



Clinical and Histopathological Findings in Breast Cancer Patients Undergoing Endometrial Sampling: A Retrospective Study

Endometrial Örnekleme Yapılan Meme Kanseri Tanılı Hastaların Klinik ve Histopatolojik Sonuçlarının Retrospektif Olarak Değerlendirilmesi

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ABSTRACT

Objectives: To evaluate the clinical and histopathological findings of breast cancer patients who underwent endometrial sampling and to determine the relationship between endocrine therapy type and abnormal endometrial pathology.

Methods: This retrospective study included 48 breast cancer patients who underwent endometrial sampling between 2010 and 2021. Clinical data such as age, menopausal status, symptoms, and type/duration of endocrine therapy were recorded. Histopathological results were categorized as normal, benign, premalignant, or malignant. Statistical analyses were performed using SPSS 22.0, and a p value <0.05 was considered significant.

Results: The mean age was 55±8.16 years, and 50% of patients were postmenopausal. Tamoxifen was used in 75%, and aromatase inhibitors in 8.3% of patients. Abnormal uterine bleeding was the leading indication for biopsy (85.4%). Benign polyps were the most common abnormality (39.6%), followed by hyperplasia (6.3%) and carcinoma (4.2%). No significant differences in abnormal endometrial pathology were observed between tamoxifen and aromatase inhibitor users (p>0.05). Treatment duration, menopausal status, and receptor profile were not associated with endometrial pathology.

Conclusion: Benign polyps were the most frequent abnormal endometrial findings among breast cancer patients undergoing endometrial sampling, while premalignant and malignant lesions were rare. The type or duration of endocrine therapy did not significantly affect the risk of endometrial pathology. Invasive evaluation should be guided by symptoms rather than routine screening.

Keywords: Aromatase inhibitor; breast cancer; endometrial biopsy; endometrial pathology; tamoxifen.

ÖZET

Amaç: Endometrial örnekleme yapılan meme kanseri tanılı hastaların klinik ve histopatolojik sonuçlarını değerlendirmek ve endokrin tedavi türü ile endometrial patoloji arasındaki ilişkiyi incelemektir.

Yöntem: Bu retrospektif çalışmaya, 2010–2021 yılları arasında endometrial örnekleme uygulanan 48 meme kanseri hastası dahil edilmiştir. Hastaların demografik özellikleri, menopozal durumları, klinik semptomları ve endokrin tedavi türü/süresi kaydedildi. Histopatolojik bulgular normal, benign, premalign ve malign olarak sınıflandırıldı. İstatistiksel analizler SPSS 22.0 kullanılarak yapıldı ve p<0,05 anlamlı kabul edildi.

Bulgular: Hastaların ortalama yaşı 55±8,16 yıl olup, %50'si postmenopozal dönemdeydi. Hastaların %75'i tamoksifen, %8,3'ü aromataz inhibitörü kullanmaktaydı. Endometrial biyopsi için en sık endikasyon anormal uterin kanamaydı (%85,4). En sık saptanan patoloji benign polipler (%39,6) olup, endometrial hiperplazi (%6,3) ve karsinom (%4,2) daha nadir görüldü. Endokrin tedavi türü ile anormal endometrial patoloji arasında anlamlı bir ilişki saptanmadı (p>0,05).

Sonuç: Endometrial örnekleme yapılan meme kanseri hastalarında en sık benign polipler izlenirken, premalign ve malign patolojiler nadirdir. Endokrin tedavi türü ve süresinin endometrial patoloji riskini anlamlı olarak artırmadığı görülmüştür. İnvaziv değerlendirme, semptom varlığında planlanmalıdır.

Anahtar sözcükler: Aromataz inhibitörü; meme kanseri; endometrial biyopsi; endometrial patoloji; tamoksifen.

Breast cancer, the most common malignancy in women, affects approximately one in eight in developed countries and represents the second leading cause of cancer-related death among women.^[1] Its incidence increases with age, and family history, obesity, and nulliparity are well-established risk factors.^[2] Despite these risks, survival outcomes remain favorable, with 5- and 10-year survival rates of about 73% and 61%, respectively.^[3]

Hormone therapy plays a central role in breast cancer management, with selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), fulvestrant, and luteinizing hormone-releasing hormone (LHRH) agonists being commonly employed. Among these, tamoxifen remains the most extensively utilized SERM for estrogen receptor–positive tumors.^[4] However, its estrogenic activity on the endometrium has been associated with an increased risk of endometrial pathology.^[5] Documented endometrial abnormalities include polyps, hyperplasia, and carcinoma, and evidence suggests that the risk of endometrial cancer is approximately threefold higher in tamoxifen users compared with non-users, particularly with higher cumulative doses and prolonged treatment.^[6] By contrast, AIs appear to confer a lower risk of endometrial pathology and cancer compared with tamoxifen.^[7]

In this study, we retrospectively evaluated breast cancer patients who underwent endometrial sampling (biopsy or curettage) at our institution. The objectives were: (1) to determine the prevalence and spectrum of endometrial histopathological findings in these patients, and (2) to assess associations between clinical factors—such as menopausal status, symptoms, and duration/type of endocrine therapy—and the likelihood of abnormal pathology. Our aim is to provide evidence to guide the gynecological management of breast cancer patients receiving tamoxifen or aromatase inhibitors (AIs), particularly in determining when an invasive evaluation is necessary.

Methods

Study Design and Patient Population

This retrospective observational study was conducted at a single tertiary care hospital. A total of 48 breast cancer pa-

tients who underwent endometrial sampling between 2010 and 2021 were identified from the institutional pathology database. Eligible patients had a history of breast cancer at any stage and had undergone endometrial biopsy or dilatation and curettage during or after adjuvant endocrine therapy (tamoxifen and/or aromatase inhibitors). Both premenopausal and postmenopausal women were included. Patients with a prior diagnosis of endometrial cancer or those who underwent biopsy for reasons unrelated to breast cancer follow-up were excluded.

Data Collection and Variables

Clinical and demographic data were retrieved from electronic medical records. Variables included age, reproductive history, menopausal status, presenting symptoms, indication for endometrial sampling, type and duration of endocrine therapy, and receipt of chemotherapy or radiotherapy. Missing data were managed using a complete-case (listwise deletion) approach; patients with unavailable information for essential variables were excluded from the analyses.

Histopathologic Evaluation

Endometrial specimens were obtained by dilatation and curettage, pipelle biopsy, or hysteroscopic-guided biopsy. Histopathological findings were categorized as proliferative, secretory, or atrophic/inactive endometrium, as well as pathological entities such as polyps, hyperplasia, and carcinoma. All pathological diagnoses were classified according to the World Health Organization (WHO) and European Society of Gynaecological Oncology (ESGO) guidelines to ensure standardized terminology and reproducibility.

Statistical Analysis

Data are presented as mean±standard deviation (SD), median with range, or number (percentage), as appropriate. Continuous variables were compared using the Student's t-test or Mann–Whitney U test, and categorical variables were analyzed with the chi-square test or Fisher's exact test, where appropriate. Multivariate logistic regression analysis was performed to identify independent predictors of abnormal endometrial pathology. Odds ratios (ORs) with 95% confi-

dence intervals (CIs) were calculated. All statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided $p < 0.05$ was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Ethics Committee of Gazi University (Approval No. 231). Patient confidentiality was maintained in accordance with the Declaration of Helsinki. Given the retrospective design, potential sources of selection bias were acknowledged.

Results

A total of 48 breast cancer patients were included, with ages ranging from 43 to 79 years (mean 55 ± 8.16). The mean parity was 2.21 ± 0.97 (range 0–6), and 3 patients (6.3%) reported a family history of cancer. At the time of endometrial evaluation, 24 patients (50%) were postmenopausal. Most patients had undergone mastectomy (91.7%), while 8.3% had breast-conserving surgery. Adjuvant radiotherapy was administered in 68.7% and chemotherapy in 81.3%. Endocrine therapy was common: 75% of patients received tamoxifen

and 8.3% an aromatase inhibitor (AI), while 16.7% did not receive endocrine therapy (Table 1). Baseline characteristics were similar between the tamoxifen and AI groups, with no significant differences in age, gravidity, or parity ($p > 0.05$).

Abnormal uterine bleeding was the leading indication for biopsy (85.4%), whereas 14.6% were asymptomatic and underwent evaluation as part of follow-up. The clinical presentation varied substantially with menopausal status: incidental ultrasound findings predominated in premenopausal women (78.9%), whereas postmenopausal women presented overwhelmingly with bleeding (89.7%).

Endometrial sampling was most frequently performed by dilatation and curettage (71%), followed by pipelle biopsy (21%) and hysteroscopic-directed biopsy (8%). Histopathology revealed no significant pathology in 50% of cases (atrophic or proliferative endometrium). Benign polyps were the most frequent abnormal lesion (39.6%), followed by atrophic endometrium (31.3%) and proliferative endometrium (18.8%). Premalignant or malignant lesions were relatively rare, with 3 cases of hyperplasia (6.3%; 2 non-atypical, 1 atypical) and 2 cases of endometrioid carcinoma (4.2%). Comparison of demographic features according to endometrial pathology outcomes revealed no significant differences in age (57.54 ± 7.83 vs. 53.54 ± 8.16 years, $p = 0.09$), gravidity (2.79 ± 1.35 vs. 3.13 ± 1.42 , $p = 0.40$), or parity (1.96 ± 0.80 vs. 2.46 ± 1.06 , $p = 0.07$) (Table 2).

Premalignant and malignant endometrial lesions were further analyzed according to endocrine therapy type (Table 3). All cases of endometrial hyperplasia, including two non-atypical and one atypical lesion, were observed in patients receiving tamoxifen. Among carcinoma cases, one patient was receiving tamoxifen and one was receiving an aromatase inhibitor. No premalignant or malignant lesions were identified in patients who did not receive endocrine therapy.

Table 1. Baseline demographic and clinical characteristics

Variables	Min-Max	Mean±SD
Age	43-79	55±8.16
Parity	0-6	2.21±0.97
Variables	n	%
Endocrine therapy type		
Tamoxifen	36	75
Aromatase inhibitor users	4	8.3
No endocrine therapy	8	16.7
Menopausal status		
Menopause	24	50
premenopause	24	50
Family cancer history		
Family history present	3	6.3
Family history absent	45	93.7
Presenting complaint		
Abnormal uterine bleeding	41	85.4
Routine check-up	7	14.6

Descriptive statistics were used. Continuous variables are presented as mean±standard deviation and minimum–maximum values, while categorical variables are expressed as numbers and percentages.

Table 2. Demographic features according to endometrial pathology outcomes

Variables	Normal pathology results	Anormal pathology results	p
Age	57.54±7.83	53.54±8.16	0.09
Gravidity	2.79±1.35	3.13±1.42	0.4
Parity	1.96±0.80	2.46±1.06	0.07

Data are presented as mean±standard deviation. Comparisons between groups were performed using independent samples t-test.

Table 3. Distribution of premalignant and malignant endometrial lesions according to endocrine therapy

Pathology	Tamoxifen (n=36)	Aromatase inhibitor (n=4)	No endocrine therapy (n=8)
Non-atypical hyperplasia	2 (5.6%)	0	0
Atypical hyperplasia	1 (2.8%)	0	0
Endometrial carcinoma	1 (2.8%)	1 (25.0%)	0

Data are presented as number (percentage). Percentages were calculated within each treatment group. Premalignant lesions include both atypical and non-atypical endometrial hyperplasia. No statistical comparison was performed due to the small number of cases.

When outcomes were compared by treatment groups, tamoxifen and AI users demonstrated similar rates of abnormal pathology (50% vs. 50%, $p>0.05$). Patients who received chemoradiotherapy had a numerically lower frequency of abnormal pathology (46.2%) compared with those who did not (66.7%), but this difference was not significant. Longer endocrine therapy duration (≥ 36 months) was associated with a higher proportion of abnormal pathology (53.7% vs. 28.6%), although the difference did not reach statistical significance (OR=2.8, 95% CI: 0.5–16.6, $p>0.05$). Finally, receptor profile was not associated with endometrial outcomes: abnormal findings were detected in 54.5% of triple-positive and 46.2% of triple-negative tumors, without a significant difference ($p>0.05$).

Discussion

In this retrospective study of 48 breast cancer patients undergoing endometrial sampling, we found that approximately half of the cohort exhibited no significant endometrial pathology, while benign polyps represented the most frequent abnormal finding. Malignant or premalignant lesions were uncommon, identified in less than 11% of cases. Importantly, the risk of abnormal pathology did not differ significantly between patients treated with tamoxifen and those receiving aromatase inhibitors, nor was it clearly influenced by adjuvant chemotherapy/radiotherapy, treatment duration, or tumor receptor status. Our findings suggest that the likelihood of clinically significant endometrial pathology in this cohort was low, regardless of the type of endocrine regimen or breast cancer subtype.

In our study, the mean age of patients with abnormal pathology (including polyps, hyperplasia, and carcinoma) was

lower than that of patients with normal findings; however, this difference did not reach statistical significance. Consistently, when patients with and without abnormal endometrial biopsy results were compared, neither age nor menopausal status showed a significant association.^[8] In contrast, a nationwide cohort study demonstrated that tamoxifen use is associated with a significantly increased risk of endometrial cancer in older and postmenopausal women.^[9]

Most patients presented with vaginal bleeding, especially those in the postmenopausal group. Recent findings indicate that among postmenopausal breast cancer patients on tamoxifen, asymptomatic individuals with increased endometrial thickness (e.g., ≥ 5 mm) have significantly lower rates of premalignant or malignant pathology compared to symptomatic individuals.^[10]

The predominant pathological finding was endometrial polyps (39.6%), followed by hyperplasia (6.3%) and carcinoma (4.2%), while nearly half of the patients (49.9%) had normal histology. In the present study, all cases of endometrial hyperplasia, including both atypical and non-atypical forms, were observed in patients receiving tamoxifen, which is consistent with the well-established estrogen agonistic effects of tamoxifen on the endometrium and its association with endometrial proliferation, hyperplasia, and carcinoma.^[11] These findings align with data from a large population-based cohort study, which reported incidence rates (per 1,000 person-years) of endometrial polyps, hyperplasia, and carcinoma as 20.13, 13.49, and 2.01, respectively, among premenopausal tamoxifen users.^[6]

While our study found no statistically significant difference in the incidence of endometrial pathology between tamoxifen and aromatase inhibitor users, previous large-scale investigations have shown a substantially reduced risk of endometrial cancer with AI therapy. Specifically, aromatase inhibitor users experienced a 48% lower incidence of endometrial cancer compared with tamoxifen users ($p<0.05$).^[12] Additionally, long-term followup data revealed a threefold lower 10-year incidence of endometrial cancer among AI users (0.4%) compared to those on tamoxifen (1.2%).^[13] Similarly, it has been demonstrated that patients who switched from tamoxifen to an aromatase inhibitor experienced a reduction in endometrial thickness, supporting the role of AIs in reversing tamoxifen-induced endometrial changes.^[14]

In this study, the incidence of endometrial hyperplasia and carcinoma did not differ significantly between patients treat-

ed with tamoxifen or aromatase inhibitors for ≥ 36 months compared with those treated for shorter durations. However, large-scale investigations have consistently demonstrated that longer tamoxifen exposure and higher cumulative doses are associated with a significantly increased risk of endometrial cancer, with extended use beyond 5 years approximately doubling the incidence compared with standard treatment.^[11] Meta-analyses have confirmed this time- and dose-dependent effect, showing that each additional year of tamoxifen further increases the relative risk.^[15] Additionally, a large retrospective analysis found that longer-term use of tamoxifen (approximately 2 years or more), particularly in postmenopausal breast cancer patients, was associated with a significant increase in endometrial cancer risk compared to shorter-term treatment.^[5]

Endometrial pathology did not differ significantly with respect to hormone receptor status among breast cancer patients. In line with this, previous studies have reported that the incidence of endometrial cancer does not differ substantially between hormone receptor-positive and receptor-negative patients, and that cases arising after either subtype exhibit comparable clinicopathological characteristics and prognoses.^[16]

This study has several limitations that should be acknowledged. To begin with, its retrospective design may have introduced selection and information bias. The relatively small sample size, despite the long study period of 11 years, may be attributed to the strict inclusion criteria and the retrospective design of the study. Moreover, the study was conducted in a single tertiary care center with a relatively small sample size, particularly in the subgroup of patients using aromatase inhibitors, which limits the generalizability of our findings. In addition, we did not include a control group of breast cancer-free patients, making it difficult to compare the absolute risk of endometrial pathology. Another limitation is that data regarding cumulative dose and duration of tamoxifen beyond three years were limited, which may have reduced our ability to detect long-term effects. Finally, because endometrial sampling was performed based on clinical indications rather than uniform screening, some asymptomatic cases might have remained undetected. Larger, multicenter prospective studies are warranted to validate and expand upon these results.

Conclusion

This retrospective study found that benign polyps were the most common abnormal finding in breast cancer patients

who underwent endometrial sampling, while premalignant and malignant lesions were rare. There were no significant differences in the risk of developing endometrial pathology based on the type of endocrine therapy administered, the duration of treatment, the administration of additional chemotherapy or radiotherapy, or tumor receptor status. Our findings suggest that the likelihood of clinically significant endometrial pathology in this patient group is relatively low, indicating that invasive evaluations should be planned based on symptoms and individualized rather than for routine screening purposes. However, our results are not generalizable due to the small sample size and single-center design. Therefore, larger-scale, prospective studies are needed.

Disclosures

Ethics Committee Approval: The study was approved by Gazi University Ethics Committee (No: 231, Date: 27.12.2021).

Informed Consent: Due to the retrospective nature of the study, informed consent was waived.

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