

A Study of Correlation of Clinical Variables with Presenting Stage and Type of Endometrial Cancer at a Tertiary Care Hospital - A Retrospective Study

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Abstract

Introduction: The prevalence of gynecological cancers has been increasing in the Asian population. With the recent changing trend in lifestyle and reproductive profile of women, the number of cases being diagnosed with endometrial cancer is increasing.

Aim: The aim of this study is to evaluate the correlation of various clinical risk factors of endometrial carcinoma on the histopathology and presenting stage of the disease.

Materials and Methods: A hospital-based, retrospective study included 100 patients of endometrial carcinoma presented at the Institute of Obstetrics and Gynaecology, Chennai, India, between January 2016 and June 2019. The correlation of age (≤ 40 years and > 40 years), parity status (parous and nulliparous), menstrual status (premenopause and postmenopause), diabetes, hypertension, duration of complaint (≤ 6 months and > 6 months), and body mass index (BMI) with the stage of the disease (clinical/radiological and pathological stages) and histological class was analyzed.

Results: The mean age of patients was 56.4 ± 11.3 years. Among the 100 patients, a total of 62 (63.6%) patients had presented with clinical/radiological stage-I, of which 6 patients had defaulted for treatment and 6 patients had the stage-IV disease. Of the 88 patients who underwent staging laparotomy, 59 (67%) patients had pathological stage-I carcinoma and 3, 18, and 8 patients presented in stage II, III, and IV disease, respectively. Histopathological evaluation revealed endometrioid adenocarcinoma as the most common type, in 79 patients (79%). No significant correlation of any of the risk factors on clinical/radiological, pathological as well as on histopathology was observed.

Conclusion: The study did not state the statistically significant association of age, parity status, menopause, diabetes, hypertension, BMI, and the duration of complaints with the histological class of endometrial carcinoma and presenting clinical and pathological stages of endometrial carcinoma.

Key words: Clinical factors, Endometrial cancer, Pathological correlation

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the Western world and is the second-most common gynecological malignancy in developing countries.^[1,2] Anciently, endometrial carcinoma was a disease of developed countries, but due to changing trends in the lifestyle and

reproductive profile of women, the prevalence of endometrial carcinoma is increasing in developing countries as well. The etiological factors responsible for the development of endometrial carcinoma are increasing age (> 55 years), obesity, hypertension, diabetes, nulliparity, menopause, high level of estrogen/endometrial hyperplasia, genetic mutation, and tamoxifen use (breast cancer).^[2-4] Abnormal uterine bleeding (e.g., menometrorrhagia and postmenopausal bleeding) is a typical presenting symptom in women with endometrial carcinoma. Endometrial carcinoma is primarily a disease of postmenopausal women and only 20–25% of cases occur in the premenopausal population (age < 45 years).^[2,3]

Conventionally, endometrial carcinomas have been classified on the basis of clinical, endocrine, and epidemiological

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characteristics as Type-I tumors (estrogen-dependent, and associated with endometrial hyperplasia) and Type-II tumors (estrogen-independent and associated with endometrial atrophy). Histopathological characteristics of endometrial carcinoma categorize it into different subtypes such as endometrioid adenocarcinoma, serous adenocarcinoma, serous endometrioid intraepithelial carcinoma, clear-cell carcinoma, mixed epithelial carcinoma, mucinous adenocarcinoma, endometrial stromal sarcoma, papillary serous carcinoma, squamous cell carcinoma, and malignant mixed Müllerian tumor.^[4,5] There are lack of data on correlation of various etiological factors with clinic-pathological stages and with the histopathological class of endometrial carcinoma.

Aim

The aim of this study is to study the effect of various clinical variables on the histopathological and clinical/pathological stages of endometrial carcinoma.

MATERIALS AND METHODS

This hospital-based, retrospective study was conducted at the Institute of Obstetrics and Gynaecology, Chennai, India. The study included 100 patients who were diagnosed and treated for endometrial carcinoma between January 2016 and June 2019. The baseline demographic details, clinical, staging, and a histopathological class of endometrial carcinoma of all the patients were collected in a retrospective manner from the medical records of the oncology department of the hospital. The demographic details such as age, medical history, body mass index (BMI), marital and parity status, age of menopause, and family history of cancer; and clinical signs and symptoms reported during presentation were also identified from the records the stages of endometrial cancer were derived according to the International Federation of Gynaecology and Obstetrics (FIGO) 2009 classification as clinical/radiological stages (by computed tomography chest and abdomen) and pathological stages (by staging laparotomy). The details of histopathological type with grade were also derived.

The correlation of age (≤ 40 years and > 40 years), parity status (parous and nulliparous), menstrual status (premenopause and postmenopause), coexisting illnesses such as diabetes, hypertension, duration of complaint (≤ 6 months and > 6 months), and BMI with the stage of the disease (clinical/radiological and pathological stages), and histological class was analyzed. BMI was classified as per the Asian criteria for BMI into eight groups – underweight: < 18.5 kg/m², normal: 18.5–22.9 kg/m², overweight: 23–24.9 kg/m², preobese: 25–29.9 kg/m², obese

type-1: 30–40 kg/m², obese type-2: 40.1–50 kg/m², and obese type-3: > 50 kg/m².

The statistical analyses were performed using the SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA). The Chi-square, Gamma Statistic, and Fisher's exact tests were used when appropriate to assess the relationships between clinic-pathologic variables and clinical variable and two-sided $P < 0.05$ was considered statistically significant. Quantitative data are presented as a mean and standard deviation, and qualitative data are presented as frequency and percentage.

RESULTS

The study included retrospective data of 100 patients who were diagnosed with endometrial carcinoma. The mean age of patients was 56.4 ± 11.3 years. Among all, 91 (91%) patients were diagnosed with endometrial carcinoma after the age of 40 years. The disease was diagnosed after an average of 15.3 ± 7.5 years postmenopause. Total 6 cases had other malignancies along with endometrial carcinoma, which includes two cases of ovarian carcinoma, 2 cases of breast carcinoma, 1 case of cervical carcinoma, and 1 case of ovarian and cervical carcinoma. Table 1 displays the demographic details of the patients. Among all clinical presentation, abnormal vaginal bleeding was found as the most common sign of endometrial carcinoma in 63 (85.1%) postmenopausal and 18 (69.2%) premenopausal women. Other complaints observed in patients with endometrial carcinoma were white discharge, abdominal pain, and abdominal mass.

The staging of endometrial carcinoma was observed as: (i) clinical/radiological stage and (ii) pathological stage. A total of 62 (62.6%) patients were presented with clinical/radiological stage-I carcinoma and 59 (67%) patients with pathological stage-I carcinoma.

Histopathological evaluation of the present study revealed endometrioid adenocarcinoma in 78 patients, among which 39 (49.4%) patients diagnosed with well-differentiated (Grade-1), 22 (27.8%) with moderately-differentiated (Grade-2), and 17 (21.5%) with poorly-differentiated (Grade-3). Three patients were diagnosed with clear-cell adenocarcinoma. Seven patients were diagnosed with endometrial stromal sarcoma with 6 low-grade well-differentiated sarcomas and 1 high-grade undifferentiated sarcoma. Mucinous endometrial adenocarcinoma was discovered in 3 patients, of which 2 were well-differentiated (Grade-1) and 1 was moderately-differentiated (Grade-2). Only 1 case of poorly-differentiated squamous cell carcinoma was observed. Furthermore, staging laparotomy

was performed in 88 patients and among them, >50% myometrial invasion was observed in 62 (70.5%) patients and <50% myometrial invasion in 26 (29.5%) patients.

Furthermore, we have analyzed the correlation of baseline demographic criteria (age, parity status, menstrual status,

diabetes, hypertension, BMI, and duration of complaints) with clinical/radiological stage [Table 2], pathological stage [Table 3] and histo-pathological class of endometrial carcinoma [Table 4]. However, no significant association of any of the risk factors on clinical/radiological, pathological as well as on histopathological type was observed. As endometrioid adenocarcinoma has been found as a most common type of endometrial carcinoma, we have also analyzed the association of baseline demographics with the occurrence of well, moderately, and poorly differentiated adenocarcinoma of the endometrium. No significant association of any of the parameter was found in our study [Table 5].

Table 1: Baseline demographic details of all the patients

Characteristics	Number of patients=100
Age, years (mean±SD)	56.4±11.3
Age group, n (%)	
≤40 years	9 (9%)
>40 years	91 (91%)
Diabetes mellitus, n (%)	30 (30%)
Hypertension, n (%)	45 (45%)
BMI, kg/cm ² (n=97) (mean±SD)	26.5±6.0
Marital status, n (%)	
Married	92 (92%)
Unmarried	8 (8%)
Parity	
Parous, n (%)	85 (85%)
Age of parous (mean±SD)	57.0±10.8
Nulliparous, n (%)	15 (15%)
Age of nulliparous (mean±SD)	53.3±13.5
Menopause, n (%)	
Yes	74 (74%)
No	26 (26%)
Menopause years (mean±SD)	15.3±7.5

SD: Standard deviation

DISCUSSION

The present study evaluated the correlation of various etiological parameters (age, parity status, menopause, diabetes, hypertension, BMI, and duration of complaint) of endometrial carcinoma with histopathological class and stages of the disease. Approximately 75% of patients were clinically diagnosed with early-stage disease (FIGO stage-I and -II).¹¹ Age is considered the main risk factor, with most cases occurring in women over the age of 50 years. Women with age >55 years have 1.4 relatively higher risks of the development of endometrial carcinoma.^{16,71} In our study,

Table 2: Correlation of various etiological variables with clinical/radiological stages of endometrial carcinoma

Characteristics	Clinical/radiological stages (n=99)								P-value	Gamma correlation
	I n=62 (%)	II n=6 (%)	III-A n=8 (%)	III-B n=3 (%)	III-C1 n=13 (%)	III-C2 n=1 (%)	IV-A n=1 (%)	IV-B n=5 (%)		
Age										
≤40 years	4 (6.5)	1 (16.7)	1 (12.5)	0	3 (23.1)	00	00	0	0.326	-0.269
>40 years	58 (93.5)	5 (83.3)	7 (87.5)	3 (100)	10 (76.9)	1 (100)	1 (100)	5 (100)		
Parity										
Parous	50 (80.6)	5 (83.3)	7 (87.5)	3 (100)	13 (100)	0	1 (100)	5 (100)	0.072	-0.435
Nulliparous	12 (19.4)	1 (16.7)	1 (12.5)	0	0	1 (100)	0	0		
Menopause										
Premenopausal	16 (25.8)	0	6 (75.0)	0	3 (21.4)	1 (100)	0	0	0.929	0.018
postmenopausal	46 (74.2)	6 (100)	2 (25.0)	2 (100)	11 (78.6)	0	1 (100)	5 (100)		
Diabetes										
No	44 (71.0)	3 (50.0)	6 (75.0)	0	10 (71.4)	1 (100)	1 (100)	4 (80.0)	0.965	0.009
Yes	18 (29.0)	3 (50.0)	2 (25.0)	2 (100)	4 (28.6)	0	0	1 (20.0)		
Hypertension										
No	31 (50.0)	3 (50.0)	6 (75.0)	0	10 (71.4)	1 (100)	1 (100)	2 (40.0)	0.25	-0.201
Yes	31 (50.0)	3 (50.0)	2 (25.0)	2 (100)	4 (28.6)	0	0	3 (60.0)		
BMI range (kg/m ²)										
Underweight <18.5	3 (5.0)	1 (16.7)	0	0	1 (7.1)	0	1 (100)	0	0.071	-0.225
Normal: 18.5–22.9	11 (18.3)	1 (16.7)	2 (28.6)	1 (50.0)	2 (14.3)	1 (100)	0	1 (20.0)		
Overweight: 23–24.9	9 (15.0)	1 (16.7)	1 (14.3)	1 (50.0)	3 (21.4)	0	0	1 (20.0)		
Preobese: 25–29.9	15 (25.0)	3 (50.0)	3 (42.9)	0	5 (35.7)	0	0	2 (40.0)		
Obese type-1:30–40	20 (33.3)	0	1 (14.3)	0	3 (21.4)	0	0	1 (20.0)		
Obese type-2: 40.1–50	2 (3.3)	0	0	0	0	0	0	0		
Duration of complaint										
≤6 months	44 (73.3)	5 (83.3)	8 (100)	1 (33.3)	9 (69.2)	1 (100)	1 (100)	3 (60.0)	0.966	0.009
>6 months	16 (26.7)	1 (16.7)	0	2 (66.7)	4 (30.8)	00	0	2 (40.0)		

BMI: Body mass index

Table 3: Correlation of various etiological variables with pathological stages of endometrial carcinoma

Characteristics	Pathological stages (n=88)								P-value	Gamma correlation
	I-A n=23 (%)	I-B n=36 (%)	II n=3 (%)	III-A n=8 (%)	III-B n=2 (%)	III-C1 n=8 (%)	IV-A n=1 (%)	IV-B n=7 (%)		
Age										
≤40 years	2 (8.7)	1 (2.8)	0	1 (12.5)	0	1 (12.5)	0	2 (28.6)	0.393	-0.288
>40 years	21 (91.3)	35 (97.2)	3 (100.0)	7 (87.5)	2 (100)	7 (87.5)	1 (100)	5 (71.4)		
Parity										
Parous	21 (91.3)	26 (72.2)	3 (100.0)	8 (100.0)	2 (100)	8 (100)	1 (100)	4 (57.1)	0.751	0.068
Nulliparous	2 (8.7)	10 (27.8)	0	0	0	0	0	3 (42.9)		
Menopause										
Premenopausal	9 (39.1)	5 (13.9)	0	5 (62.5)	0	2 (25.0)	0	2 (28.6)	0.623	0.089
postmenopausal	14 (60.9)	31 (86.1)	3 (100)	3 (37.5)	2 (100)	6 (75.0)	1 (100)	5 (71.4)		
Diabetes										
No	18 (78.3)	24 (66.7)	2 (66.7)	6 (75.0)	1 (50.0)	4 (50.0)	1 (100)	5 (71.4)	0.353	0.16
Yes	5 (21.7)	12 (33.3)	1 (33.3)	2 (25.0)	1 (50.0)	4 (50.0)	0	2 (28.6)		
Hypertension										
No	14 (60.9)	15 (41.7)	1 (33.3)	5 (62.5)	1 (50.0)	4 (50.0)	1 (100.0)	5 (71.4)	0.860	-0.028
Yes	9 (39.1)	21 (58.3)	2 (66.7)	3 (37.5)	1 (50.0)	4 (50.0)	0	2 (28.6)		
BMI range (kg/m ²)										
Underweight:<18.5	2 (8.7)	1 (2.9)	0.0	1 (14.3)	0	0	1 (100)	1 (14.3)	0.333	-0.124
Normal: 18.5–22.9	3 (13.0)	8 (23.5)	0.0	1 (14.3)	1 (50.0)	1 (12.5)	0	3 (42.9)		
Overweight: 23–24.9	5 (21.7)	4 (11.8)	1 (33.3)	1 (14.3)	0	2 (25.0)	0	0		
Preobese: 25–29.9	4 (17.4)	11 (32.4)	2 (66.7)	3 (42.9)	1 (50.0)	2 (25.0)	0	1 (14.3)		
Obese type-1: 30–40	8 (34.8)	10 (29.4)	0	1 (14.3)	0	3 (37.5)	0	1 (14.3)		
Obese type-2: 40.1–50	1 (4.3)	0	0	0	0	0.0	0	1 (14.3)		
Duration of complaint										
≤6 months	16 (72.7)	27 (77.1)	2 (66.7)	8 (100)	0	5 (62.5)	1 (100)	7 (100)	0.514	-0.12
>6 months	6 (27.3)	8 (22.9)	1 (33.3)	0.0	2 (100)	3 (37.5)	0	0		

BMI: Body mass index

Table 4: Correlation of various etiological variables with the histological class of endometrial carcinoma

Characteristics	Histopathology (n=99)									P-value	Gamma correlation
	EA n=78 (%)	ESS n=7 (%)	CCA n=3 (%)	MEA n=3 (%)	PSC n=3 (%)	EAV n=2 (%)	MMT-CH n=1 (%)	MEC (EA+PSC) n=1 (%)	SCC n=1 (%)		
Age											
≤40 years	5 (6.3)	2 (28.6)	0	1 (33.3)	0	1 (50.0)	0	0	0	0.183	-0.454
>40 years	74 (93.7)	5 (71.4)	3 (100)	2 (66.7)	3 (100)	1 (50.0)	1 (100)	1 (100)	1 (100)		
Parity											
Parous	67 (84.8)	7 (100)	2 (66.7)	2 (66.7)	3 (100)	1 (50.0)	1 (100)	1 (100)	1 (100)	0.968	-0.009
Nulliparous	12 (15.2)	0	1 (33.3)	1 (33.3)	0	1 (50.0)	0	0	0		
Menopause											
Premenopausal	19 (24.1)	4 (57.1)	0	1 (33.3)	1 (33.3)	0	0	0	1 (100)	0.545	-0.167
postmenopausal	60 (75.9)	3 (42.9)	3 (100)	2 (66.7)	2 (66.7)	2 (100)	1 (100)	1 (100)	0		
Diabetes											
No	53 (67.1)	7 (100)	2 (66.7)	2 (66.7)	3 (100)	1 (50.0)	0.0	0	1 (100)	0.264	-0.283
Yes	26 (32.9)	0	1 (33.3)	1 (33.3)	0	1 (50.0)	1 (100)	1 (100)	0		
HTN											
No	42 (53.2)	6 (85.7)	00	2 (66.7)	2 (66.7)	1 (50.0)	0	1 (100)	1 (100)	0.541	-0.145
Yes	37 (46.8)	1 (14.3)	3 (100)	1 (33.3)	1 (33.3)	1 (50.0)	1 (100)	0	0		
BMI range (kg/m ²)											
Underweight:<18.5	3 (3.9)	3 (50.0)	0	0	0	0	0	0	0	0.107	-0.254
Normal: 18.5–22.9	15 (19.5)	0	2 (66.7)	1 (33.3)	0	1 (50.0)	0	1 (100)	0		
Overweight: 23–24.9	13 (16.9)	1 (16.7)	0	0	0	1 (50.0)	1 (100)	0	0		
Preobese: 25–29.9	22 (28.6)	2 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	0	0	0	0		
Obese type-1: 30–40	22 (28.6)	0	0	0	2 (66.7)	0	0	0	1 (100)		
Obese type-2: 40.1–50	2 (2.6)	0	0	0	0	0	0	0	0		
Duration of complaint											
≤6 months	57 (74.0)	6 (85.7)	2 (66.7)	3 (100)	2 (66.7)	1 (50.0)	1 (100)	1 (100)	0	0.946	-0.018
>6 months	20 (26.0)	1 (14.3)	1 (33.3)	0	1 (33.3)	1 (50.0)	0	0	1 (100)		

HTN: Hypertension, BMI: Body mass index, EA: Endometrioid adenocarcinoma, ESS: Endometrial stromal sarcoma, CCA: Clear cell adenocarcinoma, MEA: Mucinous endometrial adenocarcinoma, PSC: Papillary serous carcinoma, EAV: Endometrial adenocarcinoma villoglandular type, MMT-CH: Malignant mixed mullerian tumor - carcinosarcoma of homologous type, MEC: Mixed epithelial carcinoma, SCC: Squamous cell carcinoma

Table 5: Correlation of various etiological variables with development endometrioid adenocarcinoma

Characteristics	Endometrioid adenoca (n=78)			P-value	Gamma correlation
	WD (Grade-1) n=39 (%)	MD (Grade-2) n=22 (%)	PD (Grade-3) n=17 (%)		
Age					
≤40 years	1 (2.6)	1 (4.5)	3 (17.6)	0.122	-0.629
>40 years	38 (97.4)	21 (95.5)	14 (82.4)		
Parity					
Parous	32 (82.1)	21 (95.5)	13 (76.5)	0.961	-0.014
Nulliparous	7 (17.9)	1 (4.5)	4 (23.5)		
Menopause					
Premenopausal	10 (25.6)	4 (18.2)	5 (29.4)	0.985	-0.004
postmenopausal	29 (74.4)	18 (81.8)	12 (70.6)		
Diabetes					
No	29 (74.4)	11 (50.0)	12 (70.6)	0.349	0.178
Yes	10 (25.6)	11 (50.0)	5 (29.4)		
Hypertension					
No	22 (56.4)	9 (40.9)	10 (58.8)	0.784	0.052
Yes	17 (43.6)	13 (59.1)	7 (41.2)		
BMI range (kg/m ²)					
Underweight: <18.5	1 (2.7)	0 (0.0)	2 (11.8)	0.886	-0.02
Normal: 18.5–22.9	8 (21.6)	3 (13.6)	3 (17.6)		
Overweight: 23–24.9	7 (18.9)	4 (18.2)	2 (11.8)		
Preobese: 25–29.9	9 (24.3)	8 (36.4)	5 (29.4)		
Obese Type-1: 30–40	10 (27.0)	7 (31.8)	5 (29.4)		
Obese Type-2: 40.1–50	2 (5.4)	0	0		
Duration of complaint					
≤6 months	25 (65.8)	14 (66.7)	12 (70.6)	0.75	-0.065
>6 months	13 (34.2)	7 (33.3)	5 (29.4)		

BMI: Body mass index, WD: Well differentiated, MD: Moderately differentiated, PD: Poorly differentiated

only 9% of women with age <40 years were diagnosed with endometrial carcinoma. No statistically significant correlation of patient's age with histopathological class and clinical and pathological stage were found in our study.

Obesity is considered as a key factor which leads to the development of about 30% of all cancers in humans and increasing BMI has strong associated with endometrial cancer incidences and mortality. A recent meta-analysis revealed that with each increase in BMI of 5 kg/m², the woman's risk of developing endometrial cancer significantly increase by 1.59.^[8,9] In obese women, the exposure of estrogen to endometrial tissue is more due to excessive estrogen production by the conversion of androgens in the fat. A study by Cauley *et al.*^[10] also proved in that obese (BMI >30) postmenopausal women have >40% increases in both circulating estrone and estradiol levels compared to normal (BMI <27) postmenopausal women. Literature states that high-BMI has good prognostic features, including low-grade tumor, endometrioid histology, and presentation at the early stage. However, patients with low BMI are expected to have high-grade tumors, nonendometrioid histology and may present at advanced stages of endometrial carcinoma with poorer clinical outcomes.^[7] In our study also, 22 patients with BMI ≥30 kg/m² were presented with clinical stage I of endometrial carcinoma, 19 patients presented with pathological stage IA and IB.

Most of the patients (n = 24) with BMI of ≥30 kg/m² were diagnosed with endometrial adenocarcinoma. However, no significant correlation between BMI and obesity was observed with histological class and clinical/pathological stages of endometrial carcinoma.

Nulliparity is associated with a two-fold increase in the risk of development of endometrial carcinoma. The reason behind this might be related to the absence of progesterone in women who are infertile, which resulting in continuous unopposed estrogen stimulation. However, multiple factors might be involved in this, and it might be related to the individual's hormonal profile during life. It has been found that nulliparous women have a significantly increased number of endometrial shedding events during their menstrual lives compared to parous women which might increase the risk of endometrial carcinoma in such women.^[2-4] In our study, we tried to establish correlate nulliparity with the stages of endometrial carcinoma and histological grades, but no such association was found between them which guided toward conduction of larger studies to prove this. Diabetes and hypertension were also found to increase the risk of development of endometrial carcinoma by 1.8–2.0-fold and 1.5-fold, respectively.^[3] The present study also analyzed the correlation between diabetes and hypertension with histological class and clinical and pathological stages, but no significant correlation has been

proved. It was also found that premenopausal women were presented with early stage of endometrial carcinoma and with less complexly differentiated tumors, but in our study, it was not established.^[2,3]

Among all histological subtypes of endometrial carcinoma, endometrial adenocarcinoma is the most common type diagnosed in around 50–60% of cases. Endometrial adenocarcinoma is further graded into three types depending on the differentiation of tumor as well-differentiated, moderately differentiated, and poorly differentiated carcinoma. Here, in this study, we also analyzed the role of various risk factors of endometrial carcinoma (age, parity status, menopause, diabetes, hypertension, BMI, and duration of complaint) with tumor differentiation in endometrial adenocarcinoma. However, no significant association was noted of each risk factor with the differentiation of tumor cells in endometrial adenocarcinoma.

CONCLUSION

From the results of the present study, it can be concluded that age, parity status, menopause, diabetes, hypertension, BMI, and duration of complaints have no association with the histological class of endometrial carcinoma and

also with clinical and pathological stages of endometrial carcinoma. However, larger trials are required to prove this with more number of patients of endometrial carcinoma.

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