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Genitourinary/Gynecologic Cancer

Prognostic Factors for Survival in Patients with Carcinoma Endometrium

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Abstract

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Objective The study aimed to see the clinical outcome and to identify prognostic factors for survival in patients with carcinoma endometrium.

Methods Patients registered at Regional Cancer Centre, Thiruvananthapuram, Kerala, India, with carcinoma endometrium from January 2009 to December 2013 were identified from hospital registry. Data regarding patient demographics, tumor characteristics, treatment schedules, and follow-up were collected using a structured proforma. Survival estimates were generated using the Kaplan–Meier method. Univariate analysis was done using chi-square and Fisher's exact tests. Multivariate analysis using the Cox regression model was performed to determine the impact of prognostic factors on outcome. The statistical analysis was done using SPSS software version 11.

Results The median follow-up of the 686 patients was 95 months (range 3–178 months).There were 432 stage 1 (63%), 100 stage II (14.6%), 108 stage III (15.7%), and 46 stage IV patients (6.7%). The 5-year overall survival was 89.2%. Prognostic factors for survival on univariate analysis were age 60 years or older, nonendometrioid histology, high-grade tumor, cervical stromal involvement, para-aortic node involvement, negative progesterone receptor expression, deep myometrial invasion advanced stage, surgery versus no surgery, serosal involvement, and ovarian and fallopian tube involvement. However, on multivariate analysis, age over 60 years, higher histological grade, advanced stage, and deep myometrial and parametrial invasion were associated with significantly poorer survival.

Conclusion We found that age over 60 years at presentation, higher grade, advanced stage, deep myometrial invasion, and parametrial invasion were associated with poorer survival.

Keywords

- prognosis
- radiotherapy
- surgery
- survival
- uterine neoplasms

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Introduction

Incidence of endometrial cancer is on the rise in India.[1] The publications of the outcome of patients and the prognostic factors of endometrial cancer are few from India. Dietary and hormonal factors are probably the cause for the increasing incidence.[1] The study aimed to see the clinical outcome and to identify prognostic factors for survival.

Materials and Methods

Following approval from the institutional review board, case files of all patients with endometrial carcinoma registered at Regional Cancer Centre (RCC), Thiruvananthapuram, Kerala, India, from January 2009 to December 2013 were retrieved from the hospital database. During this period, a total of 757 endometrial cancer patients were registered at the center. Patients who were registered for a second opinion, for brachytherapy alone, and who presented with recurrence were excluded from the study. After these exclusions, 686 patients were available for analysis. Each of these patients' records were reviewed and data on patient characteristics, disease characteristics, staging evaluation, and treatment factors were recorded. The outcome of treatment, recurrence, morbidity data, and last follow-up updates were documented and entered into a structured proforma. Survival estimates were generated using the Kaplan–Meier method. Univariate and multivariate analyses were done using the Cox regression model to determine the impact of prognostic factors on outcome. Overall survival (OS) was defined as the period from the date of diagnosis until the date of death. Various patient, tumor, and treatment-related factors were correlated with OS.

Results

The mean age of the 686 patients was 57 years (range 25–85 years). The majority of the patients (60.5%) were less than 60 years old. Comorbid illnesses were present in many; 20.7% had both diabetes and hypertension. The majority of the patients were postmenopausal (80%) at presentation. Most of the patients were multiparous (93.1%). Only 3.2% of the patients had a family history of malignancy. The pathological type was endometrioid in 78% and nonendometrioid in the rest (12%), which included papillary serous carcinoma, mucinous carcinoma, malignant mixed Mullerian tumor, adenosquamous carcinoma, and poorly differentiated carcinoma. The majority of the patients had total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) 66.9%, and 22.3% of patients had TAH with BSO and bilateral pelvic lymph node dissection and 3% had omentectomy along with lymph node dissection. The histological grade was 3 in 35.4% and the rest were grades 1 and 2. ►Table 1 shows patient characteristics. After surgery, intermediate-risk patients were treated with vaginal brachytherapy; high-risk patients were treated with pelvic radiotherapy with or without chemotherapy. Patients with grade 3 onwards received chemotherapy with or without radiotherapy. The 5-year OS probability for the entire group was 89.2%. At a median follow-up of 95 months, 126 patients (18.3%) relapsed. In these relapsed patients, 44 were locoregional failures (central pelvis and pelvic nodes) and 82 were distant failures (outside pelvis). Among the distant relapses, common sites affected were the lung followed by peritoneum, nonregional lymph nodes, liver, bone, and brain. Prognostic factors for survival on univariate analysis were age over 60 years; nonendometrioid histological type; high grade of the tumor; cervical stromal involvement; para-aortic node involvement; deep myometrial invasion (>50%); adnexal, parametrial, and serosal involvement; peritoneal deposits; advanced stage; inoperability; and pelvic and para-aortic nodal metastasis. However, on multivariate analysis patients with age over 60 years, histological grade 3, higher stages of 3 and 4 and myometrial invasion more than 50%, and parametrial invasion had significantly poorer survival. ►Table 2 shows the univariate analysis and ►Table 3 shows the multivariate analysis. Old age was associated with poor survival.

Discussion

After the Gynecologic Oncology Group (GOG) 33 study, various prognostic factors were identified and risk grouping was done.[2] The study showed that deep myometrial invasion and grade 3 disease was associated with higher chances of lymph nodal metastasis. In other studies age, tumor grade, lymphovascular space invasion, depth of infiltration, and progesterone receptor status were found important.[3–5]

GOG 99 and Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) trials defined risk groups for women to predict who may benefit from adjuvant therapy. PORTEC group defines high intermediate risk (HIR) as those with two of the following: age older than 60 years, grade 3 diseases, or ≥50% myometrial invasion.[6] GOG defines HIR based on age and the number of risk factors (grade 2–3, the presence of LVSI (lymphovascular space invasion), or outer one-third myometrial invasion). Patients aged more than 70 years must have one risk factor, those aged 50 to 70 years must have two risk factors, and those younger than 50 years must have all three risk factors.[7] Analysis of pooled data from PORTEC 1 and PORTEC 2 showed patient age, tumor grade, and LVSI were highly predictive of locoregional relapse, distant relapse, and OS.[3] Age has been identified as a predictor of recurrence and survival in many studies.[8,9]

Many trials have used age cutoff around 60 years.[9] In an analysis based on the Surveillance, Epidemiology, and End Results database, it was reported that cancer-specific mortality is higher in older women, even after adjusting for treatment differences.[9]

In a few studies, age was not a significant factor for mortality.[10] The ESMO ESTRO ESGO (European Society of Medical Oncology - European Society for Radiotherapy & Oncology - European Society of Gynecological Oncology) consensus guidelines have not considered age as a risk factor for prognostic grouping.[11]

We have grouped patients into two groups as in the PORTEC study group as we had only a few patients older

Table 1 Patient characteristics

Parameters		Frequency	Percentage
Age	<60 years	415	60.5
	≥60 years	271	39.5
Menopausal status	Premenopausal	137	20
	Postmenopausal	549	79.9
Parity	Nulliparous	46	6.3
	Multiparous	640	93.7
Histology	Endometrioid	535	78
	Nonendometrioid	151	12
Grade of endometrioid cancer	1	86	12.5
	2	357	52
	3	243	35.4
Myometrial invasion	No	29	4.2
	<50%	314	45.8
	≥50%	343	50
Pelvic lymph node–positive		64	9.3
Para-aortic node–positive		42	6.1
Estrogen receptor	Positive	98	14.3
	Negative	83	12.1
Progesterone receptor	Positive	144	21
	Negative	41	6
CEA	Positive	91	13.3
	Negative	61	8.9
Stage of disease	1A	289	42.1
	1B	142	21
	2	100	14.6
	3	107	15.8
	4	46	6.8
Type of surgery	TAH + BSO	459	66.9
	TAH + BSO + PLND ± PALN sampling	153	22
	TAH + BSO + PLND + omentectomy	22	3
	Other surgeries	52	7
	No surgery	30	4.3

Abbreviations: CEA, carcinoembryonic antigen; PALN, para-aortic lymph node; PLND, pelvic lymph node dissection; TAH + BSO, total abdominal hysterectomy with salpingo-oophorectomy.

than 70 years. Older women had higher-grade tumors ($p < 0.002$) and more advanced-stage disease ($p < 0.001$). They are less likely to undergo pelvic lymph node dissection along with hysterectomy and adjuvant treatment because of comorbidities. A significant association between age and survival could be identified in our study and age above 60 years carried poorer survival.

Regarding other risk factors which were associated with poor outcome in our study, one was the histological grade of endometrial carcinoma. Grade 3 was associated with an 81.3% OS probability at 5 years compared to 94% in grade 2 tumors. The histological grade is the most established factor for recurrence in most reports.[3,4] The grade was not a significant factor in a few studies.[8]

Depth of myometrial infiltration was a significant factor for relapse and survival in many studies.[10] In our study, myometrial invasion of more than half was associated with 82.6% 5-year survival probability compared to 95.4% for those with less myometrial invasion. Depth of infiltration could be related to worse histological grade also.

The advanced stage is associated with poor outcome. The 5-year survival for stage I disease is approximately 80 to 90%, stage II is 80%, stage III is 50 to 70%, and stage IV is 20% according to the literature considering the prognostic value

Table 2 Univariate analysis of overall survival

Factors	*p*-Value	Hazard ratio (HR)	95.0% Confidence interval (CI) for HR	
			Lower	Upper
Age (>60 years vs. ≤60 years)	0.006	1.863	1.194	2.907
Parity (multiparous vs. nulliparous)	0.350	1.616	0.591	4.422
Menopausal status (post vs. pre)	0.154	1.565	0.846	2.895
Comorbid conditions (no illness)	0.137			
Comorbid conditions (diabetes vs. no illness)	0.412	1.348	0.661	2.749
Comorbid conditions (hypertension vs. no illness)	0.164	1.536	0.84	2.808
Comorbid conditions (diabetes + hypertension vs. no illness)	0.023	1.902	1.093	3.310
Surgery (not done vs. done)	0.001	5.878	2.684	12.871
Nonendometriod vs. endometriod	0.001	2.617	1.652	4.144
Grade (1)	0.001			
Grade (2 vs. 1)	0.816	0.906	0.394	2.080
Grade (3 vs. 1)	0.019	2.593	1.168	5.757
Stage (1)	0.001			
Stage (2 vs. 1)	0.632	1.211	0.552	2.658
Stage (3 vs. 1)	0.001	4.741	2.82	7.97
Stage (4 vs. 1)	0.001	9.557	4.938	18.499
Myometrial invasion (>50% vs. <50%)	0.001	5.137	2.924	9.026
Ovarian/fallopian tube invasion (yes vs. no)	0.001	3.010	1.659	5.462
Serosal invasion (yes vs. no)	0.001	3.506	1.686	7.292
Endocervix extension (yes vs. no)	0.243	1.399	0.797	2.457
Cervical stroma invasion (yes vs. no)	0.001	2.374	1.427	3.95
Parametrial invasion (yes vs. no)	0.001	6.035	3.008	12.107
Peritonial deposits (yes vs. no)	0.001	5.336	2.743	10.38
Lymphovascular invasion (yes vs. no)	0.009	3.352	1.353	8.306
Para-aortic lymph node metastasis (yes vs. no)	0.001	4.500	2.478	8.173
Pelvic node metastasis (yes vs. no)	0.001	3.256	1.901	5.576
Lung metastasis (yes vs. no)	0.021	3.900	1.229	12.374
ER (negative vs. positive)	0.470	1.344	0.603	2.999
PR (negative vs. positive)	0.022	2.703	1.156	6.322
Carcinoembryonic antigen (CEA) (negative vs. positive)	0.988	0.993	0.385	2.561
Adjuvant treatment (no vs. yes)	0.068	1.545	0.969	2.464

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

of stage for 2009 International Federation of Gynecology and Obstetrics (FIGO) classification.[12] In our study also advanced stage was associated with poor outcome.

Parametrial invasion in endometrial cancer is not always a continuation of cervical stromal invasion. Other factors that are associated with parametrial invasion are more than half of myometrial invasion, lymph node metastasis, ovarian metastasis, and lymphovascular space invasion. It reflects the advanced stage of the disease and is associated with poor outcome.[13] The parametrial invasion was a bad factor affecting survival in multivariate analysis in our study. The 5-year OS for patients who had no serosal involvement was 83.5% versus 75% for those who had serosal involvement. We could find serosal involvement significant for poor survival on univariate analysis only.

Creasman et al showed adnexal involvement was associated with a higher risk for lymph node involvement.[2] Forty-nine patients had ovary or fallopian tube involvement in the present study. The patients who had either ovarian or fallopian tube involvement had an inferior 5 years OS of 73.6% compared to 90.4% of patients who did not have adnexal involvement. These patients are staged as stage 3A indicating grave prognosis in FIGO and Union for International Cancer Control (UICC) staging.

Table 3 Multivariate analysis of overall survival

Factors	*p*-Value	Hazard ratio (HR)	95.0% Confidence interval (CI) for HR	
			Lower	Upper
Age (>60 years vs. ≤60 years)	0.008	1.845	1.175	2.897
Grade (1)	0.024			
Grade (2 vs. 1)	0.184	0.560	0.238	1.317
Grade (3 vs. 1)	0.826	1.099	0.474	2.551
Stage (1)	0.001			
Stage (2 vs. 1)	0.846	0.923	0.412	2.071
Stage (3 vs. 1)	0.003	2.535	1.38	4.654
Stage (4 vs. 1)	0.001	5.413	2.661	11.012
Myometrial invasion (>50% vs. <50%)	0.001	3.031	1.632	5.629
Parametrial invasion (yes vs. no)	0.041	2.247	1.035	4.879

The 5-year OS of patients with pelvic node involvement was 74.5% compared to 90.7% for patients without pelvic node involvement, and OS of patients with para-aortic nodal involvement was only 65%.

Nonendometrioid histology was associated with poorer survival in most studies affecting survival.[4,14] This was significant in univariate analysis for us but not in multivariate analysis. Most of our patients with nonendometrioid histology presented with the advanced-stage disease may be the reason it was not significant in the multivariate analysis.

Progesterone receptor (PR)–negative tumors have been examined by other authors previously and found to be an adverse feature.[5] We could test estrogen receptors (ER) in 181 patients, 83 were negative and 98 were positive. Progesterone receptors were tested in 185 patients, out of which 41 were negative. There was no significant difference in the survival probability in our patients based on hormone receptor status.

Surgery is the primary curative modality for endometrial cancer. Inoperable patients had a very poor outcome. For the patients who had undergone total hysterectomy with or without pelvic lymph node dissection, the 5-year survival was 90.1%. Our analysis did not show any significant difference between TAH and BSO and TAH and BSO with pelvic lymph node dissection.

Recently there is a lot of enthusiasm in the search for molecular factors that are useful to predict chances of recurrence in endometrial carcinoma. Abnormal p53, mismatch repair deficiency, presence of POLE mutation, and no specific molecular profile have been described for risk grouping of patients after surgical treatment.[15] The PORTEC 4 trial is examining the value of the approach.

Limitations of the Study

Being retrospective analysis, data on toxicities associated with treatment were not properly documented. Data on patients who were lost to follow-up were updated using telephonic conversations and personal letters. Many of the patients had primary surgery outside the center (TAH + BSO) and adjuvant treatment was delivered based on slide review report and post op imaging.

Conclusion

Patients older than 60 years diagnosed with endometrial cancer had poorer survival. Other well-established factors like a deep myometrial invasion, grade 3 tumors, advanced stage, and parametrial invasion also had a poorer outcome. Adjuvant treatment recommendations for this cancer need further refinement. Newer molecular typing is required for better stratification of patients for the selection of adjuvant treatment.

Disclaimers

None.

IRB Approval

Approved by the scientific committee, institutional review board, Regional Cancer Center, Thiruvananthapuram, Kerala, India. IRB number: 09/2018/08

Conflict of Interest

None declared.

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