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RESEARCH

Histological and molecular determinants in fertility-sparing treatment of endometrial cancer

Endometriyal kanserin fertilite koruyucu tedavisinde histolojik ve moleküler belirleyiciler

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Abstract

Purpose: The aim of this study was to evaluate the clinical outcomes, molecular signatures, and prognostic implications of histological features, including squamous metaplasia (SM), in endometrial cancer (EC)/ atypical hyperplasia (AH) patients under the age of 40 years with early-stage EC or AH and who received fertility-sparing treatment.

Materials and Methods: This retrospective study included 16 patients who met the following criteria: EC or AH, aged ≤40 years, with no myometrial invasion or ≤50% depth of invasion, and a strong desire for fertility. The treatment consisted of oral progestins (megestrol acetate [MA]) combined with LNG-IUS for 3–12 months. Investigations included immunohistochemical analyses to assess the expression levels of p53 and mismatch repair proteins (MSH2, MSH6, MLH1, and PMS2). The cases were divided into three molecular groups (MMR-deficient [MMRd], p53 mutant [p53abn], and p53 wild-type [p53wt]).

Results: All tumors were p53 wild-type (p53wt). Complete remission (CR) occurred in 38% (6/16) of cases, and stable disease was observed in 62% (10/16). SM was observed in 37.5% (6/16) of patients, and only one SM-positive patient achieved CR (p=0,182). Four patients (3 spontaneous, 1 assisted reproductive technologies) conceived 3 full-term pregnancies. CR was not associated with age, BMI, comorbidities, or the type of treatment.

Conclusion: By highlighting the potential association between SM and lower CR rates, we provide a basis for future investigations into the clinical significance of this histological feature. SM may indicate resistance to hormonal therapy.

Keywords: Endometrial cancer, fertility-sparing treatment, squamous metaplasia, p53wild type.

Öz

Amaç: Bu çalışmanın amacı erken evre endometriyal kanser (EK)/atipik hiperplazi (AH) tanısı almış ve fertilite koruyucu tedavi (FST) uygulanan, 40 yaş altı endometriyal kanser (EK)/atipik hiperplazi (AH) hastalarında skuamöz metaplazi (SM) dahil olmak üzere histolojik özelliklerin klinik sonuçlarını, moleküler özelliklerini ve prognostik etkilerini değerlendirmektir.

Gereç ve Yöntem: Çalışmamız retrospektif olarak dahil edilme kriterlerini karşılayan 16 hasta üzerinde yapıldı. Dahil etme kriteri EK veya AH olan, ≤40 yaş, miyometriyal invazyon (MI) olmaması veya invazyon derinliğinin ≤%50 olması ve fertilite isteğiydi. Tedavi olarak, 3-12 ay boyunca oral progestinler (Megestrol asetat (MA)/LNG-RİA ile kombine) verildi. p53 ve MMR (MSH2, MSH6, MLH1 ve PMS2) ekspresyon düzeyleri immünohistokimyasal (IHC) olarak değerlendirildi. Vakalar üç moleküler gruba ayrıldı (MMR eksik-MMRd, p53 mutant-p53abn ve p53 doğal tipi-p53wt).

Bulgular: Tüm hastalar, p53wt grubundaydı. Tam remisyon (CR) vakaların %38'inde (6/16) görülürken, stabil hastalık %62'sinde (10/16) görüldü. SM vakaların %37,5'inde (6/16) görüldü ve sadece bir SM pozitif hasta CR'a ulaştı. Dört hasta (3 spontan, 1 yardımcı üreme teknikleri) gebelik elde etti. CR; yaş, vücut kitle indeksi, komorbidite veya tedavi tipi ile ilişkili değildi.

Sonuç: Sonuçlarımız; SM ile düşük CR oranları arasındaki potansiyel ilişkiyi vurgulayarak, bu histolojik özelliğin klinik önemi üzerine gelecekteki araştırmalar için bir temel oluşturmaktadır. Skuamöz metaplazi, hormonal tedavi direncinin bir göstergesi olabilir.

Anahtar kelimeler: Endometriyal kanser, fertilite koruyucu tedavi, skuamöz metaplazi, p53 wild type.

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INTRODUCTION

Endometrial cancer (EC) is among the most prevalent gynecological malignancies worldwide, with a notable prevalence in the postmenopausal population. However, a significant proportion of cases approximately 7% occur in women aged <45[1]. This observation holds particular significance for younger demographics, particularly those planning to conceive. Total hysterectomy accompanied by bilateral salpingo-oophorectomy (TH+BSO), the most commonly performed surgical procedures, presents a considerable challenge as these interventions lead to the irreversible loss of reproductive potential. In light of these challenges, fertility-sparing treatment (FST) has emerged as a promising option for patients diagnosed with early-stage and low-grade endometrial cancer. This approach is typically implemented in young women diagnosed with FIGO stage IA, grade 1 endometrioid adenocarcinoma, characterized by the absence of myometrial invasion and metastasis[2]. Treatment protocols include the administration of oral progestin agents, such as medroxyprogesterone acetate or megestrol acetate, in combination with levonorgestrel-releasing intrauterine systems (LNG-IUS). Studies have demonstrated that these methods yield complete remission rates of up to 80%[2,3]. However, treatment response rates may vary, and the patient selection criteria need to be clarified.

The significance of molecular classification in the context of FST is increasing, with systems such as the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) used to identify patients with low-risk molecular profiles, including p53 wild type (p53 wt). Additionally, patients with POLE mutations have the most favorable prognosis and are considered suitable candidates for FST[3]. Some studies have shown that treatment responses in MMRd cases may worsen[4-6].

This study aimed to examine the clinical characteristics, treatment outcomes, and prognostic value of the molecular classification of patients with EC undergoing FST. In addition to molecular properties, the aim was to reveal the relationship between SM and FST. This article highlights existing gaps in the literature and presents the results of our current experience to clarify patient selection criteria and develop personalized treatment approaches.

MATERIALS AND METHODS

Sample

This retrospective case series study analyzed patients with EC and atypical hyperplasia who were treated with FST at the Department of Gynecologic Oncology and Medical Pathology, Çukurova University Faculty of Medicine between 2010 and 2021. The inclusion criteria for the study population were as follows: female patients aged ≤ 40 years at the time of diagnosis with either grade 1 or 2 endometrioid cancer or atypical hyperplasia, as confirmed through histopathological examination. The disease must be classified as FIGO stage IA, with either no myometrial invasion or invasion limited to less than 50% of the myometrium. Furthermore, patients must desire fertility preservation, and there should be no signs of pelvic or distant metastases, as confirmed by a thorough clinical evaluation and magnetic resonance imaging (MRI).

The application of these stringent criteria ensured a well-defined study population suitable for investigating fertility-preserving interventions in early-stage EC. The exclusion criteria prioritized patient safety and methodological rigor. Patients with grade 3 or aggressive histological subtypes, myometrial invasion exceeding 50%, incomplete clinical data, or poor treatment compliance were excluded. These criteria ensure the validity of the research and patient safety. During the study period at our clinic, 44 patients underwent FST. The results of 16 patients who met the inclusion criteria and whose follow-ups were conducted at our clinic (clinical and pathological) were evaluated.

Procedure

This study was conducted in accordance with the Declaration of Helsinki. The Non-Interventional Clinical Research Ethics Committee of Cukurova University, Faculty of Medicine, granted approval (IRB number: 108, Date: February 12, 2021).

The implemented treatment protocol consists of a comprehensive hormonal therapy regimen combined with regular monitoring. The primary therapeutic approach involves the administration of oral progestins, specifically megestrol acetate at doses of 160–320 mg daily. In select cases, oral therapy is augmented with a levonorgestrel-releasing intrauterine system (LNG-IUS) to enhance

therapeutic efficacy. The duration of hormonal treatment is typically 6–12 months, with individual variations based on patient response and clinical requirements. The follow-up protocol includes regular assessments to monitor the treatment response and disease progression. Patients undergo dilatation and curettage (D&C) or endometrial biopsy via hysteroscopy at three-month intervals to evaluate endometrial response, and MRI is performed regularly to assess and monitor potential myometrial invasion. This comprehensive monitoring approach enables a proper evaluation of treatment efficacy and allows for timely adjustments to the therapeutic strategy when necessary. A clinical database was created to gather and analyze patient information. The database included parameters such as the patient's age, body mass index (BMI), and relevant comorbidities, including diabetes, hypertension, and metabolic syndrome. The presence of polycystic ovary syndrome (PCOS) was noted, as it could affect the treatment results.

Histopathological assessments were conducted on the tissue samples to identify endometrioid adenocarcinoma or grade 1 atypical hyperplasia. The presence of squamous metaplasia (SM) was also a significant finding. Treatment-related data included detailed documentation of progesterone therapy, specifically megestrol acetate alone or in combination with a levonorgestrel-releasing intrauterine system (LNG-IUS). The duration and number of treatment cycles were also recorded. Clinical outcomes, including complete remission (CR) rates, stable disease, and pregnancy outcomes, were systematically recorded.

This study distinguished between spontaneous pregnancies and those achieved through assisted reproductive techniques. Treatment efficacy was evaluated using clearly defined outcome measures, with primary outcomes focusing on direct tumor response and secondary outcomes evaluating the broader clinical effects. The primary endpoints included the complete remission (CR) rate, defined as complete regression of the tumor, and the stable disease rate, which indicates the persistence of existing pathology without progression or regression of the tumor. These primary outcome measures provide a direct indication of the treatment effectiveness in controlling or eliminating the tumor. The secondary outcomes examined the overall effects of the treatment. Pregnancy rates, including both spontaneous pregnancies and those achieved through assisted reproductive techniques, were assessed to measure the impact of treatment on reproductive function. In addition, the recurrence rate, that is, the proportion of cases in which the tumor recurred after achieving complete remission, was assessed to understand the long-term effectiveness of the treatment. These secondary measures provide valuable insights into the overall impact of treatment on patient outcomes.

IHC Analysis

Detailed characterization of the patient cohort was performed using molecular analyses of tumor tissue biopsies. The investigations included immunohistochemical (IHC) analyses to assess the expression levels of p53 and mismatch repair proteins (MSH2, MSH6, MLH1, and PMS2). The cases were divided into three molecular groups: MMR-deficient (MMRd), p53 mutant (p53abn), and p53 wild-type (p53wt) groups. Paraffin blocks were obtained using a Leica histocore multicut microtome, and 5-micron sections were taken on positively charged slides.

The prepared slides were stained with iView Blue Detection Mouse monoclonal antibody to p53 (Cellmarque, p53(D07) using kit (Ventana) kit Merck SA, Germany), MSH6 (Cellmarque, (44) Mouse monoclonal antibody, Merck SA, Germany), MSH2 (Cellmarque (G219-1129) Mouse monoclonal antibody, Merck SA, Germany), MLH1 (Cellmarque (G168-728) Mouse monoclonal antibody, Merck SA, Germany), and PMS 2 (GenomeMe (IHK412). BenchMark XT (ISH protease 2, Ventana) automated mouse monoclonal antibody (BC, Canada) was used for staining.

The evaluation was performed by two pathologists using an Olympus BX46 microscope. Strong diffuse nuclear and cytoplasmic positivity (>80%) and diffuse p53 negativity were considered as mutations. According to the percentage of nuclear staining in tumor cells for MSH6, MSH2, MLH1, and PMS, it was considered stable if 1% or more of the tumor cells showed nuclear staining. Defective expression of one or more MMRs was characterized as MMRd.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 20.0. Normality tests, such as the Shapiro-Wilk test, were performed on continuous variables. Categorical variables were expressed as numbers and percentages, and

comparisons between groups were performed using Pearson's chi-square test. All analyses used a two-tailed approach at a significance level of 0.05.

RESULTS

In this study, 16 patients who underwent FST were evaluated based on their clinical, pathological, and molecular characteristics. The mean follow-up duration was 54.1±43.8 months, with a median of 58 months. The mean age of the patients was 32.6±5.0 years (range: 25–40 years), and the mean body mass index (BMI) was 32.2±6.9 kg/m² (range: 22–46 kg/m²). The majority of patients (93.8%, n=15) were nulliparous, and 25% (n=4) were diagnosed with PCOS. Comorbidities included diabetes mellitus (DM) in two patients (12.5%), hypertension (HT) in one patient (6.25%), and metabolic syndrome in one patient (6.25%). Histopathological evaluation revealed atypical hyperplasia in one patient (6.25%), and the remaining 15 patients (93.8%) were diagnosed with grade 1 endometrioid adenocarcinoma. MRI findings showed no evidence of myometrial invasion (MI) in seven cases (44%), MI less than 50% in eight cases (50%), and MI greater than 50% in one case (6.25%). Two patients underwent laparoscopic lymphadenectomy, and no nodal involvement was detected in either patient. The diagnostic methods included dilation and curettage (D&C) in 14 cases (87.5%) and hysteroscopy in two cases (12.5%). SM was identified in six patients (37.5%). The demographic and diagnostic characteristics of the study group are presented in Table 1

Table 1. Demographics and diagnostic characteristics.

Parameter	Details	p-value*
Age (years)	32.6 ± 5.0 (range: 25–40)	0.717
BMI (kgm²)	32.2 ± 6.9 (range: 22–46)	0.513
Comorbidities		0.786
None	12 (75%)	
DM	2 (12.5%)	
HT	1 (6.25%)	
Metabolic syndrome	1 (6.25%)	
Nulliparity	15 (93.8%)	-
PCOS	4 (25%)	0.569
Histology		-
Atypical Hyperplasia	1 (6.25%)	
Endometrioid	15 (93.8%)	
Grade		-
Grade 1	16 (100%)	
MRI-detected MI		0.850
None	7 (44%)	
<50% invasion	8 (50%)	
≥50% invasion	1 (6.25%)	
Diagnostic Method		0.691
Dilation & Curettage	14 (87.5%)	
Hysteroscopy	2 (12.5%)	
Stage		-
Stage 1a	15 (93.8%)	
Stage 1b	1 (6.25%)	
Squamous Metaplasia		0.182
Present	6 (37.5%)	
Absent	10 (62.5%)	

*:The p-values refer to comparisons used to assess the potential impact of these variables on achieving complete remission.
BMI: Body Mass Index; MI: Myometrial Invasion; MRI: Magnetic Resonance Imaging; DM: Diabetes mellitus; HT: Hypertension; PCOS: Polycystic ovarian syndrome.

The progesterone treatment regimen consisted of megestrol acetate alone in 11 patients (68%) and megestrol acetate plus a levonorgestrel-releasing intrauterine system (LNG-IUS) in five patients (32%). The duration of hormonal therapy varied: 2 patients (12.5%) received treatment for 3 months, 6 patients (37.5%) for 6 months, 4 patients (25%) for 9 months, and 4 patients (25%) for ≥12 months.

Complete remission (CR) was achieved in six patients (38%), and stable disease was observed in 10 patients (62%). Among the six patients who achieved CR, four pregnancies were recorded, resulting in three live births. Two pregnancies occurred spontaneously, and two were achieved using ART. Three recurrences were noted in the CR group: one case developed ovarian metastasis after delivery and underwent laparoscopic bilateral salpingo-oophorectomy (BSO), while two cases experienced endometrial recurrence during follow-up. During follow-up, 12 patients underwent surgery: five underwent hysterectomies with bilateral salpingectomies (BS), seven underwent hysterectomies with BSO, and one underwent oophorectomy following hysterectomy. FST cases were molecularly classified as p53 wild-type (p53wt). Statistical analysis revealed no significant correlation between complete remission and the following factors: age (p=0.717), BMI (p=0.513), presence of comorbidities such as DM, HT, or metabolic syndrome (p=0.786), PCOS diagnosis (p=0.57), MRI-detected MI status (p=0.85), diagnostic method used (D&C vs. hysteroscopy; p=0.69), and type of progesterone administration (p=0.37). One of the three recurrence cases after CR involved ovarian metastasis after delivery. Two other cases showed endometrial recurrence during the follow-up period. The treatment and follow-up data of the patients are presented in Table 2.

Although SM was detected in 6 cases, only 1 achieved CR (Figure 1). However, this finding was not statistically significant (p = 0.182).

Table 2. Treatment and follow-up characteristics

Characteristics	**n (%)**	**p-value**
Progesterone Type		0.377
Megestrol acetate	11 (68%)	
Megestrol Acetate combined with LNG IUS	5 (32%)	
Treatment Cycle Duration		
3 months	2 (12.5%)	
6 months	6 (37.5%)	
9 months	4 (25%)	
12 months	4 (25%)	
Complete Remission	6 (38%)	
Stable Disease	10 (62%)	
Pregnancy Outcome (n=4)		
ART	2 (50%)	
Spontaneous	2 (50%)	
Live Births	3 (75%)	
Recurrence After CR	3 (50%)	
Surgical Treatment	12 (75%)	
Hysterectomy + Bilateral Salpingectomy	5 (42%)	
Hysterectomy + BSO	6 (50%);	
Post-hysterectomy Oophorectomy	1 (8%)	

ART: Assisted Reproductive Technology; BSO: Bilateral salpingo-oophorectomy; CR: Complete remission; LNG IUS: Levonorgestrel releasing intrauterine system.

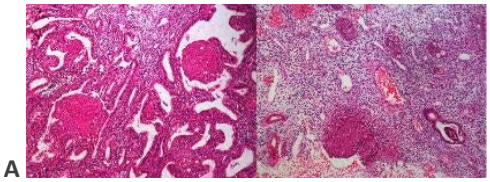

Figure 1. In the first biopsy sample, a case diagnosed with endometrioid carcinoma Figo grade 1 with squamous differentiation on a polyp basis was observed (A), and in the second biopsy sample, a polyp fragment containing squamous morule was observed (B).

DISCUSSION

FST for young women with early-stage EC and atypical hyperplasia has emerged as a viable option that balances oncological safety and the preservation of reproductive potential. This study contributes to the growing body of evidence by analyzing the clinical, pathological, and molecular characteristics of 16 patients who underwent FST and evaluating their treatment outcomes. Our findings support and enhance the existing literature, offering new insights into the prognostic factors and challenges associated with FST.

The remission rate observed in our cohort (38%) was lower than the pooled regression rates reported in meta-analyses, which ranged from 76% to 88.9% across treatment modalities and patient selection criteria[7-9]. This difference might be due to variations in the sample size, treatment protocols, or follow-up periods. For instance, studies have shown that combining hysteroscopic resection with progestin therapy can considerably increase remission rates compared to progestin therapy alone[7]. However, our study used only oral progestins and LNG-IUS, which may explain the relatively modest results. Recurrence remains a significant challenge in FST, with relapse rates ranging from 20% to 40.6% in previous studies[7-9]. In our cohort, three patients (43%) experienced recurrence after remission, including one case of ovarian metastasis. Myometrial invasion in a significant proportion of our cases (%56) may explain our low CR and recurrence rates. This highlights the importance of long-term monitoring and underscores the need to identify the predictive markers of recurrence. Molecular classification, such as ProMisE, has shown promise in stratifying patients by risk profile[10]. For example, mismatch repair-deficient (MMRd) tumors are associated with higher recurrence rates[4,5,11-13], whereas POLE-mutated tumors exhibit favorable outcomes[10,14]. The presence of p53abn in EC, which is thought to be an early-stage cancer, is the most important molecular marker that determines poor prognosis. Current guidelines indicate that these cases are not appropriate for FST[2]. Among patients who underwent FST, the p53 wt /NSMP group is the largest, accounting for 70-80% of cases, and all participants in our study were classified in this group[10]. However, emerging evidence suggests that heterogeneity exists even within p53wt tumors, which may influence treatment response and recurrence risk. Screening for mutations such as L1-CAM, CTNNB1, PTEN, and ARID1 is recommended to enhance the characterization of the molecular features of this group[15-17]. Molecular subtyping influences both the duration of treatment and the intervals between relapses. For instance, POLE-mutated tumors achieve complete remission more rapidly and have longer relapse-free intervals compared to MMRd or p53-abnormal tumors[10].

Given the limited number of cases documented in the existing literature, it is currently not feasible to provide definitive evaluations of the molecular type in patients undergoing FST. Nevertheless, integrating molecular profiling into standard clinical practice has the potential to enhance patient selection and inform personalized treatments.

SM, a histological finding observed in endometrial tissue, has been a subject of debate regarding its clinical and prognostic significance in EC and atypical hyperplasia[18]. In our study, SM was identified in 37.5% of patients undergoing FST. Among these cases, only one achieved CR, while the remaining five exhibited stable disease. Although this finding did not reach statistical significance ($p = 0.182$), it raises important questions about the potential impact of SM on treatment outcomes and warrants further investigation. Our findings suggest that SM may indicate reduced responsiveness to hormonal therapy in FST. This observation is consistent with studies showing that recurrence may be higher in early-stage endometrioid endometrial carcinoma cases characterized by SM[19-21]. A study revealed a potential correlation between specific histological patterns, including morular metaplasia and mixed glandular-squamous features, and extended treatment durations or reduced CR rates[22]. The molecular underpinnings of SM remain poorly understood but are likely multifactorial. Studies have suggested that SM may be

associated with specific molecular subtypes of EC[23, 24]. These subtypes are generally considered more responsive to hormonal therapy; however, the interplay between molecular classification and histological features, such as SM, warrants further exploration. Given these findings, it is essential to consider histological features, such as SM, during patient selection and treatment planning for FST. Incorporating detailed histopathological assessments into clinical practice can identify patients who may benefit from alternative or adjunctive therapeutic strategies, such as combining hysteroscopic resection with hormonal therapy.

SM is a relatively common histological finding in patients undergoing FST. Our study contributes to the limited body of literature examining the role of SM in FST for EC and AH. By elucidating the potential relationship between SM and lower CR rates, we established a basis for subsequent research aimed at elucidating the clinical significance of this histological feature. However, our findings are limited by the small sample size and retrospective design, which may reduce the generalizability of our results. The fact that the POLE mutation has not been evaluated is another limitation.

Although our study did not demonstrate a statistically significant impact of SM presence on remission rates, the observed trend toward lower CR rates underscores the need for further research on its clinical implications. Larger prospective studies are needed to validate these observations and determine whether SM should be considered a prognostic factor in FST. Incorporating histopathological features, such as SM, into the patient selection criteria, along with the exploration of their molecular correlates, has the potential to enhance the efficacy of fertility-preserving strategies. This approach may improve outcomes for young women attempting to balance oncological safety with reproductive objectives.

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