Uterine Cancer

Clinical Outcomes of Uterine Body Cancers Treated in a Tertiary Cancer Center

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Abstract

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Objectives This article reports the clinical outcomes of uterine body cancers in South Indian population. The primary outcome of our study was overall survival (OS). The secondary outcomes were disease-free survival (DFS), patterns of recurrence, toxicities of radiation treatment, and the association of patient, disease, and treatment characteristics with survival and recurrence.

Materials and Methods Records of the patients diagnosed as malignancy in uterus and treated with surgery alone or with adjuvant treatment from January 2013 to December 2017 were retrieved after Institute Ethics Committee approval. Demographic, surgical, histopathology, and adjuvant treatment details were retrieved. Patients of endometrial adenocarcinoma were stratified according to the European Society of Medical Oncology/European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology consensus for analysis and overall outcomes irrespective of histology were also analyzed.

Statistical Analysis For the survival analysis, Kaplan–Meier survival estimator was used. Cox regression was used to test the significance of association of factors with outcomes in terms of hazard ratio (HR).

Results A total of 178 patient records were retrieved. The median follow-up of all patients was 30 months (0.5–81 months). The median age of the population was 55 years. Most common histology was endometrioid type of adenocarcinoma (89%), sarcomas comprised only 4%. The mean OS of all patients was 68 months ($n = 178$), median was not reached. Five-year OS was 79 %. Five-year OS rates observed in low, intermediate, high-intermediate, and high-risk were 91, 88, 75, and 81.5%, respectively. The mean DFS was 65 months, median not reached. The 5-year DFS was 76%. The 5-year DFS rates observed were 82, 95, 80, and 81.5% for low, intermediate, high-intermediate, and high-risk, respectively. Univariate analysis using Cox regression showed increase in hazard for death in case of node positivity, HR 3.96 (p 0.033). The HR for disease recurrence was 0.35 ($p = 0.042$) in patients who had received

Keywords

- endometrial cancer
- ESMO-ESGO- ESTRO consensus risk
- FIGO staging
- recurrence pattern
- survival pattern

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adjuvant radiation therapy. No other factors had any significant impact on death or disease recurrence.

Conclusion The survival outcomes in terms of DFS and OS were comparable with other Indian and Western data reported in the published literature.

Introduction

Endometrial cancer is one of the commonly prevalent malignancies worldwide. The higher incidence is probably due to the increased prevalence of high-risk factors such as obesity, diabetes, hypertension, and exogenous or endogenous hyperestrogenism in developed nations. The outcomes are better in endometrial cancer due to its earlier stage of presentation.[1] As per the estimates of GLOBOCAN 2020, cancers of corpus uteri is the sixth most common malignancy among females worldwide (417,367 new cases, 4.5%).[2] About 75 to 80% of histology are of endometrioid adenocarcinoma which is the most common, which carries good prognosis.[3] Overall survival (OS) is approximately 96% which drops to 67% in lymph node positive disease.[4] Serous and clear cell histology make up about 10 and 4%, respectively, both have worse prognosis due to the nature of advanced stage at presentation.[5] Uterine sarcomas are a rare group that constitute 3 to 9% of malignant uterine body tumors and less than 1% of all gynecological malignancies.[6] Aggressive biology and propensity to local recurrence and distant dissemination characterized by less favorable outcomes with 2-year actuarial survival of 36%. The majority of endometrial cancers are being diagnosed as early-stage disease with a good prognosis after surgery alone. Identifying the patients with early-stage disease with highest risk for recurrence who needs adjuvant therapy and also avoiding overtreatment considering the risk of toxicities for low-risk group is challenging. Postoperative adjuvant therapy is based on the presence of adverse prognostic factors from the surgical staging. The decision on adjuvant therapy has been defined according to various risk stratifications based on international trials to assess the overall benefit of such treatment. Data on survival outcomes in Indian population is less. We had proposed to study the clinical outcomes of uterine body cancers treated in a tertiary cancer care center in South India.

Materials and Methods

Our study was a retrospective record-based study. The records of all patients diagnosed as malignancy in uterus and treated with surgery alone or with adjuvant treatment in the departments of Obstetrics and Gynaecology and Radiation Oncology, JIPMER from January 2013 to December 2017 were retrieved. Institutional ethical committee permission was obtained prior to the start of the study. The details such as age, comorbidities, parity (nulliparous/multiparous), menopausal status, surgery details, and postoperative histopathological report from which histology type, grade of tumor, myometrial invasion, lymphovascular space invasion, pathological stage, and nodal staging were collected. The details of adjuvant treatment received, type of radiation, duration and dose, brachytherapy and chemotherapy details, type of recurrences, metastases, status at last follow-up, and treatment received for recurrences were recorded. Revised International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system was applied to the group. Patients were stratified into various risk groups based on risk stratification by European Society of Medical Oncology/European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology (ESMO-ESGO-ESTRO), depending on histopathological details. Further analysis and factors affecting outcome were analyzed according to risk grouping. OS and disease-free survival (DFS) were calculated as the time between completion of treatment and date of occurrence of the event. An event in OS analysis was taken as death of the patient due to any cause or date of last follow-up. An event in DFS analysis was taken as disease recurrence at local or distal or both sites or death due to disease or date of last follow-up. Data entry and analysis were done using SPSS version 21. For the survival analysis, Kaplan–Meier survival estimator was used. Cox regression was used to test the significance of association of factors with outcomes in terms of hazard ratio (HR).

Results

A total of 198 patient records diagnosed with uterine body tumors between January 2013 and December 2017 were identified from the departments of Obstetrics and Gynaecology and Radiation Oncology, JIPMER. Of these, 20 records were found to be either simple or complex endometrial hyperplasia on postoperative histologic examination and so were excluded from the study. ►**Fig. 1** shows the flow of details retrieved from records.

Patient Characteristics

The median age of the population was 55 years. The median follow-up duration was 30 months (range, 0.5–81 months). Fifty-seven percent had medical comorbidities in which 8 patients (4%) were previously treated for carcinoma breast. Eighty-nine percent were postmenopausal and 5% of population were nulliparous. The FIGO (2018) stage of presentation included 50% stage I (IA and IB), 10% II, 20% III, and 4% IV. ►**Table 1** shows demographics and patient characteristics. ►**Table 2** shows treatment and disease characteristics.

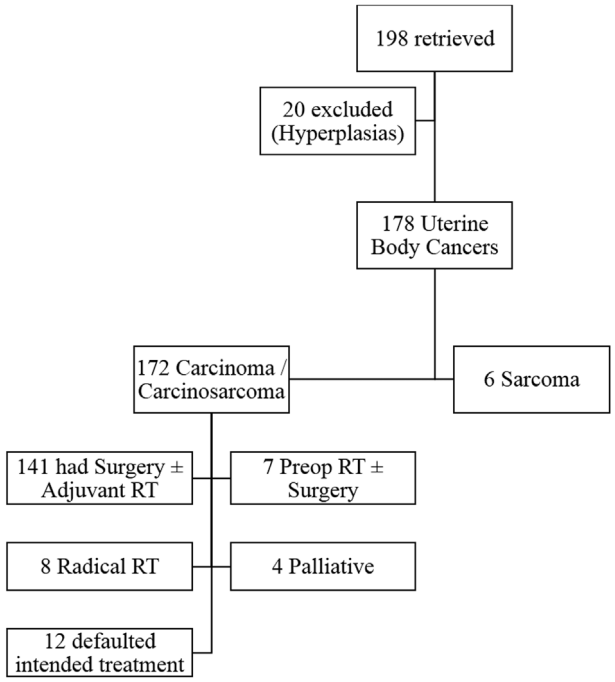

Fig. 1 Flowchart showing details retrieved from records.

Treatment Details

Surgery

Among 178 patients, 158 had undergone surgery (57% extrafascial hysterectomy with bilateral salpingo-oophorectomy [BSO], 27% total abdominal hysterectomy [TAH] with BSO). Seventy-seven patients had either sampling or pelvic lymph node dissection (PLND) or pelvic and para-aortic nodal dissection. Patients who had upfront surgery (141) were classified according to the ESMO-ESGO-ESTRO consensus risk stratification based on the postoperative histopathology examination. Fifty-three patients (30%) had high-risk features, 27 patients (15%) under intermediate risk, 6 patients (4%) under high-intermediate risk, and 20 patients (11%) were low risk. Risk group could not be stratified for 35 patients in view of inadequate histopathology details. Two percent patients were metastatic at presentation.

Radiation Treatment

Radiation therapy was delivered to 87 patients. Seventy-two patients received adjuvant radiation, 7 patients had preoperative therapy followed by surgery (in view of advanced disease at presentation), and 8 patients had radical radiation since they were found to be unfit for surgery in view of their medical comorbidities. Radiation was delivered in the form of whole pelvic external radiation alone to 5 patients, 17 had high dose rate brachytherapy alone and 65 had received both external beam and brachy. Whole pelvic radiation was delivered to the dose of 46 to 50 Gy at 2 Gy per fraction by conventional 2/4-field box technique using cobalt-60 or 6 MV beams.

Chemotherapy

Adjuvant chemotherapy was given for stage III and above. Data on chemotherapy usage from the daycare records was not available for most of the patients. Among the information available, 23 patients had received chemotherapy. Adjuvant chemotherapy was delivered to 15 patients, 1 had received neoadjuvant, and 7 had received palliative chemotherapy. The chemotherapy comprised of four to six cycles of carboplatin and paclitaxel in all patients.

Table 1 Demographics and patient characteristics

Parameters ($N = 178$)	Number	Percentage (%)
Age		
≤ 60 y	105	59
> 60 y	73	41
Risk factors		
Postmenopausal	152	89
Nulliparous	9	6
Hypertension	71	40
Diabetes mellitus	58	33
Hypothyroidism	13	7
Carcinoma breast	8	4
Stage		
IA	45	25
IB	45	25
II	17	10
IIIA	7	4
IIIB	11	6
IIIC1	16	9
IIIC2	2	1
IVA	3	2
IVB	4	2
Unknown	28	16
Histology		
Endometrioid adenocarcinoma	158	89
Serous adenocarcinoma	4	2
Clear cell adenocarcinoma	3	2
Carcinosarcoma	4	2
Poorly differentiated carcinoma	3	2
Leiomyosarcoma	3	2
Low grade stromal sarcoma	2	1
Undifferentiated sarcoma	1	1

Overall Survival

The mean OS of all patients is 68 months ($n = 178$), median was not reached. Five-year OS is 79%. The mean OS for carcinoma/carcinosarcoma is 68 months ($n = 172$ patients), for which median was not reached and the 5-year OS is 78%. Among the 6 patients with sarcoma, 2 patients were lost to follow-up, 4

Table 2 Treatment and disease characteristics

Parameter ($N = 178$)	Number of patients	Percentage (%)
Type of surgery		
EFH + BSO	101	57
TAH + BSO	49	27
Radical hysterectomy	8	4
No surgery	15	9
Unknown	5	3
Lymph node dissection		
Not done	95	53
Sampling	5	3
PLND	71	40
PLND + PALND	2	1
Unknown	5	3
Grade		
1	78	44
2	24	13
3	12	7
Unknown	64	36
Myometrial invasion		
< 50% invasion	57	32
> 50% invasion	68	38
Unknown	53	30
Lymphovascular space invasion		
Positive	26	15
Negative	69	39
Unknown	83	46
Nodal status		
Positive	20	11
Negative	62	35
Unknown	96	54
Radiation		
Adjuvant	72	40
Preoperative	7	4
Radical	8	4
Palliative	2	1
No radiation	74	42
Unknown	15	8
Chemotherapy		
Adjuvant	15	8
Neoadjuvant	1	1
Palliative	7	4
No chemotherapy	107	60
Unknown	48	27

Abbreviations: BSO, bilateral salpingo-oophorectomy; EFH, extrafascial hysterectomy; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; TAH, total abdominal hysterectomy.

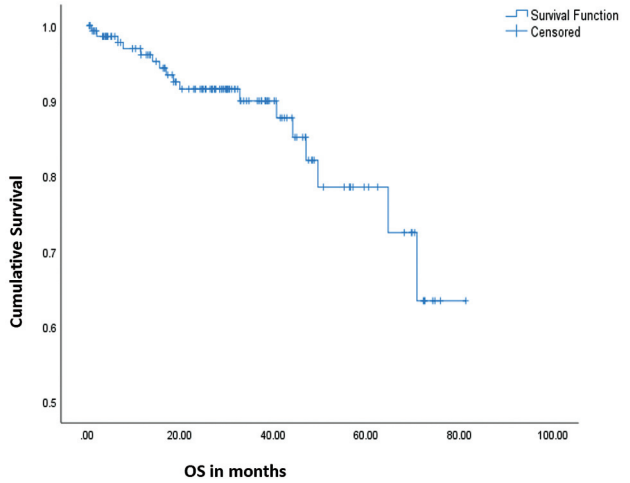

Fig. 2 Kaplan–Meir survival curve—overall survival.

were alive at the time of last follow-up date among which 3 are free of disease and 1 had distant recurrence. Median survival is not reached for stage I. Forty months for stage II, 71 months for stage III, and 8 months for stage IV. ►**Fig. 2** shows Kaplan–Meier survival curve for OS.

Disease-Free Survival

DFS was calculated only for patients who had undergone upfront surgery. Accordingly, out of 141 patients of carcinomas/carcinosarcoma analyzed, 10 recurrences were found in which 6 had vault recurrence, 3 were distant, and 1 at both sites. No recurrences were identified in patients who had received adjuvant radiation. The mean DFS was 65 months, median not reached. The 5-year DFS was 76%. There was no significant difference in DFS among the different risk groups (p 0.517). All the 6 vault recurrences were planned for further treatment with radical radiation, 4 of them completed treatment. Two patients are alive with no evidence of disease at the last follow-up. ►**Fig. 3** shows Kaplan–Meier DFS.

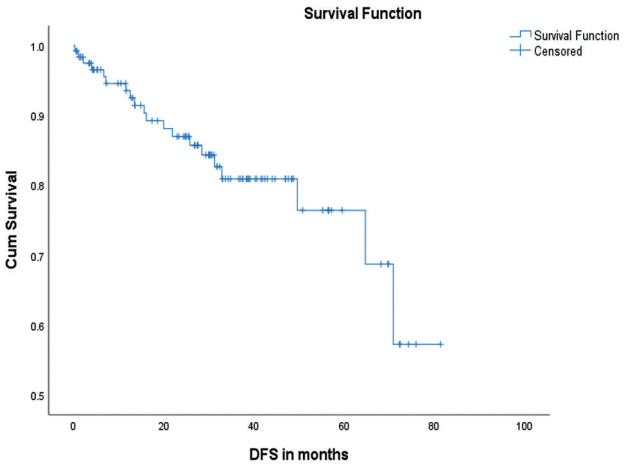

Fig. 3 Kaplan–Meir survival curve—disease-free survival.

Table 3 Univariate analysis of association of factors for death and recurrence

Parameter	HR for death	*p*-Value	HR for recurrence	*p*-Value
Node positive	3.96 (1.11–14.07)	**0.033**	2.79 (0.84–9.25)	0.092
LVSI positive	2.19 (0.63–7.6)	0.218	1.56 (0.49–4.96)	0.450
Grade 3	1.50 (0.32–6.97)	0.602	1.05 (0.23–4.68)	0.944
MMI > 50%	0.87 (0.28–2.71)	0.817	0.41 (0.15–1.12)	0.084
Received adjuvant radiation	0.68 (0.23–2.04)	0.493	0.35 (0.12–0.96)	**0.042**
LND done	1.27 (0.43–3.74)	0.665	0.62 (0.25–1.52)	0.299
Age > 60	1.33 (0.46–3.82)	0.589	1.07 (0.44–2.59)	0.887

Abbreviations: HR, hazard ratio; LND, lymph node dissection; LVSI, lymphovascular space invasion; MMI, myometrial invasion.
Note: Boldfaced values indicate significant p value <0.05.

Univariate Analysis

Univariate analysis using Cox regression showed increase in hazard for death in case of node positivity, HR 3.96 (p 0.033). No other factors were found to be significantly affecting the hazard for death. The HR for recurrence in patients who had received adjuvant radiation therapy is 0.35 (p 0.042). ►Table 3 shows univariate analysis of association of various parameters for death and recurrence.

Discussion

This is a retrospective study performed in a tertiary cancer care center to evaluate the outcomes of uterine body cancers treated over a 5-year span. Initially, we intended to analyze the outcomes of both carcinomas and sarcomas, but subsequent analysis was done only on carcinomas due to poor numbers in the latter. The majority of our study population were in stage I (50%) comparing the proportion reported from Tata Memorial Hospital (TMH), Mumbai (68%), which was studied on only early-stage disease.[7] In terms of complete surgical staging including lymph node dissection, approximately 51% (55 of 107 patients) of stage I and II underwent either sampling or pelvic with or without para-aortic nodal dissection. Mahantshetty et al reported 47% of complete surgical staging which was defined as TAH + BSO and bilateral PLND and was 51% in Kumar et al study.[7,8] Among the patients who did not receive any adjuvant treatment, in the low-risk group 6% presented with recurrence (1 in 15 patients), 8% (1 in 12 patients) in the intermediate-risk group, 33% (1 in 3 patients) in the high-intermediate group, and 6% (1 in 17 patients) in the high-risk group.

Besides, there were six more local recurrences where information on risk category was not available. All these six cases did not receive adjuvant radiotherapy (RT). All patients with recurrence were planned for further treatment with radical radiation, four of whom had completed the intended treatment. Two patients were still alive and disease free till the time of last follow-up. The recurrence rate was higher in the high-intermediate risk group which did not receive adjuvant radiation, explaining the need of adjuvant RT in this setting. Recurrence rates were low in the high-risk group which might be explained by the adjuvant treatment received by majority of the patients. The overall incidence of locoregional recurrence rates in the low-, intermediate-, and high-risk groups was reported as 5, 12, and 14% in the PORTEC-2 trial, 10, 7, and14% by Mahantshetty et al, 10, 8, and 6% by Kumar et al, respectively.[7–9] In our study, as the risk category of all patients with local recurrences were not available, the overall recurrence rates (local/distant/both) for both treated and untreated cases observed is reported as 5, 3.5, 16, and 2% in the low, intermediate, high-intermediate, and high-risk groups.

The 5-year OS and 5-year DFS of high-intermediate cases in PORTEC-2 as defined by "age > 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and stage 2A disease, any age," were reported as 84 and 82%, respectively, in the vaginal brachytherapy arm, and 79 and 78%, respectively, in the external beam RT arm.[9] Our study had defined high-intermediate risk as per the ESMO-ESTRO-ESGO risk stratification,[1] and survival rates were found to be 75% (5-year OS) and 80% (5-year DFS). Our 5-year OS rates observed in low, intermediate, high-intermediate, and high-risk were 91, 88, 75, and 81.5%, respectively. Mahantshetty et al found 5-year OS of 97, 98, and 85% in low-, intermediate-, and high-risk, respectively, whereas Kumar et al reported them as 96, 82 and 68%, respectively.[7,8] Similarly, the 5-year DFS rates observed in our study were 82, 95, 80, and 81.5% for low, intermediate, high-intermediate, and high-risk, respectively, while in the other study, the rates were 84, 85 and 60%, respectively.[7]

As per PORTEC-1, with age ≥ 60, the HR for relapse was 3.2 and HR for death was 3.1 ($p = 0.003$ and $p = 0.02$). In our study it was 1.07 ($p = 0.5$) and 1.33 ($p = 0.8$) for relapse and death, respectively. In the same PORTEC-1 study, grade 3 disease had HR for death of 4.9 ($p = 0.0008$), but it is not significant in our study with HR of 1.5 ($p = 0.6$) for death. The patients who did not receive RT had high HR for relapse 3.9, $p < 0.0001$, in the PORTEC-1 group. Similarly, in our study, patients who had received RT had less HR for relapse 0.35, $p = 0.04$, which was significant. Other factors like myometrial invasion > 50% and grade 1 were not found to be significant in both PORTEC-1 and our study.[10,11]

In univariate and multivariate analysis in the study from TMH, Mumbai,[7] tumor grade and type of radiation had significant impact in OS and grade and invasion of myometrium impacted DFS. Lymphadenectomy was not found to

have significant impact on OS and progression-free survival in our study population. There was even no significant impact in early-stage endometrioid cancers in the study from TMH, Mumbai.[7]

The retrospective nature of our study is a major limitation since the outcomes depended profoundly on the availability of patient data. We were able to retrieve as much information from the records as possible from both the departments of Obstetrics and Gynaecology and Radiation Oncology. We had limited information on risk categorization, disease recurrence, and chemotherapy treatment. Data regarding radiation toxicities in bowel/bladder/vagina was very scarce to generate any meaningful information.

Conclusion

The survival outcomes in terms of DFS and OS were comparable with the literature. Higher risk of death in node positive patients and high risk of recurrence in patients not receiving adjuvant treatment was found.

Institutional Ethics Committee Approval
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Conflict of Interest
None declared.

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