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REVIEW/DERLEME

Mismatch repair defects in endometrial cancer

Mismatch repair gen defektlerinin endometrium kanserindeki önemi

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ABSTRACT

Endometrial cancer is the most commonly diagnosed gynecologic malignancy among women worldwide and may be classified on the basis of different molecular, pathologic and genetic alterations. Identification of mismatch repair-deficient (MMRd), which occur in up to 30% of all endometrial cancers (EC), has become unavoidable for therapeutic management, clinical desicion making, and prognosis. Although microsatellite instability is associated with a more favorable outcome in colorectal cancer, its relationship with prognosis in EC is not yet clear.

Keywords: Endometrial Cancer, Mismatch Repair, Prognosis

ÖZ

Endometrium kanseri dünya genelinde en yaygın görülen jinekolojik kanserdir ve farklı moleküler, patolojik ve genetik değişikliklere göre sınıflandırılır. Yaklaşık %30 oranında görülen mismatch repair defekti (MMRd)'nin tespiti, tedavi yönetimi, klinik karar verme süreci ve prognoz ile ilişkisinden dolayı vazgeçilmez bir duruma gelmiştir. Kolorektal kanserlerde mikrosatellit instabilite daha iyi prognozla ilişkili olmasına rağmen, bu ilişki endometrium kanserinde henüz netlik kazanmamıştır.

Anahtar Kelimeler: Endometrial Kanser, Mismatch Repair, Prognoz

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INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer among women in developed countries and the fourth most common malignancy overall. (1) This type of cancer mostly develops in postmenopausal women. (2) The mean age at diagnosis of patients with endometrial cancer is 63 years and 70% is limited to the corpus uteri at diagnosis. Also, up to 14% of cases (2) occur in premenopausal women as a result of a high body mass index (BMI). (3) The lifetime incidence is 3%, and although most women present at an early stage and have a good prognosis, some women present with advanced disease, experience relapses, and have a poor prognosis. (1) Patients with advanced and recurrent EC constitute a major therapeutic challenge, with 5-year overall survival rates of only 17% in patients with distant organ involvement. (4) Approximately 80% of women with early-stage EC have a favorable prognosis, with 5-year overall survival rates of 95%. (5)

The standard treatment for endometrial cancer is surgery that includes bilateral salpingoophorectomy and total hysterectomy with evaluation of the lymph nodes. (6) Clinical and surgical histopathological features help stratify according to risk categories to determine the type and need for adjuvant therapy. (6) The major diagnostic challenge is to determine which patients with early stage EC have low-risk disease with a <5% risk of recurrence and to decide whether they can be treated with surgery alone as opposed to patients with high-risk disease who need adjuvant therapy. (7)

Over the past decade, numerous studies have investigated prognostic factors, including pathologic type, histologic grade, lymphovascular involvement, and tumor staging, but were insufficient to determine reproducibility. Therefore, research has turned to gene carcinogenesis, such as molecular changes, to provide a new prognostic classification. (8)

Understanding the molecular alterations involved in endometrial cancer provides an opportunity to (1) improve upon the current histologic classification system, (2) enhance diagnostic testing modalities, and (3) personalize treatments through the incorporation of targeted therapies. Here, we highlight from a clinical perspective, the implications of emerging molecular characteristics on classification of subtypes, development of diagnostic testing, and therapeutic options.

HEREDITERY NON-POLYPOSIS COLORECTAL CANCER (LYNCH SYNDROME)

Lynch syndrome, also called hereditary non-polyposis colorectal cancer, is associated with pathogenic variants in mismatch repair (MMR) genes (MSH2, MLH1, MSH6 and PMS2). (9) Endometrial cancer is the second most common malignancy in patients with Lynch syndrome (after colorectal cancer). (10) It is inherited autosomal dominantly, composes for 2-5% of all endometrial cancers (11) and occurs 10 years earlier. In 2007 the Society of Gynecologic Oncology (SGO) published guidelines to assist in identifying patients for whom genetic risk assessment might be useful (Table 1). (12) The SGO specifically recommended risk assessment for women with a greater than approximately 20-25% probability of having Lynch syndrome, and also identified the class of patients at 5-10% risk for Lynch syndrome where genetic risk assessment might be useful.

Table 1. Risk of Malignancy Criteria for Genetic Risk Assessment for Lynch Syndrome

Patients with a greater than approximately 20-25% probability of having Lynch syndrome and for whom genetic risk assessment is recommended:
• Patients with endometrial or colorectal cancer who meet the amended Amsterdam criteria: ▪ At least three relatives with Lynch-related cancer in a lineage (colorectal cancer, cancer of the endometrium, small intestine, ureter, or renal pelvis); ▪ An affected person must be a first-degree relative of the other two; ▪ At least two consecutive generations must be affected; ▪ At least one Lynch-related cancer must be diagnosed before age 50. • Patients with synchronous or metachronous endometrial and colorectal cancer diagnosed with the first cancer before the age of 50. • Patients with synchronous or metachronous ovarian and colorectal cancer diagnosed with their first cancer before the age of 50. • Patients with colorectal or endometrial cancer with evidence of MMR gene defect (microsatellite instability (MSI) or immunohistochemical (IHC) loss of MLH1, MSH2, MSH6 or PMS2 expression). • Patients with a first- or second-degree relative with a known MMR gene mutation.
Patients with a greater than approximately 5-10% probability of having Lynch syndrome and for whom genetic risk assessment may be useful:
• Patients with endometrial or colorectal cancer diagnosed before age 50. • Patients of any age with endometrial or ovarian cancer with synchronous or metachronous colon or other Lynch syndrome-associated tumors. • Patients with endometrial or colorectal cancer and first-degree relatives with Lynch syndrome-related tumor[1] diagnosed before age 50. • Patients with colorectal or endometrial cancer diagnosed at any age, with two or more first-degree relatives[2] with tumors associated with Lynch syndrome,[1] regardless of age. • Patients with a first- or second-degree relative[2] who meet the above criteria.

[1]Tumors associated with Lynch syndrome include tumors of the colorectal, endometrial, stomach, ovary, pancreas, ureter, and renal pelvis, biliary tract, and brain (glioblastoma, as often seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small intestine. [2]First and second degree relatives are parents, siblings, children, aunts, uncles, nieces, grandparents, and grandchildren.

While family history remains an important component in identifying individuals who may benefit from genetic risk assessment for Lynch syndrome, tumor testing for MMR defect is increasingly used to triage patients who may be at risk for germline DNA mutation. (13) These tumor tests include IHC and MSI analysis for four MMR proteins (MLH1, MSH2, MSH6 and PMS2). For IHC-based triage, the absence of a specific MMR protein in the tumor is considered abnormal. Both tumor and normal tissues are required for MSI-based triage.

Immunohistochemistry can also guide which of the four DNA MMR genes should be sequenced. This can be performed in most pathology laboratories and has become the approach of choice for the initial assessment of the MMR pathway in endometrial cancers. In 2014, the American College of Obstetricians and Gynecologists (ACOG) published an application with an IHC-based algorithm to assess the likelihood of Lynch syndrome in endometrial tumors (Figure 1). (14)

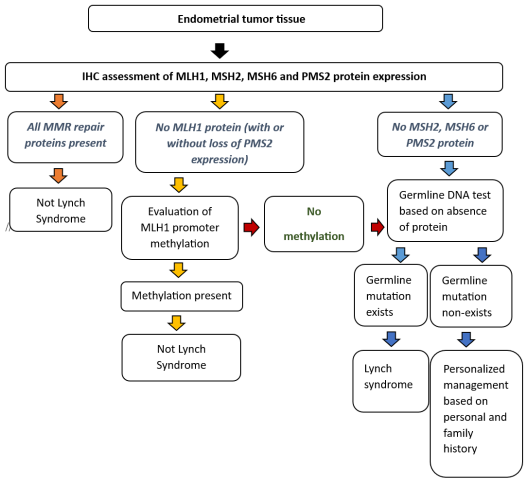

Figure 1. Algorithm for using IHC assessment of MMR protein expression to triage endometrial tumors for the possibility of Lynch Syndrome.

MMR DEFICIENT (MMRd) ENDOMETRIAL CANCER

Most endometrial cancers are sporadic, though some hereditary cases are caused by germline mutations, predominantly in MMR genes. (15) The MMR deficient (MMRd) molecular group represents 20–30% of EC cases, and is analogous to MSI in the initial genomic classification. (16)

Microsatellite instability (MSI) is defined by the expansion or contraction of the length of microsatellite pathways in the tumor compared to the corresponding DNA from the germline or normal tissues and is detected using polymerase chain reaction (PCR) based methods. (17) Microsatellites show the same number of nucleotide repeats of tumor and healthy tissue in the same individual, but can cause diffuse changes in the number of repeats in case of MMR loss.(18) MSI testing categorizes tumors as having high microsatellite instability (MSI-high), low microsatellite instability (MSI-low), or as being microsatellite stable (MSS).(19)

Tumors that are MMRd or MSI-high can originate through three pathways: germline MMR mutations in DNA mismatch repair proteins MLH1, PMS2, MSH2, MSH6, named Lynch syndrome; somatic MMR gene mutations occasionally labelled as Lynch-like; and homozygous methylation of the MLH1 gene promoter named sporadic.(20) MSI-test is more laborious, requires non-neoplastic tissue, is more expensive, and does not provide information on the gene affected both approaches (MMRd by IHC and MSI-test) require the analysis of MLH1 promoter methylation status in cases with loss of MLH1/PMS2 expression. Several studies have compared MSI testing and MMR assessment in endometrial cancer patients, and found reasonable concordance between the two methodologies. Discordance between MSI-high and MMR deficiency ranged from 2–8% in several studies from different institutions. (21) The International Society of Gynecological Pathology (ISGyP) guidelines therefore recommend MMR-IHC as the preferred test. (22) Tumors considered to be MSI-low are of much lower prevalence and not as well understood, but in practice these tumors are usually considered to be similar to MSS tumors.[23] MSI-low tumors, which comprise approximately 3% of endometrial tumors. (24)

Testing for MMR status/MSI in endometrial carcinoma patients has been shown to be relevant for four reasons:

(1) diagnostic, as MMRd/MSI is considered a marker for endometrioid type endometrial carcinoma;

(2) pre-screening to identify patients at higher risk for having Lynch syndrome;

(3) prognostic, as identified by The Cancer Genome Atlas (TCGA);

(4) predictive for potential utility of immune checkpoint inhibitor therapy.

Clinically, many studies have sought to evaluate other characteristics of MSI-high or MMR deficient endometrial tumors. (23) Histologically, some patterns have emerged. (23) Tumors with MMR deficiency or MSI-high are more commonly associated with endometrioid histology (25) and may be more frequently associated with poor prognostic factors such as advanced stage, deep myometrial invasion, high grade and lymphovascular space invasion (LVSI) (26) and has been found to be associated with an intermediate prognosis for EC. (16) From a demographic perspective, there was no age group or BMI association with MMRd. (27) Some studies show better survival outcomes (26-28), some show worse survival outcomes (29-30), and many show no association at all. (31-32)

The role of adjuvant chemotherapy in MMRd EC has been questioned by the molecular analysis of PORTEC-3. (7) This trial assessed chemotherapy used in addition to adjuvant radiation in high-risk EC. (7) The molecular analysis found no benefit with the addition of chemotherapy in the MMRd group, with the

5-year overall survival 84% in the radiation only group versus 79% in the chemoradiation group (p=0.445). (33) Adjuvant radiation on the other hand, may play a more important role in MMRd EC, compared with other EC molecular subtypes. (7) Pre-clinical work has shown increased sensitivity to radiation in MSH2 deficient cell lines. (34) In a review of 128 patients with stage Ib/II grade 3 endometrioid endometrial cancer, Reijnen et al. showed that adjuvant radiation was associated with improved disease specific survival in the MMRd group, but not in MMR-proficient cases. (35) A more recent study compared adjuvant chemotherapy and radiation with chemotherapy alone in advanced MSI-high EC, and found an improved progression-free survival with the addition of radiation. (36) There is so far insufficient evidence for the role of MMR status for response to radio or chemotherapy. (35) This evidence suggesting MMRd EC may have an increased sensitivity to radiation needs to be validated in prospective studies.

Cancers that have a high mutational burden have a substantially increased production of tumour mutated antigens (neoantigens), which correlates significantly with improved patient survival. (37) The increased neoantigens results in a high abundance of tumour-infiltrating lymphocytes (TIL), in particular CD8+ cytotoxic T cells, with an upregulated T-cell mediated antitumour response. (38) Cancer cells have two mechanisms to avoid the host immune response; the first involving the cytotoxic Tlymphocyteassociated protein 4 (CTLA-4) pathway, and the second linked with programmed cell death-1 (PD-1) and PD ligand (PD-L1). (39) Activated T cells express PD-1, and its interaction with PD-L1 decreases T cell activity. (40) Expression of PD-L1 on the surface of tumor cells causes the tumor to avoid host T-cell activity. (41) Therefore, blocking of the PD-1 interaction with PD-L1 in such cancers is likely to enhance the host immune response and have an antitumor effect. (42) Pembrolizumab (anti-PD-1) was the first immune checkpoint inhibitor shown to have favourable objective response rates (ORR) in metastatic or recurrent MMRd colorectal and non-colorectal cancers. (43-44) A subsequent study by the same group evaluated 86 patients with MMR deficiency with 12 different tumor types, including 15 patients with endometrial cancer (second only to colorectal cancer). (43) Although survival estimates are not mature, the progression-free survival at two years for this study was estimated at 53%, which is significantly higher than what would be expected for this population. (43) Pembrolizumab, an anti-PD-1 drug, has received FDA approval for the treatment of recurrent MMR-deficient or MSI-high tumors based on impressive response. (43-45) In a recently published phase 3 trial: the combination of pembrolizumab and lenvatinib were shown to improve both overall survival (OS) and progression-free survival (PFS) when compared to second or subsequent line chemotherapy in MMR proficient patients. (46) Two very important recent studies regarding the combination of immunotherapy with chemotherapy in advanced endometrial cancer showed promising results for pembrolizumab (47) and dostarlimab. (48) Combination and maintenance therapy with both of aforementioned immune check-point inhibitors altered the standard regimen for advanced endometrial cancer.

In conclusion, MSI and MMR protein assessments have already been extensively evaluated in endometrial cancer patients. Over the years new methods have been developed to stratify EC patients into a low-, intermediate-, or high-risk category. These developments are promising in guiding individualized surgical and adjuvant treatment. Tailored EC treatment prevents under- and overtreatment, that can result in suboptimal survival or unnecessary complications and toxicity. Major progress has been made with the introduction of the molecular classification. However, with

implementation of new methods the proven traditional methods, such as surgical staging and certain clinic-pathological biomarkers (i.e., LVSI) should not be ignored. Especially stage, which, alone, has been the most important prognostic factor up till now. The future lies in combinations of traditional and new stratification methods. Based on the results of ongoing research, the method to accurately assess the risk category in each patient will continuously be refined.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Decleration

Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

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