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Radiotherapy

A RETROSPECTIVE STUDY OF DEMOGRAPHICS AND SURVIVAL ANALYSIS IN CARCINOMA ENDOMETRIUM PATIENTS TREATED AT TERITIARY CARE CENTRE FROM 2014-2019

Dr. Sarilla Lavanya	Resident, Department of Radiation Oncology, GSL Medical College, Rajamahendravaram.
Dr. M. V. Ravi Teja	Resident, Department of Radiation Oncology, GSL Medical College, Rajamahendravaram.
Dr. V. Sree Dhatri	Resident, Department of Radiation Oncology, GSL Medical College, Rajamahendravaram.
Dr. P. B. Ananda Rao*	Professor and Head, Department of Radiation Oncology, GSL Medical College, Rajamahendravaram. *Corresponding Author

ABSTRACT **AIM:** To study the demographics, treatment and survival analysis in patients diagnosed with carcinoma endometrium **METHODS:** All patients diagnosed with endometrial cancer treated between January 2014 and July 2019 were included in the study. The details regarding demographics, treatment, post operative histopathology, and outcomes were taken from the case records.All patients were followed upto August 2022. **RESULTS:** There were 65 patients with median age was 59 years (Range 36 - 77years), with majority of them (61patients) are postmenopausal. 63 patients underwent surgery and 1 patient received radical radiotherapy and 1 patient received palliative chemotherapy. TAH+BSO was done in all patients and lymphnode dissection was done in 54 patients. 48 patients received adjuvant radiotherapy and 25 patients received adjuvant chemotherapy. Predominant postoperative histology is endometrial adenocarcinoma. The pathological stage distribution was stage IA in 15 patients, stage IB in 19 patients, stage II in 5 patients, stage IIIA in 8 patients, stage IIIB in 3 patients and 8 patients in stage IIIC and stage IV in 5 patients. 23 patients had grade I tumors, 11 patients had grade II tumors, and grade III tumors in 7 patientS. Based on the ESMO risk classification, 14 patients had low risk, 16 patients had intermediate and 6 high intermediate, 23 patients were at high risk, and 6 in the advanced risk category. Median follow up is 3years. 3year DFS is 93% and OS is 95%. **CONCLUSION:** Diagnosis of carcinoma endometrium have increased all over the world in recent years. We have also found the same trend in our institute. One hypothesis for the increased incidence may be due to increase in risk factors like high and rising rates of obesity, few children and diabetes. It is most common in postmenopausal women. Risk factors includes elderly age, menopause, obesity were significant in present study. Other risk factors were not statistically significant. Endometrioid adenocarcinoma is the most common histology with early stage among all surgically treated patients. DFS and OS are good in well differentiated, early stage endometrial cancers and but very poor in and poorly differentiated, stage 3 and stage 4 patients.

KEYWORDS : Endometrial carcinoma, Risk factors, Survival, Surgery, Radiotherapy.

INTRODUCTION:

Endometrial cancer is a cancer that arises from the endometrium (the lining of the uterus)

STATISTICS:

GLOBOCON 2020:

Endometrial (or corpus uteri) cancer is the 6th most commonly occurring cancer in women and the 15th most common cancer overall and it constitutes 4.5% of all cancer cases worldwide (1). It is the third most common malignancy in Indian women.

The declining incidence of cervical cancer and the predicted rise of endometrial cancer in this century mean that endometrial cancer will be a significant issue in India (2)

RISK FACTORS:

Increasing age, Obesity, Diabetes mellitus, High estrogen levels, Nulliparous, Early menarchy and Late menopause, Estrogen replacement therapy during menopause when not balanced with progestin, Tamoxifen therapy are the risk factors for carcinoma endometrium (3)

TREATMENT OF CHOICE:

The primary treatment of choice for endometrial cancer is surgery. It consists of hysterectomy with bilateral salpingo-oopharectomy. Lymphadenectomy is performed for tumors of histologic grade II or above. The topic of lymphadenectomy and what survival benefit it offers in stage I disease is still being debated (4) . In women with presumed stage I disease, a 2017 systematic review found no evidence that lymphadenectomy reduces the risk of death or relapse of cancer when compared with no lymphadenectomy (5). Adjuvant chemotherapy has been found to increase survival in stage III and IV cancer (6). Adjuvant radiotherapy is commonly used as an adjuvant therapy in endometrial cancer. It can be delivered through vaginal brachytherapy (VBT), which is becoming the preferred route due to its reduced toxicity, or external beam radiotherapy (EBRT) (7)

MATERIAL AND METHODS:

This was descriptive retrospective analysis of all endometrial cancer patients who were treated in between January 2014 and July 2019 at a tertiary cancer care centre, GSL cancer hospital, Rajahmundry, Andhra Pradesh. Patients with sarcoma of endometrium were excluded from the study. A total of 65 Carcinoma Endometrium patients were included in the study. All patients were followed up to August 2022.

The medical records of 65 patients were reviewed, and parameters such as age, parity, menopausal status, underlying co-morbidities, and clinical indications, staging details, details about outside surgery, details of procedures at our centre, histopathological findings (tumor size, histology, type, grade, stage, myometrial invasion, lymphovascular invasion, the involvement of the cervix, and involvement of the margins, ESMO risk, and nodal status), adjuvant treatment, sites of failure, the present status of the patient ,date of progression, and date of death were recorded.

STATISTICAL ANALYSIS

SPSS 16 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics was performed. The time-to-event analysis was done by Kaplan–Meier method. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of first failure. Overall survival (OS) was calculated from the date of diagnosis to the date of death. Patients who were alive were censored at their last follow-up. COX regression analysis was performed to identify factors affecting DFS and OS. The factors tested were age (>55 years or 55 years and below), stage (I–II vs. III–IV), Grade (1–2 vs. 3), obesity (BMI of >30 vs <30)

RESULTS

DEMOGRAPHICS:

A total of 65 patients were treated at our centre during the period from Jan 2014- July 2019. All patients were followed up to August 2022. Median age was 59 years (Range 36 - 77years).

61 patients were post-menopausal. 4 patients were premenopausal. Co-morbid illness included 14 patients has DM-2 alone, 22 patients has hypertension and 16 patients has both DM-2 and Hypertension and 4 patient has history of CAD. None of the patient has history of OCP uses. 2(3%) patients have BMI ≤18.5 and 12(18.46%) patients are with BMI >18.5 - 24.9 and 30(46.15%) patients are with BMI 25 - 29.9 and 21(32.3%) had BMI of ≥30 Per vaginal bleeding is most common symptoms with 54 patients in our series and lower pelvic pain present in 15 patients.

Pre operative diagnosis of ca endometrium was established in all 65 patients Pre operative workup was done adequately with biopsy in all 65 patients, in which ultrasound was done in 53 patients and MRI/CT pelvis in 52 patients.

SURGERY:

Patients diagnosed with endometrial carcinoma were surgically staged. Total abdominal hysterectomy, bilateral salphingo-oophorectomy, staging laparotomy, including pelvic (external iliac, internal iliac, obturator and common iliac nodes) and para-aortic lymphadenectomy based on the risk categories and extent of disease was performed.

Total abdominal hysterectomy and Bilateral salpingo oophorectomy was performed in 63 patients. One patient is unfit for surgery. 1 patient was diagnosed to have distant metastasis. Pelvic lymph node dissection was done in 54 patients.

One patient who is unfit for surgery received radical treatment of EBRT of 4500cGy in 25# followed by brachytherapy of 600cGy in 3#. And one patient who is diagnosed to have metastasis received 6 cycles of cisplatin+paclitaxol

PATHOLOGICAL FACTORS:

The predominant histology was endometrioid adenocarcinoma in 57 patients. 2 patients had papillary serous carcinoma and mixed carcinoma histology was present in 4 patients Tumors were staged according to the FIGO 2018 staging system of endometrial cancers. 37 patients had grade I tumors, 15 patients had grade II tumors, and grade III tumors in 11 patients. The stage distribution was stage IA in 15 patients, stage IB in 19 patients, stage II in 5 patients, stage III A in 8 patients, stage IIIB in 3 patients and 8 patients in stage IIIC and stage IV in 5 patient. 16 patients had less than 50 % myometrial invasion, while 44 patients had more than 50 % invasion. 21 patient had lymphovascular space invasion. Cervical stromal involvement was present in 11 patients. 41 patients had node-negative disease, and 13 patients had node-positive disease.

Based on the ESMO risk classification, 14 patients had low risk, 16 patients had intermediate and 6 high-intermediate, 23 patients were at high risk, and 6 in the advanced risk category

ADJUVANT TREATMENT:

Adjuvant treatment was received by 48 patients. 3 patients received brachytherapy alone, 42 patients received external beam radiation (EBRT) and brachytherapy and 3 patients received only EBRT and defaulted for brachytherapy. 6 patients defaulted adjuvant treatment after surgery. One patient died after surgery. 8 patients kept in regular followup. The median EBRT dose was 50Gy (45–50.4 Gy) and median brachytherapy dose was 6Gy/# (total 3-4#)

Adjuvant chemotherapy was received by 25 patients. 2patients defaulted after 2cycles of chemotherapy. The chemotherapy regimen was paclitaxel and carboplatin in 21 patients and 4patients received cisplatin. The median chemotherapy cycles were 6

Recurrences:

10 patients had recurrence within 3 years follow-up period. 6 had distant metastasis and 4 had local recurrence. The site of distant metastasis was lung.

OUTCOMES:

The median follow up was 2.5 years. The 3 year DFS and OS were 93% and 95% respectively. The DFS and OS of each stage are shown in Table 1. The factors affecting DFS and OS on multi-variate analysis are shown in Table 2.

Table 1

STAGE	DFS –3YEAR	OS-3YEAR
I	95%	97%
II	91%	93%
III	82%	81%
IV	42%	38%
ALL	93%	95%

Table 2

VARIABLE	HAZARD RATIO	P VALUE
ELDERLY AGE	8.12	0.04
OBESITY	12.05	0.02
GRADE III	5.28	0.02
STAGE III-IV	6.45	0.03

DISCUSSION

Carcinoma endometrium is one of the most common gynecological malignancy at our centre. The median age in our study was 59 years. Age is one of the risk factor for endometrial carcinoma with risk increases with age. In western countries the percentage of EC patients of 80 years of age or older increased more than four times with median age at diagnosis was 65 years [8]. while studies reported from India show a median age consistently near 50 years. This reflects the differential life expectancy in the state in which the centre is located. In present study,the majority (61patients) of patients were postmenopausal and 7 patients are nulliparous, and none of the patients have relavant family history and history of ocp usage Comorbid illness included 14 patients has DM-2 alone and 16 patients has both DM-2 and Hypertension. 30 patients are overweight with BMI - 25 - 29.9 and 21 patients are obese with BMI of ≥30 which reflects obesity as a main risk factor [9]. These factors are considered to be known risk factors associated with endometrial cancers [10]. None of the patients have a history of smoking and alcohol intake.

Endometrial cancer is most commonly diagnosed at endometrial biopsy in symptomatic patients. The most common presentation of endometrial cancer is postmenopausal bleeding pv, which is true is present study also. No generally applicable screening test is available. In developing countries and low resource countries pelvic ultrasound is the most common imaging in gynecological cancers[11]. Most of the endometrial carcinomas are incidental findings who receive pelvic ultrasound for another indication Transvaginal US is often the initial imaging examination for women with dysfunctional (postmenopausal or intermenstrual) uterine bleeding. However, once the diagnosis of endometrial cancer has been made, contrast-enhanced MRI should be performed which helps to distinguish patients who need more aggressive therapy [12]. In present study, Pre operative workup was done adequately with biopsy in all 65 patients, in which ultrasound was done in 53 patients and MRI/CT pelvis in 52 patients.

Staging: In 2009, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging system for carcinomas of the vulva, cervix, and endometrium [13]. The primary changes made for endometrial cancer included the grouping of stages IA and IB together as stage IA with the loss of prior IC and the division of stage IIIC (metastasis to the pelvic and/or paraaortic lymph nodes) into stage IIIC1 (positive pelvic nodes) and IIIC2 (positive paraaortic lymph nodes). Specifically the old staging system defined stage IA as no invasion into the myometrium, stage IB as less than 50% invasion into the myometrium, and stage IC as equal to or greater than 50% invasion into the myometrium, whereas the new FIGO 2009 system defines stage IA as cancer confined to the uterus with less than 50% myometrial invasion, and stage IB as equal to or greater than 50% myometrial invasion, with both IA and IB including any tumor grade. This was modified after data from the FIGO Annual Report showed no difference in survival between previous stage IA grade 1 or 2 and stage IB grade 1 or 2 tumors. The other significant change involved patients with positive pelvic or paraaortic lymph nodes. Under the old FIGO guidelines, patients with positive pelvic and/or paraaortic lymph nodes were staged as IIIC, and under the new system patients with positive pelvic lymph nodes are separated from those with positive paraaortic +/− pelvic lymph nodes, stage IIIC1 and IIIC2, respectively. This change was made because many studies demonstrated worse survival for patients with positive paraaortic lymph nodes when compared to positive pelvic lymph nodes.

Total abdominal hysterectomy with bilateral salpingo-oopharectomy is the standard surgery procedure for carcinoma endometrium and it is followed in our study. Pelvic lymphnodes removal is part of surgery in

most of the patients which judgment mainly decided with pre-operative imaging. Para-aortic lymphnodes removal was based on clinical suspicion. Omitting lymph node dissection may be reasonable for patients with low risk of lymphnode metastasis[14]. Open approach done in all patients of present study and lymphnode dissection was done in 54 patients . The median intraoperative time was 180 min (100–300 min). The median postoperative stay was 7 days (5–30 days) which is comparable to other studies. One patient died with postoperative complicatations within one week after surgery. *Chen et al* indicated that silent metastases to the omentum frequently are neglected clinically in patients with stage I endometrial carcinoma during primary surgery and that a routine omental biopsy should be part of the procedure. Furthermore, for patients with high-risk variables, a complete omentectomy ought to be considered [15]. In present study omentectomy was done in 54 patients.

Endometrioid adenocarcinoma most common histology in our group with 57 patients Postoperative histopathological examination shows LVSI positive in 21 patients which is one of the factors in ESMO risk classification in carcinoma endometrium. Adjuvant radiation therapy done in 48 patients. Depending on the risk stratification either EBRT alone or VBT alone or both was delivered to the patients. 25 patients received adjuvant chemotherapy. Most common chemotherapy regimen used in present study is carboplatin. In *Behbakht et al,* they analysed prognostic indicators of survival in advanced endometrial cancer. They concluded that median survival was better in stage III compared with stage IV. Survival is better with surgery followed by radiotherapy. And patients without vaginal extension and parametrial involvement survived better [16].

Coronado et al done a study of survival analysis in endometrial carcinoma by type of surgery done. In their study, DFS, OS, and specific survival related to EC (SS) were significantly higher for minimally invasive surgery compared to open surgery but when matched by age, body mass index, comorbidities, histological type, grade, myometrial invasion, and FIGO stage, DFS, OS, and SS amounts were similar between the MIS and OP groups. So finally they concluded that the surgical approach for women with EC does not impact DFS or OS amounts when matched by homogeneous groups [17]. The recurrence pattern in this study is similar to those reported in other Indian and Western studies [18]. Local recurrence rate is 15% in patients of present study with median 3 years follow-up. In our institute, surveillance protocol is history and clinical examination done in every 1 month for 6 months then 2-3 months for next 6 months, 4-6months in 2nd and 3rd year and yearly once their after. USG done every 6months. CT/MRI is adviced when clinically indicated. DFS and OS are good in early stage endometrial cancers but very poor in stage 3C and stage 4 patients. Survival is worse in old age, obese patients, which is similar to certain studies like Patel et al[19]

CONCLUSION

Diagnosis of carcinoma endometrium have increased all over the world in recent years. We have also found the same trend in our institute. One hypothesis for the increased incidence may be due to increase in risk factors like high and rising rates of obesity, few children and diabetes. It is most common in postmenopausal women. Risk factors includes elderly age, menopause, obesity were significant in present study. Other risk factors were not statistically significant. Endometrioid adenocarcinoma is the most common histology with early stage among all surgically treated patients. DFS and OS are good in well differentiated, early stage endometrial cancers and but very poor in and poorly differentiated, stage 3 and stage 4 patients.

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