

# A Fifteen Years Audit of Endometrial Cancer Referred for Adjuvant Treatment to a Tertiary Care Hospital in Northern India

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## ABSTRACT

**Introduction:** Endometrial cancer is the seventh most common cancer in women worldwide with Age Standardised Incidence Rate (ASIR) of 8.4 per lac. In Indian subcontinent, the incidence is lesser and the ASIR is 2.1/100,000 women. However, its incidence is on the steady rise in developing part of the world including India. Surgery is the primary treatment and adjuvant radiotherapy is given in patients with high-risk of recurrence and significant change has happened in the management in the last 20 years. From India limited literature is available for management practices for endometrial cancer.

**Aim:** To assess the referral patterns, demography, staging, surgical practices, adjuvant treatment and follow-up policies for endometrial cancer in a tertiary care hospital in northern India.

**Materials and Methods:** A retrospective cross-sectional study was done for patients having endometrial cancer treated between January 2000-December 2015 in a tertiary care hospital in northern India in January 2022. A total of 93 patients having endometrial cancer were referred for radiotherapy. For these patients, their referral patterns, demography, staging, surgical practices, adjuvant treatment and follow-up policies were analysed, retrospectively. Disease Free Survival (DFS) and Overall Survival (OS) were computed by Kaplan-Meier method.

**Results:** The median age at presentation was 55 years. Postmenopausal vaginal bleeding was the commonest symptom 78 (83.87%). Ultrasonography 23 (24.73%) was the preferred first imaging modality. Type 1 endometrioid carcinoma was 75 (80.64%) and total abdominal hysterectomy with bilateral salpingo-oophorectomy was done in 82 (88.17%). Adjuvant External Beam Radiotherapy (EBRT) with Brachytherapy (BT) was given in 61 (65.59%), EBRT alone in 7 (7.52%) and BT alone given in 11 (11.83%). Median EBRT dose was 50.4 Gy. Vaginal cylinder applicator was used in 69 (95.83%) out of 72 patients receiving BT. A 6.0 Gy/# to a total of 2 fractions were given in 57 (79.16%). Median treated length of vagina was 3 cm (range 2-8 cm). Five year DFS and OS was 25% and 25% and 64% and 62% respectively in worst and best case scenario. Ten (10.75%) patients, all having high-risk had multiple visceral and local recurrence.

**Conclusion:** In patients with endometrial cancer, total abdominal hysterectomy with bilateral salpingo-oophorectomy is commonest surgical practice with adjuvant radiotherapy given in patients with high risk of recurrence. In a developing country like India, assuring uniformity of treatment protocols is a challenging task.

**Keywords:** Brachytherapy, Radiotherapy, Surgery

## INTRODUCTION

Endometrial cancer is the seventh most common cancer in women worldwide (14<sup>th</sup> most common cancer overall), with ASIR of 8.4 per lac [1]. It is the commonest genital cancer in women in developed countries. In Indian subcontinent, the incidence is lesser and the ASIR is 2.1/100,000 women [1]. However, due to change in lifestyle and urbanisation endometrial cancer is on the steady rise in developing part of the world including India [2-4]. It is a disease of postmenopausal women with peak incidence in 6<sup>th</sup> and 7<sup>th</sup> decade of life. The prognosis is better than other gynaecological cancers, as it presents at early stage at diagnosis. The risk factors of endometrial carcinomas are older age, early age at menarche, late age at menopause, lower parity, use of hormone replacement therapy, obesity, diabetes mellitus, hypertension, high-fat and low fibre diet [5-8]. Surgery has been the primary modality of treatment and patients at high-risk of recurrence benefit with adjuvant radiotherapy [9-11]. However, there is a significant change in the management of carcinoma endometrium over the last 2-3 decades. Recently, there is a decreasing trend for the use of adjuvant pelvic radiotherapy in completely surgically staged patients to decrease the long-term toxicity [10-12].

A service evaluation was carried out to critically review the process involved in the management of endometrial cancer, a relatively less common cancer in this part of the world, to document factors (patient related, disease and intervention including timelines)

believed to influence the outcome of endometrial cancer. The aim of present study was to look for referral patterns, demography, staging, surgical practices, adjuvant treatment and follow-up policies in patients being referred for adjuvant treatment to a tertiary care hospital in northern India.

## MATERIALS AND METHODS

The present cross-sectional study was done in Department of Radiotherapy, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India between January 2000 to December 2015, data was analysed in January 2022. This type of audit study is a part of departmental service evaluation process and Informed written consent was obtained from all patients in accordance with departmental and institute policies. A total of 2,314 gynaecological cancer patients were registered in the Department of Radiotherapy.

**Inclusion criteria:** Patients having histopathological diagnosis of endometrial cancer, any stage, referred for adjuvant treatment in form of external beam radiotherapy or BT or chemotherapy were included in the study.

**Exclusion criteria:** Non availability of medical records, patients not coming after first consultation, no histological proof of endometrial cancer and patients having uterine sarcoma were excluded from the study.

Of these, 116 (5%) patients had endometrial cancer; rest included cervical cancer, vaginal and ovarian cancers. Of 116 patients, five cases of uterine sarcomas and 18 patients who did not report after first consultation were excluded. Thus, the present study included 93 patients having endometrial cancer for further analysis. Medical records were retrieved for their referral patterns, demography, staging, surgical practices, adjuvant treatment and follow-up policies in patients of endometrial cancer. Initial assessment included pelvic examination and endometrial tissue biopsy. For staging ultrasound abdomen, Contrast Enhanced Computed Tomography (CECT) and later on Magnetic Resonance Imaging (MRI) recently were used. The standard surgery was total abdominal hysterectomy and bilateral salpingo-oophorectomy but no routine lymphadenectomy was practiced in general. Patients were staged according to FIGO staging system [13]. In histopathological review, data was collected for histological type, grade, depth of invasion, >1/2 myometrium involvement and lymphovascular emboli. Staging was based on the information gleaned from the discharge summaries, examination findings at presentation to the department, imaging, and histology whenever available/provided. Criteria for adjuvant radiotherapy was assessed based on age, grade and depth of myometrial invasion and stage, risk group and physician's choice [11,12]. Adjuvant RT were consisted of EBRT with or without BT. Patients were kept on clinical and radiological follow-up as per existing departmental follow-up policy i.e., three monthly for first two years, six monthly for next two years and thereafter once a year. Imaging in form of ultrasonography and or CECT scan was done when indicated.

## STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, central tendency using mean, median, and mode was performed. DFS and OS was calculated from the date of registration to the date of first failure and date of death or late of last follow when alive at the time of analysis in January 2022 respectively using Kaplan–Meier method. Death due to any cause or loss to follow-up was considered as an event for survival analysis.

## RESULTS

**Demography:** The demographic profile of 93 endometrial cancer patients is shown in [Table/Fig-1]. The median age at presentation was 55 years with about one fifth 23 (24.73%) of patients were more than 60 years of age. The median duration of symptoms at the time of presentation was six months. Postmenopausal vaginal bleeding was the commonest symptom 78 (83.87%).

Referral pattern of patients showed that community gynaecologists are the commonest speciality performing the surgery 30 (32.26%). Ultrasonography alone 23 (24.73%) was the preferred first imaging modality with no records of radiological imaging details were found in 28 (30.11%). FIGO stage I–IV disease was 45 (48.39%), 11 (11.83%), 20 (21.50%) and 2 (2.15%) 15 (16.13%) of patients could not be staged due to inadequate documentation [Table/Fig-1].

## Treatment Details

**Surgery:** Average number of radical hysterectomy done per month at the centre is 1-2 per month. Reason is that ours is a low gynaecological cancer volume centre without having a full-fledged department of obstetrics and gynaecology and also being a tertiary referral centre. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done in 82 (88.17%). Pelvic Lymph Node Dissection (PLND) was done in 31 (33.33%) only and lymph node sampling was done in 5 (5.37%). When looked at level of dissection status, it was found that 26 (27.95%) patients had pelvis lymph node dissection only and extended nodal dissection was

Characteristics	N (%)
<b>Age (years)</b>	
≤60	70 (75.27)
>60	23 (24.73)
Mean, median (range)	55.9, 55, (37-80)
<b>Menopausal status</b>	
Premenopausal	12 (12.90)
Postmenopausal	73 (78.50)
Unknown	8 (8.60)
<b>Referral pattern</b>	
Institute's gynaecologist	10 (10.75)
Community general surgeon	11 (11.83)
Community gynaecologist	30 (32.26)
Community oncosurgeon	14 (15.05)
Others (dedicated cancer facility)	28 (30.11)
<b>Prestaging imaging modality</b>	
MRI	2 (2.15)
CECT	15 (16.13)
USG	23 (24.73)
MRI+USG	9 (9.68)
CECT+USG	12 (12.90)
PET	2 (2.15)
MRI+CECT	2 (2.15)
No records	28 (30.11)
<b>Diagnosis</b>	
Type-I (Endometroid Ca)	75 (80.64)
Type-II (Non endometroid Ca)	9 (9.68)
Endometrial Ca, NOS	9 (9.67)
<b>Risk group</b>	
Low-risk	4 (4.30)
Low intermediate	37 (39.78)
High intermediate	22 (23.66)
High	19 (20.43)
Unknown	11 (11.83)
<b>FIGO stage</b>	
I	45 (48.39)
II	11 (11.83)
III	20 (21.50)
IV	2 (2.15)
Unknown	15 (16.13)
<b>Primary treatment record</b>	
Total abdominal hysterectomy and bilateral salpingo-oophorectomy	82 (88.17)
Simple/subtotal hysterectomy	7 (7.53)
Vaginal hysterectomy	2 (2.15)
Inoperable	2 (2.15)

[Table/Fig-1]: Demography profile (n=93).

MRI: Magnetic resonance imaging; CECT: Contrast enhanced computed tomography; USG: Ultrasound; PET: Positron emission tomography; NOS: Not otherwise specified; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy

done in 8 (8.60%). Median number of pelvic lymph nodes dissected was 10 each and nodes were positive in 5 (13.88%) patients out of 36 patients in whom either PLND or pelvic lymph node sampling was done.

**Histopathological details:** Type 1 endometroid carcinoma was commonest histopathological type 75 (80.64%). Histopathological examination, depth of invasion and Lympho-vascular emboli is shown in [Table/Fig-2]. According to the criteria used in the Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC)

Variable	N (%)
<b>Grade</b>	
I	33 (35.48)
II	23 (24.73)
III	13 (13.98)
Unknown	24 (25.81)
<b>Depth of invasion</b>	
Only endometrium	6 (6.45)
<1/2 myometrium	26 (27.96)
>1/2 myometrium	38 (40.86)
Unknown	23 (24.73)
<b>LVI</b>	
LVI positive	9 (9.68)
LVI negative	21 (22.58)
Unknown	63 (67.74)

[Table/Fig-2]: Depth of invasion, Grade and LVI status (n=93).

trial, considering age, grade and depth of myometrial invasion and stage, 37 (39.78%) had low intermediate risk was commonest endometrial cancer risk category [10].

### Adjuvant Treatment Details

**External Beam RT (EBRT):** Based on physicians discretion adjuvant EBRT with vaginal BT was given in 61 (65.59%), EBRT alone 7 (7.52%), BT alone in 11 (11.82%) while observation alone without adjuvant RT/brachytherapy in 11 (11.82%). 3 (3.22%) patients who presented with metastatic/recurrent/advanced cases received palliative treatment. Patients received a median radical EBRT dose of 50.4 Gy (range 20-55Gy) in 25-28 fractions. RT technique was conventional in 50 (73.52%), conformal RT 8 (11.76%) and intensity modulated RT in 10 (14.70%). Until 2008, 28 patients (41.17%) received treatment on telecobalt machine and 2009 onwards 40 (58.82%) were treated on linear accelerator.

**Brachytherapy (BT):** All patients received High Dose Brachytherapy (HDR). A varied BT dose schedule and vaginal treatment length was used based on physician discretion. A 6Gy/fraction for three or four fractions was given when radical BT alone was treatment of choice or 6Gy/fraction for two fractions after adjuvant EBRT. BT was delivered by vaginal cylinders in 69 (95.83%), tandem and ovoids in 2 (2.77%) and remained unknown in 1 (1.38%). A total of 21 (22.58%) patients did not receive BT because they had low-risk disease and were kept on either follow-up or received EBRT alone. Two patients were given 9-9.5 Gy/fraction for total of two fractions. The median treated length of vagina was 3 cm (range 2-8 cm) and upper third vagina was treated in 47(65.27%) [Table/Fig-3,4].

Brachytherapy (BT) dose and fraction schedule	N (%)
6.0 Gy/# x2 fractions	57 (79.17)
6.0 Gy/# x3 fractions	5 (6.94)
6.0 Gy/# x4 fractions	6 (8.33)
7.0 Gy/# x2 fractions	1 (1.39)
9 Gy/# x2 fractions	1 (1.39)
9.5 Gy/# x2 fractions	1 (1.39)
Unknown	1 (1.39)

[Table/Fig-3]: Brachytherapy (BT) dose and Fraction schedule (n=72)\*.  
(\*Only 72 Patients received Brachytherapy (BT))

**Chemotherapy:** Chemotherapy was delivered in 12 (12.90%) patients either in advanced Stage-III and IV or as concurrent weekly Cisplatin chemotherapy. The number of chemotherapy cycle as concurrent ranged 4-6 while in adjuvant setting it ranged from 2-6 cycles.

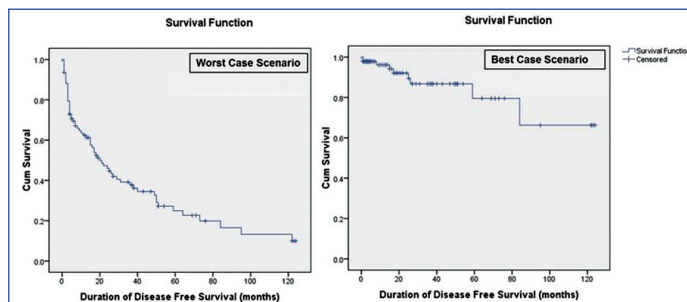
Treated length of vagina	N (%)
Full length	5 (6.94)
Half length	9 (12.5)
Upper third	47 (65.28)
variable length	5 (6.94)
Unknown	6 (8.33)

[Table/Fig-4]: Treated length of vagina (n=72)\*.

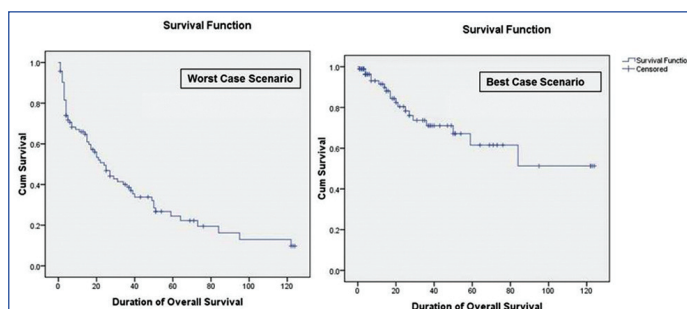
(\*Only 72 Patients received Brachytherapy (BT))

**Toxicity:** Vaginal stenosis was recorded as per Common Terminology Criteria for Adverse Events (CTC) v3.0 [12]. No vaginal toxicity was seen in 24 (33.33%) while Grade-I, II, III vaginal toxicity was seen in 13 (18.06%), 3 (4.17%) and 3 (4.17%) respectively and it was not documented in 29 (40.27%).

**Survival outcomes:** DFS and OS was computed based on worst and best case scenario. Reason for doing this analysis was because there was 60% lost to follow-up and patients were either disease free or having local or systemic disease at the time of last recorded follow-up. For computing outcomes in worst case scenario, all the lost to follow-up cases were considered having disease recurrence and dead while for best case scenario, all the lost to follow-up cases were considered to be disease free and alive. Five year DFS was 25% and 64%, respectively in worst and best case scenario. Five year OS was 25% and 62%, respectively in worst and best case scenario [Table/Fig-5,6]. Therefore, it stands to logic that the actual DFS and OS should be in between these two extreme case scenarios.



[Table/Fig-5]: Disease Free Survival (DFS) in months (worst and best case scenario) n=93.



[Table/Fig-6]: Overall Survival (OS) survival in months (worst and best case scenario) n=93.

**Relapse:** Ten (10.75%) of the patients had relapse, all belonged to high-risk group. Relapsed occurred at multiple sites like para-aortic lymph nodes, liver, lung, bones and local recurrence.

## DISCUSSION

The present study is a long-term audit of endometrial cancer patients treated over a period of 15 years at tertiary care referral centre from northern part of India. Present study analysed the referral patterns, demography, staging, surgical practices, adjuvant treatment and follow-up policies. Present study revealed that postmenopausal vaginal bleeding was the commonest symptom 78 (83.87%) and ultrasonography 23 (24.73%) was the preferred first imaging modality in this part of the world. Total abdominal hysterectomy with

bilateral salpingo-oophorectomy 82 (88.17%) was the commonest surgery procedure being practiced. Postsurgery, two-third of the patients received adjuvant EBRT with vaginal BT. Vaginal cylinder applicator was used in 69 (95.83%) out of 72 patients receiving BT. A 6Gy/fraction for two fractions after postoperative EBRT was the treatment of choice.

Median age in this study was 55 years similar to other studies from India except a rural-based tertiary care cancer centre from south India reported by Dessai S et al., where it was 59 years [14]. The median age at diagnosis of endometrial cancer is 62 years in the USA and above 60 years in the European countries west, whereas studies reported from India showed a median age around 50 years [11,12,14-19]. In a hospital-based study of endometrial cancer survival in by Tata Memorial Hospital, Mumbai from western India reported the median age of 54 years similar to present study [17].

In a study from Pakistan by Tanvir I et al., out of 52 epithelial endometrial cancer, 42 (80%) had endometrioid carcinoma and maximum patients belonged to age group of 51-60 years which is similar to present study results [20].

There is huge difference in the treatment facility being availed or provided to patients in this part of the world. There is lack of dedicated cancer centres where gynaecological/surgical oncologists are present. Upper class and upper middle socio-economic class patients go to higher centre where dedicated gynaecological or surgical oncologists, onco pathologists with state of the art histopathological laboratory, high end radiation facility is available. Whereas in the state of Uttar Pradesh and neighbouring states making northern part of India, very few centres have these facilities. In present study, nearly half of the patients were referred after undergoing total abdominal hysterectomy with bilateral salpingo-oophorectomy surgery by community based gynaecologists or general surgeons and only 6% patient's surgeries were performed by surgical oncologists or gynaecological oncologist. Reasons for patients not going or getting the dedicated comprehensive cancer centre are multifactorial like poor socio-economic status, long duration stay and accommodation issue, lack of awareness of treatment options available, etc.

Due to lack of awareness, in this part of the world, even community doctors are not clued up with the multidisciplinary approach for management of cancer. Ground reality is that patients go to local gynaecologist or general surgeon first and due to either lack of facility or other logistics reasons, proper radiological evaluation is not done. As present study data shows that in majority of patients only ultrasound was done while CT scan and MRI were done in only 18% of patients. This often results in inadequate surgery for endometrial cancer. There is also lack of standardisation for surgical practices like PLND practices. Only 31 (33%) of the patients underwent standard surgical procedure. It is known that inadequate surgery carries has higher risk of local and distant recurrence. This is evident from the result of present study where survival rates are poor as compared to published literature from other parts of the world [14-20].

Standardisation of pathology reporting is an important issue. Due to reasons mentioned above, there is an urgent need to set a state of the art pathology lab and uniform histopathology reporting system. A low-risk intermediate and high-risk intermediate category can be defined on good histopathological report only. This is very important for deciding the need and type of adjuvant radiotherapy (EBRT or BT or both) treatment which will have impact on recurrence, toxicity and survival.

In low-risk group, patients were offered either BT or observation only. In low intermediate risk, most common treatment was EBRT alone followed by observation alone followed by combined EBRT and BT. In high intermediate risk group, all patients received EBRT and BT. In high-risk group, in our set-up, most of the patients

were having advanced disease so that they were offered palliative treatment only. This was followed by EBRT alone followed by combined EBRT and BT. In high risk group, combined EBRT and BT was given to patients. The PORTEC trial found that there is no survival benefit with adjuvant external radiation [10]. The ASTEC /EN5 trial which was published in recommended that external radiation therapy should not be given as a routine for intermediate and high-risk endometrial cancers [21,22]. The PORTEC 2 trial said that vaginal BT alone is an effective adjuvant treatment in the high intermediate risk patients with carcinoma endometrium [23].

There have been changes in treatment practices over 15 years, till 2008 combined EBRT and BT were given. After that with better surgico-pathological details and newer treatment guidelines, combined EBRT and BT has decreased significantly with patient are being kept on observation also.

Present study showed median EBRT dose 50.4 Gy which was similar to other studies from India and west. The median dose received by BT only patients in present study was 6 Gy per fraction and the median fractions were also similar to published literature [14-20]. Vaginal toxicity is an important issue as this directly impacts the sexual life. Currently, we are treating only proximal 3 cm of vagina to have improved sexual function without compromising the local control along with conformal radiotherapy treatment at linear accelerator to decrease the pelvic toxicity.

Bertelsen K et al., have reported 5-year OS rate for the entire population (stage I-IV) of 77% [24]. Chen T et al., in German national data set form 11 registry included 30,906 patients diagnosed with endometrial cancer from 1997-2006. The 5-year OS was 91% for localised 51% for regional, and 20% for distant stage [25]. Tangjitgamol S et al., have reported the 5-year OS to be 83.4% [26]. Mahantshetty U et al., had showed that nulliparous women has poor prognosis than parous women. It has also shown that age at diagnosis, extent of disease, family history, diabetes, hypertension and treatment are important determinants for prognosis [17]. The outcomes (OS) reported in the Malabar cancer centre was comparable to the outcome reported in Western and Indian studies which was not the reflecting in present study [14-22]. Present study identify the reasons for poor outcomes as the following; firstly all patients who lost to follow-up were considered dead for the purpose of analysis as in worst case scenario. Secondly, being a retrospective study, retrieval of data was difficult. Missing data is expected in such type of retrospective data collection. It is also expected since long-term follow-up were reported.

Lost to follow-up is an important issue especially in the Indian subcontinent. Most of the available literature is silent about this issue. Pertinent factors like the lack of education, awareness and financial limitations are the main reasons for the high lost to follow-up rate which exists in the patients. This gains more importance in a healthcare system where the patient pays from his/her pocket for his/her treatment and follow-up visits, commute, patient attrition, change of address and telephone numbers of patients and lack of long-term motivation on the part of the family are important contributors for high lost to follow-up rates. Present study found, recurrence pattern was similar as reported in both Indian and western studies. High-risk disease had local and distant recurrences which are salvageable either by radiation or surgery [14-22]. There are not many published endometrial cancer survival data from India due to factors like lack of structured documentation, limited centres where treatment facility is available, poor patient follow-up and no proper death registry system.

### Limitation(s)

Limitations are that it is a retrospective study and higher lost to follow-up limits robustness of the survival outcome data analysis.

## CONCLUSION(S)

In this part of the India, median age of presentation of endometrial cancer patients is one decade earlier compared to western population. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is commonest surgical procedure. However, in a resource constrained setting, assuring uniformity of management approach and care and determining patterns of failure in an infrequent disease such as endometrial cancer is a challenging task given various avenues of service providers and poor compliance to follow-up.

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