Original Article

Elastosonographic Evaluation of Endometrium in Women Using Tamoxifen for Breast Cancer

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Abstract

Objectives: A prospective case–control study was carried out to assess the value of elastosonography in identifying endometrial pathology in women using Tamoxifen (TAM) for breast cancer. **Materials and Methods:** In total, 66 women using TAM for breast cancer were enrolled for the study with 61 premenopausal and 61 postmenopausal healthy controls. Ultrasonographic findings (strain ratio, endometrial thickness) were evaluated in regard to the duration of TAM usage, histopathological findings, and menopausal status. **Results:** Patients with endometrial cancer (EC) and cystic endometrial hyperplasia (CEH) were found to have longer duration of TAM usage, increased endometrial thickness, and higher strain ratios compared with controls. A significant positive correlation was found between duration of TAM usage, endometrial thickness, and the strain ratios. Endometrial thickness and the strain ratios were significant predictors for groups under risk. Cutoff values for endometrial thickness, strain ratios, and duration of TAM usage were 12.55 mm, 2.46, and 18 months in premenopausal group and 7.75 mm, 7.70, and 32 months in postmenopausal group to predict risky population, respectively. **Conclusion:** Endometrial tissue strain ratio was found to be significantly increased in cases with endometrial pathologies. Addition of elastosonography modality to B-mode may improve the diagnostic accuracy during the follow-up of women using TAM for breast cancer.

Keywords: *Breast cancer, elastosonography, endometrium, Tamoxifen*

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Introduction

Ultrasound strain imaging is relatively a new technique, which is performed using a transducer obtaining radiofrequency echo data during manual freehand compressions of the tissue. This modality images the strain or stiffness distribution throughout an organ in response to an applied stress. The technique is currently being used mainly for differential diagnosis of masses in breast and thyroid imaging. Although preliminary results had been reported for applications in gynecology and obstetrics, the technique is still not in routine clinical practice.[1-5] The majority of elastosonographic studies in obstetrics discipline is focused on uterine cervix but not endometrium.[6,7]

Tamoxifen (TAM) is a triphenylethylene with a selective estrogen-receptor modulator (SERM) action that has estrogen agonistic or antagonistic effects in different tissues depending on estradiol concentration.[8] TAM is a widely used medication prescribed as an adjuvant therapy in treatment of breast cancer at any stage irrespective of nodal and receptor status.[9] The usual recommended dose is 20 mg/day; higher doses add on increased toxicity without any proven additional benefits.[10] The effect is paradoxic with antiestrogenic effect on mammary tissue, while estrogenic on endometrium and coagulation system leading to a potential risk of developing endometrium cancer and venous thrombosis during treatment of breast cancer.[11,12]

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Various effects of TAM on endometrium other than cancer can be observed during ultrasonographic examination including endometrial thickening, polyps, heterogeneous endometrial echo texture, and accumulation of endometrial fluid. The histopathological reports of endometrial tissue samples ranged from adenomatous endometrial polyps, endometrial cystic atrophy, adenomatous hyperplasia to mucosal endometrial adhesions.[13-17] Although the optimal endometrial screening modality still remains controversial, transvaginal sonography alone is usually adequate in asymptomatic patients. However, a more detailed evaluation is needed in patients where the endometrial line is irregular. Although being an invasive procedure, endometrial tissue sampling is still the gold standard to rule out a malignancy and used liberally by many gynecologists.[18,19]

Finding a noninvasive way to accurately diagnose the cause for uterine bleeding in women on TAM would avoid the physician to perform unnecessary interventions. In this article, we present preliminary results that illustrate the ability of ultrasound strain imaging to differentiate endometrial pathologies [endometrium cancer (EC) and cystic endometrial hyperplasia (CEH)] from normal endometrium in regard to elastosonographic changes in stiffness and elasticity of endometrium in women with breast cancer who are under TAM therapy.

Materials and Methods

Selection of groups

A prospective case–control study was performed at a tertiary referral hospital between March 2015 and August 2015. The study was approved by the scientific and bioethical review board (IRB No. 11.03.2015/735).

About 66 women with history of breast cancer who are under TAM therapy (20 mg/day) were included in the study. Because of potential changes in the elasticity of endometrium and adjacent myometrium, all patients with adenomyosis, submucosal fibroids, a history of previous uterine surgery (including myomectomy), endometrial interventions such as endometrial ablation, polyp removal, hysteroscopic interventions (except diagnostic hysteroscopy), endometrial sampling within one year, women having ultrasonographically detected retroverted uterus, presence of intrauterine device, and those under hormone replacement therapy or refusing to participate were excluded from the study. The women with the sonographic finding of a retroverted uterus were excluded because of the technical difficulty of compressing a retroverted uterus not as easily as an anteverted uterus even with transvaginal approach. The control group was comprised of 122 healthy subjects in two groups with the same criteria of exclusion: 61 in premenopausal and 61 in postmenopausal period [Figure 1]. Written informed consents were obtained from all the participants.

Elastosonographic evaluation of endometrium

All ultrasonographic examinations including B-mode scanning and elastosonography were performed by using the same commercially available ultrasound equipment (Hitachi RTE, HI VISION, Preirus, Japan) and the same transvaginal transducer (V53W transvaginal probe) with a frequency range of 5–7 MHz. The images were acquired by the same single operator, blinded to the study design, and having >10 years of experience in obstetrical sonographic imaging. All examinations were performed in dorsal lithotomy position with an empty bladder. Endometrium was visualized in the sagittal plane of uterus with a clear view of endometrium and adjacent myometrium. After placing the endovaginal probe in the anterior fornix of vagina, a clear view of endometrium was obtained. Elastosonography was performed by freehand technique (applying light repetitive compressions to the region of interest, each lasting around 1 s). Dual mode screen was used for displaying B-mode and elastosonography side-by-side on screen. A sinusoidal wave form was obtained after four to five compression–decompression cycles. We selected the most symmetrical waveform and compared the radiofrequency signals at the peak of the compression and at the through of the decompression in the same cycle. Elastosonographic color mapped images were translucent and overlapping the gray scale images. A color scale ranging from blue to red representing the degree of tissue elasticity was displayed on the screen; red signals representing the tissues with highest elasticity and blue signals representing tissues with lowest elasticity. The reference point for elastosonography was the adjacent myometrial tissue. Circles ranging from 3 to 5 mm were placed to the region of interest (ROI) of both the endometrium (A) and the adjacent myometrium (B). The stiffest endometrial tissue area was selected in patients receiving TAM. Strain ratios demonstrated as B/A value were calculated and displayed automatically by the embedded software of the sonographic equipment [Figure 2].

Statistics

The data were analyzed by the commercially available software, Statistic Package for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.), and Microsoft Office Excel 2007 software for calculations of Youden Index. The relevance of the distribution of continuous variables such as age, endometrial thickness and duration of TAM usage in months were evaluated with Shapiro–Wilk test. The continuous variables were expressed as median [interquartile range (IQR)] and categorical

variables as *n* (%). Mann–Whitney *U*-test was used to compare the study group with control group in regard to age, parity, and endometrial thickness. Receiver operating characteristic (ROC) analyses were performed in order to find out if endometrial thickness, and B/A values in elastosonography could predict the risk group for pathological endometrial changes (endometrium cancer and cystic endometrial hyperplasia). The area under curve (AUC) ± standard error (SE) of AUC in ROC analyses was given within 95% confidence interval. The cutoff values for endometrial thickness and B/A were calculated with Youden index. The sensitivities and specificities of cutoff values were calculated. Spearman's Rho correlation coefficient is calculated for the relation between the endometrial thickness, duration of Tamoxifen usage in months, and B/A values of elastosonography. A $P < 0.05$ was considered as statistically significant.

Results

The median of age and parity were 48.50 (IQR = 11.00) years, 3.00 (IQR = 2.00) for 66 patients in TAM

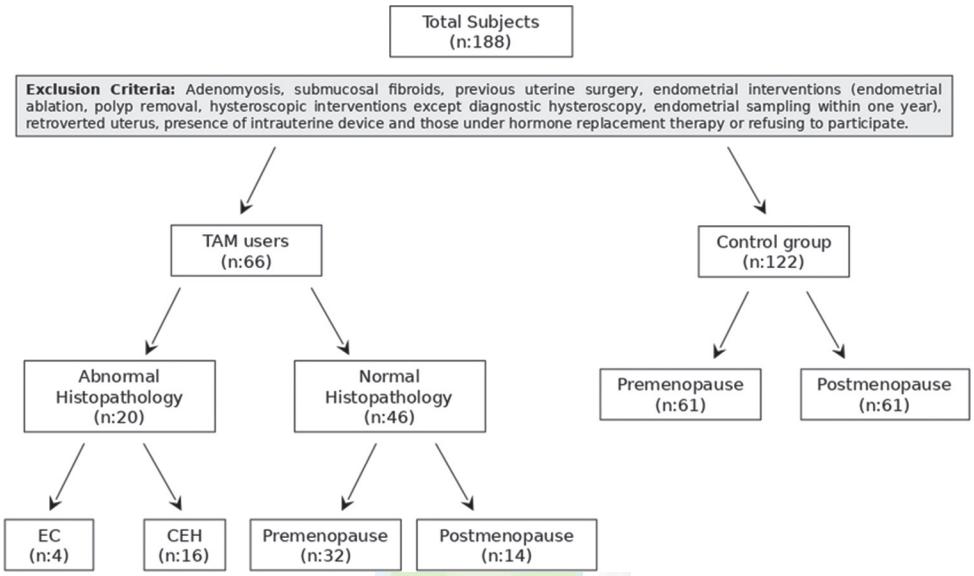

Figure 1: Patient selection and distribution. TAM=Tamoxifen; EC=Endometrial cancer; CEH=Cystic endometrial hyperplasia

Table 1: Descriptive statistics of cases

	TAM[1] Users				Controls		
	Abnormal histopathology		Normal histopathology				
	End. Ca.[2] (*n*=4)	CEH (*n*=16)	Premenopausal (*n*=32)	Postmenopausal (*n*=14)	General (*n*=122)	Premenopausal (*n*=61)	Postmenopausal (*n*=61)
Age (year)							
Median (IQR)	62.50 (13.00)	49.50 (12.00)	46.00 (5.00)	53.00 (9.00)	50.00 (22.00)	35.50 (10.00)	57.00 (5.00)
Min - Max	60.00 - 76.00	41.00 - 55.00	40.00 - 51.00	40.00 - 60.00	31.00 - 63.00	31.00 - 49.00	50.00 - 63.00
Parity							
Median (IQR)	2.50 (3.00)	3.00 (2.00)	3.00 (1.00)	4.00 (4.00)	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)
Min - Max	0.00 - 4.00	2.00 - 4.00	0.00 - 5.00	0.00 - 5.00	0.00 - 5.00	0.00 - 4.00	0.00 - 5.00
Duration of TAM use (month)							
Median (IQR)	37.00 (25.00)	24.00 (32.00)	12.00 (12.00)	6.00 (21.00)	-	-	-
Min - Max	12.00 - 44.00	6.00 - 48.00	6.00 - 30.00	4.00 - 28.00	-	-	-
Endometrial thickness (mm)							
Median (IQR)	20.90 (7.63)	14.30 (6.70)	9.85 (2.15)	7.90 (5.33)	3.00 (1.05)	3.20 (0.95)	2.60 (0.90)
Min - Max	12.30 - 22.40	7.30 - 23.00	7.80 - 18.30	7.30 - 14.80	1.80 - 5.00	2.30 - 5.00	1.80 - 4.10
B/A ratio							
Median (IQR)	51.15 (5.88)	3.71 (1.19)	1.98 (1.38)	1.86 (1.55)	1.14 (0.24)	1.05 (0.16)	1.27 (0.28)
Min - Max	46.01 - 53.66	1.42 - 9.50	0.87 - 3.09	1.04 - 5.89	0.83 - 2.78	0.83 - 1.27	1.00 - 2.78

[1]Tamoxifen, [2]Interquartile range

using group and 50.00 (IQR = 22.00) years, 3.00 (IQR = 1.05) for 122 women in control group, respectively. The median of duration of TAM usage was 12.00 (IQR = 12.00) months. The descriptive statistics of TAM users and the controls were summarized in Table 1. The distribution of endometrial thickness and B/A ratios across groups using TAM were shown in Figures 3 and 4, respectively.

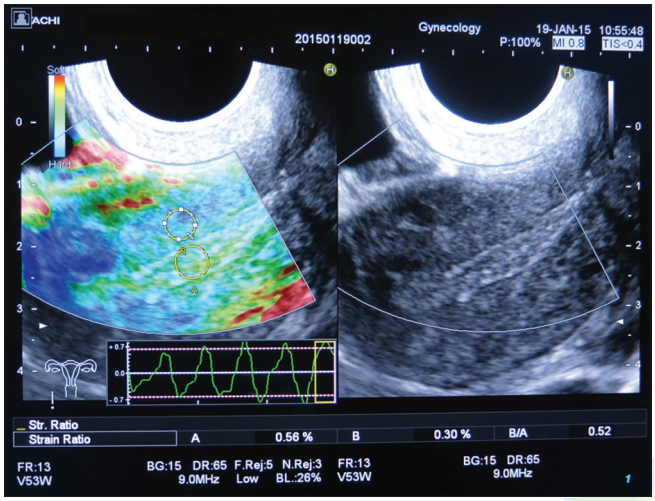

Figure 2: Elastosonography technique

Endometrial sampling was performed for all women using TAM, with 20 of them having the complaint of uterine bleeding. After histopathological examination, there were 4 patients diagnosed to have endometrium cancer and 16 patients to have complex endometrial hyperplasia, all having the complaint of uterine bleeding. All of the four cases of endometrium cancer were within the postmenopausal TAM users. Median age of the four patients with histologically confirmed endometrial cancer was 62.50 (IQR = 13.00) years. The medians of parity, duration of TAM usage, and endometrial thickness in endometrial cancer patients were 2.50 (IQR = 3.00), 37.00 (IQR = 25.00) months, 20.90 (IQR = 7.63) mm, respectively.

The strain ratios were found to be significantly higher in cases with endometrium cancer ($P < 0.001$) [Table 1]. Because of very low number of cases with endometrium cancer, endometrium cancer and endometrial hyperplasia cases were united to form a new group named "abnormal pathology group" in order to be evaluated statistically. The median age of abnormal pathology group was 54.00 (IQR = 12.00) years, while median age of remaining 46 patients with no complaint of uterine bleeding and normal histopathological examination was 48.00 (IQR = 6.00) years, and groups

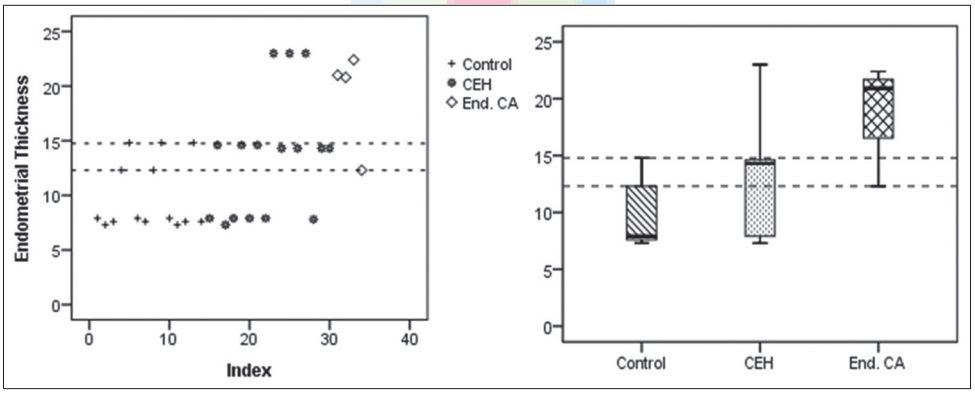

Figure 3: Distribution of endometrial thickness across groups using TAM. (Normal histopathology group using TAM is assigned here as control group). TAM=Tamoxifen; CEH=Cystic endometrial hyperplasia; End. ca.=Endometrium cancer

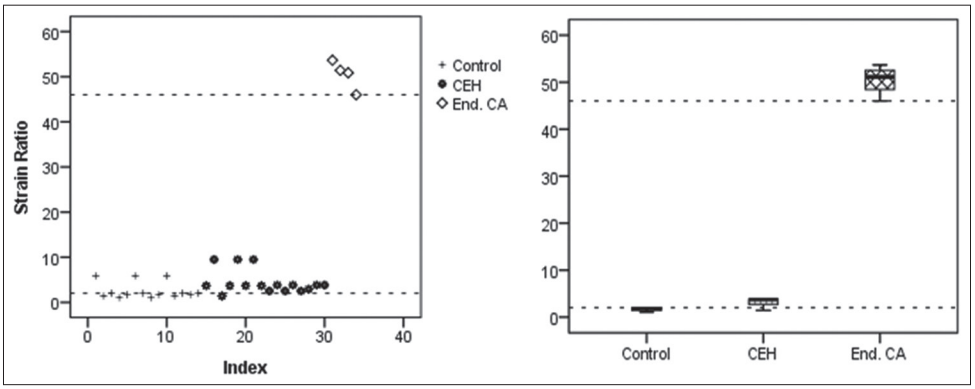

Figure 4: Distribution of strain ratios (B/A) across groups. TAM=Tamoxifen; CEH=Cystic endometrial hyperplasia; End. ca.=Endometrium cancer

Table 2: Comparison of cases with abnormal histopathology and with normal histopathology in the group of TAM users

	TAM[1] Users						*P*-values*		
	Abnormal histopathology, Median (IQR[2])			Normal histopathology, Median (IQR)					
	General (*n*=20)	Premenopausal (*n*=8)	Postmenopausal (*n*=12)	General (*n*=46)	Premenopausal (*n*=32)	Postmenopausal (*n*=14)	*P*1[a]	*P*2[b]	*P*3[c]
Age (year)	54.00 (12.00)	43.00 (2.00)	55.00 (7.00)	48.00 (6.00)	46.00 (5.00)	53.00 (9.00)	0.176	0.013	0.106
Parity	3.00 (2.00)	2.00 (2.00)	3.00 (2.00)	3.00 (2.00)	3.00 (1.00)	4.00 (4.00)	0.807	0.908	0.322
Duration of TAM use (months)	24.00 (31.00)	24.00 (12.00)	37.00 (36.00)	12.00 (18.00)	12.00 (12.00)	6.00 (21.00)	0.002	0.076	0.006
Endometrial Thickness (mm)	5.79 (13.05)	14.30 (8.70)	13.45 (11.35)	9.60 (3.20)	9.85 (2.15)	7.90 (5.33)	0.028	0.012	0.106
B/A	3.82 (6.38)	3.37 (1.29)	9.50 (45.95)	1.98 (1.33)	1.98 (1.38)	1.86 (1.55)	<0.001	<0.001	0.001

[1]Tamoxifen, [2]Interquartile range, *Obtained from Mann-Whitney *U*-test, [a]*P*-value obtained from comparing all patients with abnormal histopathology and Tamoxifen usage to those with normal histopathology and Tamoxifen usage, [b]*P*-value obtained from comparing premenopausal patients with abnormal histopathology and Tamoxifen usage to those with normal histopathology and Tamoxifen usage, [c]*P*-value obtained from comparing postmenopausal patients with abnormal histopathology and Tamoxifen usage to those with normal histopathology and Tamoxifen usage

Table 3: Comparisons of TAM users with abnormal histopathology and controls (not using TAM) in premenopausal and postmenopausal patients

	TAM[1] users with abnormal histopathology Median (IQR[2])			Control (not using TAM) Median (IQR)			*P* values*		
	General (*n*=20)	Premenopausal (*n*=8)	Postmenopausal (*n*=12)	General (*n*=122)	Premenopausal (*n*=61)	Postmenopausal (*n*=61)	*P*1[a]	*P*2[b]	*P*3[c]
Age (year)	54.00 (12.00)	43.00 (2.00)	55.00 (7.00)	50.00 (22.00)	35.50 (10.00)	57.00 (5.00)	0.106	0.004	0.917
Parity	3.00 (2.00)	2.00 (2.00)	3.00 (2.00)	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	0.616	0.920	0.734
Duration of TAM use (months)	24.00 (31.00)	24.00 (12.00)	37.00 (36.00)	-	-	-	-	-	-
Endometrial thickness (mm)	5.79 (13.05)	14.30 (8.70)	13.45 (11.35)	3.00 (1.05)	3.20 (0.95)	2.60 (0.90)	<0.001	<0.001	<0.001
B/A ratio	3.82 (6.38)	3.37 (1.29)	9.50 (45.95)	1.14 (0.24)	1.05 (0.16)	1.27 (0.28)	<0.001	<0.001	<0.001

[1]Tamoxifen, [2]Interquartile range, *Obtained from Mann-Whitney *U*-test, [a]*P*-value obtained from comparing all patients with abnormal histopathology and Tamoxifen usage to those with normal histopathology and without Tamoxifen usage, [b]*P*-value obtained from comparing premenopausal patients with abnormal histopathology and Tamoxifen usage to those with normal histopathology and without Tamoxifen usage, [c]*P*-value obtained from comparing postmenopausal patients with abnormal histopathology and Tamoxifen usage to those with normal histopathology and without Tamoxifen usage

were comparable with regard to the ages (z = 1.352, P = 0.176, Table 2). Patients with histologically confirmed endometrial pathologies were found to have higher duration of TAM use, thicker endometrium, and higher B/A ratios compared with normal histopathology group ($P < 0.05$) [Table 2]. Median age of 8 premenopausal patients under TAM medication who had endometrial pathology was 43.00 (IQR = 2.00) years, whereas median age of 61 premenopausal patients without TAM medication was 35.50 (IQR = 10.00) years and the difference between groups was statistically significant (z = 2.875, P = 0.004) [Table 3].

In correlation analysis of postmenopausal TAM users, a significant positive correlation was found between the duration of TAM usage and the endometrial thickness and the B/A ratios. However, insignificant result was obtained when only premenopausal group was included in the analysis ($P > 0.05$) [Table 4].

When the statistical analyses were performed according to the united group of endometrium cancer and cystic endometrial hyperplasia as endometrial pathology, endometrial thickness and the B/A ratio of both premenopausal and postmenopausal patients were found to be significant predictors for groups under risk ($P < 0.05$). Cutoff values of endometrial thickness and B/A ratios were 12.55 mm (87.5% sensitivity, 81.2% specificity) and 2.46 (100% sensitivity, 84.4% specificity) in premenopausal period, whereas it was

7.75 mm (with 91.7% sensitivity, 42.9% specificity) and 7.70 (58.3% sensitivity, 100% specificity) in postmenopausal group to predict risky population, respectively. Cutoff values for the duration of TAM usage were 18 months (62.5% sensitivity, 71.9% specificity) and 32 months (58.3% sensitivity, 100% specificity) in premenopausal and postmenopausal groups, respectively [Table 5].

Table 4: Correlation of endometrial thickness and B/A ratios with the duration of TAM usage

	TAM* users	
	rho	*P*
Premenopausal		
Endometrial thickness	−0.092	0.573
B/A	0.039	0.812
Postmenopausal		
Endometrial thickness	0.409	0.038
B/A	0.498	0.010
Pre + Postmenopausal		
Endometrial thickness	0.068	0.586
B/A	0.342	0.005

*TAM=Tamoxifen

The statistical analyses of EC and CEH groups were also performed as separate groups. The groups of EC, CEH patients, and TAM users with normal pathology were analyzed in regard to endometrial thickness and B/A ratios to find out cutoff values. Nonparametric analyses were performed and the correct classification probability of TAM users with normal pathology, EC, and CEH patients in regard to endometrial thickness and B/A ratios were found to be 78.6%, 43.8%, and 75% for endometrial thickness and 78.6%, 93.8%, and 100% for B/A ratios, respectively. The cutoff values of endometrial thickness and B/A ratios were, respectively, 12.30 mm and 2.0 to discriminate CEH from normal pathology group and 14.80 mm and 46.01 to discriminate EC from CEH [Table 6].

Table 5: The areas under the ROC curve for endometrial thickness and B/A ratio of TAM users

Groups	Variables	AUC±St.E.	%95 CI	Cut-off	*P*	Sensitivity	Specificity
TAM users (all)							
	Endometrial thickness (mm)	0.671±0.083	0.509 - 0.833	≥11.55	0.028	0.700	0.761
	B/A	0.910±0.039	0.834 - 0.986	≥2.46	<0.001	0.950	0.826
	Duration of TAM usage (month)	0.736±0.068	0.604 - 0.869	≥29.00	0.002	0.400	0.957
Premenopausal TAM Users							
	Endometrial thickness (mm)	0.785±0.112	0.566 - 1.000	≥12.55	0.014	0.875	0.812
	B/A	0.926±0.042	0.843 - 1.000	≥2.46	<0.001	1.000	0.844
	Duration of TAM usage (month)	0.705±0.096	0.517 - 0.894	≥18.00	0.076	0.625	0.719
Postmenopausal TAM users							
	Endometrial thickness (mm)	0.690±0.106	0.482 - 0.898	≥7.75	0.100	0.917	0.429
	B/A	0.863±0.077	0.713 - 1.000	≥7.70	0.002	0.583	1.000
	Duration of TAM usage (month)	0.810±0.087	0.639 - 0.980	≥32.00	0.007	0.583	1.000
EC vs control[1]							
	Endometrial Thickness	0.929±0.074	0.784 - 1.000	≥17.80	0.011	0.750	1.000
	B/A	1.000±0.000	1.000 - 1.000	≥25.95	0.003	1.000	1.000
CEH vs control[2]							
	Endometrial Thickness	0.696±0.100	0.501 - 0.892	-	0.067	-	-
	B/A	0.790±0.095	0.603 - 0.977	≥2.265	0.007	0.938	0.786
EC vs CEH[3]							
	Endometrial Thickness	0.703±0.133	0.443 - 0.963	-	0.219	-	-
	B/A	1.000±0.000	1.000 - 1.000	≥27.755	0.002	1.000	1.000

TAM=Tamoxifen; EC=Endometrial cancer; CEH=Cystic endometrial hyperplasia. [1]Discrimination of patients with EC from those with normal pathology in postmenopausal TAM group, [2]Discrimination of patients with CEH from patients with normal pathology in postmenopausal TAM group, [3]Discrimination of patients with EC from patients with CEH in all TAM users (TAM users with normal histopathology were designated as controls)

Table 6: Diagnostic test summary measures for EC, CEH, and normal pathology in TAM users

	VUS	95% CI of VUS	Cutoff points (Normal pathology/CEH; CEH/EC)	CCP (Normal pathology; CEH; EC)
End. thickness	0.423	0.191 - 0.682	12.30; 14.80	0.786; 0.438; 0.750
B/A	0.790	0.581 - 0.949	2.00; 46.01	0.786; 0.938; 1.000

VUS=Volume under surface; CEH=Cystic endometrial hyperplasia; EC=Endometrium cancer; CCP=Correct classification probability

Discussion

The most appropriate method in follow-up of sonographic endometrial thickness of breast cancer patients under TAM is still not clear. Although the tissue sampling is still the gold standard, it is an invasive method and not appropriate as a monitoring tool in these patients. We aimed to find out whether the diagnostic accuracy could be increased with the addition of real-time tissue elastosonography modality to B-mode sonography. In our study, we found that the endometrial tissue strain ratios were significantly increased (stiffer tissue, decreased elasticity) in cases with endometrial pathologies. Patients with EC and CEH were found to have longer duration of TAM usage, increased endometrial thickness, and higher strain ratios compared with controls. A significant positive correlation was found between duration of TAM usage, endometrial thickness, and the strain ratios. Endometrial thickness and the strain ratios were significant predictors for groups under risk. Cutoff values for endometrial thickness, strain ratios, and duration of TAM usage were 12.55 mm, 2.46, and 18 months in premenopausal group and 7.75 mm, 7.70, and 32 months in postmenopausal group to predict risky population, respectively.

The endometrial thickness alone is usually not accepted as the only indication for endometrial sampling by most of the clinics in breast cancer patients using TAM. Based on the results of many studies, the main and the only indication for endometrial sampling in our clinic is the presence of uterine bleeding in patients using TAM. In a review about the pathogenesis and biology of endometrial neoplasia, several studies about the endometrial changes caused by the use of TAM and aromatase inhibitors (anostrozole) in breast cancer were compared.[20] TAM had been shown to cause more benign endometrial abnormalities, such as polyps, thickening of endometrium, and endometrial hyperplasia, whereas aromatase inhibitors had the advantage of reversing most of these effects and causing endometrial atrophy. However, the reversal effect of aromatase inhibitors in switching therapy did not affect unspecific endometrial thickenings and endometrium cancer.[21-23] Moreover, Seoud *et al*. reported that there was no close correlation between endometrial thickness and endometrial pathologies.[24] It still needs further research whether any other pathway exists in development of cancer on the endometrial hyperplasia or endometrial polyp base.

Tamoxifen-associated malignant endometrial tumors (TAMET) were compared with spontaneous endometrial cancers in a study by Wilder *et al*. Both the clinical behavior and the expression of estrogen and progesterone receptors were significantly different between the groups.[25] An increasing trend to develop well-differentiated mucinous endometrium cancers in patients under TAM had been reported.[26] The different tumor biology of TAMET, development of malignancy irrespective of the sonographic endometrial thickness, and suspicious relation of endometrial hyperplasia transformation into malignancy, all question the effectiveness of transvaginal B-mode sonographic measurement of endometrial thickness as a tool in follow-up of these patients. Studies about the prevention and reduction of endometrial hyperplasia in patients under TAM by using long-term levonorgestrel-releasing intrauterine systems (LNG-IUS) suggested that endometrial polyp and endometrial hyperplasia formation had been reduced with LNG-IUS use. However, none of these studies were sufficiently powerful to detect a significant difference in development of cancer of the endometrium under TAM effect.[27]

The cutoff value to detect endometrial abnormalities by TVUS was reported as 6 mm with 85.1% sensitivity and 55.7% specificity in a prospective, well-designed study of 138 postmenopausal TAM user women with breast cancer.[28] The cutoff value in ROC curve of postmenopausal TAM users for endometrial abnormalities was 7.75 mm in our study and was found to be higher than the cutoff value reported in that study. This may be related with the different durations of TAM usage in both studies; a median of 37 months in our study group and 23 months in the study of Fong K *et al*.

One of the weakness of our study is the small sample size. As the number of endometrial cancer cases is small, possible diagnostic value of elastosonographic indices and other parameters in differentiation of endometrium cancer and endometrial hyperplasia could not be studied. As far as we observed during the study, the thickness of the endometrium and endometrial changes were not distributed homogenously throughout the endometrium and the peripheral endometrial tissue adjacent to the myometrium had the lowest elasticity (higher B/A ratio, hence stiffest tissue) in patients under TAM therapy. Moreover, the stiffness of this region adjacent to the myometrium was not evenly distributed within itself. Even with higher sample sizes, the main limitation inherent to endometrial changes due to TAM would be the uneven distribution of tissue elasticity changes within the endometrium. Although it is beyond the scope of this study and it is hard to make an assumption because of the small sample size, we just want to share our observation on some special patterns of distribution unique to specific endometrial pathologies. For example, the pattern of patchy distribution of softer areas within stiffer (low resistance) endometrium, including the areas

close to the myometrial border, was more common in patients whose endometrial samplings reported to be CEH. In contrast, centralized softer areas (distal to the myometrial junction) surrounded with stiffer areas and relatively homogenous stiffer endometrium near the myometrial border were observed in the patients reported to be EC.

There are two modalities of elastosonographic imaging: compressive or strain elastosonography and shear-wave elastosonography. Both the imaging method and the force applied for tissue compression are different in these two techniques. Whereas stress is applied by repeated manual compression of the transducer in strain elastosonography, shear-wave elastosonography uses an acoustic radiation force impulse generated by a focused ultrasound beam instead of manual generation of force. Thus, the method is largely dependent on examiner's experience in strain elastosonography but highly reproducible and with lower intra and inter observer differences in shear-wave elastosonography.[29,30] Apart from the generation of force applied, the diagnostic performance of elastosonography is largely dependent on the diameter and localization of ROI. A wider compression power is exposed on the tissue near to the probe when compared with a region distal to the probe. In a similar manner, laterality of the ROI also results in compression axis to be lower when compared with the central located ROI.[31] All these factors should be taken into account both during performing the technique and evaluation process of the results.

An elastosonographic scoring system for endometrial imaging using pattern of distribution may be a useful tool in sonographic follow-up of breast cancer patients using TAM. There are already two elastosonographic scoring systems used in breast imaging defined by Rizzatto *et al*. and Ueno *et al*. in which the patterns of distribution of elasticity were graded from 1 to 5; benign lesions having the score of 1 to 3 and malignant lesions as scores of 4 or 5.[32,33] There is no such study on scoring the distribution of elasticity of endometrium. Our data may be used in future for developing a scoring system that may be useful for differential diagnosis of endometrial changes during TAM usage.

Conclusion

The management of endometrial sonographic findings in breast cancer patients using TAM is still unclear. In this study, we found that the endometrial tissue strain ratios were significantly increased (stiffer tissue, decreased elasticity) in cases with endometrial pathologies. Addition of real-time tissue elastosonography modality to B-mode sonography may improve the diagnostic accuracy. Although still needing validation with large scale studies, the cutoff values for endometrial thickness and B/A ratios found in our study are valuable in clinical decision process before invasive procedures in TAM users.

Compliance with ethical standards

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the scientific and bioethical review board of Kecioren Training and Research Hospital, Ankara, Turkey (IRB No. 11.03.2015/735).

Informed consent

Informed consents were obtained from all individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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