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Recurrence Patterns in Endometrial Cancer: A Retrospective Analysis

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***Abstract**:*
***Aim:** To assess the pattern of failure of patients with endometrial cancer and to analyze the variables predictive of the risk of local and distant disease recurrence.*
***Materials And Methods:** The clinical and pathologic case records of patients with histologically proven carcinoma endometrium treated at Department of Radiotherapy Father Muller Medical College between 2014 to 2017 were reviewed. Out of 45 patients who took radiotherapy (which include either EBRT OR Vaginal brachytherapy) 33 patients were included in the analysis.*
***Results:** The median age of the 33 patients was 57.6 years. Out of the 33 patients selected 16(48%) belong to stage I, 2(6%) belong to stage II and 15(45%) belong to stage III.All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy +/- pelvic lymphadenectomy. Patients were staged retrospectively according to the International Federation of Gynaecology and Obstetrics (FIGO) classification 2009. Total external beam radiation dose was 50Gy in 25 Fractions. Patients with invasion equal to or more than half of the myometrium, grade 3 disease, cervical or adnexal involvement, LVSI received weekly Injection Cisplatin 40mg/m2 along with radiotherapy. Vaginal brachytherapy was delivered to a dose of 4Gy or 5Gy per session to a total of three or four sessions. Following surgery or adjuvant treatment patients with extra pelvic metastasis received palliative chemotherapy (paclitaxel+ carboplatin). The relapse was loco regional in 4 patients and distant in 2 patients. 1 patient had both loco regional and distant failure. Neither local recurrence nor distant failure was significantly associated with patient age, cervical involvement, myometrial invasion, tumour grade, LVSI, FIGO stage, histological type and lymph node status.*
***Conclusion:** None of the highrisk features of endometrial cancer were independent predictors of loco regional or distant failure.Majority of the patients in the study who received adjuvant treatment did not have a loco regional or distant failure.Further study with a bigger sample size is warranted to have a better understanding of patterns of failure in endometrial cancer.*
***Keywords:** Carcinoma endometrium, Recurrence patterns, Radiotherapy, Brachytherapy, Chemotherapy*

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I. Introduction

Endometrial cancer is the most common gynecological malignancy in the West, but in India, the incidence rates are low.Most of these cancers present at an early stage and are associated with a good prognosis.Tumor stage, patient age, histological type, tumor grade, myometrial invasion, lymph-vascular space involvement (LVSI) and lymph node status are significant prognostic variables. [(1-7)]The standard surgery consists of laparotomy, peritoneal washing, extra-fascial total hysterectomy and bilateral salpingooophorectomy with or without lymph node dissection, although laparoscopic or robot-assisted laparoscopic hysterectomy can represent a feasible and safe surgical approach in expert hands.[(8)]External pelvic radiotherapy reduces loco regional recurrences without improving survival and appears to offer a benefit in terms of clinical outcome only in patients with both deep myometrial invasion and poorly differentiated grade. [(9)] Recent studies suggest a possible role for adjuvant platinum-based chemotherapy in association with radiotherapy for high-risk disease. [(10)]Data from the literature have shown that the recurrence rates range from 11 to 23%, and most of failures develop within 3 years. [(2,3,5,11,12)]Endometrial cancer relapses in less than one fifth of the cases, and recurrent disease may be vaginal (approximately 15% of failures), pelvic (35%) or distant (50%). [(6,12)]

II. Materials & Methods

The clinical and pathologic case records of patients with histologically proven carcinoma endometrium treated at Department of Radiotherapy Father Muller Medical College between 2014 to 2017 were reviewed.Out of 45 patients who took radiotherapy (which include either EBRT OR Vaginal brachytherapy) in the department of radiotherapy father muller medical college 33 patients were included in the analysis. These 33 patients have undergone surgery and radiotherapy at Father Muller Medical College Mangalore.

All patients underwent total abdominal hysterectomy and bilateral salpingooophorectomy +/- pelvic lymphadenectomy. Patients were staged retrospectively according to the International Federation of Gynaecology and Obstetrics (FIGO) classification 2009.The histological classification was performed according to the World Health Organization classification. Patients with invasion equal to or more than half of the myometrium, or grade 3 disease, or cervical or adnexal involvement or LVSI (Lymphovascular invasion) received adjuvant external beam radiation, with or without vaginal brachytherapy and chemotherapy.Total external beam radiation dose was 50Gy, 2Gy per fraction, 5 fractions per week over 5 weeks along with weekly Injection Cisplatin 40mg/m2 given concurrently with radiation. Vaginal brachytherapy was delivered to a dose of 4Gy or 5Gy per session to a total of three or four sessions. Patients with paraaortic lymph node metastasis diagnosed by pathologic sampling during surgery received extended field radiotherapy to a total dose of 50Gy with a four field anterior posterior and lateral technique. Following surgery or adjuvant treatment patients with extra pelvic metastasis received palliative chemotherapy (paclitaxel+ carboplatin)

Periodical surveillance included physical examination, and abdominal-pelvic ultrasound every 3-4 months for the first 2 years from surgery.Chest X-ray was performed every 6 months for the first 2 years, every year thereafter. Further investigations were performed when appropriate.

III. Statistical Analysis

Patient age, histological type, tumor grade, myometrial invasion, LVSI, cervical involvement, FIGO stage, lymph node status and adjuvant treatmentwere analyzed for association with recurrence risk. Peritoneal, hematogenous, and lymph node recurrences outside the retroperitoneal area (i.e. inguinal, or axillary and supraclavicular) were considered as distant failures. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Microsoft word and Excel have been used to generate graphs, tables

IV. Results

The mean age of the 33 patients was 57.6 years. Out of the 33 patients selected 16(48%) belong to stage I, 2(6%) belong to stage II and 15(45%) belong to stage III. Adjuvant therapy was given to all 33 patients. 28 patients received adjuvant EBRT+/- chemotherapy. 5 patients received only adjuvant vaginal brachytherapy. 2 patients received adjuvant chemotherapy (Table 1).

26 patients (78%) who received adjuvant treatment had no failures on follow up till date.The relapse was loco regional in 4 patients and distant in 2 patients. 1 patient had both loco regional and distant failure (Table 2).

Among the 7 patients who failed 2 patients belong to stage I and 5 patients belong to stage III. In the 2 patients that failed in stage 1 one patient had tumor size of 7.5cm and the other had >50%myometrial invasion (Table 3). Neither local recurrence nor distant failure was significantly associated with patient age, cervical involvement, myometrial invasion, tumour grade, LVSI FIGO stage, histological type and lymph node status as the sample size was too low for comparison.

Table 1: Patient characteristics

Characteristic	NUMBER
Mean Age(years)	57.6
FIGO Stage	
I	16
II	2
III	15
Histological type	
Endometrioid Adenocarcinoma	28
G1	15
G2	10
G3	3
Clear cell adenocarcinoma	1
Serous adenocarcinoma	4

Myometrial invasion <50% ≥50%	 13 20
Node metastases Positive Negative	 8 25
Treatment modalities Surgery+RT Surgery+RT+chemo	 31 2

Table 2: Details of Initial failures

FIGO STAGE	GRADE 1	GRADE 2	GRADE 3
I	11/16 (68.75%)	4/16 (25%)	1/16 (6.25%)
II	1/2 (50%)	1/2 (50%)	0
III	3/15 (20%)	5/15 (33.33%)	7/15 (46.66%)

Table 3: Stages And Grades

Characteristic	Number	Site
Locoregional	N=4	Central Pelvis (4)
Distant	N=2	Bone (1) Liver (1) Brain (1)
Locoregional+Distant	N=1	Vault (1) Spleen (1)
Total	N=7	

Table 4: Recurrence rate and site of failures

Figo Stage	Rate	Local	Distant
I	3/16(18.75%)	2	1
Ii	0/2(0)	0	0
Iii	5/15(33.3%)	3	2
Total	8/33(24.2%)	5	3

Table 5: loco regional recurrence rate according toclinical pathological variables

CHARACTERISTIC	PATIENTS, (n=)	RECURRENCE, n(%)	p Value
Age (years) <61 ≥61	 16 17	 3(18%) 2(11.8%)	 ns
FIGO stage I-II III	 18 15	 2(11.1%) 3(20%)	 ns
Histological type Endometrioid Non-endometrioid	 28 5	 4(14.2%) 1(20%)	 ns
FIGO grade G1-G2 G3	 25 8	 4(16%) 1(12.5%)	 ns
Cervical involvement No Yes	 21 12	 3(14.28%) 2(16.7%)	 ns
Myometrial invasion <50% ≥50%	 15 18	 2(13.3%) 3(16.66%)	 ns
LVSI No Yes	 24 9	 4(16.6%) 1(11.1%)	 ns
Lymph Node status Negative Positive	 25 8	 4(16%) 1(12.5%)	 ns

V. Discussion

A systematic review of 16 non-comparative retrospective studies on the role of follow-up assessed 2922 patients who were clinically free of disease following potentially curative treatment [(6)]. The overall recurrence rate was 13% and the risk of failure was associated with surgical stage, histological type, myometrial invasion, tumor grade and lymph node status. Overall, 68% to 100% of relapses occurred within the first 3 years, and 61% of these (range, 38% to 86%) involved distant sites. In the series of the Mayo Clinic, tumor recurred in 142 (23%) of 610 endometrial cancer patients. [(2, 3, 5)] The relapse was peritoneal in 37 cases, hematogeneous in 60, and lymphatic in 44. As far as the 60 hematogeneous recurrences are concerned, 42 (70%) involved the lung, 9 (15%) the liver, 5 (8%) other sites, and 4 (7%) involved multiple sites. [(2)] Of the 44 lymphatic failures, 6 (14%) were pelvic, 16 (36%) were para-aortic, 12 (27%) were both pelvic and para-aortic, and 10 (23%) involved other node-bearing areas. [(3)] Poor histological differentiation, LVSI and deep myometrial invasion have been reported to be predictors of local recurrence [(1,11,13).]

In the series of the Mayo Clinic, non-endometrioid histology (relative risk (RR)=11.58, $p<0.001$), positive peritoneal cytology (RR=6.72, p=0.009), lymph node metastasis (RR=5.10, p=0.02), and cervical involvement (RR=3.10, p=0.04) were independent predictors of peritoneal recurrence. [(5)] In the same series, hematogeneous failure occurred in 5% of patients with myometrial invasion less than one half versus 23% of those with deeper myometrial invasion, and myometrial infiltration was found to be the only independent predictor of this type of recurrence (RR=6.0, p=0.003).

VI. Conclusion

None of the highrisk features of endometrial cancer like patient age, cervical involvement, myometrial invasion, tumor grade, LVSI FIGO stage, histological type and lymph node status were independent predictors of locoregional or distant failure because of low sample size.Majority of the patients in the study who received adjuvant treatment did not have a locoregional or distant failure. Further study with a bigger sample size is warranted to have a better understanding of patterns of failure in endometrial cancer.

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