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Lynch syndrome in patients treated for endometrial cancer

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Summary

Objective: To evaluate the patients with familial Lynch syndrome, who were treated for endometrial cancer in Gynecology Department of Ankara Oncology Education and Research Hospital. *Materials and Methods:* Staging surgery was performed in all patients diagnosed with endometrial cancer. Total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy, bilateral pelvic-para-aortic lymph node dissection (BPPLND), and peritoneal cytology were performed. The patients were referred to radiation oncology clinic with their final pathology report, postoperatively. Adjuvant radiotherapy was performed in patients deemed necessary. *Results:* Familial Lynch syndrome was detected in four of 93 patients. All of the Lynch cases were diagnosed with FIGO Stage I endometrial adenocarcinoma. The mean age of Lynch syndrome patients was 51.5 years. Two of these 93 patients were synchronous colon and endometrial cancer and one of these 93 patients was metachronous colon and endometrial cancer, but Lynch syndrome was not diagnosed in these three patients according to Amsterdam criteria. *Conclusion:* Diagnosis of patients with Lynch syndrome and identification of at-risk people is very important because if it is diagnosed at early stage, better survival rates could be expected.

Key words: Lynch syndrome; Endometrial cancer; Colon cancer.

Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries, and its incidence and importance has increased over the years. Approximately 5% of endometrial cancers are hereditary, and the Lynch syndrome is responsible for most of them. The Lynch syndrome is seen in 2-3% of endometrial cancers.

The Lynch syndrome also called hereditary non-polyposis colorectal cancer (HNPCC), is the most common hereditary colorectal cancer syndrome. It can be caused by mutations in one of the DNA mismatch repair genes (MSH 2, MLH 1, PMS 1, PMS 2 or MSH 6) [1]. It is an autosomal dominant genetic disease characterized by early onset of hereditary colorectal tumors, hereditary gynecological cancers (endometrium and ovary), and other carcinomas such as gastric, pancreatic, brain, hepatobiliary, and small intestine. Colorectal and endometrial cancer are the characteristic tumors of the Lynch syndrome. Females with Lynch syndrome are more prone to have endometrial and ovarian cancers later in life. Prognosis prediction and early diagnosis of the syndrome is important in order to plan appropriate treatment.

The aim of this study is to highlight the importance of family history in treatment of endometrial cancers, regarding rare presence of Lynch syndrome in these malignancies. Otherwise, cancer may be treated with missing the big picture of an underlying Lynch syndrome, which is particularly essential for screening patients, and their first-degree relatives for other cancers.

Materials and Methods

The patients with familial Lynch syndrome, who have been treated for endometrium cancer in Gynecology Department of Ankara Oncology Education and Research Hospital between 2013 and 2015, were evaluated in this study. Staging surgery was performed in all patients after the necessary preparations. Following the midline incision peritoneal cytology was performed and the abdomen was explored. Total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy and bilateral pelvic-para-aortic lymph node dissection (BPPLND) were performed. The patients' postoperative processes were usual and they were referred to radiation oncology clinic with their final pathology report. Adjuvant radiotherapy was performed to patients deemed necessary. Because of all patients with Stage I, chemotherapy was not applied. Lynch syndrome diagnosis were performed according to Amsterdam II and revised Bethesda criteria (Table 1) [2, 3]. Patients and relatives were followed regularly according to potential malignancy risk groups by the relevant clinic.

Results

Familial Lynch syndrome was detected in four of 93 patients, who were treated for endometrial cancer in Gynecology Department of Ankara Oncology Education and Research Hospital from January 2013 to August 2015 (4.3%). Two of these 93 patients were synchronous colon and endometrial cancer and they were not diagnosed for Lynch syndrome according to Amsterdam II and Bethesda criteria. One of these 93 patients was metachronous colon and endometrial cancer. All of the patients were admitted to gynecology clinic with abnormal uterine bleeding. The

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Table 1. — *Amsterdam II and revised Bethesda criteria.*

Amsterdam II Criteria [2]	Revised Bethesda Criteria [3]
There should be at least three relatives with a Lynch associated cancer (colorectal, endometrium, small bowel, ureter or renal pelvis) and • One should be a first degree relative to the other two • At least two successive generations should be affected • At least one should be diagnosed before age 50 • Familial adenomatous polyposis should be excluded • Tumors should be verified by pathological examination	Just one these criteria need to be met: • Diagnosed with colorectal cancer before the age of 50 years; • Synchronous or metachronous colorectal or other HNPCC-related tumours (which include stomach, bladder, ureter, renal pelvis, biliary tract, brain (glioblastoma), sebaceous gland adenomas, keratoacanthomas, and carcinoma of the small bowel), regardless of age; • Colorectal cancer with a high-microsatellite instability morphology that was diagnosed before the age of 60 years; • Colorectal cancer with one or more first-degree relatives with colorectal cancer or other HNPCC-related tumours. One of the cancers must have been diagnosed before the age of 50 years (this includes adenoma, which must have been diagnosed before the age of 40 years); • Colorectal cancer with two or more relatives with colorectal cancer or other HNPCC-related tumours, regardless of age.

results of the biopsies were reported as endometrial adenocarcinoma. The mean age of patients was 51.5 years. The follow-up schedule, the disease free survival, and the overall survival can be seen in Table 2.

Case 1

A 52-year-old, G2P2 patient was admitted to gynecology clinic with menometrorrhagia. Patient had past history of colon cancer seven years prior and it was managed by right hemicolectomy. Histopathological examination of endometrial biopsy revealed endometrial adenocarcinoma. She underwent TAH+BSO+BPPLND+omentectomy+peritoneal cytology. Histopathological examination of the tumor was found to protrude into the uterine cavity, which was infiltrating less than half of the myometrium, consisted of well-differentiated glandular structures, with no infiltration at cervix and vagina. The ovaries were normal. Thirty pelvic and paraaortic lymph nodes removed by the lymphatic dissection were found to be reactive. Omental and peritoneal cytology were normal. According to these findings, she was diagnosed with FIGO Stage IA endometrial adenocarcinoma. There was no indication of adjuvant therapy for endometrial cancer. Her family history included colon cancer in her mother 36 years of age, in her brothers at 34, 50, and 47 years of age, in her sister at 50 years of age, and in her uncle at 45 years of age. Her family history in six family members had a history of colorectal cancer and four of these were diagnosed at a younger age (below 40 years). According to this family history and to Amsterdam II and Bethesda criteria, she was diagnosed with Lynch syndrome. In this patient the recurrence developed in the iliac lymph nodes. She died due to cerebrovascular events.

Table 2. — *Characteristics of patients.*

	Case 1	Case 2	Case 3	Case 4
Age (years)	52	38	61	55
GPYA	G2P2	G3P2A1	G12P4A8	G3P2A1
Presenting symptom	Menometrorrhagia	Menometrorrhagia	Postmenopausal bleeding	Menometrorrhagia
Preoperative histopathological diagnosis	Endometrial adenocarcinoma	Endometrial adenocarcinoma	Endometrial adenocarcinoma	Endometrial adenocarcinoma
Postoperative histopathological diagnosis	Endometrial adenocarcinoma	Endometrial adenocarcinoma	Endometrioid type adenocarcinoma	Endometrioid type adenocarcinoma
Stage of endometrial cancer	Stage IA	Stage IA	Stage IB	Stage IA
Adjuvant therapy	-	-	RT	-
Follow-up time	22	16	20	3
History of colon cancer	+	-	+	-
Relative diagnosed with Lynch syndrome	6	3	4	4
Number with disease in several generations	2	2	2	2
Relative with a Lynch syndrome diagnosed before age 50 years	6	3	3	3
Presence of synchronous or metachronous cancer	-	-	-	-
Comorbidity	CVE	-	-	-
Disease free survival (months)	19	Disease free	Disease free	Disease free
Overall survival (months)	22	16	20	3
Status	Exitus	Alive	Alive	Alive

CVE: cerebrovascular event.

Case 2

A 38-year-old, G3P2A1 patient was admitted to gynecology clinic with menometrorrhagia and her endometrial biopsy report was Grade 1 endometrial adenocarcinoma. After staging surgery she was diagnosed with FIGO Stage I endometrioid type endometrial adenocarcinoma. Her family history included colon cancer in her mother 50 years of age, colon cancer in her sister at 32 years of age, and colon cancer in her uncle at 43 years of age. Her family members underwent surgery for colon cancer under the age of 50 years. Her family fulfilled the Amsterdam II criteria for Lynch syndrome. Currently, the follow-up of patient is continuing as normal.

Case 3

A 61-year-old, G12P4A8 patient was admitted to gynecology clinic with postmenopausal bleeding. She was treated for colon cancer when she was 33-years-old. Histopathological examination of endometrial biopsy revealed endometrial adenocarcinoma. After the staging surgery she was diagnosed with FIGO Stage IB endometrioid type adenocarcinoma. The external beam radiation therapy and intracavitary radiotherapy were completed followed by surgery. The follow-up in January 2015 were normal. Her family history included colon cancer in her father at 49 years of age, in her brother at 28 years of age, endometrial cancer in her sister at 31 years of age, and endometrial cancer in her other sister at 55 years of age. This patient was the sister of Case 4.

Case 4

A 55-year-old, G3P2A1 patient was admitted to gynecology clinic with abnormally uterine bleeding. Her endometrial biopsy report was endometrial adenocarcinoma. After the staging surgery, she was diagnosed with FIGO Stage IA endometrioid type adenocarcinoma. This patient was the sister of Case 3. Their family history was revealed that three of their family members had a history of colorectal cancer which was diagnosed before 50 years of age. These cases were diagnosed with Lynch syndrome according to Bethesda criteria.

Discussion

In this paper all patients were diagnosed at an early stage thanks to early abnormal uterine bleeding. Because they had a familial history and/or second malignancy, surgical staging was performed in all patients. From January 2013 to August 2015, a total of 93 endometrial cancer patients were operated in Gynecology Department of Ankara Oncology Education and Research Hospital and four of them were diagnosed with Lynch syndrome (4.3%). In de la Chapelle study, Lynch syndrome was defined as carriership of a deleterious MMR gene mutation. By screening for MMR gene mutations in unselected colorectal or endometrial cancer patients, it was found that the prevalence of Lynch syndrome in colorectal and endometrial cancer patients is 1-3% [4]. Population prevalence of Lynch syndrome is approximately 1 in 600 to 1 in 3,000 individuals [4, 5]. The incidence of Lynch syndrome in women who presented with endometrial cancer was approximately 2.3% in one population-based study [6], which is comparable to the 2.2% incidence of Lynch syndrome in patients who present with colorectal cancer [7]. In our case series, all of the cases presented with abnormal uterine bleeding and they were diagnosed with endometrial cancer at a rate of 4.3% in endometrial cancer population.

The Lynch syndrome is an autosomal dominant cancer-susceptibility syndrome caused by a germ-line mutation in one of the MMR genes [8]. The germline mutations or alteration of MMR genes are prevalently found in MLH1, MSH2, and less frequently in MSH6 and PMS2 genes and lead to high risk of colorectal and endometrial cancer [8]. About 2% of all colorectal cancer occurs in the context of the autosomal dominantly inherited Lynch syndrome [9]. Mutation carriers have 60-80% more risk of developing colorectal cancer than other people [10].

Lynch syndrome is characterized by predisposition to early onset colorectal cancer and cancers of the endometrium, small intestine, ovary, hepatobiliary system, kidney, and ureter [11]. Women with the Lynch syndrome have a 40–60% lifetime risk of endometrial cancer and a ten- to 12% lifetime risk of ovarian cancer [12-14]. Based on available data, the risk of colorectal cancer at age 70 for women with Lynch syndrome is estimated to be 18–61%, compared with 1.7% in the general population [15]. The risk of endometrial cancer at age 70 for women with Lynch syndrome is estimated to be 16–61% and may equal or exceed their risk of colorectal cancer [15]. The risk of ovarian cancer at age 70 for women with Lynch syndrome is estimated to be 5–10%, compared with approximately 1% in the general population [16]. In women with Lynch syndrome, the life-time risk of disease is high and many at-risk women are premenopausal and it is unknown whether they will have recognizable abnormal bleeding as an early symptom [17]. All of the patients in the present case series was admitted to the clinic due to abnormal uterine bleeding.

A retrospective review of women with gastrointestinal and gynecologic metachronous malignancies (i.e., separate malignancies arising at different times) and documented Lynch syndrome found that in more than one half of cases, the gynecologic cancer was the presenting cancer [18]. Importantly, when endometrial cancer was the presenting diagnosis, there was a median of 11 years before the diagnosis of colon cancer; thus, women's healthcare providers frequently have the opportunity to identify women at risk and prevent subsequent metachronous Lynch syndrome-associated malignancies through implementation of appropriate risk-reduction strategies. Although the number of the present patients is not sufficient for a retrospective study,

the findings in this case series are consistent with the literature. The present authors aimed to prevent Lynch syndrome-associated malignancies in patients which presenting with endometrial cancer.

Endometrial cancer that is associated with Lynch syndrome occurs at a significantly younger age than in the general population [19]. The average age is around age 50 years (compared with a mean of 60 years in the general population) [19]. In the present series, one of the patients was 38-year-old but the other patients were 52.61- and 55-years-old, respectively. These findings were consistent with the literature.

Family history is very important in Lynch syndrome. Better management and diagnosis of Lynch syndrome in these patients and their families is required prior to the treatment in order to cope with the adverse outcomes. It is important to determine the family history in patients presenting with colorectal cancer because colorectal cancer is more prevalent in patients with Lynch syndrome [20]. Positive family history and presentation of ovarian cancer, endometrial cancer or colorectal cancer at younger age (below 40 years) are effective markers of recognition of Lynch syndrome and can lead to a reduced mortality and morbidity rates by early diagnosis [21]. All of the patients in the present case series were diagnosed with Lynch syndrome according to their family history.

Recognition and diagnosis of Lynch syndrome is extremely important so that appropriate screening programs and/or risk-reducing surgery can be initiated to prevent development and promote early detection of cancers [22]. Molecular screening and subsequent instrumental surveillance are very effective in identifying colorectal cancers at earlier stages and reducing the number of deaths from secondary cancers in Lynch syndrome patients [22]. The molecular tests are using of the term *Lynch syndrome* to specify families that transmit an inherited mutation in one of the genes that encode proteins in the DNA MMR complex (*MLH1, MSH2, MSH6,* and *PMS2*), regardless of whether any pedigree criteria has been fulfilled [1].

Before the availability of genetic testing, the Amsterdam Criteria, developed in 1990, were used to identify families for research studies of Lynch syndrome [23]. These criteria demonstrate high specificity, but because of their low sensitivity, they were not useful as referral guidelines. One of the limitations of these initial criteria was that extracolonic malignancies were not included as defining diagnoses. To address this issue, these criteria were revised to include extracolonic cancer in 1999 [2]. Given the limitations of the Amsterdam Criteria, the Bethesda Guidelines were developed in 1997, and subsequently revised in 2004, to provide more clinically useful recommendations for which patients with colorectal cancer should be considered for further evaluation of Lynch syndrome [24]. These criteria incorporate age of diagnosis, tumor characteristics, and personal and family cancer history. Diagnostic testing optimally begins with tumor testing in affected individuals who meet the revised Bethesda guidelines, as a way to select those who are most likely to benefit from further genetic evaluation [24]. A deleterious mutation in a MMR gene confirms the diagnosis. The diagnosis is considered likely if the clinical presentation is consistent with clinical criteria. In 2007, the Society of Gynecologic Oncologists provided guidelines to assist in identifying patients for whom genetic risk assessment may be helpful which are listed in Table 3. They specifically recommended that women who have a greater than approximately 20–25% chance of having Lynch syndrome be offered risk assessment. They also identified a category of patients who have

Table 3. — *Society of Gynecologic Oncologists criteria for offering genetic risk assessment for Lynch syndrome.*

Patients with greater than approximately 20−25% chance of having Lynch syndrome and for whom genetic risk assessment is recommended:	Patients with greater than approximately 5−10 % chance of having Lynch syndrome and for whom genetic risk assessment is recommended:
• Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria as listed below: - At least three relatives with a sentinel Lynch-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) in one lineage; - One affected individual should be a first-degree relative of the other two; At least two successive generations should be affected; At least one Lynch-associated cancer should be diagnosed before age 50. • Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50 • Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50 • Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. microsatellite instability (MSI) or immunohistochemical loss of expression of MLH1, MSH2, MSH6 or PMS2) • Patients with a first or second degree relative with a known mismatch repair gene mutation	• Patients with endometrial or colorectal cancer diagnosed prior to age 50 • Patients with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch syndrome-associated tumor at any age • Patients with endometrial or colorectal cancer and a first-degree relative with a Lynch syndrome associated tumor[a] diagnosed prior to age 50 • Patients with a first or second-degree relative[b] that meets the above criteria

[a] Lynch syndrome-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 carcinoma of the small bowel.
[b] First and second degree relatives are parents, siblings, children, aunts, uncles, nieces, nephews, grandparents, and grandchildren.

Table 4. — *Risk-reduction recommendations for women with Lynch syndrome.*

Gastrointestinal	Gynecologic	Urologic
Colonoscopy every 1-2 years beginning at age 20-25 (or age 30 for women with MSH-6 mutations)	Patients should be aware that abnormal vaginal bleeding warrants evaluation	Annual urinalysis starting at age 25-30
Esophagogastroduodenoscopy (EGD) every 2-3 years beginning at age 30-35	Screening with annual endometrial biopsy and transvaginal ultrasound beginning at age 30	
Capsule endoscopy every 2-3 years beginning at age 30-35	Chemoprevention with oral contraceptives or progestins	
Chemoprevention with aspirin or NSAIDs	Risk-reducing hysterectomy with bilateral salpingo-oophorectomy between age 35 and 40 and when childbearing is complete	

a 5–10% risk for Lynch syndrome and for whom genetic risk assessment may be helpful [25]. In contrast to the Amsterdam Criteria, the Bethesda Guidelines have a relatively high sensitivity but low specificity for identifying individuals with Lynch syndrome. The authors also diagnosed the Lynch syndrome according to Amsterdam II and Revised Bethesda criteria.

When tumor testing is not feasible or if there is an extremely strong family history suggestive of Lynch syndrome, proceeding directly to testing for germline mutations in the MMRs remains an option [9]. A positive gene test confirms the diagnosis, but a negative test does not ensure lower risk unless a mutation has been previously identified in an affected family member [1, 26]. Despite major advances in diagnostic capabilities, there will be families for whom no testing is feasible (no tumor or no affected person available for testing) or in which testing is negative but in which the clinical suspicion for Lynch syndrome is still strong [26]. No laboratory test or combination of tests is completely sensitive nor specific for diagnosing or excluding Lynch syndrome. Clinical judgment should not necessarily be overridden by laboratory results if the clinical presentation for Lynch syndrome is compelling [9].

It is important to note that about 45% of families that fulfill strict Amsterdam criteria will not have evidence of a DNA MMR mutation or deficiency of DNA mismatch repair in their tumor [9]. These families (designated familial colorectal cancer type X) appear to have increased risks of colorectal cancer compared with the general population, but lower risks than seen in those with Lynch syndrome [9]. The optimal screening for familial colorectal cancer type X has not been defined and clinical judgment is required to determine if Lynch syndrome screening guidelines are appropriate, based on the profile of cancer in the family, or if less aggressive screening may be advised [9].

More than 75% of women with Lynch syndrome who develop endometrial cancer present with Stage I disease, similar to sporadic endometrial cancer [17, 19]. Three of the present cases were Stage IA, the other case was Stage IB. In Boks *et al.* study, the overall five-year survival rate was 88% [17]. Similarly, because of abnormal uterine bleeding, all patients were diagnosed at an early stage.

Most of endometrial cancer associated with Lynch syndrome histological type is endometrioid type. Except that serous, clear-cell, and malign mixed Müllerian tumors have also been reported [17, 19, 27]. In Broaddus *et al.* study 43 of 50 (86%) endometrial cancers were endometrioid histology, with the remaining being papillary serous carcinoma, clear cell carcinoma, and malignant mixed Müllerian tumors [19]. Although tumor localization in general endometrial cancer usually originates from the uterine corpus, in Lynch syndrome associated endometrial cancers, the tumor localization originates from the lower uterine segment. These tumors may be misdiagnosed as cervical adenocarcinoma. These tumors are more invasive and high-grade tumors than the tumors which originated from the uterine corpus [28]. All of the present cases, the type of the tumors were endometrioid type adenocarcinoma and originated from the uterine corpus.

Although it is known that the majority of (sporadic) endometrial cancers are detected at an early stage, about 10–15% of patients with such tumours will ultimately die from metastatic disease. In view of this significant mortality and the high risk of developing endometrial cancer in families with Lynch syndrome, most authors advise surveillance of the endometrium [29]. They suggested that surveillance may lead to the detection of premalignant lesions, and suggested that it may also lead to the detection of endometrial cancer at an early stage. Screening modalities that have been suggested include transvaginal ultrasound and endometrial sampling [29]. Women with a known or suspected mutation in a DNA mismatch repair gene, or who are at risk based on a documented mutation in the family, should be offered annual endometrial biopsy beginning at age 30 to 35 years [9]. The authors followed the patients and their relatives as recommended in Table 4 [9, 30].

Endometrial screening can theoretically decrease the amount of treatment needed by detecting cancer at an earlier stage, when surgery alone can be curative [9].

British [31] investigators evaluated the outcome of surveillance of 269 women from families suspected of having Lynch syndrome. The surveillance programme consisted of ultrasound every one to two years. It did not lead to the detection of premalignant lesions or endometrial cancer.

However, two women presented with symptoms at six and 24 months after a normal ultrasound and were diagnosed with endometrial cancer. Both tumours were in an early stage (FIGO Stage I). In another study from the Netherlands, 41 women from families with Lynch syndrome underwent surveillance by transvaginal ultrasound (TVU) followed by aspiration biopsy in suspected cases [32]. After a mean follow-up of five years, premalignant lesions, that is, complex atypia, were detected in three patients. There was one interval cancer diagnosed eight months after a normal ultrasound. This tumour was at an early stage. Another study of 175 subjects from Finland reported the results of surveillance by TVU and aspiration biopsy [33]. Complex atypia was found in five patients, endometrial cancer was found in 11, and there were two interval cancers. Out of the 11 screen-detected cancers, six cancers were identified only by aspiration biopsy and not by TVU.

Given the high risk for endometrial cancer and the moderately increased risk for ovarian cancer, women with Lynch syndrome must decide between screening or prophylactic surgery. While there are no data regarding the efficacy of screening for gynecologic cancers in Lynch syndrome, there is evidence of efficacy for prophylactic surgery [9].

Schmeler *et al.* [14] report on a retrospective cohort of 315 women who had MMR mutations, in which 61 had prophylactic surgery and were then followed up for approximately ten years. No endometrial or ovarian cancers developed in those who had surgery, whereas 33% of those who did not have surgery developed endometrial cancer and 5.5% developed ovarian cancer. These data indicate that prophylactic hysterectomy and oophorectomy is a reasonable option for those with Lynch syndrome, following a careful discussion of the risks, benefits, and limitations of this procedure. Given the average age at diagnosis of gynecologic cancers, it may be reasonable to offer this option to women aged 35 years or older who do not want to preserve fertility.

To perform laparotomy for colon surgery, occult endometrial carcinomas can be found at the time of surgery. This finding emphasizes the need to maintain a high index of suspicion during prophylactic surgery in women with the Lynch syndrome [14]. The uterus and ovaries should be carefully assessed at the time of surgery; the pathologist should be advised of the high risk of endometrial and ovarian cancer, and the specimens should be carefully examined intraoperatively, with frozen sections obtained if indicated. The surgeon should be prepared to perform a complete staging operation, if necessary [14]. Therefore in women with Lynch syndrome who need to undergo laparotomy for colon surgery, consideration should be given to concurrent prophylactic hysterectomy and oophorectomy [9].

In conclusion, the surveillance by gynecological examination, TVU, and aspiration biopsy beginning from age 30–35 years may lead to the detection of premalignant lesions and early cancers (category of evidence III, grade C). Prophylactic hysterectomy and salpingo-oophorectomy may be an option for women with Lynch syndrome, since they substantially reduces site-specific cancers (grade C) [29, 32]. Further research is needed to determine the efficacy of these screening methods in comparison with prophylactic surgery in reducing morbidity and mortality from endometrial and ovarian cancer in women with Lynch syndrome.

Newly diagnosed endometrial and colorectal cancer patients and their at-risk relatives are a much easier target population for screening and this approach leads to more informative genetic test results, at an economical cost particularly in women with a mutation associated with Lynch syndrome [34]. The limitation of this study is the absence of a genetic assessment, which is essential for supporting the diagnosis.

Proper diagnosis of patients with Lynch syndrome and identification of at-risk people is very important because if it is diagnosed at early stage it can be easily managed. Endometrial biopsy every one to two years, beginning at age 30–35 years, is recommended for women with Lynch syndrome and should undergo colonoscopy every one to two years, beginning at age 20–25 years or two to five years before the earliest colon cancer diagnosis in the family, whichever is earlier. Clinical management of these patients commonly involves surgery such as hysterectomy and oophorectomy to reduce the risk, once childbearing is complete.

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