

## “UNIQUE CLINICOPATHOLOGIC FEATURES OF ENDOMETRIAL MALIGNANCY IN A TERTIARY CARE INSTITUTE – A FIVE YEAR INDIAN RURAL EXPERIENCE”

### **Abstract:**

Endometrial cancer is one of the commonest female genital tract cancers in many countries. The endometrium is one of the ten leading sites for cancer in Indian females. This cross sectional study was conducted to determine cases of endometrial malignancy occurring over a five year period at a rural tertiary care teaching institute and found that the rural Indian population exhibits some unique features in relation to this malignancy. The malignancies occur at earlier ages and occur in women with high parity. Pre surgical curettings may not be positive in all patients and a high index of clinical suspicion guides diagnostic and therapeutic interventions.

**Keywords:** Gynecology, oncology, endometrium

### **Introduction:**

Endometrial cancer is one of the commonest female genital tract cancers in many countries. Worldwide there were about 287,000 new cases of endometrial cancer in the year 2008 accounting for 4.8% of all cancers in females [1]. It is the commonest female genital tract malignancy in the United States with age adjusted incidence rate 24.1 and the age-adjusted death rate 4.2 per 100,000 women per year for the year 2005 to 2009 [2]. A uniform increase in incidence is reported in many South and East European countries [3] and the increase is seen more consistently in post menopausal women throughout Europe. The endometrium is one of the ten leading sites for cancer in Indian females with age adjusted incidence rates varying from 4.8 to 2.7 per 100,000 across different cancer registries [4]. Developing countries are experiencing a rising trend in the incidence of this cancer and obesity has been implicated as an important risk factor for this association [5]. In addition barriers to health care access, inadequate facilities, gender related inequality, as well as therapeutic inclination towards health care rather than a preventive approach preclude early diagnosis [6] and are inherent obstacles in the health care system. The pattern of endometrial carcinoma in rural India has not been investigated and this study was undertaken to determine if our population displayed any unique characteristics in relation to this malignancy in a resource poor rural setting.

### **Methods:**

This is a cross sectional study carried out at a rural tertiary care institute in central India. The source population included all gynecology patients admitted in the department of obstetrics and gynecology over a five year period. Patient related data is stored in our hospital database as the Hospital Information System (HIS). We conducted a systematic search of all inpatients admitted at our institute with the diagnosis of endometrial cancer in the discharge summary. Inclusion criteria were all patients that had a confirmed diagnosis of endometrial cancer by histopathological examination at our institute and primarily managed at our institute. All possible data regarding demographic profile, investigations, and management was extracted by a single trained data extractor. Exclusion criteria were patients that had been primarily managed at other institutes and referred to our hospital even if they had a histopathological documentation of carcinoma endometrium as their investigations were usually performed at other places and other details were not available.

**INTERNATI**Data was analyzed using Stata version 10. Mainly descriptive statistics were used and chi square test was used for comparative statistics. If data was not available despite all efforts, then the analysis was carried out only on available values and the sample size was clearly mentioned in results and tables.

### Results:

Over a five year period from 2007 to 2012, 42 cases of carcinoma endometrium were diagnosed in our institute. The overall mean age of the patients was  $53.23 \pm 10.28$  years ranging from 38-75 years (Table 1). Maximum cases (38.10%) were seen in the age 40-50 years. Mean age of menstruating women was  $41 \pm 3.6$  years ranging from 38-45 years and of post menopausal women was  $55.27 \pm 9.59$  years ranging from 40-75 years. Approximately 72% of post menopausal patients were within the age group of 41-60 years. About 80% of all the patients were <60 years old at the time of diagnosis. The mean parity was  $3.09 \pm 1.64$  and 85.51% were para two or higher.

Most of the patients (85.71%) were menopausal at the time of diagnosis (Table 2). Out of these, 83.33% had attained menopause at <50 years of age and 44.44% at <40 years of age. Amongst the post menopausal patients, 39% were diagnosed with endometrial malignancy within 5 years of menopause, 61.1% within 10 years, and 72.21% within 15 years. 14.29% patients were still menstruating at the time of diagnosis. The total menstruating period from menarche till menopause was  $\leq 25$  years in 19.05% and  $\leq 30$  years in 52.38%.

One of the commonest complaints at the time of admission was post menopausal bleeding in 66.67% followed by pain in abdomen in 57.14%. One patient presented with lump in abdomen as the chief complaint. A mass was palpable on abdominal examination in 23.8% patients. In 61.9% patients the uterus was 10 weeks size on vaginal examination. All patients >10 years menopausal had uterine size <8 weeks and this was statistically significant compared to women that had attained menopause within the last 10 years or were still menstruating ( $p = 0.009$ ).

The mean endometrial echo (N=32) was  $18.18 \pm 11.24$  mm and ranged from 3-39 mm (Table 3). There was no significant difference ( $p = 0.93$ ) between endometrial echo in women within 15 years of menopause and more than 15 years post menopausal ( $p = 0.93$ ). The echo was similar in women menstruating or within 10 years of menopause compared with more than 10 years menopausal women ( $p = 0.81$ ). The thickness was <5 mm in 66.6% of patients with "no tissue" reported after histopathological examination of endometrial curettings. Additional features mentioned about the endometrium in ultrasonography were a collection or irregular echo in 10% each, endometrial mass in 30%, blurred or cystic echo in 5% each, and the endometrium was unremarkable in 40%.

Ultrasonography was suggestive of malignancy in 38.1%. *Papanicolaou* smear was suggestive of high grade intra epithelial lesion in 4.76% and suspicious of malignancy in another 4.76%. Endometrial sampling by fractional curettage was suggestive of malignancy in 71.43%. In 14.29% cases no tissue was obtained after curetting. Both ultrasonography and histopathology of endometrial samples were available in 20 patients, at least one suggested malignancy in 71.43% and both in 38.1% cases.

Wertheim's hysterectomy was performed in 47.62% and type II modified radical hysterectomy in 4.76%. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed in 28.57%.

The commonest histopathologic type after surgery was Adenocarcinoma in 71.43%. Squamous variant of endometrial cancer was seen in 11.11% in age <50 years, 57.14% of women in the age group of 50-60 years, and in none of the patients aged  $\geq 60$  years. Two thirds (66.67%) of the patients were stage I at the time of diagnosis and only 5.56% had distant spread of disease.

### Discussion:

Endometrial malignancy occurs in the peri and post menopausal age. The incidence of this cancer is increasing especially for the type I variant which is estrogen dependent, occurs at an earlier age with better prognosis [7]. The mean age in a Japanese study was  $59.4 \pm 10.5$  years [8]. The mean age was  $53.28 \pm 10.28$  years, the peak age 55-60 years, and median age 55 years in our study which is lesser than the age reported in western studies [7, 9]. This may be because most of the malignancies in our study were type I which occur at an earlier age. However, in our study the mean age of patients with type I cancer was not different from those with type II cancers ( $P = 0.99$ ). This indicates that type II malignancies also occur at a younger age in this subpopulation. Another interesting observation was that all patients above the age of 60 years had type I cancer. Thus the age distribution of endometrial cancer appears to be different in our population from the western. A Pakistani study reported the mean age as  $56.7 \pm 12.4$  years which is similar to our study [10].

Multiparity protects against endometrial cancer [8, 11]. Giving birth to at least one child is associated with 35% risk reduction and the risk decreases with every subsequent birth [12]. Older ages at first [12] as well as last [12, 13] birth are associated with lower risk. In our study, 66.66% patients were para three or higher. However, early marriages and low age at first pregnancy are common in India. More than 50% of the women marry before the legal age of marriage that is 18 years and the median age at marriage is 17.2 years. Half of the women between the age of 20-49 have first birth before the age of 20 years [14]. We feel that early pregnancy and childbirth provide a progestogenic environment conducive to disfavor endometrial malignancies but the effect wanes off after some time and the risk begins to increase after that period. If pregnancy occurs at an older age the effect persists till the perimenopausal age which is a high risk period for development of endometrial carcinoma. Hence, as women in India complete their families early, the protective effect of parity and older age at first birth do not seem to be the operating factors. This may be one reason for parity not playing a protective role in this group. We also feel that this may be the reason for endometrial cancer occurring at an earlier age when the protective effect of early pregnancy has waned off. Albrektsen et al found that parity and time interval since last child birth positively influenced survival in endometrial cancer patients and the effect was most significant in endometrioid variant of carcinoma [15].

Early menarche and late menopause are implicated as risk factors in many studies [8, 16-18]. Menarche  $\geq 15$  yrs has 34% less risk compared to menarche before 11 years and menopause  $\geq 55$  yrs has 53% more risk than menopause between 45-49 years [18]. The hypothesis is greater exposure to estrogen during the reproductive period leading to endometrial hyperplasia and then malignancy. MacPherson C et al report the relative risk of endometrial cancer at menopause 45-49 years of age as 0.62 and the relative risk begins to increase after 33 years of ovulation [16]. Approximately 60% of our patients attained menopause before the age of 45 years and 19.05% had menstruated  $\leq 25$  years from menarche until menopause. So, a longer reproductive period does not appear to be the major risk factor operating in this set of patients. Unfortunately, information regarding other risk factors like irregular cycles and obesity was lacking in the data which may be responsible for carcinoma endometrium.

The commonest presenting feature is post menopausal bleeding or irregular bleeding in perimenopausal women [9, 19]. Bhurgri et al report post menopausal bleeding in 86.4% and purulent discharge in 4% cases [10]. Post menopausal bleeding was one of the chief complaints in 66.66% of total patients and 77.78% of postmenopausal patients. The remaining menopausal women presented with pain in abdomen and white discharge as the chief complaint. One patient presented with a lump in abdomen as the only complaint. This is important as every menopausal patient may not present with bleeding and other symptoms like pain and abnormal vaginal discharge must not be ignored.

Endometrial thickness on Ultrasonographic examination has been evaluated as a predictive tool for carcinoma endometrium and a study found an endometrial thickness of  $\leq 4$ mm in women with post menopausal bleeding was associated with 5.5% chance of actually having a pathology [20]. However, symptomatic post menopausal women are at greater risk of having malignancy even with lesser endometrial thickness compared to asymptomatic women with thicker endometrial [21]. Duration since menopause did not affect the endometrial thickness in our study and thickness was similar in women post menopausal more than 10 years compared to menopausal within 10 years. Goldstein SR reviewed role of transvaginal sonography or endometrial biopsy in patients with post menopausal bleeding and found that the chance of having an endometrial cancer in a patient with post menopausal bleeding and an endometrial echo of  $\leq 4$ mm is 1 in 917 and endometrial biopsy is more likely to yield samples insufficient for histopathological evaluation by Pipelle biopsy in these patients [22]. Ultrasonography was suggestive of malignancy in only 38% cases in our study. Associated pathologies like fibroid and adenomyosis may indicate a hyper estrogenic environment conducive for development of cancer.

Fractional curettage is a part of the diagnostic work up in our institute and was performed in all patients and histopathology revealed carcinoma in 71.43%. Atypical metaplasia was reported in a patient with infiltrating variety of cancer. The reliability of pre-hysterectomy curettings depends upon the endometrial thickness [22] and degree of tumor differentiation [23]. Accuracy of tumor typing depends upon the actual type of tumor and sensitivity ranged from 46-64% in one study [24]. The sensitivity for detecting carcinoma with four site biopsy was 88% in a recent Japanese study [25]. The problem arises in patients with thin endometrial echo on transvaginal sonography. They are less likely to yield enough tissue to provide an adequate sample for diagnosis [26]. This may be the reason for all fractional curettage samples not yielding a positive result.

As this is a rural setup and patients generally do not report for follow up, we prefer to perform a hysterectomy in post menopausal women if the clinical index of suspicion is high in favor of malignancy. The disease was confined to uterus in 66.6% and local spread in 27.8% and is similar to the SEER data 2012 statistics[2] indicating the slow growing nature of this malignancy. The commonest post surgical histopathologic type was Adenocarcinoma (type I tumor).

The incidence of type I tumors is increasing and is related to increased estrogen states [7]. Developing countries are experiencing an epidemic of obesity and India is not immune to the phenomenon. Kalra and Unnikrishnan report an increase in obesity and metabolic syndrome amongst ever married women of reproductive age from 11% to 15% and the rural population is not an exception[27, 28]. This may be one reason for high rate of type I tumors in older age groups in this subpopulation.

**Table I: Demographic profile**

Characteristic	Proportion	N
<b>Age (years)</b>		
< 40	4.76	2
40-50	40.47	17
50-60	35.71	15
60-70	14.29	6
≥ 70	9.52	4
<b>Parity</b>		
0	9.52	4
1	4.76	2
2	19.05	8
3	23.81	10
4	28.57	12
≥ 5	14.29	6

**Table II: Clinical profile**

Characteristic	Proportion	N
<b>Complaints at admission (N=42 in each subgroup)</b>		
Pain in abdomen	57.14	24
Post menopausal bleeding	66.67	28
Menorrhagia	28.57	12
White discharge per vaginum	33.33	14
Other complaints	14.29	6
<b>Size of uterus on per vaginum examination (N=42)</b>		
< 6weeks	28.57	12
6 to 10 weeks	35.71	15
10 to 15 weeks	11.90	5
15 to 20 weeks	19.04	8
≥ 20 weeks	4.76	2
<b>Menopausal status (N=42)</b>		
Menstruating	14.29	6
Post menopausal	85.71	36
<b>Duration since menopause (N= 36)</b>		
≤ 5years	38.18	14
>5 but ≤10 years	22.22	8
>10 but ≤15 years	11.11	4
>15 but ≤20 years	8.33	3
>20 years	19.44	5

**Table III: Ultrasonography, Histopathology and staging of endometrial malignancy.**

	Proportion	N
<b>Endometrial echo thickness (N=42)</b>		
≤5mm	14.29	6
>5mm	61.90	26
Other*	23.81	10
<b>Diagnosis on USG (N=42)</b>		
Carcinoma	38.10	16
Adenomyosis	2.38	1
Collection	4.76	2
Fibroid	9.52	4
Normal	19.05	8
Thick endometrium	21.42	9
Not available	4.76	2
<b>Histopathological diagnosis after endometrial sampling (N=42)</b>		
Carcinoma	71.43	30
Atypical hyperplasia	7.14	3
Atypical hyperplasia with metaplasia	7.14	3
No tissue	14.29	6
<b>Type of surgery (N=42)</b>		
TAH with BSO <sup>#</sup>	28.57	12
Extended total hysterectomy <sup>§</sup>	4.76	2
Wertheims hysterectomy	47.62	20
No surgery <sup>**</sup>	19.05	8
<b>Histopathological type of malignancy after surgery (N=34)</b>		
Adenocarcinoma	71.43	30
Adenosquamous carcinoma	14.29	6
Malignant mixed mullerian tumor	4.76	2
Pseudo sarcomatous squamous cell carcinoma	4.76	2
Squamous cell carcinoma	4.76	2
<b>FIGO stage (N=36)</b>		
Ia	16.67	6
Ib	13.88	5
Ic	36.11	13
IIb	5.56	2
IIIa	16.67	6
IIIc	5.56	2
IVb	5.56	2

\*endometrial echo was not mentioned in these cases: in one ultrasonography report, endometrium was completely occupied by a mass, the echo was blurred in one, one had an endometrial collection, normal endometrium was the

only reported feature in one report, and report was not available for one patient.

# TAH with BSO is Total abdominal hysterectomy with bilateral salpingoophorectomy.

\$ Extended total hysterectomy is removal of uterus with bilateral tubes and ovaries with upper 1/3<sup>rd</sup> of vagina and clamping the broad ligaments 1cm away from uterus.

\*\* surgery was not performed in 8 patients of which 6 were either medically unfit for surgery or had advanced stage disease in which surgery was not possible and 2 patients were not willing to undergo surgery.

#### **Limitations:**

Retrospective data and missing values limit our study. Also information about other variables like obesity, contraception, family history etc was missing and may have influenced our results.

#### **Conclusions:**

Endometrial carcinoma exhibits some unique clinicopathologic features in Indian rural women. It occurs at an earlier age compared to the western counterparts and type I cancers are more common even with advancing age. The protective effect of parity may be missing in this subgroup due to early childbearing and early completion of family. These patients have a thick endometrium on Ultrasonographic examination independent of the duration since menopause. The uterus is enlarged to a greater extent in patients that are menstruating or within ten years of menopause. The tumors are confined to the uterus in two third patients and the commonest variant is Adenocarcinoma. Pre surgical endometrial curettings may not always yield a positive diagnosis of malignancy and clinical suspicion plays a vital role in the rural setup.

#### **Declaration of conflict of interest:**

The authors report no conflicts of interest. The study was not funded by any organization and there are no financial conflicts of interests.

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