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Clinical Group

Archives of Nursing Practice and Care

DOI http://dx.doi.org/10.17352/anpc.000019

ISSN: 2581-4265 CC By

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**Dates: Received:** 11 February, 2017; **Accepted:** 21 February, 2017; **Published:** 22 February, 2017

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**Keywords:** Endometrial cancer; Survival; Prognostic factors

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Research Article

# Survival Determinants in Endometrial Cancer Patients: 5-Years Experience

## Abstract

**Aim:** The aim of the study was to explore five years survival in women with endometrial cancer.

**Material and methods:** A retrospective review of 146 patients with endometrial cancer treated at Baskent University Hospital Gyne-oncologic Clinic in Ankara, Turkey between 2010 and 2015 was performed. Demographic and clinic-pathological data were compared with survival.

**Results:** The median age of the patients was 61.4 y±5.3 years (36-82). The overall 5-years survival was 89%. Multivariate Cox regression model revealed that the FIGO stage, grade, age, histological type, myometrial invasion, and lymph node involvement were all predictive factors on survival ($p<0.05$). However, the menopausal status, age at menopause, parity, BMI, comorbidities, ECOG performance score, therapy modality, HR status, and family history were not associated with survival ($p>0.05$).

**Conclusion:** The results of our study, several clinic-pathological prognostic factors of EC have been identified on survival. These results provided significant evidence that early foresight of EC survival. Further prospective randomized studies are necessary to clarify the role of these factors.

## Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in the world, especially in industrialized countries. There were an estimated 320,000 new cases with 50,327 deaths of EC each year and its incidence is rising worldwide [1]. The incidence of EC varies in different regions of the world; in the USA 23.3/100,000, in Europe 16/100,000, and in Canada 19.5/ 100,000 women per year. Low rates occur in Africa (3.3/100,000) and Asia (3.8/ 100,000) [2]. In Turkey, too, EC is the most frequently seen gynecologic cancer (8.4/10000) in women following breast cancer [3].

Although there is no any effective screening modality, 75% of the women are diagnosed at the early stage because of the predominantly postmenopausal bleeding symptoms [4,5]. In advanced stage, treatment failure is more common and there are important subgroups within this diagnosis with poor survival so there is still a significant mortality from the disease [6]. The overall 5-year survival for all stages is 86%; patients; when diagnosed at a local or regional stage, the 5-year survival rate is 97% and 67% respectively, while distant stage survival decreases to 16% [7]. In order to improve survival of EC patients, clinic-pathological prognostic factors have been studied previously [5-12]. Unfortunately, the importance of predictive factors for the prognosis of patients with EC has not yet been fully established. As a result of the limited prospective data about why some patients with EC have recurrent disease the detailed levels of prognostic value of factors are still being discussed. Therefore, estimating survival of EC is remarkable that provide an understanding of the disease course. The purpose of the study was to investigate the predictive factors that affect survival of patients with EC.

## Material and Methods

Totally 146 patients with the diagnosis of EC treated at the Department of Gynecologic Oncology, Baskent University Ankara Hospital in Turkey between 2010 and 2015 were analyzed retrospectively. Patients of whom all of the pathological examinations were not performed in our hospital were excluded from the study. Patients with unknown treatment data, or missing information were excluded. The follow-up consisted of three months for first three years, six months for next two years, and then yearly reviews. The research was approved by the University of Baskent Institutional Review Board.

The data were collected by using three different forms between April 2016 and January 2016 through hospital-based cancer registry; 1) The Patient Information Form, 2) The Charlson Comorbidity Index (CCI), and 3) The Eastern Cooperative Oncology Group (ECOG) Performance Scale.



**Citation:** Pinar G, Ayhan A (2017) Survival Determinants in Endometrial Cancer Patients: 5-Years Experience. Arch Nurs Pract Care 3(1): 012-015. DOI: http://dx.doi.org/10.17352/anpc.000019

1) The Patient Information Form; This form includes 15 questions to define individual and medical characteristics of the women with EC such as age, body mass index (BMI), menopause status, menopause age, hormone receptor (HR) status, parity, subtype, stage, grade, type of therapy, lymph node involvement and myometiral invasion. Histology was classified based on the International Classification of Diseases for Oncology (ICD-O) as endometrioid and non-endometrioid. Stage categories were based on the International Federation of Gynecology and Obstetrics (FIGO) stages I, II III and IV [13]. Survival time was calculated from date of diagnosis until death. BMI values of patients were classified as underweight (BMI <18.5 kg/m$^2$), normal (BMI 18.5-24.9 kg/m$^2$), overweight (BMI 25-29.9 kg/m$^2$), and obese (BMI ≥30 kg/m$^2$) according to World Health Organization (WHO) criteria [14].

2) The Charlson Comorbidity Index (CCI); Comorbidity was measured for each patient using the CCI, categorized as 0, 1, or ≥2, with a higher score indicating a larger number or greater severity of comorbidities. The CCI, ranging from 0 to 29, consists of a weighted sum of 17 major illnesses (e.g., myocardial infarction, stroke, diabetes, liver disease, dementia, renal disease) [15].

3) European Cooperative Oncology Group (ECOG) Performance Scale; This scale was developed by the Eastern Cooperative Oncology Group (ECOG) in 1982 to classify a patient according to their functional impairment, compare the effectiveness of therapies, and assess the prognosis of a patient (from 0 to 5, with 0 denoting perfect health and 5 death) [16].

The statistical program SPSS version 18 (SPSS, Inc, Chicago, IL) was used to process the results. Data were given as percent or mean ± standard deviation (SD). Statistical analysis was performed Chi-square, Fisher's exact tests, Multivariate Cox Regression and Kaplan-Meier survival analysis. The level of significance was established at $p<0.05$.

## Results

Detailed characteristics of the patient set are shown in Table 1. Totally, 146 women with EC who met the inclusion criteria were included in the study. The median age of the patients was 61.4 y ±5.3 years (min:36, max:82), 54.1 % patients were younger than 60 years and average age of menopause was 50.6±5.24 years (min: 41-max: 56). The mean parity was 3.21±4.5, ranging from 0 to 14 and 58.2% were overweight + obese.

According to the 1988 FIGO criteria, 116 (79.4%) patients had stage I-II and 30 (20.6%) had stage III-IV disease. Grades of the disease were grade-I in 90 (61.6%) and grade ≥II in 56 (38.4%) patients. EC was classified as endometrioid (n=124) and non-endometrioid type (n=22). Lymph node involvement was found in 26 patients (17.8%), the depth of myometrial invasion was smaller than 50% in 94 patients (64.3%), and HR status was positive in 112 patients (76.7%). Among patients with EC, 31.5% had CCI- 0, and 68.5% had CCI- ≥1. ECOG performance status was "0-1" (67.1%), "≥2" (32.9%) in patients' last hospitalizations (Table 1). The most common symptom at presentation for patients was postmenopausal bleeding (88.9%). Twenty-five percent of women had cancer stories in their families. All patients underwent primary surgery (a hysterectomy with bilateral salpingo-oophorectomy). Lymphadenectomy was performed on forty-five patients with/without omentectomy and bowel surgery. Postoperative external-beam pelvic radiotherapy (EBRT) and/or brachytherapy (BT) were administered to the majority of the patients (82.2%).

**Table 1:** Clinical characteristics of the women with EC and survival analysis.

| Variables | N | % | 5-y survival Median: 89% | $x^2$/p |
|---|---|---|---|---|
| **Age** (Mean: 61.4 y ±5.3) | | | | |
| ≤60 | 79 | 54.1 | 88.4 | **5.394** |
| >60 | 67 | 45.9 | 71.5 | **0.002** |
| **Menopausal status** | | | | |
| Premenopausal | 20 | 13.7 | 94.4 | 0.026 |
| Postmenopausal | 126 | 86.3 | 81.5 | 0.761 |
| **Age at menopause** (Mean: 50.6±5.24) | | | | |
| ≤50 | 63 | 43.2 | 80.3 | 0.493 |
| >50 | 83 | 56.8 | 85.4 | 0.164 |
| **BMI** | | | | |
| Normal (18.5-24.9 kg/ m$^2$) | 61 | 41.8 | 84.5 | 1.254 |
| Overweight + Obese (≥25 kg/m$^2$) | 83 | 58.2 | 81.9 | 0.232 |
| **Parity** (Mean: 3.21±4.5) | | | | |
| Yes | 129 | 85.4 | 81.9 | 1.022 |
| No | 17 | 14.6 | 80.0 | 0.056 |
| **Grade** | | | | |
| I | 90 | 61.6 | 88.1 | **7.942** |
| II-III | 56 | 38.4 | 64.4 | **0.014** |
| **Stage** | | | | |
| I-II | 116 | 79.4 | 91.7 | **6.661** |
| III-IV | 30 | 20.6 | 56.2 | **0.020** |
| **Subtype** | | | | |
| Endometrioid | 124 | 84.9 | 93.4 | **11.670** |
| Non-endometrioid | 22 | 15.1 | 71.5 | **<0.001** |
| **Lymph node involvement** | | | | |
| Positive | 26 | 17.8 | 69.4 | **10.230** |
| Negative | 120 | 82.2 | 88.7 | **<0.001** |
| **Myometrial invasion** | | | | |
| ≤50 % | 104 | 74.3 | 92.6 | **9.781** |
| >50 % | 42 | 25.7 | 66.0 | **<0.001** |
| **CCI** | | | | |
| 0 | 46 | 31.5 | 88.4 | 0.452 |
| ≥ 1 | 100 | 68.5 | 79.2 | 0.462 |
| **ECOG** | | | | |
| 0-1 | 98 | 67.1 | 83.5 | 0.309 |
| 2-3 | 48 | 32.9 | 80.0 | 0.135 |
| **HR status** | | | | |
| Positive | 112 | 76.7 | 89.0 | 1.200 |
| Negative | 34 | 23.3 | 78.4 | 0.356 |

HR: Hormone receptor, BMI: Body Mass Index, CCI: The Charlson Comorbidity Index, ECOG: European Cooperative Oncology Grou.



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Survival analysis was performed in the evaluation of 146 patients. The median of survival was 89%. HR status, BMI, CCI, menopause status, age at menopause, family history, ECOG performance status and treatment type were not significant for the survival of the EC (p>0.05). Lower stage and grade of disease, endometriod subtype, lymph node involvement, and depth of myometrial invasion ≤ 50% were prognostic factors for better survival (p<0.05). Increased age was associated with decreased survival (p<0.05) (Table 1).

Similarly, on multivariate analysis; advanced age was significantly associated with worse OS (HR, 1.4 [95% CI, 1.3–1.4] than younger women. Non-endometrioid was associated with worse OS than endometrioid cancers (HR, 1.3 [95% CI, 1.2–1.5). Higher grade (HR, 1.1 [95% CI, 1.1–1.3), stage (HR, 2.0 [95% CI, 1.1–2.8), myometrial invasion (HR, 1.3 [95% CI, 1.1–1.6), and lymph node involvement (HR, 1.2 [95% CI, 1.0–1.3) had significantly poorer OS rates (Table 2).

## Discussion

EC is most common amongst postmenopausal women and the main symptom is irregular or postmenopausal bleeding so the prognosis is generally favorable [5]. In our study, postmenopausal bleeding was seen in 88.9% of patients. In accordance with our study, Keskin et al. also reported postmenopausal vaginal bleeding as the most common complaint [7]. Over the past few decades, several studies have demonstrated the prognostic importance of different parameters [6-12]. In this study, 5- years survival of patients was 89%. The previous study confirmed that in these data on survival. Gottwald et al. [12], found that the 5-year survival for EC was 87%. Ayhan et al. [17], reported that the 5-year overall survival rate of entire group was 86% [17]. Karateke et al. [9], documented that 5- year survival of patients with EC was 76.9%. In a study by Craighead et al. [10], a 5-year survival rate of 65% was identified. By contrast, Jhingran et al. [18], reported a 5year survival rate of only 42%.

In this study, older women were found to have a poorer prognosis, survival declined with increased age (p<0.05). Analysis of 165 women of EC indicated that old age was associated with poor survival [11]. Bristow et al. [8] and Ferlay et al. [19], demonstrated that EC survival decreases in older patients. However, Karateke et al. [9], Gottwald et al. [12], and Bajracharya and Juan [6], found age at diagnosis was not significant predictor of survival for EC.

When diagnosed at a local or regional stage, the 5-year survival rate is 96% and 67% respectively, while distant stage survival decreases to 16%. [20]. Bajracharya and Juan [6], found that stage was among the most important prognostic factors in EC. In a large study conducted by Karateke et al. [9], five years survival rates in patients with sage 1-IV disease were 83.3%, 80%, 62.5% in stage III and 33.3%, respectively. Craighead et al. [10], demonstrate that disease stage was the most important prognostic factor affecting survival. Our findings match well with previous studies, these rates in patients with stage I-II and II-IV disease were 91.7%, and 56.2%, respectively. Consequently, staging became one of the most important prognostic factors (p<0.05) and this was similar to the results of previous studies.

In the literature, tumor grade is also known to affect survival [5,6,9]. In this study showed there was a significant correlation between histological grades (88.1% for grade I and 64.4% for grade II-III) as prognostic factors (p<0.05). In the other study, 5 years survival rates of grade 1-3 EC were 71-88% for grade I, 60-79% for grade 2 and 32-65% for grade 3 [20]. In the present study, five years survival rates were 93.3% for grade I, 77.3% for grade II and 60% for grade III, and these rates were consist with literature. Consequently, the overall survival analyzes showed a statistically significant difference among grade I-III (p<0.05).

In general, patients with tumors of non-endometrioid subtypes have a worse prognosis than those with tumors of endometrioid subtypes [12,20]. In this study, patients with non-endometrioid subtype (71.5%) were lived shorter than those with endometrioid type (93.4%) (p<0.05). According to Karateke et al. [9] and Bajracharya and Juan [6], non-endometrioid type of endometrial carcinoma tends to have lower survival rates as compared to endometrioid type. In contrast to this, Craighead et al. [10], documented that subtypes of EC on endometrial carcinoma prognosis was not remarkable (p>0.05).

Previous studies showed that the depth of myometrial invasion ≤ 50% were independent prognostic factors for better survival [6,9,12,21]. In a large study, five years survival rates of patients with or without deep myometrial invasion were found as 60% and 80%, respectively [20]. In our study, myometrial invasion had a significant impact on survival. Five years survival rates were differed between patients with tumor confined to inner $^{1}/_{2}$ of myometrium and those had beyond this level (92.6%, 66.0%, respectively, p<0.05). The results do not match well with those of Lim et al. [11] and Ayhan et al. [22], deeper myometrial invasion was not associated with prognosis for women with EC.

Based on the available scientific evidence, lymph node involvement is also known to affect survival in EC [11]. In this study, significant difference by means of five years survival was found between patients with lymph node involvement and those with no involvement (69.4% and 88,7%, respectively, p<0.05). Fader et al. [5] and Ayhan et al. [22], reported that the most important prognostic factor in EC is nodal involvement.

**Table 2:** Multivariate Cox regression model of OS (5-year).

| Variables | HR | %95 CI | P |
|---|---|---|---|
| Age at diagnosis (≤60y vs >60y) | 1.43 | 1.31-1.49 | 0.002 |
| Stage (III-IV vs I-II) | 2.01 | 1.13-2.80 | 0.020 |
| Subtype (endometrioid vs others) | 1.34 | 1.23-1.53 | 0.001 |
| Grade (1 vs ≥ 2-3) | 1.15 | 1.11-1.34 | 0.003 |
| Lymph node involvement (+/-) | 1.23 | 1.06-1.36 | 0.031 |
| Myometrial invasion (≤ 50 % vs >50 %) | 1.32 | 1.18-1.67 | 0.015 |

HR: hazard ratio, CI: Confidence Interval.



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## Conclusion

In the result of this study, the median 5-year survival for OC was 89%. Age at diagnosis, histological subtype, stage, grade, depth of myometrial invasion and lymph node involvement have been identified as predictors of survival. The results of our work may contribute to better understand its clinical behavior. Further multicenter randomized studies are necessary on large number of patients to prove the role of these factors, which leads to improve the survival.

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