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Original Research Article

Evaluation of endometrial abnormalities in breast cancer patients on tamoxifen therapy

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ABSTRACT

Background: Breast cancer is the most common malignancy in women. Tamoxifen, widely used as adjuvant therapy, has anti-estrogenic effects on breast tissue but may induce endometrial changes due to estrogenic stimulation. To evaluate endometrial abnormalities in postmenopausal breast cancer patients receiving tamoxifen therapy.
Methods: This cross-sectional study was conducted at the Department of Gynaecological Oncology, NICRH, Dhaka, over one year. Seventy-five postmenopausal breast cancer patients who had received tamoxifen for more than six months were enrolled. All underwent transvaginal ultrasound (TVS) and 32 patients subsequently had histopathological evaluation. Data were analyzed using SPSS v23.
Results: The mean age was 58.03±7.96 years. TVS revealed endometrial thickness of 4–7.9 mm in 58.6%, 8–11.9 mm in 8%, 12–15.9 mm in 12%, 16–19.9 mm in 6.7% and ≥20 mm in 14.6% of patients, with a mean thickness of 11.22±6.68 mm. Thickness ≥8 mm was significantly associated with longer tamoxifen use ($p<0.05$). Histopathology (n=32) showed 25% normal endometrium, while 75% had abnormalities: polyps (28.1%), hyperplasia without atypia (25%), hyperplasia with atypia (9.4%), atrophy (9.4%) and carcinoma (3.1%). A significant correlation was found between TVS findings and histopathology ($p=0.044$).
Conclusions: Nearly two-fifths of patients developed endometrial thickening >8 mm and three-quarters of those biopsied had abnormal histopathology, including hyperplasia with atypia and carcinoma. Long-term tamoxifen therapy in postmenopausal women may predispose to endometrial pathology, warranting regular surveillance with TVS and prompt biopsy for suspicious cases.

Keywords: Atypia, Endometrium, Hyperplasia, Tamoxifen, TVS

INTRODUCTION

Breast cancer is the is the second most common cause of death from cancer among women in the world.[1] In 2018, 26.4% of the women was diagnosed newly with breast cancer and it is the most prevalent cancer of top 5 cancer in females of South-Eastern Asia. The incidence of breast cancer in Bangladesh in 2018 among the female is 19% and for both sex it is 8.5%. The 5 year prevalence for both sex for breast cancer is 35.19%.[2] In the treatment of breast cancer tamoxifen is used as the first targeted agent.[3] Use of Tamoxifen in treatment is associated with an increased risk of developing both endometrial cancer and benign gynaecologic symptoms, which demand prompt diagnosis and therapy.[4,5] Many studies generally define an

endometrial thickness of 4.0- 5.0 mm as the normal cut-off value in postmenopausal women.[6] But endometrial thickness equal to or greater than 8 mm are usually suspicious. Though endometrial thickness in Tamoxifen varies from patient to patient, in some cases it may result in a spectrum of endometrium abnormalities including benign alterations such as endometrial polyps, endometrial hyperplasia, endometrial cystic atrophy, adenomyosis and endometrial carcinoma.[7] So, the main objective of the present study was to evaluate endometrial abnormalities in postmenopausal breast cancer patients on Tamoxifen therapy.

METHODS

This cross sectional (prospective) study was conducted in the Department of Gynaecological Oncology, NICRH, Mohakhali, Dhaka for a period of 1 year, from September 2014 to October 20145. A total of 75 patients were taken as study sample according to inclusion and exclusion criteria. Purposive sampling according to inclusion and exclusion criteria. All the postmenopausal breast cancer patients taking Tamoxifen 20 mg/ day as adjuvant therapy for >6 months for breast cancer were approached for this study. Patients who received hormone therapy prior to the diagnosis of breast cancer along with or without Tamoxifen and patients who had gynaecological pathology prior to the diagnosis of breast cancer were excluded from the study. A pre-structured data collection sheet was used as a research tool. Consent of study participants were taken and then they were subjected to TVS. Protocol was strictly followed. Data were recorded with confidentiality, entered and analyzed using SPSS version 23.

RESULTS

Majority of the respondents were 51-60 years group (57.3%), 41-50 years group (16.0%), 61-70 years 12% and >70 years 14.7%. Mean age was 58.03±7.96 years with range of 48-74 years. Majority of occupation of study population were housewife (76.0%) followed by 20.0% service holder and 4.0% were businessman. Study patients were distributed according to endometrial thickness (n=32), where 1 patient had endometrial thickness less than 8 mm. In 4-7.9 mm endometrial thickness 1 atrophic endometrium found after histopathology. 8-11.9 mm endometrial thickness there were 4 normal endometrium, 1 endometrial polyp and 1 atrophic endometrium after histopathology. In 12-15.9 mm endometrial thickness there were 4 normal endometrium, 2 endometrial polyp, 2 endometrial hyperplasia without atypia and 1 atrophic endometrium after histopathology. In 16-19.9 mm endometrial thickness there were 1 endometrial polyp, 3 endometrial hyperplasia without atypia and 1 endometrial hyperplasia with atypia after histopathology. In ≥20 mm endometrial thickness there were 5 endometrial polyp, 3 endometrial hyperplasia without atypia, 2 endometrial hyperplasia with atypia and 1 endometrial cancer after histopathology. Risk factors for endometrial cancer in symptomatic and asymptomatic postmenopausal breast cancer patient treated with Tamoxifen were tabulated above. There was significant differences in BMI among groups (p=0.032). Duration of tamoxifen use was significantly associated with presence of symptoms of endometrial abnormalities in the participants (p-value 0.002 and 0.001). Significant relation between endometrial thickness and duration of tamoxifen treatment showed in table 6. More the duration of Tamoxifen use, higher the endometrial thickness (p= <0.001).

Table 1: Distribution of study population according to age group and occupation (n=75).

Demographic characteristics	Number of participants	%
Age (in year)		
41-50	16	16
51-60	57.3	57.30
61-70	12	12
>70	14.7	14.70
Mean ±SD	58.03	±7.96
Range (min-max)	48	74
Occupation		
Housewife	76	76
Service holder	20	20
Businessman	4	4

Endometrial thickness was significantly higher in symptomatic patients (p<0.001) as well as heterogenous echotexture (p=0.012). Transvaginal ultrasonographic endometrial findings showed normal endometrial thickness in 44 (58.6%) patient and thickened endometrium in 31 (41.3%) patient. 58 (77.3%) showed homogenous echotexture and 17 (22.7%) showed heterogenous with cystic echotexture. Regarding histopathological findings, 8 patients (25.0%) had normal endometrium and 24 patients (75%) had endometrial abnormalities. Eleven patients (34.38%) had endometrial hyperplasia among which 25% without atypia and 9.38%

with atypia, 9 patient (28.12%) had endometrial polyp, 3 patient (9.38%) had atrophic endometrium and 1 patient (3.12%) had endometrial cancer. The findings showed significant correlation (p=0.044) between endometrial thickness and histopathologic findings.

Table 2: Distribution of study patients according to endometrial thickness (n=32).

Endometrial thickness (in mm)	Number of patients (n=32)	%
4-7.9	1	1
8-11.9	6	6
12-15.9	9	9
16-19.9	5	5
≥20	11	11

Table 3: Histopathological findings of patients in relation to endometrial thickness (n=32).

Histopathological findings						
Endometrial thickness	**Normal endometrium**	**Endometrial polyp**	**Endometrial hyperplasia without atypia**	**Endometrial hyperplasia with atypia**	**Atrophic endometrium**	**Endometrial cancer**
4-7.9mm	0	0	0	0	1	0
8-11.9mm	4	1	0	0	1	0
12-15.9mm	4	2	2	0	1	0
16-19.9mm	0	1	3	1	0	0
≥20mm	0	5	3	2	0	1
In Total	8	9	8	3	3	1

Table 4: Risk factors for endometrial cancer in postmenopausal breast cancer patients treated with Tamoxifen (n=75).

Variables	Symptomatic (n=9)	Asymptomatic (n=66)	P value
Age at menarche, years (Mean±SD)	12.44±0.73	12.88±1.42	0.372*
Age at menopause, years (Mean±SD)	47.22±1.39	47.44±1.91	0.744*
Weight, kg (Mean±SD)	56.61±7.24	51.08±8.15	0.057*
Height, m (Mean±SD)	1.39±0.03	1.4±0.03	0.214*
BMI, kg/m² (Mean±SD)	29.26±2.85	26.04±4.27	**0.032***
Parity, (Mean±SD)	2.78±0.44	2.45±1.11	0.393*
DM, N (%)	2(22.2%)	6 (9.1%)	0.346!
HTN, N (%)	3 (33.3%)	16 (24.2%)	0.556!

*P-value determined by independent t-test; !P-value determined by chi-square test.

Table 5: Correlation of duration of Tamoxifen use with symptom of endometrial abnormalities and endometrial thickness (n=75).

Duration of tamoxifen use				
Endometrial abnormalities				
Variables	**>6 months to <3 years**	**>3 years**	**Mean±SD duration, (months)**	**P value**
Symptomatic (n=9)	1 (11.1%)	8 (88.9%)	44.22±2.48	0.001!
Asymptomatic (n=66)	45 (68.2%)	21 (31.8%)	35.00±8.06	0.002*
Endometrial thickness				
<8 mm (n=44)	34 (77.3%)	12 (38.7%)	32.84±5.68	0.001*
≥8 mm (n=31)	10 (22.7%)	19 (61.3%)	40.74±9.69	<0.001!

*P-value determined by independent t-test; !P-value determined by chi-square test.

Table 6: Correlation in TVS findings of endometrial thickness and echotexture in symptomatic and asymptomatic post-menopausal breast cancer patients under tamoxifen therapy (n=75).

TVS findings	Total(n=75)	Symptomatic (n=9)	Asymptomatic (n=66)	P value
Endometrial thickness (in mm)				
4-7.9	44 (58.6%)	1 (11.1%)	43 (65.2%)	<0.001!
8-11.9	6 (8%)	0	6 (9.1%)	
12-15.9	9 (12%)	0	9 (13.6%)	
16-19.9	5 (6.7%)	2 (22.2%)	3 (4.5%)	
≥20	11 (14.6%)	6 (66.7%)	5 (7.6%)	
Mean endometrial thickness, mm (Mean±SD)	11.22±6.68	20.44±7.88	9.97±5.46	<0.001*
Endometrial echotexture				
Homogenous	58 (77.3%)	4 (44.5%)	54 (81.8%)	0.012!
Heterogenous with cystic areas	17 (22.7%)	5 (55.5%)	12 (18.2 %)	

*P-value determined by independent t-test; !P-value determined by chi-square test.

Table 7: Histopathological findings of endometrium in breast cancer patients under tamoxifen therapy (n=32).

Histopathological findings	Total (n=32)	%
Normal endometrium	8	25
Abnormality	24	75
Endometrial polyp	9	28.12
Endometrial hyperplasia without atypia	8	25.00
Endometrial hyperplasia with atypia	3	9.38
Atrophic endometrium	3	9.38
Endometrial cancer	1	3.12

Table 8: Correlation between endometrial thickness and histopathological findings in the study patients (n=32).

Endometrial thickness						
Histopathological findings	**4-7.9 mm**	**8-11.9 mm**	**12-15.9 mm**	**16-19.9 mm**	**≥20 mm**	**P value***
Normal endometrium	0	4	4	0	0	0.044
Endometrium polyp	0	1	2	1	5	
Endometrial hyperplasia without atypia	0	0	2	3	3	
Endometrial hyperplasia with atypia	0	0	0	1	2	
Atropic endometrium	1	1	1	0	0	

*p value was determined by chi-square test.

DISCUSSION

In this cross sectional study, among 75 study subjects, majority were from 51-60 years group (57.3%) with mean of 58.3±7.96 years. The study was similar with previous other studies.[8–10] Majority study population were housewife (76.0%) followed by the result of Rahman S study.[11] In our study, a comparison of risk factors for endometrial cancer between gynecologically symptomatic and asymptomatic groups showed no significant difference in the study except BMI (p=0.032). It was found that mean age at menarche in symptomatic and asymptomatic patients were 12.44±0.73 years and 12.88±1.42 years while mean age at menopause were 47.22±1.39 years and 47.44±1.91 years respectively. In a research of WHO scientific group, menopausal age group was mentioned 47-48 years for developing countries.[12] Similar result was found in India where mean menopausal age was 47.35 years in urban Indian women and 49.56 years in rural Indian women.[13] Another closest finding was discovered among Nepalese women where 46.3±4.78 years were mean menopausal age.[14] Mean duration of Tamoxifen use in gynecologically symptomatic and asymptomatic patients were 44.22±2.48 months and 35.00±8.06 months in our study. Among symptomatic patients, 88.9% was taking Tamoxifen for more than 3 years while 68.2%

asymptomatic patients taking Tamoxifen for 6months to 3 years. A statistical relationship was observed between these two groups and also a relation was marked between duration of tamoxifen use and symptoms of patients.[15] To determine mean endometrial thickness of 11.22±6.68 mm (ranging between 6 mm and 45 mm) Transvaginal ultrasound was used. Among the patients, 8% presented endometrial thickness between 8 mm and 11.9 mm and 14.6% were ≥20 mm where, symptomatic patients had significantly higher thickness than asymptomatic patients (p<0.001).

Additionally, echotexture was homogeneous in 77.3% of cases and heterogenous with cystic areas in 22.7% patients. The findings were similar to other authors.[16,17] About 44 (58.7%) patients showed endometrial thickness of less than 8 mm while 31 (41.3%) showed endometrial thickness of 8 mm or more. A statistically significant (p=0.001) value was identified where about 61.3% patients who used Tamoxifen for ≥3 years had endometrial thickness of 8mm or more which. On the other hand, mean duration of Tamoxifen use was also statistically higher among patients with endometrial thickness ≥8 mm (p<0.001). In Cohen et al, study, also noticed significant relation between endometrial thickness and duration of Tamoxifen treatment (p 0.025) as in the present study.[18]

According to the histopathological findings, a normal endometrium was observed in 8 (25.0%) and endometrial abnormalities in 24 (75%) patients where eleven patients (34.38%) had endometrial hyperplasia where 25% were without atypia and 9.38% with atypia. 9 patients (28.12%) had endometrial polyp, atrophic endometrium in 3 (9.38%) cases. Only 1 case (3.1%) with endometrial carcinoma was found. A significant correlation (p=0.044) was observed between endometrial thickness and histopathological findings. Similar observation was noted by Kochar study, where he displayed normal endometrium 37%, endometrial polyp 22%, endometrial hyperplasia without atypia 19%, endometrial hyperplasia with atypia 9%, atrophic endometrium 4% and 2% endometrial cancer found after histopathology. With increased endometrial thickness, the incidence of increased abnormal histopathological findings were remarked.[19] Additionally, long time use of Tamoxifen can increase risk of endometrial cancer while compared to non-treated patients.[20-22] So, it can be concluded that patients with breast cancer using adjuvant Tamoxifen treatment should be monitored for further risk assessment.

There was no control group. Sample was collected in only one centre and the Sample size was small which might not display the actual scenario.

CONCLUSION

The average age of the study population was 58 years. About two-fifth of the total study population were found to have endometrial thickness >8mm and were indications for fractional curettage in Trans Vaginal Ultrasonography. Two-third symptomatic patient showed endometrial abnormalities on histopathological examination. Among them 9.38% patients showed endometrial hyperplasia with atypia and 3.1% had endometrial carcinoma after histopathology. So, long-term use of Tamoxifen as adjuvant therapy for carcinoma breast might lead to endometrial pathology. The study was approved by the Institutional Ethics Committee. Written consent was obtained from the patients (subjects) and their confidentiality (subjects) were strictly maintained. This study was not hazardous to environment.

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