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A Retrospective Study of the Treatment Results & Patterns of Failure of Type II Endometrial Cancer Patients Treated at Radiotherapy Department, NCI, Cairo University during the Period from January 2000 till December 2012

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Abstract

Aim of the study: To identify all clinico-pathological data, different treatment modalities and the different prognostic factors which affected the locoregional control (LC), disease-free survival (DFS), and overall survival (OS) of Type II endometrial cancer patients. Patients and methods: Data of Type II endometrial carcinoma patients who presented to the Radiation Oncology department, National Cancer Institute, Cairo University during the period from (2000-2012) were retrospectively reviewed. Results: Multivariate analysis identified stage as an independent prognostic factor for OS & DFS, and age was an independent prognostic factor for DFS and LC. Low pretreatment hemoglobin levels significantly affected OS. Conclusion: Large and multicentric clinical trials are required to further study this group of patients and define optimum treatment modalities.

Keywords

Endometrial Carcinoma, Radiotherapy, Chemotherapy

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1. Introduction

Endometrial cancer is the sixth most common cancer in women worldwide & one of the most frequently occurring female genital cancers, with 320,000 new cases diagnosed in 2012 [1].

Type II Endometrial cancer accounts for 10 to 20 percent of endometrial carcinomas. These include tumors of non-endometrioid histology: serous, clear cell, squamous, transitional cell, and undifferentiated. Uterine carcinosarcomas are also included in this subtype [2].

While the incidence of Type II tumors is low compared to Type I, excess mortality is associated with Type II EC. In an analysis of Surveillance, Epidemiology and End Results (SEER) data, Hamilton *et al*. [3] reported that while 11% of ECs were Type II, 47% of deaths in the SEER cohort occurred in this subtype. Furthermore, stage-adjusted 5-year overall survival rates for Type II tumors are significantly worse compared to Type I tumors [4].

The epidemiology and biology of Type II tumors are not well characterized, although a few studies report that Type II cases are more likely to be older, of normal weight, multiparous, and African American compared to Type I cases [5]-[12]. The tumorigenesis of Type II EC is not thought to operate through the estrogen pathway, as normal-weight and parous women have decreased estrogen exposure compared to obese and nulliparous women. Low incidence of Type II tumors makes this subtype difficult to study.

The proposed aim of this work is to study the clinical and pathological characteristics of Type II endometrial carcinoma patients. Analyze the potential prognostic factors affecting Locoregional Control, Disease-Free Survival and Overall Survival.

2. Patients and Methods

This is a retrospective study involving 91 patients with pathoologically proven Type II endometrial carcinoma, who presented to the Radiation Oncology department at the National Cancer Institute, Cairo University during the period from January 2000 to December 2012.

Data was retrieved from the patients' medical records. The collected data included the patients' names, age, menopausal status, comorbidities, obstetric history, performance status, pretreatment hemoglobin levels, presenting symptom(s), pathological subtype, FIGO stage, grade, date and type of surgery, details of adjuvant treatment and response to treatment, side effects and complications of treatment, follow-up details and patterns of failure, salvage treatment and patient status at last follow up.

Patients received external beam radiotherapy 50 Gy/5weeks, 49 patients received brachytherapy (3 patients received Low dose rate to a dose of 30 Gy and 46 patients received High dose rate brachytherapy 7 Gy × 2 fractions).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21 was used. Quantitative data were presented as mean, standard deviation, median and range as appropriate. Qualitative data were presented as frequency and percentage. Survival analysis was done using Kaplan-Meier method. Comparison between two survival curves was done using log-rank test. Cox regression was used for analysis of independent variables affecting survival. P value ≤ 0.05 was considered significant.

3. Results

This is a retrospective study which was done on patients with Type II endometrial carcinoma who were treated at the Radiation Oncology department, National Cancer Institute, Cairo University during the period between year 2000 and 2012 and included a total of 91 patients (**Table 1**).

Univariate analysis showed patients below 60 years of age had significantly fewer rates of locoregional failure compared to those above 60 years of age (local control rates were 85.7% at 5 years versus 52.5%) (p value = 0.026). On multivariate analysis, age was found to be an independent prognostic factor for local control (HR = 4.26, 95% CI = 1.27 - 14.26) (p value = 0.019). Where as for other factors no significant differences were found regarding their impact on local control (**Figure 1** and **Table 2**).

3.1. Disease Free Survival

Univaritae analysis showed there is significant improvement in disease free survival for patients less than 60 years

Table 1. Local control and different prognostic factors.

Factors	Number of patients	Local control at 3 years (%)	Local control at 5 years (%)	P value (univariate)
Age (years)				
<60	32	85.7	85.7	0.026
≥60	56	64.1	52.5	
Pretreatment Hemoglobin				
<12 g/dl	29	50.6	38.0	0.114
≥12 g/dl	17	87.5	72.9	
Pathology				
Papillary Serous	28	71.9	61.6	
Clear cell	12	85.7	85.7	0.140
Undifferentiated	8	All cases censored	All cases censored	
Carcinosarcoma	40	57.0	42.7	
Lymph nodes				
Nx	63	74.8	60.1	0.880
N0	18	69.2	69.2	
N1	7	All cases censored	All cases censored	
FIGO stage				
Early (I,II)	68	75.9	59.6	0.841
Advanced (III,IV)	20	78.1	78.1	
Adjuvant ERBT				
No	9	57.1	38.1	0.111
Yes	79	79.6	70.5	
Brachytherapy				
Yes	49	85.7	78.6	0.075
No	39	66.3	49.8	
Chemotherapy				
Yes	8	64.3	64.3	0.919
No	78	77.1	63.5	

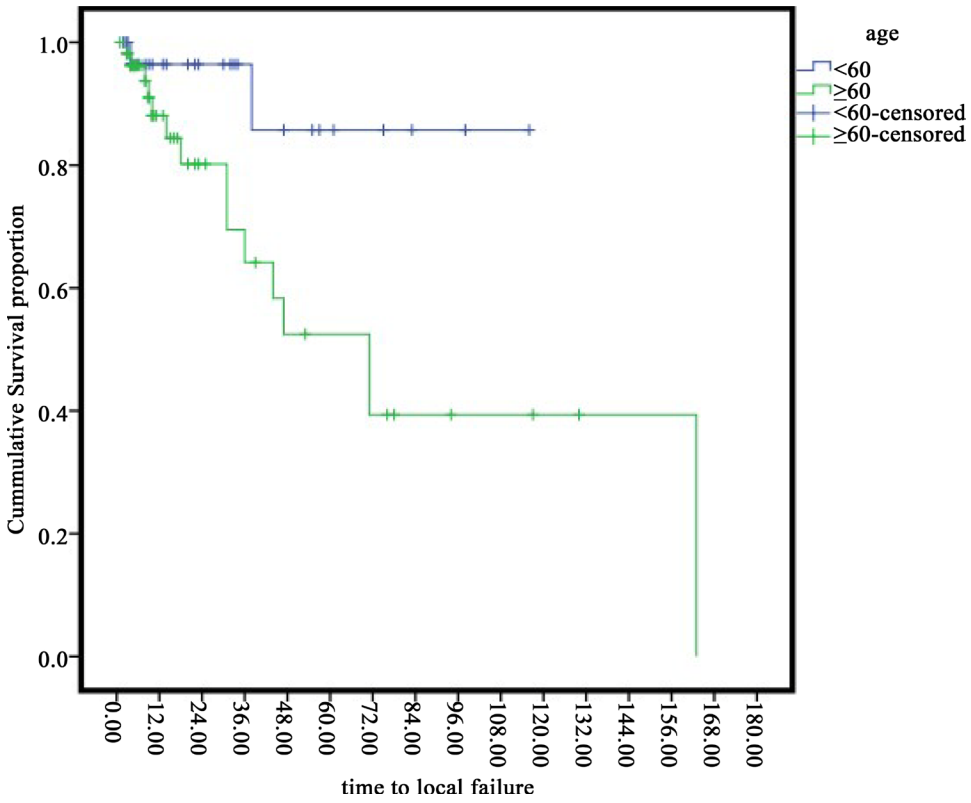

Figure 1. Impact of age on local control.

Table 2. Disease free survival and different prognostic factors.

Factors	No. of patients	3 DFS %	5 years DFS	P value (univariate)	P value (multivariate)
Age (years)					
<60	32	84.5	65.7	0.001	0.005
≥60	56	41.1	32.4		
Pretreatment Hemoglobin					
<12 g/dl	29	43.4	32.5	0.117	
≥12 g/dl	17	65.7	52.5		
Pathology					
Papillary Serous	29	44.2	44.2		
Clear Cell	12	72.9	72.9	0.666	
Undifferentiated	8	68.6	51.4		
Carcinosarcoma	39	60.6	26.9		
Lymph nodes					
Nx	64	52.1	41.4	0.089	
N0	17	94.1	70.6		
N+	7	41.7	0		
FIGO stage					
Early (I,II)	68	62.7	52.0	<0.001	0.026
Late (III,IV)	20	0	0		
ERBT					
No	8	38.1	38.1	0.694	
Yes	80	59.0	44.9		
Brachytherapy					
Yes	49	70.9	57.3	0.004	0.011
No	39	40.5	27.0		
Chemotherapy					
Yes	8	72.9	72.9		
No	78	54.3	41.2	0.273	
Factors	**No. of patients**	**3 DFS %**	**5 years DFS**	**P value (univariate)**	**P value (multivariate)**
Duration from surgery to ERBT					
≤2 months	48	59.2	50.1	0.866	
>2 months	32	59.1	29.6		

with p = 0.001, for patients with early stages there was better DFS with significant P = 0.001, also those who received brachyjtherapy they had better DFS with p = 0.004 (**Figures 2-4** and **Table 3**).

3.2. Overall Survival

Univariate analysis showed better overall survival for patients less than 60 years old with p = 0.002, also patients with stage I and II disease had better overall survival than advanced stage with p = 0.004 (**Figure 5** & **Figure 6**).

4. Discussion

Our study confirmed that age was a significant prognostic factor; advanced age (>60 years) was associated with worse local control (p = 0.026), disease-free survival (p = 0.001) and overall survival (p = 0.02). This is consistent with numerous studies, such as that conducted by Vance *et al.* to determine the prognostic significance of age in type II endometrial carcinomas in general which found that age more than 65 years is a significant adverse prognostic factor for tumor recurrence [13].

According to the FIGO 26th annual report, FIGO stage was a significant prognostic factor for survival. 5-year OS rates for stage I disease was 90% for endometrioid carcinoma and 80% - 85% type II histologies, and dropped to 29% for stage IV disease [14]. Similarly, in our study patients with advanced stage disease had significantly lower rates of DFS ($p \leq 0.001$) and OS (p = 0.004).

Previous studies conducted to evaluate the effect of adding brachytherapy to EBRT concluded that it did not confer additional benefit to local control or overall survival [15]. However, in a study by Sorbe *et al.*, the combination of brachytherapy and EBRT led to significant improvement in LC without OS benefit [16]. Most of the

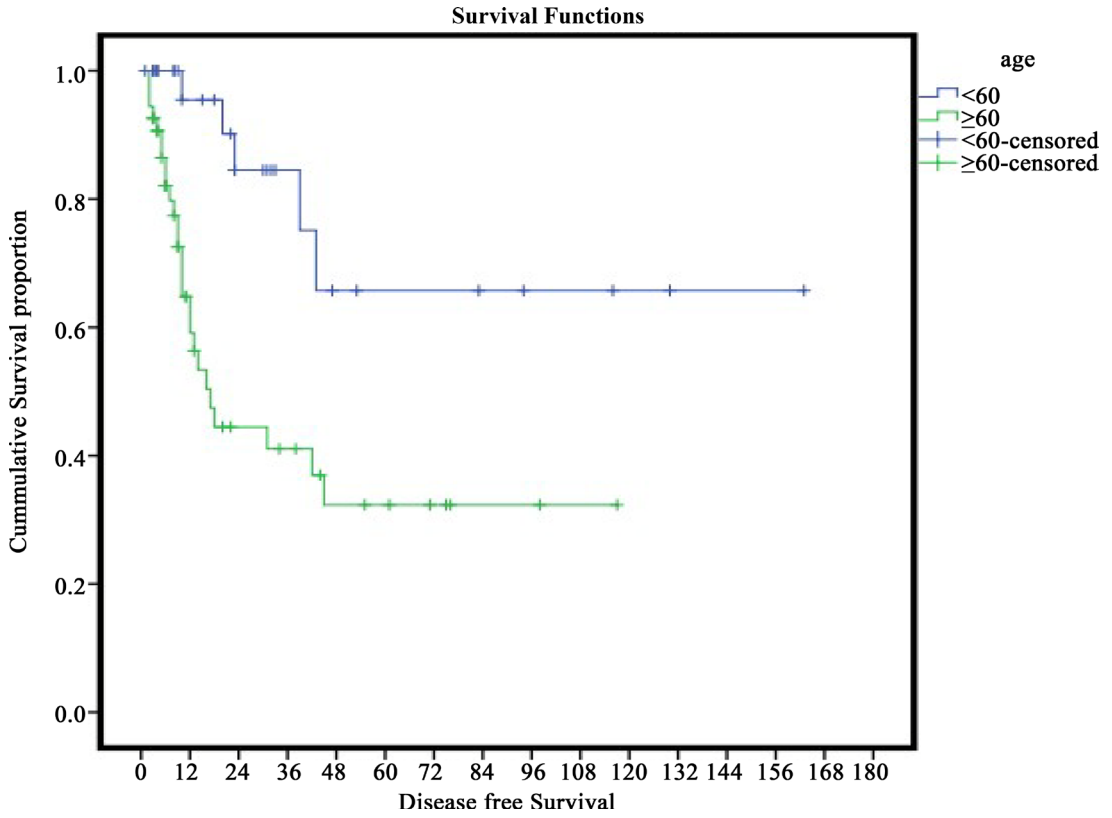

Figure 2. Impact of age on disease free survival.

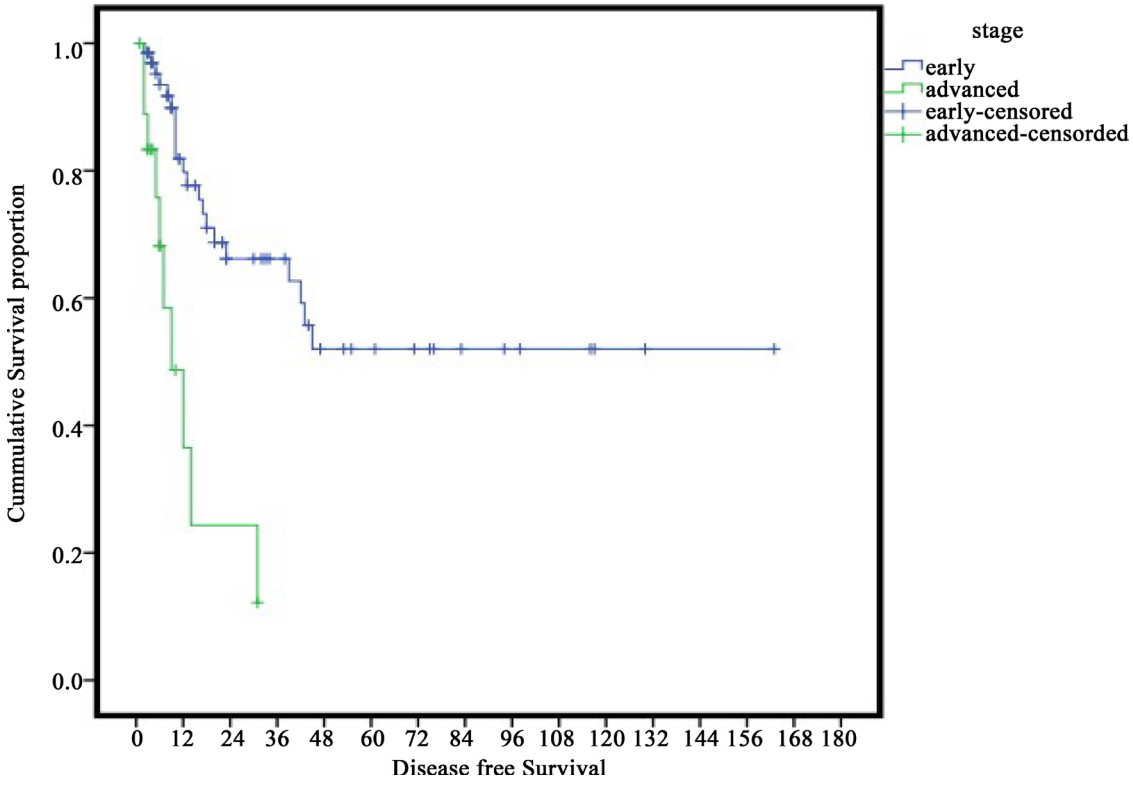

Figure 3. Impact of FIGO stage on disease free survival.

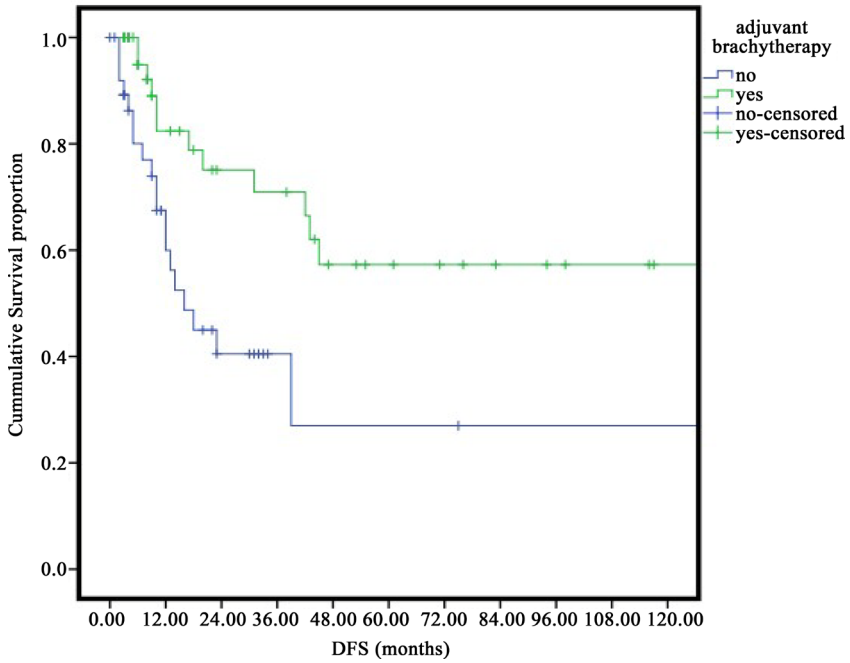

Figure 4. Impact of adjuvant brachytherapy on disease free survival.

Table 3. Overall Survival and different prognostic factors.

Factors	No. of patient	3 years OS%	5 years OS%	P value (univariate)	P value (multivariate)
Age (years)					
<60	32	84.8	84.8	0.020	
≥60	59	66.7	60.1		
Pretreatment Hemoglobin				0.009	
<12 mg/dl	31	62.5	41.7		
≥12 mg/dl	17	100	100		
Pathology					
Papillary Serous	30	85.7	85.7		
Clear Cell	12	71.1	71.1	0.341	
Undifferentiated	8	85.7	85.7		
Carcinosarcoma	41	73.4	58.7		
Lymph node status					
Nx	66	81.4	76	0.154	
N0	18	72.2	54.1		
N + ve	7	68.6	0		
FIGO stage					
Early (I,II)	68	84.9	75.1	0.004	0.041
Advanced (III,IV)	23	34.9	0		
Adjuvant EBRT					
No	10	75.0	75.0	0.910	
Yes	81	79.3	74.6		
Brachytherapy					
Yes	49	77.7	72.5	0.838	
No	42	78.7	59.0		
Chemotherapy					
Yes	9	85.7	85.7	0.467	
No	80	77.0	66.9		
Duration from surgery to ERBT					
≤8 weeks	48	92.9	82.5	0.011	0.011
>8 weeks	32	60.6	48.5		
Overall Treatment Period (OAP)					
≤8 weeks	42	76.4	50.9	0.250	
> 8 weeks	49	80.2	74.8		

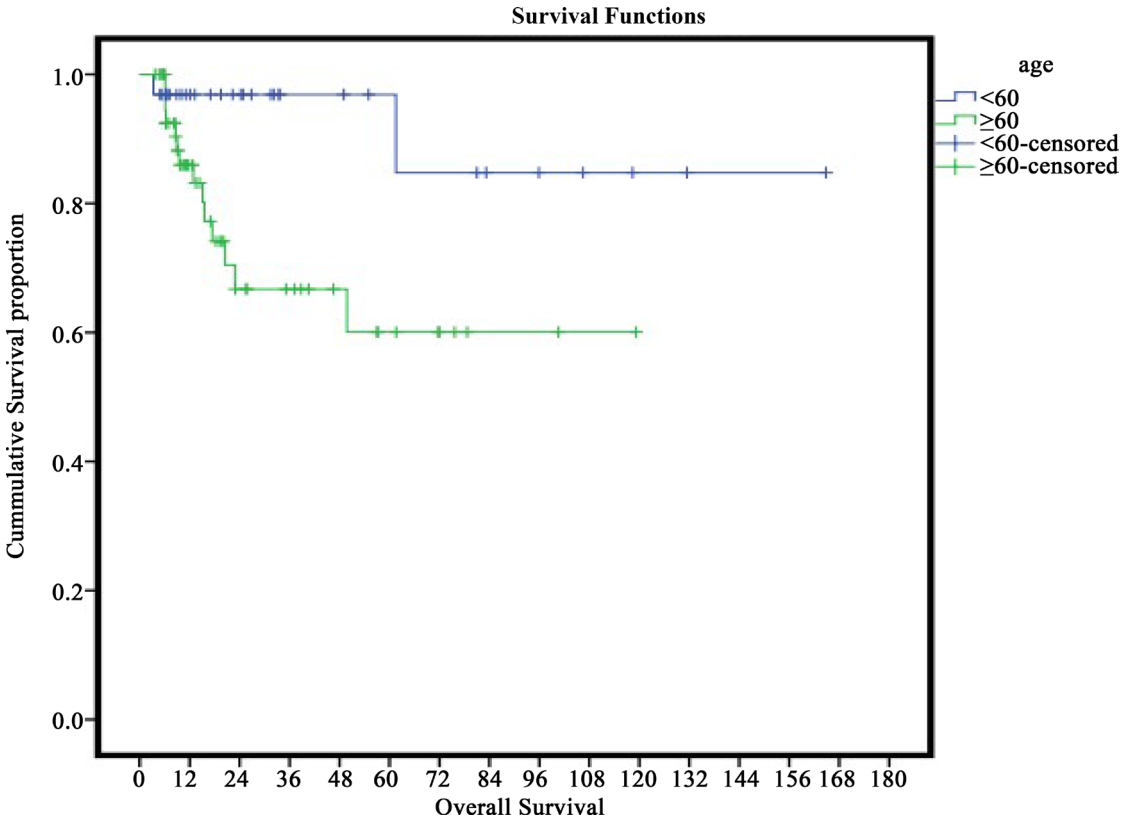

Figure 5. Impact of age on overall survival.

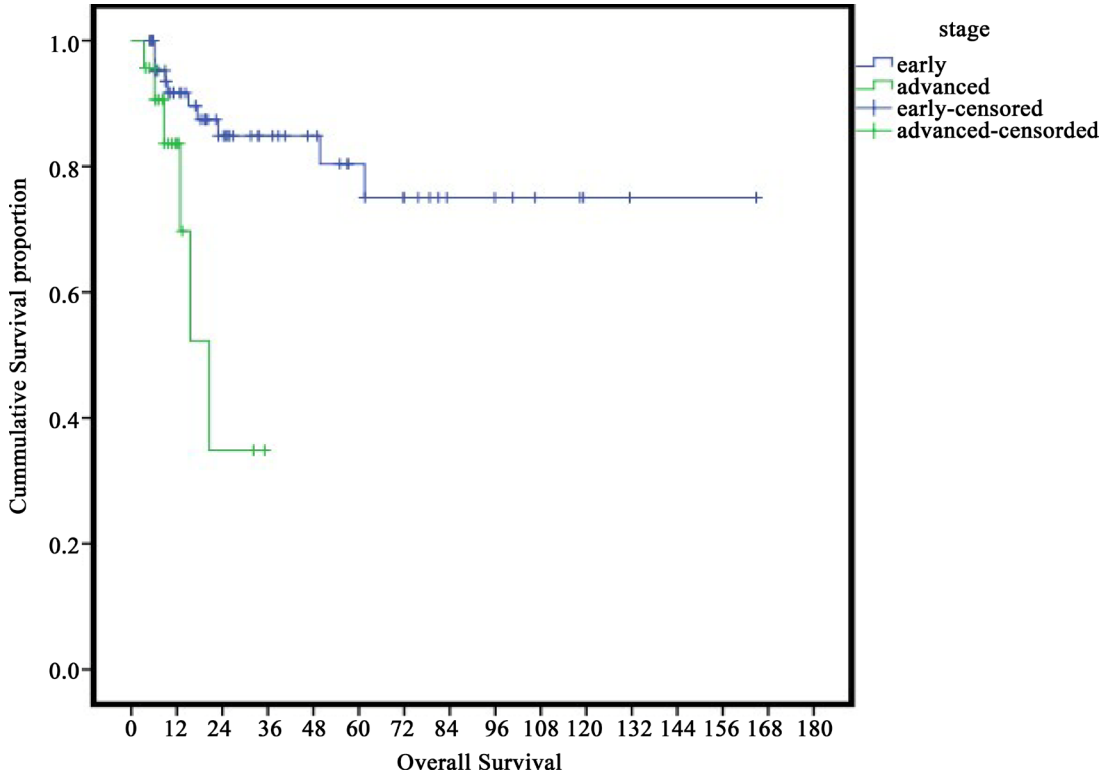

Figure 6. Impact of FIGO stage on overall survival.

patients in the current study received adjuvant brachytherapy as a boost after ending EBRT. The use of brachytherapy was associated with significantly improved DFS (p value = 0.011) and a trend towards improved LC rates (p value = 0.075) but with no improvement in OS (p value = 0.838).

The current study also showed that increasing the time interval between surgery and start of EBRT (>8 weeks) had a negative impact on OS (p = 0.011) which was also confirmed on multivariate analysis. This came close to the study done by Cattaneo *et al.* in which interval > 9 weeks was associated with poor survival outcomes [17].

Regarding the sites of locoregional recuuence, our study found that the vaginal vault was the most common (50%), followed by the pelvic region (22%). This is matching with the results of the study by Demiral *et al.* in which 46.7% recurred in the vaginal stump and 33.3% in the pelvis [18].

Our study found that the most frequent site of distant failure was the peritoneum (24.1%). This is most probably due to the fact that papillary serous and carcinosarcoma subtypes together represented the majority of our patients (78%). These subtypes have a tendency for distant failure in the abdomen, which was confirmed in multiple studies and reviews [19] [20].

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