ARAŞTIRMA MAKALESİ/ ORIGINAL ARTICLE

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Tamoksifen Tedavisi Alan Opere Meme Kanserli Hastalarda Endometrial Patolojiler, Risk Faktörleri ve Tanıda Transvajinal Ultrasonografinin Rolü

Endometrial Pathology, Risk Factors and The Diagnostic Value of Transvaginal Ultrasonography in Breast Cancer Patients Treated with Tamoxifen

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ÖZ

GİRİŞ ve AMAÇ: *Meme kanseri tedavisi için tamoksifen kullanan hastalarda tamoksifenin endometriyum üzerine yaptığı değişikliklerin histopatolojik ve ultrasonografik olarak değerlendirilmesi ile bu değişikliklerin hipertansiyon, obezite, diabetes mellitus ile ilişkisini araştırılması amaçlanmıştır.*

GEREÇ ve YÖNTEM: *Eğitim ve Araştırma Hastanesi Kadın Doğum Kliniği'nde, Ocak 2007 - Ocak 2012 yılları arasında meme kanseri nedeni ile opere olan ve tamoksifen kullanan hastalar dahil edilmiştir. Tranvaginal ultrasonografi (TVUSG) ile endometriyal görüntülemesi yapılan 128 hastada endometrial örnekleme yapulmış ve histopatolojik sonuçlar değerlendirilmiştir.*

BULGULAR: *Endometrium kanseri saptanan olgularda TMX kullanım süreleri ortalama 4,43 yıl, endometrium kalınlığı ortalama 17,83 mm, malignite saptanmayan olgularda ise tamoksifen kullanım süresi ortalama 2,72 yıl ve endometrium kalınlığı ortalama 9,3 mm idi.*

Yapılan ROC eğrisi ile endometrial kalınlık cut-off değeri 8.5 mm ve üzeri olarak alındığında endometrial patolojileri (endometrium kanseri, endometrial hiperplazi, endometrial polip) TVUSG ile %88.3 sensitivite ve %76,5 spesifisite ile belirlenebileceği saptandı. Eğer cut-off değeri 9,5 mm ve üzeri olarak alınırsa sensitivite %83.3'e gerilerken spesifisite %82,4'ye çıkmaktaydı. Endomerium kanseri saptanan olguların %100'ü hipertansif ve diabetes mellitusu olan hastalardı.

TARTIŞMA ve SONUÇ: *TMX endometrium kanseri yönünden risk faktörü olarak bilinen hipertansiyon ve diabetes mellituslu hastalarda endometrium kanseri gelişimini belirgin olarak tetiklemektedir. Bu risk ilacın kullanım süresi arttıkça artmaktadır. Risk faktörü olan hastalarda takipte ultrasonografik olarak endometrium kalınlığının cutt off değerinin 8.5 mm olarak alınması tüm endometrial patolojileri belirlemede yüksek sensitivite ve spesifisiteye sahiptir.*

Anahtar Kelimeler: *tamoksifen, endometriyal kanser, ultrasonografi*

ABSTRACT

INTRODUCTION: *The aim of the study was to demonstrate the histopathological and ultrasonographic changes of endometrial tissue due to the tamoxifen use and to evaluate the affect of hypertension, obesity and diabetes mellitus on endometrial alteration.*

METHODS: *One hundred and twenty eight patients who were administered tamoxifen at Training and Research Hospital between 2007-2012 were included to the study. Patients were checked annually with transvaginal ultrasonography underwent endometrial sampling in case of endometrial thickness > 5 mm and/or uterine bleeding.*

RESULTS: *The mean time of tamoxifen treatment and the mean endometrial thickness were 4,43 years and 17,83 mm respectively at patients with endometrial cancer. Whenever compared with those cases without malignancy, the mean time of tamoxifen treatment and the mean endometrial thickness is 2,72 years and 9,3 mm respectively.*

The specificity and the sensitivity of transvaginal ultrasonography at detecting endometrial pathologies are 76.5% and 88,3% respectively when cut-off value of endometrial thickness was accepted as 8,5 mm. When the cut-off value was accepted 9,5 mm, the sensitivity decreased to 83,3% and specificity increased to 82,4%.

DISCUSSION and CONCLUSION: *Tamoxifen precipitates the development of endometrium cancer markedly in the patients with hypertension and diabetes mellitus. The increased duration of tamoxifen use is directly proportional with increasing risk of endometrial cancer. In patients with these risk factors, the sonographic follow-up criteria of endometrial thickness cut-off value should be accepted as 8,5 mm to obtain better result with higher sensitivity and specificity.*

Keywords: *Tamoxifen, endometrial cancer, ultrasonography*

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INTRODUCTION

Breast cancer is the most common cancer in women and the most common cause of death after lung cancer worldwide (1, 2, 3). Anti-estrogen drugs have become very popular with the recent studies focused on the role of estrogen on breast cancer etiology. Tamoxifen, a non-steroid anti-estrogen agent has become the most challenging progress explored at 1973 has become an indispensable treatment option in breast cancer.

Endometrium cancer is the most common gynecologic malignancy worldwide (3, 4, 5) and the second most common gynecologic cancer in Turkey with the 1,3% mortality rate among all cancer cases according to 2006 Turkey Health Statistics data. There are several risk factors associated with estrogenic environment. TMX treatment is one of the important risk factor at patients with breast cancer.

Tamoxifen is a selective estrogen receptor modulator often used in treatment of breast cancer because of the anti-estrogenic impact (6, 7, 8) however tamoxifen has estrogenic impact on endometrial tissue (8, 9, 10) therefore the risk of development of endometrial cancer rises 2- or 3-fold. Affects and side effects are associated with the time and dose of the drug. Although the behavior of endometrial cancer is similar to the normal population at patients with 20 mg/day of tamoxifen use, at higher dose (40 mg/day) the tumor characteristics got more aggressive (8, 9).

In our retrospective study, we aim to demonstrate the relationship between endometrial hystopathology and transvaginal ultrasonography (TVUSG) in breast cancer patients treated with tamoxifen and with that underwent endometrial sampling.

MATERIAL and METHOD

Patients with breast cancer who were administered tamoxifen between 2007-2012 at the gynecology clinic of Şişli Hamidiye Etfal Training and Research Hospital were included to our study.

Age, parity, gravity, body mass index, endometrial thickness, time interval of tamoxifen treatment, hypertension and diabetes mellitus history and histopathologic diagnosis after endometrial sampling were studied retrospectively. Patients were divided in 3 groups according to the endometrial thickness such as ≤5 mm, 5-10 mm and ≥10 mm. Moreover histopathologic diagnosis was grouped depending on the presence or the absence of estrogenic effect of TMX on the endometrium.

The relationship between the most pathologic impact of estrogenic effect as endometrium cancer rate and TMX treatment duration, age, parity, menstruation time, obesity, hypertension, diabetes mellitus is studied additionally. The cut-off values targeting the sensitivity and specificity rates of endometrial thickness shown with TVUSG in order to define the endometrial cancer have measured via the ROC equation.

The body mass indexes of the patients are calculated with the help of “body weight (kg) / total body area (m2)” formula. The specification has done according to World Health Organization criteria as 18,5-25 kg/m2 is normal, 25-30 kg/m2 is overweight and ≥30 kg/m2 is obese.

For the statistical analysis of the study, SPSS 18.0 (Statistical Package for Social Sciences) for Windows application was used. The data is analysed with the help of some statistical methods such as the mean calculation and standard deviation. Also the Fisher's exact test, Ki-Square test comparing and independent samples t test are used while the qualitative data.

RESULTS

At 89 (69,5%) patients, histopathologic examination revealed endometrium under estrogen effect, however in the remaining group (n=39; 30,5%) there was no estrogen effect.

Six (4,7%) patients had endometrioid endometrial cancer, 12 (9,4%) patients had hyperplasia without atypia, 6 (4,7%) patients had complex hyperplasia with atypia, 12 (9,4%) patients had irregular proliferative endometrium, 35 (27,3%) patients had endometrial polyp and 18 (14,1%) patients had endometrium under estrogen effect. Patients with no endometrial estrogen effect, 15 (11,7%) patients had atrophic endometrium and 24 (18,8%) patients had normal endometrium epithelia. Consequently, 59 (%46,1) patients had pathological endometrial sampling such as malignancy, endometrial polyp, hyperplasia and of these

patients, 6 (%4,7) had malignancy. The distribution of these results is shown in Figure 1.

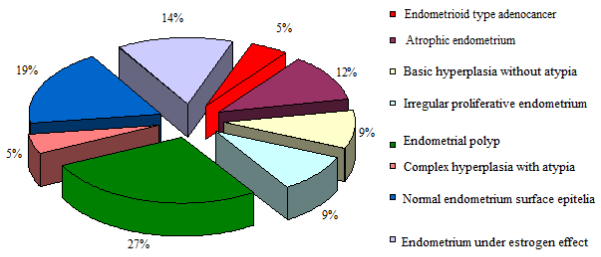

Figure-1. The distribution of endometrial sampling results.

The mean age was 50.95 (range=34-82; SD: 9,72). At patients with endometrial cancer, the mean age was 59,5 (range=53-67, SD: 6,15) and of the remaining group without malignancy (n=122) the mean age was 50,53 (range=34-82, SD: 9,68). This difference was statistically significant (p: 0.006)

The mean time of tamoxifen treatment was 2,8 years (range=0,5-6 years, SD: 1,49). At patients with endometrium cancer the mean time of tamoxifen use was 4,43 years (SD: 1,03) however patients without malignancy the mean time was 2,72 years (SD: 1,47) and it was statistically significant (p: 0,009).

The mean duration of tamoxifen treatment at patients who had endometrium under estrogen effect was 2,99 years (SD: 1,5) and of those cases without estrogen effect was 2,35 years (SD: 1,21). The increasing duration of tamoxifen use is directly proportional with the increasing number of patients with the findings of estrogen effect however this difference was not found statistically significant (p: 0,189)

In patients less than one year tamoxifen use (n=26) the percentage of any pathological presentation (endometrium cancer, hyperplasia, polyp) was 42,3%. However, at patients with tamoxifen use for 1 to 5 years or more than five year, the percentage of any pathological presentation increases to 45,2% and 55% respectively.

The mean endometrial thickness was 9,7 mm (range=3-22 mm, STD: 4,47). The mean endometrial thickness was 17,83 mm (STD: 2,78) and 9,3 mm (STD: 4,14) at patients with endometrial cancer and without endometrial cancer respectively. Endometrial thickness was over 10 mm at all patients with endometrium cancer however it differs at patients without malignancy (>10 mm (n=47, 38,5%); 5-10 mm (n=43; 35,2%) and 5< mm (n=32; 26%)).

The mean endometrial thickness was 11,8 mm (STD: 3,6) at the patients with estrogen effect meanwhile it was 4,8 mm (STD: 0,85) at patients with no estrogenic effect and it was statistically significant (p: 0,001).

At ROC curve analysis, the cut-off value was determined 8,5 mm. At this point, endometrial pathologies such as endometrium cancer, endometrial hyperplasia, polyp can be detected by transvaginal ultrasonography with the 88,3% sensitivity and 76,5 specificity. However limiting the cut-off value at 9,5 mm, sensitivity decreases to 83,3% and specificity increases to 82,4%. AUC (area under the curve): 0,883 (95% CI 0,824–0,943) (p=0,0001) (Figure 2).

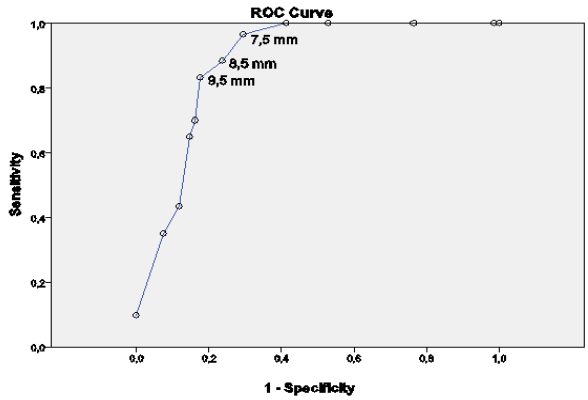

Figure-2: Endometrial thickness ROC curve cut-off value.

Table 1 shows the association between the results of endometrial sampling and the demografic features.

The mean BMI was 28,31 (STD: 4,07) (range=21,64-42,32).

The mean BMI was 38,29 (STD: 2,40) at patients with endometrial cancer while that of the malignancy-free patients the mean BMI was 27,81 (STD: 3,46). This difference found to be statistically significant (p=0,001).

The mean BMI of the cases with the findings of estrogen effect was 29,6 (STD: 3,8) while that of no

estrogen effect detected was 25,3 (STD: 2,8). Also that was found to be statistically significant (p: 0,001).

Tablo 1. The Association between The Demographic Features and The Endometrial Sampling Results

Endometrial Sampling Results		Age (year)	Parity	Endometrium Thickness (mm)	Menstrually Active Time (year)	BMI	HT	DM
Adenocancer Endometrioid Type	Mean	59,5	3,67	17,8	38,33	38,29	1,00	1,00
	Std.Deviation	6,1	1,211	2,78	2,251	2,4	0	0
Atrophic Endometrium	Mean	56,5	4,20	4,3	29,87	26,03	,40	,60
	Std.Deviation	10,03	1,082	,61	3,944	3,37	,507	,507
Basic Hyperplasia without Atrophy	Mean	52,0	3,00	13,5	30,83	30,11	,17	,58
	Std.Deviation	9,0	,953	3,14	4,933	2,58	,389	,515
Irregular Proliferative Endometrium	Mean	46,5	3,17	10,8	28,00	28,13	,33	,25
	Std.Deviation	8,76	,835	3,15	3,542	2,75	,492	,452
Endometrial Polyp	Mean	49,7	2,83	11,1	31,74	28,8	,57	,34
	Std.Deviation	8,8	1,524	2,26	5,564	3,31	,502	,482
Complex Hyperplasia with Atrophy	Mean	53,6	1,33	16,8	36,00	32,3	,83	,50
	Std.Deviation	7,5	1,366	,98	6,693	2,54	,408	,548
Normal Endometrium Surface Epithelia	Mean	49,50	3,13	5,1	30,63	24,8	,46	,21
	Std.Deviation	7,684	1,035	,85	4,959	2,3	,509	,415
Endometrium Under Estrogen Effect	Mean	49,06	3,06	9,0	28,78	28,06	,33	,39
	Std.Deviation	13,206	2,155	3,1	7,313	2,58	,485	,502
Total	Mean	50,95	3,09	9,7	30,97	28,3	,47	,41
	Std.Deviation	9,724	1,471	4,4	5,690	4,073	,501	,493

BMI:BodyMassIndex, DM:DiabetesMellitus, HT:Hypertension, TMX:Tamoxifen.

The mean parity was 3,09 (STD: 1,47). (range=0-9)

The mean parity was 3,67 (STD: 1,21) and 3,07 (STD: 1,48) at patients with endometrial cancer and without endometrial cancer and it was not statistically significant (p: 0,691).

The mean duration between menarche and menopause was 30,97 years (range=19 -46 years).

The mean menstrual-active timespan at patients with endometrium cancer was 38,33 years (STD: 2,51) and that of without any malignancy was 30,61 years (STD: 5,56) and was statistically significant (p: 0,003).

The mean menstrual-active timespan at patients with endometrium under estrogen effect was 31,25 years (STD: 6,12) and endometrium without estrogen effect was 30,33 years (STD: 4,15) and was statistically significant (p: 0,009)

68 patients had hypertension at medical records. Patients with endometrial cancer, all had hypertension. At patients with no malignancy, 54 (44,3%) patients had hypertension and 68 (55,7%) patients had no hypertension. This difference was statistically significant (p: 0,008)

52 patients had diabetes mellitus at medical records. Patients with endometrial cancer, all had diabetes mellitus. At patients with no malignancy, 46 (37,7%) patients had diabetes mellitus and ıt was statistically significant (p: 0,008)

Patients with endometrium under estrogen effect, 43 (48,3%) had hypertension and 52 (40.6%) diabetes mellitus. At the group with no endometrial estrogen influence, 17 patients (43,6%) had hypertension and 14 patients (35,9%) had diabetes mellitus. The difference was statistically significant (p: 0,010; p: 0,010).

DISCUSSION

Tamoxifen is the first selective estrogen receptor modulator used as hormonal treatment for breast cancer since 1971 (6). Tamoxifen is both an antagonist and an agonist of the estrogen receptor that's why the treatment may exhibit some unwanted estrogenic effects (6, 7, 8, 9).

Endometrial cancer risk due to tamoxifen therapy has already been confirmed and reports of endometrial cancers diagnosed among women receiving tamoxifen therapy for breast cancer began to appear in the literature as early as 1985 (10). According the published NSABP B-14 study the women treated with tamoxifen found to have significantly higher risk for developing endometrium cancer (11). Also it is found that specific risk is 0,6/1000 in the placebo group and 2/1000 in the tamoxifen group whose mean treatment duration is 35 months (11, 12, 13).

In our study, the percentage of the patients that have a malignancy according to histopathologic data was 5%. Besides that the endometrium cancer incidence is found 2,5 fold in our cases treated with tamoxifen to the general population. As it can be seen in other studies, tamoxifen has an estrogenic effect on endometrium and create a magnified risk for endometrium cancer. It is suggested by National Surgical Adjuvant Breast and Bowell Project (NSABP) that tamoxifen therapy duration of 5 years should be adequate (11). The benefits of a longer therapy are still being investigated. But prolonged usage of tamoxifen (>5 years) obviously increases the endometrium cancer risk (12, 13, 14, 15). In our study, the mean tamoxifen treatment duration of the patients with malignancy is 4,33 years while that without malignancy is 2,72 years. The incidence of endometrial pathologies of 26 patients whose tamoxifen usage was less than a year is 42,3%, 82 patients treated 1-5 years was 45,2% and 20 patients treated more than 5 years is 55%. These findings are compatible with the other published studies.

The incidence of the pathologies related to estrogen effect is found to be increased among the patients took tamoxifen therapy (16, 17). That incidence of endometrial pathologies differs between 15-61% (176). Maugeri et al. recorded the incidence of endometrial polyp in tamoxifen treatment group as 13,7% (18). Also Lahti et al. noted that as 36% (16, 17). Our results are similar to the other studies so the most common endometrial pathology is found to be polyp with 27% incidence. Additionally basic and complex

hiperplasia have 14% and endometrium cancer has 5% incidence.

It's identified that the demographic characteristics of the patients treated with tamoxifen has an impact on arousal of malignancy from an underlying endometrial polyp or a hyperplasia (18, 19, 20). The factors such as age (p: 0,008), DM (p: 0,002), menstrual-active time (p: 0,003), obesity (p:0,001) get along well with other studies focusing on combination of additional risk factors and increasing of malignancy incidance. The only factor that is not significantly different is parity (p: 0,091). Both the tamoxifen of which the estrogenic effect is an important risk factor for endometrium cancer and the demographic characteristics of the patients bunch together and generate a cumulative effect on progression of endometrium cancer. All these aspects suggest giving priority to aromatase inhibitory agents like exemestane as a fine alternative to tamoxifen in treatment of breast cancer in order to eliminate estrogenic effects on endometrium in the patients that have multiple risk factors for cancer.

Several studies take different cut-offs for endometrial ultrasonographic examination of asymptomatic postmenopausal women. Tsuda et al. establish 2,3% of endometrial pathology out of 1400 asymptomatic postmenopausal women in their study (20). When the cut-off is taken 3 mm for TVUSG they obtain 90% sensitivity and 84% specificity (20). Moreover that a low cut-off obviously cause lots of unnecessary procedures hence the increasing complication rates become inevitable. Gambacciani et al. declare only 1 cancer case out of 850 postmenopausal women in their retrospective study by stating the endometrial thickness cut-off as 5 mm. There was a suspicious benign endometrial pathology in 147 patients thereby a confirmation needed via hysteroscopy and results exposed 93,2% false positivity (22).

The leading cause of these differentiated studies is higher endometrial pathology risk among women treated with tamoxifen. Fishman et al. described their findings about increasing of endometrial thickness as much as 0,75 mm per year and approximately 12 mm (6-21 mm) increment is seen afterwards the 5 year-long tamoxifen treatment in their study (23). Markovitch et al. examined 279 patients treated with tamoxifen. The endometrial thicknesses grouped as 5-7,5 mm, 12,5-15 mm and >15 mm. There was no cancer detected under 5 mm. The detailed analysis revealed the best cut-off as 15 mm with 37,5% sensitivity and 87,2% specificity (24). Develioğlu et al. relatively evaluated 60 patients treated with tamoxifen via TVUSG and sonohisterography. The best results found as 9,5 mm for TVUSG (80% sensitivity, 74% specificity) and 5,5 mm for sonohisterograph (60% sensitivity, 91% specificity). Also, the sensitivity and specificity found as 60% and 100% respectively via sonohisteroscopy in the cases of polypoid endometrial pathologies (25).

The mean endometrial thickness of patients with malignancy found via TVUSG was 17,33 mm and that of without malignancy was 9,3 mm according to the results of our study. Endometrium cancer was seen in between 15-22 mm, hyperplasia 7-18 mm and polyp 8-18 mm. Endometrial thickness was over 10 mm in all patients with endometrium cancer but for patients without malignancy only 38,5% of detected as above 10 mm. The higher endometrial thickness of patients with malignancy is significant (p: 0,012). When the endometrial thickness cut-off value as 8,5 mm is determined, endometrial pathologies (endometrium cancer, endometrial hyperplasia, polyps) can be detected via TVUSG with 88,3% sensitivity and 76,5 specificity. However limiting the cut-off value at 9,5 mm decreases sensitivity ratio to 83,3% and increases the specificity ratio to 82,4%.

Before starting tamoxifen treatment, the patients should be informed about obesity as a avoidable risk factor and encouraged for extra-weight loss.

Hence the increased duration of tamoxifen treatment is directly proportional with the increasing endometrial thickness, TVUSG becomes an ideal advantage for screening endometrial pathologies. Also, setting the cut-off value higher to that of asymptomatic postmenopausal women's can direct preferably and substantially decrease the unnecessary procedures.

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