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What is currently known about endometrial cancer in Lynch syndrome? - review

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ABSTRACT

Introduction: About 5% of endometrial cancer cases can be genetic and inherited. Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant syndrome. Caused by a germline mutation in one of the DNA mismatch repair genes, it is responsible for most hereditary cases. Lynch syndrome is associated with the early onset and the development of many types of cancer, especially colon and endometrial cancer.

Methods: The review of publications regarding Lynch syndrome-associated endometrial cancer and methods for screening, diagnosis and its prevention.

State of knowelage: Endometrial cancers related to Lynch syndrome are mostly sentinel (they reveal the predisposition in 50% of families) and are characterized by young age at onset (commonly before 60 years). The lifetime cumulative risk of endometrial cancer for

women with Lynch syndrome is about 40% to 60%, which equals or exceeds their risk of colorectal cancer. Lynch syndrome, the current gynecologic cancer screening guidelines include annual endometrial sampling and transvaginal ultrasonography beginning at age of 30-35 years, which is very important in the early detection of this cancer. Risk-reducing surgery consisting of prophylactic hysterectomy and bilateral salpingooophorectomy should be offered to women aged 35 years or older who do not wish to preserve their fertility.

Summary: Diagnosis of endometrial cancer in patients with Lynch syndrome has important clinical implications for the individual and family members.

Key words: Lynch syndrome, endometrial cancer, mismatch repair, IHC, MRR, MSI.

Introduction

It is estimated that about 5% of endometrial cancer cases may be attributed to a site-specific inherited predisposition to cancer [1]. Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome is responsible for most hereditary cancers of the endometrium. Mutations in one of the four mismatch repair genes :hMLH1, hMSH2, hMSH6 or hPMS2, have been identified in patients with Lynch syndrome. This article aims to describe Lynch syndrome from the available literature, considering the endometrial cancer associated with this syndrome.

Background

Lynch syndrome is one of the most common autosome-dominant, inherited, cancer susceptibility syndrome. LS characterized by a high risk of malignancies, including colorectal (2%–3% of cases , lifetime risk of 52–82%) [2], endometrial (2.3 % of cases, lifetime risk of 25–60%) [3] and ovarian (lifetime risk of 4–12%) malignancies [4,5].

The diagnosis of LS is based on the identification of germline mutations in the DNA mismatch repair (MMR) genes: MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), PMS1 homolog 2 (PMS2) and/or epithelial cell adhesion molecule (EPCAM). The loss of DNA MMR leads to genomic instability by facilitating the accumulation of somatic mutations in various sequences [6,7]. Germline mutations in hMLH1and hMSH2 are responsible for over 90% of diagnosed Lynch syndrome cases. Endometrial cancer (EC) is the most common cancer associated with LS patients [8,9]. Screening and diagnosis of LS in EC patients is a great importance for sick patients, but also for their relatives who could benefit from genetic counseling and enhanced oncological surveillance [10,11].

Current Screening Strategies – Amsterdam criteria and Bethesda guidelines

Screening strategies for colorectal cancer with LS have been thoroughly verified [12,13]. However, LS-related EC (LS-EC) screening is still controversial because no consensus has

been reached on the strategies, upper age threshold or cost-effectiveness of screening [14,15]. Prior to the introduction of next generation sequencing (NGS), LS screening methods consisted of clinical diagnostic criteria based on individual and family history of cancer. These methods are relatively inexpensive. The most commonly used screening tools are the Amsterdam II clinical criteria [16] and the revised Bethesda guidelines (Table 2.)[17]. However, the disadvantages of clinical criteria are the requirement of high accuracy in collecting individual and family histories as well as actual low accuracy [6,18].

Table 1. Amsterdam criteria II [16]

There should be at least 3 relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One should be a first-degree relative of the other 2
At least 2 successive generations should be affected
At least 1 should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the CRC case(s) if any
Tumors should be verified by pathological examination

Table 2. Adapted Bethesda guidelines [17]

1a	Colorectal cancer diagnosed in a patient who is less than 51 years of age.
1b	Endometrial cancer diagnosed in a patient who is less than 46 years of age
2	Presence of synchronous or metachronous HNPCC-associated tumors*, regardless of age
3	Colorectal cancer with the MSI-H** histology*** diagnosed in a patient who is less than 61 years of age. No relatives with HNPCC-associated tumors* being diagnosed under age of 51 years
4	Patient with HNPCC-associated tumor* and one or more first-degree relatives with an HNPCC-associated tumor*, with one or more colorectal cancer, with one or more of the cancers being diagnosed under age of 51 years
5	Patient with one or more HNPCC-associated tumor* and two or more first- or second-degree relatives with HNPCC-associated tumors*, with one or more colorectal cancer, all cancers diagnosed after age of 50 years
* Hereditary non-polyposis colorectal cancer (HNPCC)-associated 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, and tumors of the small bowel ** Microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers *** Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern	

Unfortunately, the above LS screening patterns focus primarily on the colon, and it has been shown that the effectiveness of LS diagnosis in patients with gynecological cancers is poor [19]. These criteria are complex and poorly implemented in clinical practice. Therefore, other screening strategies should be used for EC patients [20].

Current guidelines

The Society of Gynecologic Oncologists (SGO) published a committee statement on the risk assessment for inherited gynecologic malignancies [21]. In these recommendations' patients are triaged to a genetic counselor or genetic testing based on the perception of risk (Table 3.) This document offered the caveat that there are patients who may not meet these extensive criteria but who may warrant genetic screening. These patients include those with few female relatives, unknown family history, or in a patient from a family in whom hysterectomy and oophorectomy was performed prior to the age of the risk of Lynch cancers [22]. However,

before qualifying the patients with endmetrial cancer at group of risk and referring them to a specialist clinic, they still require extensive family or personal history investigation.

Table 3. SGO committee statement guidelines on risk assessment for Lynch syndrome [21].

For patients with a 20–25% risk of Lynch syndrome genetic risk assessment is strongly recommended, these patients include: 1. Family pedigrees meeting Amsterdam criteria 2. Those patients with metachronous or synchronous colorectal and endometrial or ovarian cancers prior to age 50 3. Those with a 1st or 2nd degree relative with a known germline mutation in a mismatch repair gene
For patients with a 5–10% risk of having Lynch syndrome genetic testing was classified as being “helpful”, these patients include: 1. Patients with endometrial or colorectal diagnosed prior to 50 2. Patients with endometrial and/or ovarian cancer and a synchronous or metachronous Lynch-associated tumor at any age 3. Patients with endometrial or colorectal cancer and a first-degree relative diagnosed with a Lynch-associated malignancy prior to 50 4. Patients with colorectal or endometrial at any age with two or more 1st or 2nd degree relatives diagnosed with a Lynch-associated malignancy at any age 5. A patient with a 1st or 2nd degree relative who meets the above criteria

Screening algorithms

According to recent literature it is considered that IHC for the MMR proteins may be used as primary triage for Lynch syndrome. Walsh et al. retrospectively identified, by IHC, putative Lynch syndrome in 26/146 newly diagnosed endometrial cancer patients less than 50 years of age with only 6/26 patients fulfiled the Amsterdam criteria II [23]. In another retrospective study by Matthews et al., 34% of women with newly diagnosed endometrial cancer under the age of 50 were detected immunohistochemical evidence of mismatch repair deficiency [24]. Unfortunately, reservations have been raised about these tests because confirmation of a gene mutation was not performed in tumors lacking expression of a MMR protein. Lu et al. in its prospective screening in women under 50 years of age showed that IHC followed by sequencing is a feasible, sensitive option [25]. In this group of patients, 9% demonstrated germline mutations in MLH1, MSH2 or MSH6, higher than the 2.3% rate in the general population of patients with endometrial cancer as a result of Lynch syndrome. Hampel et al., in a large, prospective Lynch screening study of 562 women presenting with endometrial cancer demonstrated that the mean age at diagnosis of the 13 probands identified with Lynch syndrome was 54.1 years [26,27]. Had they used 50 years as a screening cut off, 69% of patients would have been missed. Additionally, Goodfellow et al. demonstrated a mean age of 54.8 years in 35 cases of presumptive Lynch-associated endometrial cancer [28]. These data suggest that unlike earlier studies that demonstrated the mean age of diagnosis of endometrial cancer in patients with Lynch syndrome was 48 years [29], the diagnosis of endometrial cancer in a proband with Lynch syndrome is more commonly made after the age of 50 [22].

In Xiaopei Chao et al. studies total of 111 unselected patients with newly diagnosed EC were enrolled. Six patients (5.4%) harbored a pathogenic germline mutation of MMR genes, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for identifying LS-EC were 33.3%, 88.6%, 14.3% and 95.9% for the clinical criteria; 66.7%, 75.0%, 14.3% and 97.3% for IHC of MMR proteins; 100%, 89.9%, 33.3% and 100% for MSI test; 100%, 72.4%, 20.0% and 100% for combined IHC and MSI test, respectively. The combination of IHC and MSI test had higher sensitivity and PPV than the clinical criteria ($p = 0.030$). MSI test and IHC were highly concordant for LS-EC screening (73/77, 94.8%) [6].

Endometrial tumors found in Lynch syndrome most commonly result from mutations in MSH6 and tumors resulting from mutations in MSH6 occur at a later age than those in MLH1 and MSH2 (these often occur in colon cancers with LS). Mutations in MSH6 confer a less “severe” clinical picture with regards to both CRC and EMCA. Importantly, for those individuals with a germline MSH6 mutation the cumulative risk of endometrial cancer is substantially exaggerated beyond that associated with mutation in the other MMR genes [30,31]. Several studies focused on the truncating germline mutation of MSH6 where it was shown that women had twice as frequent endometrial cancer with this mutation in contrast to those that had mutations in MLH1 or MSH2 [26,27,28, 30,32].

Westin et al. attempted to identify pathological factors of endometrial cancer in Lynch syndrome. Determined that the prevalence of Lynch among women with endometrial cancer of the lower uterine segment was 29% and concluded that in cases of pathologically confirmed endometrial cancer originating in the lower uterine segment, screening for Lynch syndrome should be considered [33]. Broaddus et al. compared three cohorts of endometrial cancer patients: those with sporadic endometrial cancer under 50 years old, those with MSI-H endometrial cancers secondary to methylation of the MLH1 promoter and those with Lynch syndrome. In this study there was no difference in deep myometrial invasion between the cohorts, additionaly although they did identify a distinctive “undifferentiated” subtype in those with MSI-H tumors secondary to methylation, they were unable to identify any distinct pathologic characteristics that could reliably distinguish between Lynch-associated and sporadic endometrial cancers [34]. In the study of Shia et al. examined morphological features and their impact on the status of MSI (which also occurs in Lynch syndrome) - the CRC, tumor infiltrating lymphocytes (TIL) and peritumoral lymphocytes (PL) in endometrial cancer were shown to be independent predictors of MSI [35]. Soslow et al. developed an algorithm for detecting patients at high risk group for endometrial cancer in Lynch syndrome based on tumor morphology and epidemiologic factors. In this algorithm, immunohistochemistry for MMR proteins was performed on:

1) all endometrioid carcinomas in patients younger than age 50,

2) endometrial carcinomas with TILs and PLs (suggestive of MSI),

3) at the discretion of the treating physician.

In a prospective evaluation of 375 hysterectomy specimens, IHC was performed on 80 tumor samples according to this algorithm [36]. The authors concluded that through this algorithm, they were able to enrich for high-risk patients.

Mode of present testing

Universal molecular testing in accordance with guidelines The National Comprehensive Cancer Network (NCCN) [14,37] for LS in all newly diagnosed EC patients should be test perform to evaluate loss of MMR function via immunohistochemical (IHC) and/or microsatellite instability (MSI) analysis independent of the clinical criteria [37,38,39]. This method of screening is cost effective and also the sensitivity and specificity are satisfactory [40]. Tissue tests can be very helpful in cases where, due to family or personal cancer, they fall into a lower risk category from 5% to 10% of the risk of Lynch syndrome, for example in people diagnosed with endometrial cancer before the age of 50 [41]. Hampel et al. published the results of prospective Lynch screening in 500 newly diagnosed colon cancer patients. The sensitivity of IHC in this population was 94%. The positive predictive value of an abnormal IHC for detecting Lynch syndrome was 23.89%; significantly higher than both age<50 (10.3%) and first-degree relative with colon cancer or EMCA (8.8%) [42]. Vasen et al. described a 93% concordance between IHC and MSI testing in colon tumors when all 4 MMR proteins were examined [43]. Cohn et al. performed IHC on 336 endometrial cancers, positive staining for MLH1 or MSH2 predicted an intact mismatch repair system in 95% of cases [44]. Modica et al. described similar results in their research; when all 4 MMR proteins were examined, they had 91% sensitivity and 83% specificity in defining the MSI-H phenotype [45].

In studies comparing the diagnostic value of IHC and MSI which given the higher rate of MSH6 mutations in endometrial cancer associated with Lynch syndrome and the lower predictive value of MSI in MSH6-associated Lynch syndrome, consideration of IHC, rather than MSI as primary screening for Lynch syndrome in patients with endometrial cancer, should be considered [26,27]. An additional limitation of MSI testing may be fact that the presence of a positive screen for MSI will not discriminate between its presence as a result of epigenetic silencing of MLH1 or loss of function of an MMR protein. This has been described in several studies [26,27,46,47,48,49]. In addition, there may be mentioned an additional BRAF V600E mutation test in the MSI method for Lynch in colon cancer patients described in the studies by Davies et al. and Bessa et al. [50,51]. Unfortunately, several studies have not demonstrated the usefulness of this mutation in detecting endometrial cancer in Lynch syndrome [52,53,54].

Screening and Prevention for Individuals with Lynch Syndrome (table 4.) [55]

Table 4.

Intervention	***Recommendation***
Colonoscopy	Every 1–2 years beginning at age 20–25 years or 10 years prior to the youngest age of cancer diagnosis in the family, whichever comes first. For MSH6 families begin at age 30.
Endometrial sampling	Every year beginning at age 30–35 years.
Transvaginal ultrasound	Every year beginning at age 30–35 years.
Urinalysis with cytology	Every 1–2 years beginning at age 25–35 years.
History and physical examination	Every year beginning at age 21 with review of systems, education, and counseling.
Colorectal resection	Generally, not recommended for primary prophylaxis, but if cancer is diagnosed, the preferred procedure is a subtotal colectomy.
Hysterectomy with bilateral salpingo-oophorectomy	Discuss as an option after childbearing is complete.

Conclusion

It is important for clinicians alike gynecologic oncologists, surgical oncologists, general surgeons, medical oncologists, primary care providers to be particularly cautious when endometrial cancer is detected. In Lynch syndrome, it usually occurs at an early stage and can be successfully cured but diagnosis of colon cancer has a significantly worse prognosis. Given the opportunity for colon cancer screening and prevention strategies to be initiated, the identification of probands with endometrial cancer as a result of Lynch syndrome will lead to a reduction in morbidity and mortality for these patients and their families. However, more research is needed to determine more effective screening methods compared to preventive surgery to reduce morbidity and mortality from endometrial cancer in women with Lynch syndrome.

Abbreviations:

LS - Lynch syndrome

HNPCC- hereditary nonpolyposis colorectal cancer

EC - endometrial cancer

LS-EC - Lynch syndrome-associated endometrial cancer

CRC - colorectal cancer

MLH1 - MutL homolog 1 gene

MSH2 - MutS homolog 2 gene

MSH6) - MutS homolog 6 gene

PMS2 - PMS1 homolog 2 gene

MMR - mismatch repair

EPCAM - epithelial cell adhesion molecule

DNA - deoxyribonucleic acid

NGS - next generation sequencing

MSI-H - microsatellite instability

SGO - Society of Gynecologic Oncologists

IHC - immunohistochemical

EMCA - Epithelial mucin core antigen

TIL - tumor infiltrating lymphocytes

PL - peritumoral lymphocytes

NCCN - National Comprehensive Cancer Network

BRAF - serine/threonine-protein kinase B-Raf

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