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Endometrial Pathology in Tamoxifen-treated Breast Cancer Patients: Correlation of Endometrial Thickness on Ultrasound, Preoperative Sampling, and Final Pathology

Tamoksifen Tedavisi Alan Meme Kanseri Hastalarında Endometrial Patoloji: Ultrasonografide Endometrial Kalınlık, Preoperatif Örnekleme ve Nihai Patoloji Arasındaki İlişki

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Abstract

Objective: This study aims to evaluate the relationship between endometrial thickness measured via transvaginal ultrasonography (TVUSG), preoperative endometrial biopsy findings, and final histopathology results, in breast cancer patients receiving tamoxifen therapy who underwent hysterectomy for benign indications.

Methods: A retrospective observational study was conducted on 77 tamoxifen-treated breast cancer patients who underwent hysterectomy between January 1, 2020; and January 1, 2025. Data included patient demographics, tamoxifen usage, TVUSG measurements of endometrial thickness, preoperative biopsy outcomes, and final hysterectomy pathology findings were collected. Statistical analyses included t-tests, Mann-Whitney U, chi-square, receiver operating characteristic (ROC) curve, and Cohen's Kappa tests.

Results: Postoperative endometrial pathology was detected in 36.4% of patients. Those with pathological findings had significantly greater endometrial thickness (11.74±6.20 mm vs. 7.93±4.27 mm; p=0.01) and longer tamoxifen use duration (4.52±2.97 vs. 2.83±2.07 years; p=0.01). ROC curve analysis revealed moderate diagnostic performance of endometrial thickness (area under the curve =0.686; 95% confidence interval: 0.565-0.807; p=0.007), with an optimal cut-off of 7.5 mm, yielding 75.0% sensitivity and 63.3% specificity. A lower threshold of 4.5 mm provided higher sensitivity (96.4%) but poor specificity (24.5%). Preoperative biopsy demonstrated limited diagnostic utility, with 35.7% sensitivity, 73.5% specificity, and a low agreement with final pathology (Cohen's Kappa =0.095; p=0.397).

Conclusion: The diagnostic accuracy of preoperative endometrial biopsy and endometrial thickness measurement was found to be limited in tamoxifen-treated patients. Individualized follow-up strategies are needed, particularly for symptomatic patients with prolonged tamoxifen use or increased endometrial thickness. Larger-scale studies are required to guide clinical management.

Keywords: Tamoxifen, breast cancer, endometrial biopsy

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Öz

Amaç: Bu çalışma, benign nedenlerle histerektomi uygulanan tamoksifen tedavisi alan meme kanseri hastalarında transvajinal ultrasonografi (TVUSG) ile ölçülen endometrial kalınlık, preoperatif endometrial biyopsi bulguları ve nihai histopatoloji sonuçları arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntem: 1 Ocak 2020 ile 1 Ocak 2025 tarihleri arasında histerektomi uygulanan tamoksifen tedavisi altındaki 77 meme kanseri hastası üzerinde retrospektif gözlemsel bir çalışma gerçekleştirildi. Hastaların demografik verileri, tamoksifen kullanım süresi, TVUSG ile ölçülen endometrial kalınlık, preoperatif biyopsi sonuçları ve nihai histerektomi patoloji bulguları değerlendirildi. İstatistiksel analizlerde t-testi, Mann-Whitney U, ki-kare, alıcı çalışma karakteristiği (ROC) eğrisi ve Cohen's Kappa testleri kullanıldı.

Bulgular: Hastaların %36,4'ünde postoperatif endometrial patoloji saptandı. Patolojik bulgusu olan hastalarda endometrial kalınlık (11,74±6,20 mm'ye karşı 7,93±4,27 mm; p=0,01) ve tamoksifen kullanım süresi (4,52±2,97 yıla karşı 2,83±2,07 yıl; p=0,01) anlamlı olarak daha yüksekti. ROC analizine göre endometrial kalınlığın tanısal gücü orta düzeydeydi (eğri altında kalan alan =0,686; %95 güven aralığı: 0,565-0,807; p=0,007). 7,5 mm'lik eşik değeri %75,0 duyarlılık ve %63,3 özgüllük sağladı. 4,5 mm'lik daha düşük eşik değeri daha yüksek duyarlılık (%96,4) ancak düşük özgüllük (%24,5) ile ilişkiliydi. Preoperatif biyopsinin tanısal değeri sınırlı olup duyarlılığı %35,7, özgüllüğü %73,5 ve nihai patoloji ile uyumu düşüktü (Cohen's Kappa =0,095; p=0,397).

Sonuç: Tamoksifen tedavisi alan hastalarda preoperatif endometrial biyopsi ve endometrial kalınlık ölçümünün tanısal doğruluğu sınırlı bulunmuştur. Özellikle semptomatik, uzun süre tamoksifen kullanan veya artmış endometrial kalınlığa sahip hastalarda bireyselleştirilmiş takip stratejilerine ihtiyaç vardır. Klinik yönetimi yönlendirebilmek adına daha geniş ölçekli çalışmalara gereksinim duyulmaktadır.

Anahtar Kelimeler: Tamoksifen, meme kanseri, endometrial biyopsi

Introduction

Breast cancer is one of the most common malignancies among women, with the majority of cases being estrogen receptor-positive. Tamoxifen, used as adjuvant therapy in these patients, acts as an estrogen antagonist in breast tissue, thereby reducing the risk of recurrence and improving survival[1,2]. Recent studies suggest that extending tamoxifen treatment up to 10 years can further enhance its therapeutic efficacy[3]. However, unlike its antagonistic effect on breast tissue, tamoxifen exhibits estrogen agonist activity in the endometrium, leading to endometrial thickening and various pathologies[4]. Studies have demonstrated that women taking tamoxifen have an increased risk of developing endometrial hyperplasia, polyps, and cancer, with the risk increasing in a dose- and duration-dependent manner[5]. Given that breast cancer and endometrial cancer share several epidemiological and genetic risk factors, the impact of tamoxifen on the endometrium warrants close attention[6]. Despite the widespread use of tamoxifen, there is still no clear consensus on the most effective strategy for endometrial surveillance in these patients. While routine screening for endometrial pathology is not recommended in asymptomatic postmenopausal women receiving tamoxifen therapy, research indicates that sonohysterography may enhance the diagnostic accuracy of ultrasonography by better detecting or ruling out anatomical abnormalities when clinically indicated[7]. Identifying factors associated with the development of endometrial pathologies in women taking tamoxifen is essential for designing individualized surveillance strategies. This is particularly relevant, as the clinical significance of these factors increases with prolonged tamoxifen use.

Most studies in this area have examined the overall risk for endometrial pathologies associated with tamoxifen use, with limited research focusing on the specific factors contributing to these pathologies[8]. Furthermore, in cases of abnormal vaginal bleeding, diagnostic modalities such as ultrasonography, hysteroscopy, and pathological examination play a vital role. The primary aim of this study is to investigate the relationship between endometrial thickness measured by transvaginal ultrasonography (TVUSG) and preoperative biopsy results, and final hysterectomy pathology in breast cancer patients receiving tamoxifen therapy. In addition, a key objective of the study is to evaluate the reliability of these two diagnostic methods in predicting endometrial pathologies and their contribution to the clinical diagnostic process.

Materials and Methods

This retrospective observational study evaluated the relationship between endometrial thickness, preoperative endometrial biopsy results, and final pathology findings in breast cancer patients who underwent hysterectomy for benign indications between January 1, 2020; and January 1, 2025. This retrospective study was conducted by reviewing the medical records of patients who underwent surgery in the gynecology clinics of our tertiary referral center during the specified period.

Female breast cancer patients who underwent hysterectomy for benign indications during the specified period were using tamoxifen, had their endometrial thickness measured by TVUSG prior to hysterectomy, underwent preoperative

endometrial biopsy with available histopathological results, and had accessible final hysterectomy pathology reports were included in the study. Decrease in hemoglobin (Hb) was defined as the reduction in Hb levels measured by comparing preoperative Hb values with those obtained at the sixth postoperative hour. The study was approved by the Local Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (decision no: 2025:03-17, date: 10.04.2025).

Patients diagnosed with endometrial or cervical malignancy, patients with a history of previous endometrial ablation, radiotherapy, or chemotherapy, patients with incomplete clinical data, and cases with missing or unavailable pathological assessment at the time of hysterectomy were excluded. The patients' demographic characteristics, clinical history, tamoxifen use status, and duration, endometrial thickness measured by transvaginal ultrasonography, perioperative data, preoperative endometrial biopsy results, and final hysterectomy pathology findings were retrospectively collected from the electronic medical record system.

Statistical Analysis

All statistical analyses were carried out using the SPSS software package (version 25.0, IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median (interquartile range), depending on the distribution of the data. Categorical variables were presented as counts and percentages. The distribution of continuous variables was assessed with the Shapiro-Wilk test. For comparisons between two groups, the independent samples t-test was applied for normally distributed data, whereas the Mann-Whitney U test was used when normality assumptions were not met. Relationships between categorical variables were examined using the chi-square test or Fisher's exact test, as appropriate, based on expected frequencies. The ability of transvaginal ultrasonographic endometrial thickness measurements to predict the presence of histopathological abnormalities was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated to determine overall diagnostic performance, and the optimal cut-off point was established using the Youden Index. Agreement between preoperative endometrial biopsy results and final pathology findings from hysterectomy specimens was analyzed using Cohen's Kappa statistic. A p-value less than 0.05 was considered statistically significant in all tests.

Results

A total of 77 patients were included in the study. The mean age of the participants was 49.05±7.88 years, and the mean parity was 2.03±1.03. The mean decrease in Hb (g/dL) was 1.58±0.84, and the mean body mass index (BMI) was 27.12±3.80 kg/m^2. The mean preoperative endometrial thickness was 8.81±5.14 mm regarding menopausal status, 68.8% (n=53) of the patients were premenopausal and 31.2% (n=24) were postmenopausal. Preoperative endometrial evaluation revealed pathological findings in 23 patients (29.8%), while 54 patients (70.1%) had normal results. Final hysterectomy pathology revealed pathological findings in 28 patients (36.4%) while 49 patients (63.6%) were classified as normal (Table 1).

Preoperative endometrial histopathology results were available for all 77 patients. The most common finding was the insufficient samples in 28 patients (36.4%). Endometrial polyps were observed in 15 patients (19.5%), endometrial hyperplasia without atypia in 5 patients (6.5%), and hyperplasia with atypia in 3 patients (3.9%). Functional endometrial phases included the secretory phase in 9 patients (11.7%) and the proliferative phase in 9 patients (11.7%). Additionally, 8 patients (10.4%) had atrophic endometrium (Table 2). Postoperative endometrial histopathology was available for all patients. The most common postoperative finding was atrophic endometrium (18 patients, 23.4%), followed by endometrial polyps (15 patients, 19.48%), endometrial hyperplasia without atypia (10 patients, 12.99%), and hyperplasia with atypia (3 patients, 3.9%). The secretory phase was identified in 16 patients (20.8%), and the proliferative phase in 13 patients (16.9%). These results indicate a wide distribution of endometrial conditions in the study population (Table 3).

Analysis of patient characteristics according to final histopathology revealed that both the duration of tamoxifen use and endometrial thickness were significantly higher in patients with endometrial pathology. Specifically, mean tamoxifen use was 4.52±2.97 years in the pathologic group compared to 2.83±2.07 years in the normal group (p=0.01). Similarly, the mean endometrial thickness measured by TVUSG was significantly greater in patients with pathologic findings (11.74±6.20 mm vs. 7.93±4.27 mm; p=0.01). No statistically significant differences were observed between the groups in terms of age, parity, BMI, menopausal status, or postoperative Hb drop (all p>0.05) (Table 4).

The diagnostic concordance between preoperative endometrial biopsy and final hysterectomy pathology in tamoxifen-treated breast cancer patients was suboptimal. Among 28 patients with pathological findings in the final hysterectomy specimens, only 10 were correctly identified by preoperative biopsy, yielding a sensitivity of 35.7%. Specificity was higher at 73.5%, with 36 out of 49 normal cases accurately detected. The overall diagnostic accuracy of the biopsy was calculated as 59.7%. Positive and negative predictive values were 43.5% and 66.7%, respectively, suggesting limited predictive performance. Cohen's Kappa coefficient was 0.095 [standard error (SE): 0.113; p=0.397], indicating poor agreement between biopsy and final pathology results, with no statistically significant concordance beyond chance. These findings highlight the limited diagnostic reliability of preoperative endometrial biopsy in this patient population (Table 5).

ROC curve analysis was performed to assess the diagnostic utility of endometrial thickness in predicting endometrial pathology. AUC was calculated as 0.686 (SE: 0.062; 95% confidence interval: 0.565-0.807; p=0.007), indicating a moderate level of diagnostic accuracy. According to the Youden index, the optimal cut-off value was identified as 7.5 mm, which yielded a sensitivity of 75.0% and a specificity of 63.3%. Additionally, a lower threshold of 4.5

Table 1. Characteristics of tamoxifen-treated breast cancer patients undergoing hysterectomy

Variables	n=77
Age (year) ± SD	49.05±7.88
Parity (n) ± SD	2.03±1.03
Decrease in Hb* (g/dL) ± SD	1.58±0.84
BMI* (kg/m²) ± SD	27.12±3.80
Endometrial thickness (mm) ± SD	9.06±5.19
Premenopausal n (%) Postmenopausal n (%)	53 (68.8%) 24 (31.2%)
Preoperative endometrium evaluation Pathological n (%) Normal n (%)	 23 (29.8%) 54 (70.1%)
Final pathology Pathological n (%) Normal n (%)	 28 (36.4%) 49 (63.6%)

Hb: Hemoglobin, BMI: Body mass index, SD: Standard deviation, *: Statistically significant

Table 2. Preoperative endometrial histopathology results

Endometrial polyp n (%)	15 (19.5%)
Endometrial hyperplasia without atypia n (%)	5 (6.5%)
Endometrial hyperplasia with atypia n (%)	3 (3.9%)
Secretory endometrium n (%)	9 (11.7%)
Proliferative endometrium n (%)	9 (11.7%)
Atrophic endometrium n (%)	8 (10.4%)
Insufficient sample n (%)	28 (36.4%)
Total	77 (100.0%)

Table 3. Postoperative endometrial histopathology results

Endometrial polyp n (%)	15 (19.48%)
Endometrial hyperplasia without atypia n (%)	10 (12.99%)
Endometrial hyperplasia with atypia n (%)	3 (3.9%)
Secretory endometrium n (%)	16 (20.8%)
Proliferative endometrium n (%)	13 (16.88%)
Atrophic endometrium n (%)	20 (25.97%)
Total n (%)	77 (100.0%)

Table 4. Comparison of clinical, demographic, and sonographic characteristics according to final endometrial pathology

	Normal n=49	Pathologic n=28	p
Age ± SD	49.49±8.451	48.29±6.847	0.6
Parite ± SD	1.9796±1.14546	2.1071±0.78595	0.3
BMI (kg/m²) ± SD	27.43±4.082	26.57±3.259	0.5
Tamoxifen use duration (years) ± SD	2.83±2.07	4.52±2.97	<0.05*
Premenopausal n (%) Postmenopausal n (%)	34 (69.4%) 15 (30.6%)	19 (67.9%) 9 (32.1%)	0.5
Endometrial thickness (mm) ± SD	7.93±4.27	11.74±6.20	<0.05*
Decrease in Hb (g/dL) ± SD	1.5±0.81	1.6±0.89	0.7

SD: Standard deviation, BMI: Body mass index, Hb: Hemoglobin, *: Statistically significant

Table 5. Diagnostic concordance between preoperative endometrial biopsy and final hysterectomy pathology in tamoxifen-treated breast cancer patients

	Final pathology: pathologic	Final pathology: normal	Total
Preoperative pathologic	10	13	23
Preoperative normal	18	36	54
Total	28	49	77

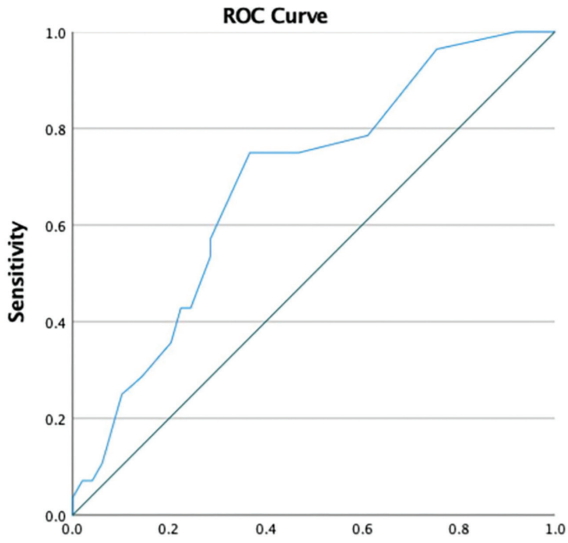

Figure 1. ROC curve demonstrating the diagnostic performance of endometrial thickness in predicting final histopathological outcomes in tamoxifen-treated breast cancer patients. AUC was 0.686 (SE: 0.062; 95% CI: 0.565-0.807; p=0.007), indicating moderate diagnostic accuracy. The optimal cut-off value determined by the Youden index was 7.5 mm, with 75.0% sensitivity and 63.3% specificity. A lower threshold of 4.5 mm yielded higher sensitivity (96.4%) but lower specificity (24.5%)

ROC: Receiver operating characteristic, AUC: Area under the curve, SE: Standard error, CI: Confidence interval

mm demonstrated higher sensitivity (96.4%) but markedly reduced specificity (24.5%), indicating an increased rate of false positives when using this more conservative cut-off (Figure 1).

Discussion

The primary aim of this study was to evaluate the relationship between endometrial thickness measured by TVUSG, preoperative endometrial biopsy results, and final hysterectomy pathology in breast cancer patients receiving tamoxifen therapy. Given tamoxifen's known estrogen agonist effect on endometrial tissue, there is growing concern regarding its potential to induce various endometrial pathologies, including hyperplasia and malignancy[9]. Understanding whether non-invasive imaging findings and biopsy results correlate with definitive surgical pathology is crucial for optimizing follow-up strategies and minimizing unnecessary interventions in this patient population. This study contributes to the existing body of literature by providing data from a surgically confirmed cohort, offering insights into the diagnostic reliability of TVUSG and endometrial biopsy in tamoxifen-treated breast cancer patients.

Preoperative endometrial biopsy demonstrated a moderate diagnostic performance, with a sensitivity of 53.6% and specificity of 71.4% in predicting pathological outcomes. The Cohen's Kappa coefficient was calculated as 0.248, indicating a low level of agreement between the preoperative biopsy and final hysterectomy pathology. While TVUSG provides moderate diagnostic discrimination, as evidenced by AUC values, biopsy is limited by sampling limitations that compromise reproducibility and concordance with final histopathological results, as reflected by the low kappa coefficient. This discordance may be explained by the heterogeneous or focal nature of endometrial lesions, insufficient tissue sampling, or pathology residing in areas not captured during biopsy[10]. A single biopsy sample may not accurately represent the entire endometrium; thus, relying solely on biopsy results may be insufficient for clinical decision-making in asymptomatic tamoxifen users. Therefore, a comprehensive assessment incorporating ultrasonographic findings, clinical symptoms, and-when indicated-surgical intervention is recommended to ensure accurate diagnosis and appropriate management.

Researchers found a statistically significant difference in tamoxifen usage duration between patients with and without endometrial pathology, indicating that longer exposure may be a contributing factor to endometrial abnormalities (4.52±2.97 years for patients with vs. 2.83±2.07 years for patients without, p=0.01). Extended tamoxifen use has been reported to increase the risk of conditions such as hyperplasia, polyps, and carcinoma due to its partial estrogen agonist effect on endometrial tissue[11]. These findings highlight the importance of implementing individualized monitoring protocols in long-term tamoxifen users, even in the absence of symptoms.

In asymptomatic patients, tamoxifen-associated subepithelial stromal hypertrophy may lead to thickened endometrium that does not accurately reflect histological pathology; it may also be affected by operator dependency and interobserver variability[12]. Consequently, standard screening tools such as TVUSG and blind endometrial biopsy have shown limited diagnostic value in detecting focal intrauterine lesions[13]. In contrast, when used selectively based on clinical indications, sonohysterography has demonstrated superior accuracy in identifying or excluding structural anomalies[14]. Although

tracking endometrial thickness may assist in risk stratification, interpretation must be approached cautiously in light of these limitations. The comparison of endometrial thickness between groups revealed a statistically significant difference, with higher measurements observed in patients with pathological outcomes. While ROC analysis demonstrated only moderate diagnostic capability (AUC: 0.686), certain threshold values showed clinical potential. A cut-off of 7.5 mm offered a balanced sensitivity and specificity, whereas lowering the threshold to 4.5 mm markedly increased sensitivity at the expense of specificity. These results underline that although thickened endometrium in asymptomatic tamoxifen users may raise suspicion, it should not be used in isolation for diagnostic decision-making due to its limited discriminative power. This interpretation is consistent with previous literature indicating that thresholds between 4 and 8 mm may hold clinical relevance in identifying endometrial pathology in tamoxifen users[15]. Moreover, reliance on endometrial thickness alone in asymptomatic individuals has been linked to unnecessary intervention[16]. Therefore, clinical symptoms-particularly postmenopausal vaginal bleeding-should remain the principal indication for further endometrial evaluation. This approach aligns with current guidelines from the American College of Obstetricians and Gynecologists, which recommend limiting endometrial assessment to symptomatic tamoxifen users[17].

This study has several strengths, including the integrated evaluation of endometrial thickness, preoperative biopsy findings, and final histopathological outcomes in a defined cohort of tamoxifen-treated breast cancer patients. The use of both TVUSG and histopathological confirmation strengthens diagnostic reliability, while ROC analysis adds clinical relevance by identifying practical threshold values. Additionally, systematic data collection enhances internal validity.

Study Limitations

However, limitations include the retrospective design, which may introduce selection bias due to the inclusion of only those patients undergoing hysterectomy for benign indications. The modest sample size restricts generalizability, and factors such as cumulative tamoxifen dose, hormonal milieu, and other endometrial risk factors were not evaluated. Moreover, the low sensitivity of preoperative endometrial biopsy observed in this study highlights its limited utility in predicting final pathology. Prospective, multicenter studies with larger populations are warranted to confirm and expand upon these findings.

Conclusion

In conclusion, the agreement between preoperative endometrial biopsy and final hysterectomy pathology was found to be low, highlighting the limited diagnostic reliability of biopsy in tamoxifen-treated patients. Likewise, endometrial thickness measured by TVUSG alone demonstrated limited predictive value for detecting pathology in asymptomatic individuals. In the presence of vaginal bleeding, endometrial biopsy should be performed even if TVUSG shows a normal endometrial thickness. Nevertheless, when endometrial thickness exceeds specific thresholds—particularly in patients with prolonged tamoxifen use—more vigilant clinical follow-up may be warranted. These findings emphasize the need for individualized surveillance strategies that strike a balance between early detection and the risk of overdiagnosis and overtreatment. To optimize endometrial monitoring and inform future clinical guidelines, further prospective, large-scale studies are required in this patient population.

Ethics

Ethics Committee Approval: The study complied with the Declaration of Helsinki, and approval was obtained from the Scientific and Ethical Committee for Medical Research at University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital before starting the system search (approval number: 2025:3-17, date: 10.04.2025).

Informed Consent: A retrospective observational study was conducted on 77 tamoxifen-treated breast cancer patients who underwent hysterectomy between January 1, 2020; and January 1, 2025.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., A.H.İ., Concept: S.K., A.K., A.H.İ., Design: İ.U., Data Collection or Processing: A.K., S.K., U.D., Analysis or Interpretation: S.K., U.D., Literature Search: A.K., S.K., U.D., Writing: S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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