Significance and prevalence of Tamoxifen related endometrial changes in patients of carcinoma breast

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Abstract- **Background**: Tamoxifen acts as an estrogen agonist on the female genital tract. The side effect of major concern is endometrial carcinoma.

   Aim: The aim of this study was to determine the prevalence and significance of endometrial changes in breast cancer patients, receiving tamoxifen and the factors influencing it.

   Materials and Methods: The cohort comprised of 10 years retrospective group (RG) and one year prospective group (PG) of patients receiving tamoxifen. Transvaginal ultrasonography (TVS) was done at scheduled intervals and fractional curettage was carried out if endometrial stripe thickness (EST) $\geq$ 15mm.

   Results: Only 12 (11.6%) patients on tamoxifen therapy developed EST $\geq$ 15mm. Two (16.66%) patients with suspicious histopathology on fractional curettage underwent TAH+ BSO. Amongst them one patient had adenosarcoma of mixed mullerian variety. In the PG, the EST increase at the initiation of tamoxifen therapy and at six monthly intervals till 1 year, was statistically significant with p-value of <0.05. This increase was consistent for a period of 2-7 years of tamoxifen usage and was mainly limited to the postmenopausal group.

   Conclusion: Routine screening has not shown to be very helpful but regular follow up especially in the presence of clinical triad i.e. vaginal bleeding, abnormal findings on clinical examination and increased EST on TVS warrants a more aggressive approach to detect uterine malignancy at an early stage.

Index Terms- Breast cancer, tamoxifen therapy, transvaginal ultrasonography, hyper-estrogenic states, endometrial cancer

I.   INTRODUCTION

The ultimate goal of endocrine therapy in breast cancer is to achieve decreased estrogen levels. Among the negative effects, tamoxifen also has a positive (agonist) estrogen agonist effect on the female genital tract.[1] This agonist effect on the endometrium can stimulate proliferation, which increases the risk of polyps, hyperplasia, and endometrial cancer by 2 to 4 fold compared with patients not receiving tamoxifen. The expected annual risk of endometrial cancer in patients on tamoxifen therapy is approximately two per thousand patients.[2] Tamoxifen doubles the risk of endometrial cancer after 1-2 years of usage and quadruples after 5 years.[3] The best way to prevent tamoxifen induced endometrial cancer is to ensure a routine baseline screening with transvaginal ultrasonography. Screening programs helps in detecting premalignant endometrial lesions because without baseline assessment, such lesions may grow or later be attributed to Tamoxifen. Endomrtrial thickness in tamoxifen patients may vary but thickness equal to or greater than 8mm are usually suspicious as compared in control subjects (9 - 13 mm vs. 4.0 - 5.4 mm).[4]. Endometrial cancer is usually associated with a measurement greater than 10mm.[5] At an EST value of 5mm, transvaginal sonography (TVS) had a positive predictive value of 9% for detecting any abnormality. The sensitivity was 90%, the specificity was 48%, but the negative predictive value was 99%.[6] The likelihood of abnormality is greater for patients who have abnormal vaginal bleeding, discharge, abnormal glandular cells on papanicolaou smear or an endometrial measurement on ultrasonography of more than 8mm, these findings should prompt an aggressive evaluation of the endometrium.[7]

   This study was designed to determine the prevalence and significance of endometrial changes in patients using tamoxifen as adjuvant therapy in breast cancer. The rationale behind this study was to detect endometrial cancers at an early stage and to determine any statistically significant association between tamoxifen and various factors like duration of tamoxifen therapy, menstrual status and hyperestrogenic states.

II.   MATERIALS AND METHODS

   This prospective observational study was conducted in the Department of Radiotherapy at Christian Medical College & Hospital, Ludhiana. Patients who received treatment for breast cancer with tamoxifen as one of the component in previous 10 years were enrolled in the retrospective group (RG). New patients enrolled over one year of commencement of study were enrolled in the prospective group (PG). Analysis of all the patients of carcinoma breast who were using tamoxifen was done with six-monthly TVS to assess the EST. A baseline TVS at the beginning of tamoxifen therapy was done in the PG group and then it was followed up every six months. Any patient who presented with EST equal to or greater than 15mm or presented symptomatically with vaginal bleeding underwent a fractional curettage.

The patients qualifying for the inclusion criteria were premenopausal and postmenopausal women irrespective of age and patients who have been treated for breast cancer, either early or advanced stages, with tamoxifen. Patients receiving concurrent treatment with other hormonal agents or who presented with prior histopathologically proven endometrial carcinoma or atypical hyperplasia were excluded from the study. In the retrospective study group, inclusion criteria and exclusion criteria were same.

The data were analyzed using SPSS (Statistical Package for Social Sciences) version 16.0 and Epi Info Version 6. Analysis was also done using cross-tables and Chi-square tests for various categories of different variables.

III.   RESULTS

One hundred and three patients came for follow up during the study period. Amongst them, 73 patients consented to undertake the above mentioned protocol and they were included in the RG. In the one year PG, all 30 patients who consented for the study protocol, were enrolled. (table1).

TABLE 1: Table showing the comparative data of the two study groups.

*Body mass index (BMI) was used for ascertaining nutritional status.

	Retrospective group (RG) (n)	Prospective group (PG) (n)
Number of patients	73	30
AGE in years (mean±SD)	48.61±10.62	47.70±7.54
Nulliparous	5	0
Primiparous	5	5
Multiparous	62	25
No information	1	0
Premenopausal	25	7
Postmenopausal	34	14
Iatrogenic menopausal	5	5
Perimenopausal	9	4
Underweight(<18.5)	5	0
Healthy weight(18.5-24.9)	25	13
Overweight(25-29.9)	20	11
Obese(>30)	23	6

TVS ultrasound was done for all patients on initiation of tamoxifen and at six-monthly intervals in PG. EST more than 5 mm on TVS was considered as endometrial thickening. Increased EST was noted in 87.37% patients. The other findings on TVS, number of patients showing space occupying lesion (SOL) and the histopathological examinations (HPE) findings are shown in (table 2).

Table 2: Representation of transvaginal sonographic findings and histopathological findings

TVS findings	RG+PG(n=103)	%
↑EST	90	87.37
Cystic changes	26	25.24
SOLs	8	7.76
Normal EST(≤ 5mm)	13	12.62
Total	103	100
	RG	**PG**
Increased endometrial stripe	9	3
Underwent fractional curettage	6	2
TAH+BSO	2	0
Histopathological findings		
Benign	4	2
Malignant	1	0

SOL= space occupying lesion, TAH+BSO = trans abdominal hysterectomy and bilateral salpingo-opherectomy

* TVS findings in both Prospective group and Retrospective group and subsequent intervention in patients with endometrial stripe >15mm, followed by patients undergoing fractional currettage and finally trans abdominal hysterectomy and bilateral salpingo-opherectomy in patients with suspicious findings and histopathological findings.

One patient showed hyperplastic polypoidal changes on fractional curettage and another patient had findings suspicious of malignancy. Both underwent transabdominal hysterectomy and bilateral salpingo-opherectomy (TAH & BSO). HPE confirmed simple hyperplasia with polypoidal growth (figure 1) in the first case and adenosarcoma of mixed mullerian type (figure 2) in the second case.

Fig 1: Figure showing H & E stained section of endometrium on low power view (10X). Stromal hyperplasia with glandular changes is visible
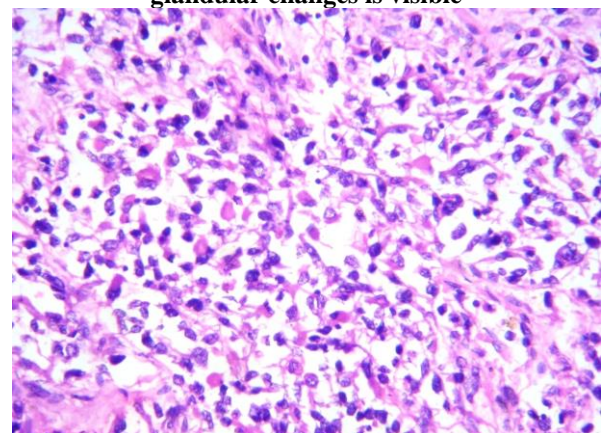
Fig 2: Figure showing H & E stained section from endometrium on high power view (40X). Spindle shaped tumour cells displaying moderate nuclear pleomorphism

Both these patients had presented symptomatically with vaginal bleeding. After hysterectomy, the first patient was switched over to letrozole, an aromatase inhibitor (AI) and the second patient with malignancy, received adriamycin based chemotherapy followed by radical radiotherapy and intravaginal brachytherapy.

Patients in the PG had tamoxifen exposure for < 1year, and amongst them none developed an EST of ≥ 15mm. In the RG, it was evident that patients using tamoxifen for 2-7 years showed a consistent pattern of increase in the EST, but due to less number of patients, it was difficult to ascertain the changes beyond seven years of usage. Eleven patients demonstrated increased EST of ≥ 15mm in RG. It was found that 54.5% (n=6) patients developed changes in EST between 3-6 years of tamoxifen, while 18.2% (n=2) patient developed changes between 2-3 years. Strikingly 27.3% (n=3) patients showed endometrial changes within one year. (Fig 3) Malignancy developed in one patient between 4-5 years of tamoxifen therapy. Figure 3 shows a graphical representation between the duration of tamoxifen therapy (years) on x-axis and the mean of EST (mm) on y-axis. The mean EST (mm) was calculated among the total number of patients who presented during the respective years for follow up and underwent TVS.
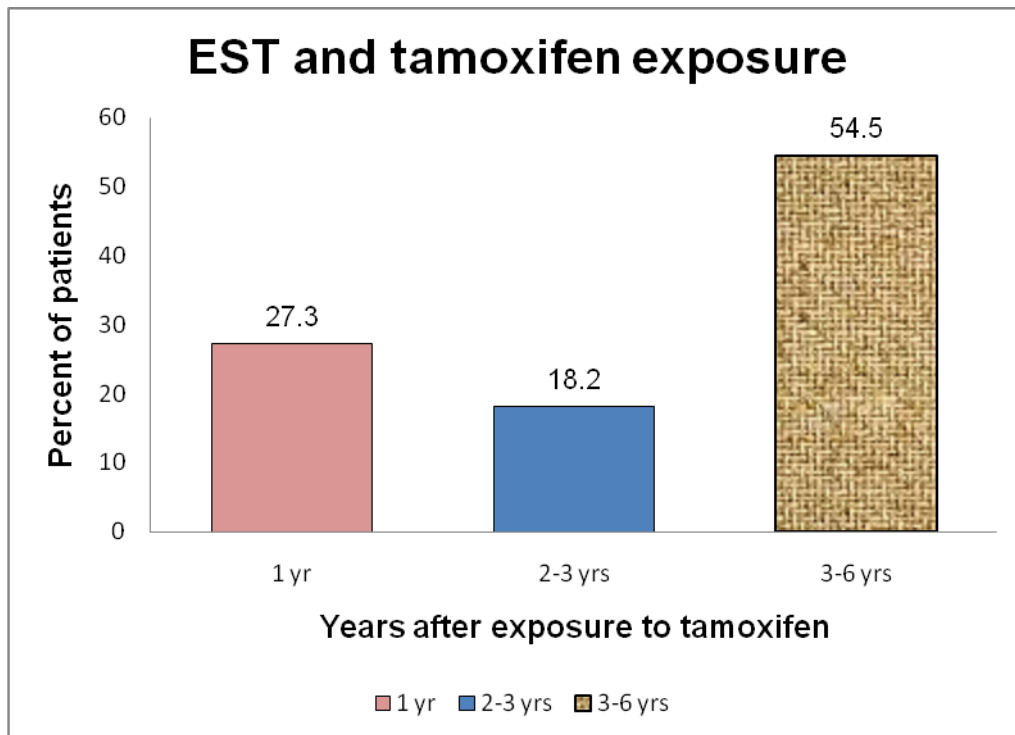

Fig 3 EST & tamoxifen exposure

The figure is showing the number of patients with EST 15mm or above after exposure to tamoxifen. Highest incidence noted in 3-6 years after exposure.

- EST= Endometrial stripe thickness

The pattern of EST changes noted was different in premenopausal and postmenopausal group of patients. There was a consistent rise in EST in postmenopausal group of patients. The EST change was not linear in premenopausal patients and was showing peak around the 3rd and 6th year of tamoxifen therapy (Fig 4).
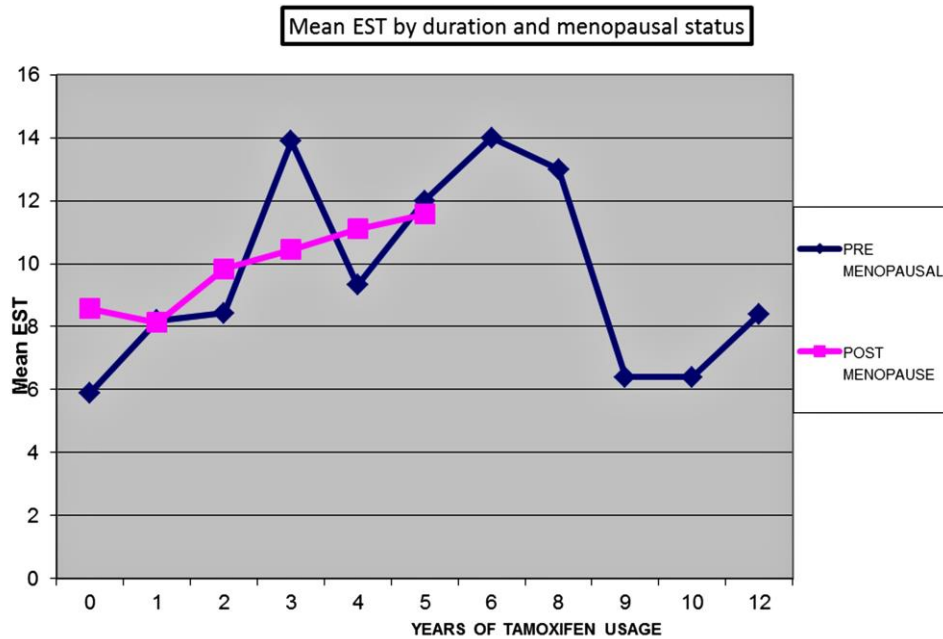
Fig 4: Line diagram comparing mean EST changes in pre and postmenopausal patients of breast cancer on tamoxifen. The EST changes were not consistent in the premenopausal patients. Peak rise in EST was noted in the 3rd and 6th years of tamoxifen therapy in premenopausal group. In the postmenopausal group, there was a consistent rise in EST from one year till 5th year of exposure to tamoxifen with peak around the 5th year.

The EST rise in the postmenopausal patients on tamoxifen therapy over time was statistically significant. The usual pattern is a decrease in EST after menopause. So, the rise in EST in postmenopausal patients could be attributed to tamoxifen exposure. In premenopausal women the increase in EST was not significant and it could be attributed to the phase of the menstrual cycle. Chi square for linear trend of the menopausal status and EST was analyzed. For premenopausal women the linear trend value was 1.575 with a p-value of 0.2095, and for postmenopausal women it was 2.270 with a p-value of 0.131. The odds ratio was 2, 4 and 3.3 at 5 yrs, 6 yrs and 7 yrs respectively. There was no significant correlation found between increased endometrial stripe thickness and hyperestrogenic states.

IV. DISCUSSION

It is estimated that tamoxifen patients have a threefold increase in endometrial proliferation and polyps, and a tenfold increase in endometrial hyperplasias compared with controls. Although the incidence of these endometrial changes is high, the chance of these conditions progressing to endometrial cancer is low; only atypical hyperplasia, an uncommon finding, was a significant (27%) risk of progression to cancer.[8]

Endometrial hyperplasia is a histological diagnosis characterized by proliferation of endometrial glands resulting in a greater gland-to-stroma ratio than observed in normal endometrium. The WHO classification of endometrial hyperplasia is based upon two factors: i) the glandular/stromal architectural pattern, which is either simple or complex. ii) The presence or absence of nuclear atypia. They are further divided into a) simple hyperplasia b) complex hyperplasia c) simple atypical hyperplasia d) complex atypical hyperplasia.[9] TVS is the first line imaging modality for screening of tamoxifen induced endometrial hyperplasia. Studies conclude that an endometrial thickness greater than 8mm on TVS had a 100% positive predictive value for endometrial disease.[10] The normal postmenopausal endometrium appears as a single echogenic line and should not exceed 5 mm as a bilayer thickness.[11] In our study, we considered the normal EST as ≤ 5mm, anything above this was taken as increased EST. Gynecological intervention was reserved for patients with EST ≥ 15mm or any symptomatic presentation. At an EST value of 5mm, TVS had a positive predictive value of 9% for detecting any abnormality. The sensitivity was 90%, the specificity was 48%, but the negative predictive value was 99%. Based on these values, over half of the women would require TVS, with a low yield (4%) of endometrial carcinomas.[12]

Amongst all the patients in the PG comprising of 30 patients, none had tamoxifen exposure at the time of baseline TVS, while among the 73 patients in the RG the period of tamoxifen exposure ranged from 1 year to 10 years. ATAC trial discussed that tamoxifen treatment results in a doubling of the risk of endometrial cancer after 1-2 years and a quadrupling after 5 years of therapy respectively.[13] The findings could be represented in figure 3, showing that tamoxifen behaves as an agonist on the endometrial lining leading to consistent increase in EST as the years of tamoxifen exposure increased. It is evident from the graph that there is progressive increase in EST from two years to five years of tamoxifen exposure.

The baseline TVS in the PG showed that none of the patients had any endometrial pathology or EST equal to or more than 15mm at initiation of tamoxifen, while in the subsequent TVS, at six monthly interval, three (10%) patients showed an increase in EST to equal to or more than 15mm, whereas in the RG one out

of 9 patients developed increase in EST to 15mm after yearly estimation. Our findings were supported by the study which observed that tamoxifen induces uterine abnormalities from as early as 3 months of therapy.[3] In the HPE, six patients had simple hyperplasia, one patient showed polypoid features and the other had features suspicious of malignancy. The other findings are tabulated in table 2. Both these patients belonged to RG. Here we would like to mention that in this study there was no baseline TVS data available for the patients in RG. In the absence of baseline TVS any endometrial lesions may grow or later be attributed to tamoxifen. In this study, out of the total 103 patients who underwent TVS all were asymptomatic except two patients, who belonged to RG and were postmenopausal, validating the statistical significance of tamoxifen induced EST in postmenopausal women. Particularly, these were the same patients who on fractional curettage had polypoidal changes and features suggesting malignancy and underwent TAH+BSO. The findings of one patient consisted of polypoid features and the other patient had adenosarcoma of mixed mullerian variety. Both these patients had presented symptomatically with vaginal bleeding. Supporting our observation, in the NSABP-P1 study most endometrial cancers were diagnosed in symptomatic group.[14] It has also been confirmed in the study by Cheng and coworkers that 67% of postmenopausal women receiving tamoxifen who reported abnormal bleeding had a pathologic finding, including 6 women (19%) with premalignant or malignant lesions. It is therefore recommended that abnormal bleeding in such patients be promptly and aggressively evaluated.[15] The prevalence of endometrial cancer in the study was 1 per 500 women, which correlates with the NSABP B-14 study.

We tried to establish a correlation between the occurrence of hyperestrogenic states and increased EST. For this we categorized our patients with increased EST and found the frequency of hyperestrogenic states i.e. increased BMI and hypertension among them. At the end we could not prove any association between them in view of p-value > 0.05. However in a meta-analysis, it was found that increase in BMI by $5kg/m^2$ increases the EST (1.59, p<0.0001).[16] It was also confirmed that obesity increases EST independently, however hypertension increase the EST in the presence of obesity.[17]

V. CONCLUSION

From the above discussion, it is evident that any patient receiving or who has previously received tamoxifen and/or who reports abnormal vaginal bleeding should be promptly evaluated. They should be advised to undergo annual gynecological examinations and should inform in case of abnormal gynecological symptoms e.g. menstrual irregularities, abnormal vaginal bleeding, lower abdominal pain or pressure symptoms. A screening program may detect premalignant endometrial precursors. If no baseline assessment is made such lesions may grow or later be attributed to tamoxifen. The thickness of normal endometrium in women receiving tamoxifen however is yet to be defined. Care must be taken, however, not to over interpret the TVS findings of the EST in tamoxifen-treated patients. The likelihood of abnormal EST is greater for patients who have abnormal bleeding, discharge than in asymptomatic tamoxifen-

users. There are no data to suggest that routine endometrial sampling in asymptomatic women taking tamoxifen to reduce the incidence of breast cancer would be beneficial. Since tamoxifen-associated endometrial cancers appear to have a similar stage, grade and histology as endometrial cancers occurring in the general population, their prognosis is generally good. Fractional curettage should be reserved for patients with any sign of abnormal vaginal bleeding, including spotting or brownish vaginal discharge. The risks of tamoxifen induced endometrial cancer must be weighed against the benefits of tamoxifen in reducing breast cancer recurrence and contralateral breast cancers..

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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