellite instability and, more recently, the hypermethylation of CpG islands). CRC represents the 2nd most common indication for oncogenetic consultation after breast cancer. In fact, nearly 5% of CRCs are linked to constitutional genetic abnormalities, including mutation of the APC (adenomatous polyposis coli) gene in familial adenomatous polyposis (FAP) or a mutation involving the DNA repair system (MMR: mismatch repair) in LS) [1].

The purpose of this review is to update the indications and surgical strategies in patients with LS.

Lynch syndrome

Definition

Lynch Syndrome (LS) is linked to a constitutional mutation in one of the genes of the MMR system involved in the repair of DNA replication errors: MLH1, MSH2, MSH6, PMS2 or an 3′ deletion of the EPCAM gene leading to the inactivation of MSH2 [2]. The loss of function of one of the four proteins composing the MMR system leads to genomic instability in the tumor cells. These DNA replication errors are particularly represented in genome sequences called microsatellites. The observation of sequence abnormalities of tumor microsatellites is called microsatellite instability (MSI). This constitutional mutation is transmitted in an autosomal dominant mode with a strong penetrance ranging from 80 to 85%. The prevalence of alterations of these genes is estimated between 1/2000 and 1/1000. Such a mutation is identified in 80% of patients with LS. In terms of distribution, 80 to 90% of mutations affect MLH1 and MSH2, while 10 to 20% affect MSH6 and PMS2; and about 3% of Lynch syndromes are linked to a deletion of the 3' end of the EPCAM gene [2]. Deletions of the 3' end of the EPCAM gene are detected by Multiplex Ligation-dependent Probe Amplification (MLPA). From a classification standpoint, the two terms LS and HNPCC (Hereditary Non-Polyposis Colorectal Cancer) were formerly used synonymously but currently identify two distinct entities. LS is defined molecularly by the finding of an authenticated genetic mutation. HNPCC syndrome is defined clinically as patients who present clinically with Amsterdam II or I criteria without a genetic mutation that has been identified to date. Finally, the term ''LS-like'' corresponds to the families of patients with a MMR system abnormality without mutation identified to date [2].

Clinical expression

LS is the most common form of hereditary CRC (3%) [3], with a prevalence of 1/440 in the general population [4]. It represents the second most common hereditary cancer-predisposing syndrome after breast/ovarian syndrome [5].

There are different spectra associated with LS, depending on the relative risk (RR) of appearance of a type of cancer. The narrow spectrum includes cancers with a high RR: CRC, endometrial cancer, urinary tract cancer (ureter and bladder) and small bowel cancers. The broad spectrum includes tumors with a lower RR: ovarian tumors, glioblastoma, cutaneous tumors (keratoacanthomas and sebaceous tumors), tumors of the bile ducts and stomach [6—13] (Table 1). Within the broad-spectrum, pancreatic tumor remains debated but two recent studies suggest an increased risk of developing pancreatic cancer in patients with Lynch Syndrome. In 2009, Kastrinos et al. reported the results of a study of 6342 individuals from 147 families with Lynch Syndrome. The risk of developing pancreatic cancer in this population was multiplied by a factor of 8.6 [14]. In 2012, Win et al. compared data from 1029 patients without MMR mutation to 446 patients with MMR mutation. Patients with a mutation in the MMR system were at increased risk of developing pancreatic cancer [15]. Moreover, in the context of the LS, tumor associations between CRC and other tumors have been described. The Turcot syndrome associates CRC and brain tumors (glioblastoma or medulloblastoma) and the Muir-Torre syndrome associates CRC and skin tumors (adenomas or sebaceous carcinomas, basal cell carcinomas, keratoacanthomas). RR and cumulative risk (CR) over the course of life are determined for each type of cancer. Whereas RR is an aid for diagnosis, CR helps define surveillance strategies. In addition, the risk of cancer varies according to the mutation found. The CR of cancer by age 70 related to LS is between 15 and 20% with a PMS2 mutation, between 30 and 69% with an MSH6 mutation, and between 40 and 80% for carriers of an MLH1 or MSH2 mutation [4]. In addition, the risk of cancer is higher in men (40—70%) than in women (20—50%).

In whom should one suspect Lynch Syndrome?

The clinical diagnosis of LS was initially based on clinical criteria (Amsterdam I and II criteria) published in the 1990s [16,17]. The Amsterdam criteria are the presence of CRC (Amsterdam 1) or narrow spectrum (Amsterdam 2) in three first-degree relatives over two generations, including at least one case occurring before 50 years of age. These criteria lacked sensitivity despite good specificity, leading to their revision as the Bethesda Criteria, which broadened the criteria and identified patients who should be screened

Table 1 Median age at diagnosis of tumors in the HNPCC spectrum.

Tumor type	Median age at diagnosis
Colorectal cancer	43 years [6]
Endometrial cancer	50 years [7]
Urinary tract cancer	62 years [8]
Small intestinal cancer	45 years [9]
Ovarian Cancer	50 years [7]
Glioblastoma	41.5 years [10]
Skin cancer	53 years [11]
Biliary tract cancer	57 years [12]
Gastric cancer	47 years [13]

for LS (Table 2) [4]. However, these criteria are insufficient since nearly one in three patients with LS would remain undiagnosed [2]. Thus, among the patients carrying a mutation of the MMR system, only 40% present with these Amsterdam criteria. Conversely, only 50 to 60% of patients fullfilling Amsterdam criteria carry a mutation. Current recommendations by the American Gastroenterological Association (AGA) [18] argue for seeking to diagnose LS in any patient with CRC regardless of age while others recommend LS screening for patients with CRC before the age of 70 [5], and only in case of Bethesda criteria for patients older than 70. While predictive scores have been published, they are little used in France [19,20].

How to diagnose Lynch Syndrome

The diagnosis of LS is based on the detection of the deficiency of the MMR system in CRC tumor tissue, expressed either by the MSI phenotype, by molecular biology, or by the loss of expression of one of the four proteins of the MMR system by immunohistochemical study. This MMR immuno-phenotyping makes it possible to orient the molecular diagnosis towards a specific gene. However, the MSI phenotype is not specific to LS. Indeed, in CRC, the MSI phenotype is linked to a bi-allelic hypermethylation of the MLH1 gene in 75 to 85% of the cases and to an inherited mutation of one of the MMR genes in only 15 to 25% of the cases. Therefore, in case of MLH1 mutation more or less associated with the PMS2 gene, the search for a BRAF mutation (V600E) in the tumor DNA is an aid to the distinction of a sporadic case that may have a V600E BRAF mutation and a LS that does not have this mutation.

Recommendations [21] are to use a single method when suspicion is low but to do both immunohistochemistry and molecular biology techniques when there is strong suspicion. If both techniques are normal, LS is virtually eliminated. On the other hand, the AGA does not recommend one technique more than another because of their respective sensitivity and specificity. Indeed, the sensitivities and specificities of the MSI test are 0.93 (0.87—0.96) and 0.79 (0.70—0.86) and those of the immunohistochemical study are 0.91 (0.85—0.95) and 0.83 (0.77—0.88), respectively.

Lynch Syndrome and colorectal cancer

Incidence

In patients with LS, the CR of developing a CRC by age 70 is between 27% and 45% [22,23]. In the ERISCAM cohort study from 40 French centers [24], this risk was 38% in men and 31% in women. It was 41%, 48% and 12%, respectively, in case of MLH1, MSH2 and MSH6 mutations. The ''MALLORCA'' international group recent performed an observational study of 1942 patients who carried a LS mutation during a monitoring program; the study identified 314 patients with a first cancer, including 151 CRCs (131 colon and 20 rectum) [25]. The diagnosis of CRC was made at a mean interval of 31.8 months after the last colonoscopy, 58% within 2.5 years and 79% 3.5 years. At age 70, the CR of all-sex CRC ranged from 20% for MSH6 mutation to 46% for MLH1 mutation. The overall survival was 94% and 91% respectively at 5 and 10 years. This same group also identified the risk of second primary cancer from a cohort of 1273 LS patients following a first cancer [26]. Of these 1273 patients who initially developed 1835 cancers (including 1161 CRC), 318 (25.7%) developed a second primary cancer, with CRC ($n = 147$) being the most frequent. The 70-year CR of CRC after first cancer ranged from 23% to 48% with MSH6 and MSH2 mutations, respectively. In contrast, the CR was comparable whether the first cancer was colorectal or not (36% versus 39%).

Characteristics

Microsatellite instability leads to the activation of oncogenes and the inactivation of tumor suppressor genes and results in accelerated carcinogenesis. Compared with sporadic CRC, LS-associated CRC is characterized by: early age (20 years younger on average); a localization in the right colon; a stage with less locally-advanced stage at diagnosis (25% stage I and 40% stage II); less distant metastasis (5%); some histological features (poorly-differentiated, mucinous component, strong T-cell infiltration, ''Crohn-like'' type); better survival after surgical resection; but poorer sensitivity to 5-FU [27]). The decreased sensitivity to 5-FU seems to be canceled by the addition of oxaliplatin, particularly in stages III [28].

Role of endoscopy

In consideration of the high incidence of CRC in LS patients, learned societies recommend early and regular endoscopic screening, i.e., every one to two years from the age of 25 onward and then annually from age 40, or starting 10 years before the age of appearance of CRC in the youngest patient in the family (AGA). Compared with no surveillance, a program of endoscopic screening increases the detection of adenoma (Odds Ratio (OR) = 3.81) while decreasing the prevalence of CRC (OR = 0.23), of metastatic CRC synchronous (OR = 0.28) and of CRC-related mortality (OR = 0.06) [4,29]; thus, without increasing the cost, it allows a gain of seven years in life expectancy [18]. At present, no randomized study has been published concerning the appropriate interval between two endoscopies, even though the majority of authors agree on a two-year interval [30]. Despite adequate surveillance, an interval CRC can develop within the two-year time span [31,32]; according to the Dutch registry, the identified risk factors are the MLH1 or MSH2 mutation, a personal history of CRC, incomplete previous colonoscopy, or incomplete polypectomy [32]. The majority of the interval CRCs reported [33—36] are stage I-II (78-95% of cases) and located in the right colon (57-62% of cases). These interval CRCs are explained not only by accelerated carcinogenesis but also by the difficulty of identifying pre-cancerous lesions [37]. More than 10 years ago, Jong et al. [38] reported that adenomas in LS patients were

Table 2 Amsterdam II Criteria: (good specificity but poor sensitivity) and Bethesda Criteria (poor specificity but good sensitivity).

Amsterdam II Criteria (all the criteria should be present)	Bethesda Criteria (at least one criterion)
At least three family members with cancers of the HNPCC narrow spectrum	Colorectal cancer before age 50
At least one of these three should be a first-degree relative	Second synchronous colorectal cancer or a metachronous colorectal cancer (regardless of age)
Involvement of at least two generations	Second cancer from the broad spectrum of HNPCC (regardless of age)
At least one cancer before the age of 50	Pathologic findings showing Microsatellite Instability at age < 60
No history of familial adenomatosis coli	Colorectal cancer with at least one first-degree relative presenting with a cancer from the broad spectrum of HNPCC before the age of 50
	Colorectal cancer with at least two first-degree relatives presenting with a cancer from the broad spectrum of HNPCC (independent of age)

significantly more often flat, small, villous and had severe dysplasia. These endoscopic findings and these interval CRCs call for very good-quality endoscopy [39]. The performance of chromo-endoscopy with indigo carmine makes it possible to highlight the relief of the mucosa and to better visualize flat villous lesions, the principal colonic lesions of LS [40] and thus to double the rate of detection of these adenomas [41]. According to a French multi-center study, chromo-endoscopy using indigo-carmine staining significantly improves diagnostic performance. Thus, in a blinded study, chromo-endoscopy doubled the percentage of diagnosed adenomas: 32/78 (41%) versus 18/78 (23%), $P < 0.001$ [40]. Finally, the timing of initial endoscopy and frequency of future surveillance should be adapted according to the location of the mutation; the risk of CRC being lower and later in case of MSH6 mutation [42].

Upper endoscopic surveillance of the esophagus, stomach and duodenum is also proposed because of the risk of gastric cancer (wide spectrum). Recent ASCO/ESMO recommendations support testing for and eradication of *Helicobacter pylori*. In populations with high incidence of gastric cancer, endoscopic monitoring is recommended every one to three years [43]. In France, endoscopic gastric surveillance is recommended to start at age 20 and every four years thereafter. In patients at risk of developing gastric cancer (atrophic gastritis, intestinal metaplasia, adenoma), follow-up upper endoscopy is recommended every two years. Upper endoscopy should include careful examination of the distal duodenum and the ampulla of Vater.

Place of prophylactic surgical treatment in Lynch Syndrome

In 2009, the French National Cancer Institute (NCI) published professional recommendations on the prophylactic cancer preventing surgery in patients with a genetic predisposition, which are still current [44]. In theory, there are three types of prophylactic surgery for LS.

Primary prophylactic surgery

There are no formal indications for primary prophylactic colorectal surgery in LS. Indeed, this corresponds to the excision of an organ that is cancer-free organ albeit at high risk of cancerization. Prophylactic colorectal surgery is not recommended when the patient is free from colonic lesions because endoscopic management reduces the risk of death by 70% [30]. Thus, according to an old statistical model, [45], the benefit of a total carcinological colectomy at the age of 25 would increase survival by 1.8 years compared with endoscopic surveillance. This primary prophylactic surgery could nevertheless be considered in some families with LS, with high penetrance and an early age of CRC.

Primary prophylactic colon surgery can be proposed for LS patients with endometrial cancer (EC) requiring a hysterectomy without preservation of adnexae. Indeed, in females with LS, EC is often referred to as ''sentinel event'' because it is first manifestation of LS in more than one in two women [46], with an earlier age of onset than in sporadic EC [46]. In LS, EC occurs significantly more commonly in patients with early menarche, nulliparity, short-term or no oral contraception (1 year) [47]. These women with LS who develop EC have an increased risk of developing a CRC. Thus, according to a previous study based on the Amsterdam criteria, Aarnio et al. found that the CR of CRC at 26 years after the development of an EC, ranged from 40 to 75% [48]. According to a recent registry study that included 127 LS patients with EC, 55% of patients ($n = 70$) developed a second cancer, more than half ($n = 40$) of which were CRC. Compared with the general population, LS women with EC have a 40-fold increased risk of developing CRC [49], which can be the basis for discussion of prophylactic colectomy at the time of total hysterectomy. There is however very little data on this specific point and on the extent of the colonic resection. The professional recommendations for prophylactic surgery of cancers with genetic predisposition published in 2009 simply recall the risk of developing a rectovaginal fistula and the need to interpose the omentum in case of colectomy and associated hysterectomy.

Moreover, in view of the risk of EC (narrow spectrum) and ovarian cancer (wide spectrum), gynecologic examination and pelvic ultrasound with measurement of the endometrial thickness are recommended every year after age 35 or starting five years before the first case of endometrial cancer in the family. Prophylactic surgery (total hysterectomy with bilateral salpingo-oophorectomy) should be discussed starting at age 45 or five years before the first endometrial cancer in the family.

Secondary prophylactic surgery

The majority of surgical indications for LS are therefore based on the treatment of either a CRC or of an endoscopically-unresectable dysplasia or adenoma. Either segmental or total colectomy can be proposed depending on the location of the lesion. For rectal lesions, a proctectomy with or without sphincter preservation or a total coloproctectomy can be discussed. In addition to location, the choice of the technique must take into account patient factors (age, co-morbidities, personal choice), the morbidity of the gesture, the functional sequelae engendered, the impact on the quality of life, and, finally, the risk of developing a metachronous lesion. These considerations are necessary in order to provide patients with the most complete enlightened information. This decision can be difficult to make because the certainty of the diagnosis of LS is not always known at the time of surgery.

Tertiary prophylactic surgery

This concerns patients who have undergone segmental colonic or rectal resection with the diagnosis of LS made post-operatively. The prophylactic strategy is based either on endoscopic surveillance or on the extension of surgical resection.

What type of surgical resection?

To simplify the presentation, we consider in this work successively the management of rectal cancer and then of colon cancer in patients with the LS.

Lynch Syndrome with Rectal Cancer (RC)

About 20—30% of patients with LS will develop RC, including 15% as an initial presentation. The American Society of Colon and Rectal Surgeons (ASCRS) recommends treatment of the rectal lesion alone, in the absence of other synchronous colon cancer localizations (level of recommendation: grade 2 C) [1]. This strategy is all the more justified if a neoadjuvant treatment is indicated. In the literature, the CR to develop a metachronous colon cancer after proctectomy ranges from 18 to 54% depending on the length of follow-up [50—52]. These variations can be explained by the fact that not all patients in whom LS was suspected on the basis of the Amsterdam Criteria proved to have LS [53]. In the series of Win et al. compiled from several registers, 21 patients (27%) among 79 patients who underwent resection of a RC complicating LS eventually developed a metachronous cancer of the colon with a median follow-up of nine years [49]. In 75% of cases, the colon cancer was located on the right and diagnosed at an early stage (I—II). At 10, 20 and 30 years, the cumulative risk of CC was respectively 19%, 47% and 69%.

Lynch syndrome with colon cancer (CC)

The recent recommendations of the ASCRS call for a total colectomy (TC) (evidence grade 1B) because of the higher risk of metachronous CC [1]. However, the ASCRS also recognizes a role for the segmental colectomy (SC) disease in view of the sequelae of TC (evidence grade 2 C). The situation is complex and necessitates adaptation on a case-by-case basis.

According to a Markov statistical model, performance of TC versus SC at the age of 27 would increase life expectancy by 2.3 years for all stages and by 3.4 years for Dukes A stage. The benefit of subtotal colectomy compared to SC decreases with age. At age 47, the advantage is 1 year and it is only 0.3 years at age 67. Thus the youngest patients are the most likely to benefit from extensive colectomy [54]. The main criticism is that it is difficult to predict the TNM stage preoperatively. However, no prospective randomized study has been published to date, comparing SC to TC for LS patients with colon cancer.

Risk of metachronous cancer: segmental colectomy (SC) or total colectomy (TC)?

To date three meta-analyses are available [55—57] with similar results, namely that TC is significantly associated with a decrease in the risk of metachronous CC. The most recent study by Malik et al. is the most complete and the most interesting because it differentiated the patients according to whether the LS was proved by a mutation of the MMR system or suspected based on clinical criteria [57]. This meta-analysis included ten studies with 1389 patients and a 100-month follow-up; SC was performed in 1119 patients and TC in 270 patients.

The risk of metachronous colon cancer at the end of follow-up was respectively 28.2 and 4.7%, (OR: 5.12, 95% CI 2.88—9.11). The relative risk of developing a metachronous lesion after SC compared to TC was 8.56, (95% CI 3.37—21.73) in patients with proven LS (MMR mutation) and 3.04, (95% CI 1.46—6.34) in patients who met the Amsterdam criteria but did not have proven MMR mutation. In summary, this study suggests that for LS patients, SC carries five times the risk of developing metachronous CRC compared to TC. However, the study has little information on the frequency of endoscopic screening or the quality of the endoscopic examination [58].

However, none of these three meta-analyses, showed SC to have a statistically significant association with decreased survival, even though all three studies suggested a survival benefit for TC [59—61]. Moreover, no data were available on the morbidity and mortality of SC *vs.* TC nor on the functional sequelae generated by each procedure. Finally, the specific mutation probably has an effect since the majority of patients who developed metachronous cancer had an MLH1 or MSH2 mutation. In the future, recommendations for extensive surgery may be based on the type of mutation.

Morbidity and mortality: segmental colectomy or total colectomy?

Few recent data from comparative series are available for morbidity and mortality following TC vs. SC. A Mayo Clinic study of 522 CRC patients who underwent SC ($n = 321$) or total colectomy ($n = 201$) showed that morbidity-mortality was comparable between the two groups, even after classification according to Dindo-Clavien. Only post-operative ileus was significantly more common after extensive colectomy (26.4—38.5% versus 10.9%), leading to a significant prolongation of hospital stay (8-9 versus 7 days). In contrast, the anastomotic leak rate (0.9—3.3% versus 1.9%) and the re-intervention rate (2.7—3.3% versus 3.7%) were comparable. Anastomotic disruption remains the most feared surgical complication as it increases morbidity and post-operative mortality. One of the most recent series of the literature,

which included 17,518 colic resections, reported an anastomotic leak rate of 3.9% [63]. Some risk factors are now well known such as smoking history, diabetes, hypoalbuminemia and emergency surgery. These factors must be taken into account during the surgical decision. These complications and especially their risk factors are all the more important since they have a demonstrated impact on the oncological results. Two recent studies report that these complications had a negative impact on overall survival, CRC-specific survival, and recurrence [64,65].

Functional sequelae and quality of life: SC or total colectomy?

In terms of functional results and quality of life, only one study specific to LS is available, from the Dutch register [66]. A total of 104 patients who responded to the questionnaires were analyzed (51 with SC and 53 with TC). The follow-up was significantly longer in the SC group (12.7 vs. 9.2 years, $P < 0.01$). If the Quality of life (QOL) scores were comparable between the two interventions according to EORTC SF36 and/or QLQ-CR38 scores, TC was significantly associated with stool frequency and its social impact compared to SC. The authors suggested that preservation of a part of the distal sigmoid and rectosigmoid below the pelvic brim would serve oncological imperatives while improving functional outcomes. Several other authors have also observed similar results. In the Cleveland Clinic series [62], TC was significantly correlated with daytime (4 vs. 1) and nocturnal (1 vs. 0) stool frequency, and with the need for medications to slow transit (19.6 vs. 0%) episodes of diurnal incontinence and perineal excoriation (18.5% *vs.* 6.9%). After adjusting for age, sex, procedure, and the interval to evaluation of functional outcome, stool frequency was related to the extensiveness of colectomy, to young age and to a short interval of the clinical evaluation. Patients whose anastomosis was within 20 cm of the anal margin had the poorest functional outcome. Two French teams have reported similar results [67,68]. In summary, extended colectomy alters the functional result in terms of the number of stools per 24 hours, the use of medication to retard transit, and even diet. Unless carcinologic reasons make extended colectomy imperative, performance of an ileo-sigmoid anastomosis to a recto-sigmoid stump of 20 to 25 cm length would be preferable to performing an ileo-rectal anastomosis.

In conclusion, unless the LS shows significant penetration in the family as evidenced by many CRCs, by a young age of first CRC, or unless the patient is unlikely to comply with a programmed endoscopic surveillance, and if there is no other indication for extended colectomy, the decision to perform a SC *vs.* TC should be made on a case-by-case basis, having fully informed the patient of the operative and functional risks as well as the risk of developing a metachronous lesion. If an extensive colectomy is performed, the preservation of 20 to 25 cm of rectosigmoid improves the functional results. Whatever the resection performed, an annual postoperative colorectal endoscopic monitoring is imperative, as well as gynecological surveillance according to the recommendations [7]. The latest European recommendations for gynecological screening for LS are a clinical examination, a pelvic ultrasound, an endometrial biopsy ± a hysteroscopy annually from the age of 35 years [69]. Only one study [70] has shown that prophylactic surgery eliminates any risk of EC and ovarian cancer. This surgery can be offered to any LS patient with proven mutations or high risk, once desired childbearing years are past, at 40—45 years. This decision must be validated in a multi-specialty consultation; the patient must be informed that this will result in menopause and possible hormone replacement therapy.

Conclusion

In conclusion, much progress has been made in the understanding of Lynch Syndrome, allowing precise identification of LS patients (thanks to the search for the MSI phenotype and/or the mutation of one of the genes of the MMR system), a better knowledge of the prevalence of CRCs and associated cancers, in particular gynecological cancers, better endoscopic monitoring of these patients, and ultimately, a decrease in the prevalence of CRC and secondary mortality due to CRC [71]. Nevertheless, LS is still relatively underappreciated among surgeons as evidenced by the low percentage (< 33%) of patients who present with CRC before the age of 50 in whom testing for LS is carried out [72,73]. Given the implications for the patient and his descendants, progress is still to be made in educating surgeons with respect to Lynch Syndrome.

Disclosure of interest

The authors declare that they have no competing interest.

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