YÜKSEK RİSKLİ VE DÜŞÜK RİSKLİ ENDOMETRİUM KANSERLERİ HASTALARDA İLERİ YAŞ KÖTÜ PROGNOSTİK BİR FAKTÖR MÜDÜR?

Is Advanced Age a Poor Prognostic Factor In High Risk and Low Risk Endometrial Cancer Patients?

Mehmet GÖKÇÜ[1], Selçuk ERKILINÇ[1], Ulaş SOLMAZ[1], Mustafa BAĞCI[1], Orhan TEMEL[1], Tuğba KARADENİZ[2], Muzaffer SANCI[1]

[1]University of Health Sciences Tepecik Education and Research Hospital, Department of Gynecologic Oncology, İzmir Turkey

[2]University of Health Sciences Tepecik Education and Research Hospital, Department of Pathology, İzmir Turkey

Mehmet GÖKÇÜ M.D.,
Selçuk ERKILINÇ M.D.,
Ulaş SOLMAZ M.D.,
Mustafa BAĞCI M.D.,
Orhan TEMEL M.D.,
Tuğba KARADENIZ M.D.,
Muzaffer SANCI M.D

İletişim:
Selçuk ERKILINÇ M.D. University of Health Sciences Tepecik Education and Research Hospital, Department of Gynecologic Oncology, Bornova, İzmir 35200, Turkey
Tel: +905549166923
e-mail:
selcukerkilinc@hotmail.com

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ÖZET

Amaç: Yüksek riskli ve düşük riskli endometrium kanserinde ileri yaşın sağkalım üzerine etkisini araştırmak

Metod: 1995-2015 yılları arasında düşük riskli 759, yüksek riskli 139 endometrium kanseri hastası çalışmaya dahil edildi. Demografik veriler, cerrahi tedavi verileri retrospektif olarak değerlendirildi. Yaşın sağkalım üzerine etkisinin araştırılması için Univariate ve multivariate regresyon analizi yapıldı.

Bulgular: Düşük riskli ve yaşlı hastalarda genç hastalarla karşılaştırıldığında dış myometrial invazyon, radyoterapi, lefovasküler invazyon anlamlı olarak daha fazlaydı. Yüksek riskli yaşlı hastlarada sadece radyoterapi oranı yüksek bulundu. Yüksek riskli düşük riskli hastalarda ileri yaş total sağkalım için bağımsız bir risk faktörü olarak bulundu

Sonuç: Hem yüksek riskli hem de düşük riskli endometrium kanserli hastalarda ileri yaş olumsuz prognostik bir faktör olarak bulunmuştur

Anahtar Sözcükler: *Endometrium kanseri; Düşük risk; Yüksek risk; İleri yaş*

ABSTRACT

Objective: To evaluate the effect of advanced age on high risk and low endometrial cancer patients.

Methods: A total of 759 patients with type I endometrial cancer and 139 patients with type II endometrial cancer between January 1995 to December 2015 were included to the study. High risk and low risk patients were devided into two groups according to age. Demographic data, surgical treatment, adjuvant treatment and survival characteristics were compared between age groups in high risk and low risk patients. To detect the independent hazard of the variables on survival univariate and multivariate Cox regression analysis was performed.

Results: Outer ½ myometrial invasion, adjuvant radiotherapy, LVSI, tumor diameter were significantly higher in advanced age groups in low risk patients. Admission of adjuvant radiotherapy was the only parameter that differed between older and younger age groups in high risk patients. Both disease free survival and overall survival were higher in younger low risk patients. Overall survival was longer in high risk and younger age patients, but disesase free survival was similar. Multivariate Cox-regression analysis revealed that advanced age was a significant independent hazard for overall survival both in high risk and low risk endometrial cancer patients (HR:1.94, 95% CI:1,0-3,4).

Conclusion: Our study suggested that advanced age was a poor prognostic factor both for low risk and high risk endometrial cancer patients.

Keywords: *Endometrial cancer; High risk; Low risk; Advanced age*

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INTRODUCTION

Endometrial cancer is the most common gynecological tumor in developed countries, and its incidence is increasing [1,2]. The progressive aging of the population is an epidemiological fact of the 21st century. The older population continues to expand as a result of reduced mortality and birth rates. People aged 65 years and older represented 12% of the population in 1990; the percentage in this group is expected to increase to 20%, by 2030 [3]. Currently 60% of all malignancies occur in people aged 65 years and older, and this proportion is expected to rise up to 70% by the year 2030 [4].

Mainly endometrial cancer is the cancer of post-menopausal period. Cumulative risk of developing endometrial cancer after age of 70 is 1.3% and the risk is increasing [5]. Increasing incidence of endometrial cancer in developed countries may be attributed to greater prevalence of obesity and metabolic syndromes and ageing of population. Previous studies found the age to be a poor prognostic factor in endometrial cancer and age was integrated in risk stratification by several study groups including PORTEC (Postoperative Radiation Therapy in Endometrial Carcinoma), GOG (Gynecologic Oncology Group), and JGOG (Japanese Gynecologic Oncology 'Group)[6-8]. Furthermore it has been shown that age plays a significant role in surgical decision and treatment plan. Elderly patients were reported to receive less aggressive surgery and adjuvant treatment than younger counterparts [9].

There are two pathologic subtypes of endometrial cancer (type I and type II) that reflect clinic and pathologic features [10]. Low risk tumors that have better prognosis contain grade 1 and 2 endometrioid tumors whereas high risk tumors contain other histologic subtypes (serous, clear cell, undifferentiated and mixed types) and grade III tumors.

There are studies on literature evaluating the effect of age in patients with endometrial cancer [11-13]. Patients in advanced ages may be treated less radical compared to the youngers as a result of increased incidence of comorbidities. So this may contribute to less favorable oncological outcomes. In the light of all this information, we aimed to evaluate the effect of advanced age on high risk and low risk endometrial cancer patients saparetely. To the best knowledge of the authors this is the first study evaluating the effect of advanced age on low risk and high risk endometrial cancer patients separately.

MATERIALS AND METHODS

Patient selection and design

All patients with histopathologically confirmed diagnosis of endometrial cancer who were treated at a single high-volume cancer center (Tepecik Education and Research Hospital) between January 1995 and December 2015, were retrospectively reviewed. Patients with pathologic diagnosis of endometrial cancer were included to the study and a total of 898 patients were encountered. The patients were divided in to two groups according to risk stratification as high risk and low risk endometrial cancer The patients that had hystologically endometrioid type grade 1 and 2 tumors were regarded as low risk patients and the other histologic subtypes and grade 3 tumors were regarded as high risk patients.. 659 patients with low risk and 139 patients with high risk were included to the study. Patients that had simultaneous tumor and received neo-adjuvant chemotherapy were excluded. Patients with missing data, who did not undergo surgical staging were also excluded. Patients with low risk and high risk were also divided into two categories according to the age as <65 and ≥65 and compared in terms of the aforementioned variables. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee of our institution.

Data collection:

Demographic data including age at diagnosis, surgery, adjuvant treatment, and follow-up information, were obtained from medical records. Histopathological findings, including tumor histology, stage, tumor diameter (TD), depth of myometrial invasion (MI), lymphovascular space invasion (LVSI), cervical stromal invasion, pelvic (P) and/or para-aortic (PA) metastasis, extrauterine spread and the size of metastatic tumors were retrieved from pathology reports. All of the pathology slides were reviewed by experienced gynecologic pathologists.

Surgery:
All patients underwent a staging laparotomy and debulking surgery. Fluid from either peritoneal washing or ascites was obtained during surgery for cytological analysis. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO), was performed in all cases. The peritoneal implants were resected in some eligible cases by stripping abdominal, and/or diaphragmatic peritoneum. The decision to perform a systematic P and PA lymphadenectomy was made at the surgeon's discretion (no lymph node sampling, only pelvic node sampling, pelvic and paraaortic sampling and systematic lymph node dissection). Disease stage was determined postoperatively based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system.

Clinical follow-up:
The patients returned for follow-up visits for every 3 months for the first 2 years, every 6 months for the next 2 years, and annually thereafter until 10 years of disease free survival. Follow-up evaluations consisted of physical and vaginal examinations, vaginal cytology, ultrasound scan and assessment of serum CA 125 values. Computed tomography or magnetic resonance imaging was performed annually. Disease free survival (DFS) was defined as the time from the date of primary surgery to the detection of recurrence or the latest observation. Overall survival (OS) was defined to be the time interval from the date of surgery to death or to date of last contact.

Statistical Analysis
The normality of data was investigated with Kolmogorow- Smirnov test and Shapiro Wilk test. Continuous variables were compared with independent t test and Mann-Whitney-U test where suitable. Categorical variables were compared with chi-square test. Survival analysis was performed with Kaplan-Meier survival curve and Log-rank test for the comparison of survival between the groups. To detect independent hazard of the variables on overall survival a univariate and multivariate Cox regression analysis was performed. A p value <0,05 was regarded as statistically significant. All statistical analyzes were performed with SPSS version 17 software package (SPSS Inc., Chicago, IL, USA).

RESULTS
Two hundered and nine patients were in the advanced age group and 689 patients were in the younger age group. Outer ½ myometrial invasion, adjuvant radiotherapy, LVSI, tumor diameter was significantly higher in advanced age in low risk endometrial cancer patients. The comparison of advanced age and younger age in low risk patients is shown on Table I.

Adjuvant radiotherapy was significantly higher in advanced age and high risk patients. All the parameters was similar between advanced age and younger age groups in high risk endometrial cancer patients. The comparison of age groups in high risk patients is shown on Table II. Survival characteristics are shown on Table III. Both disease free survival and overall survival were higher in patients <65 years old for both high risk and low risk patients. Overall survival was also higher in patients <65 but disease free survival did not differ between the age groups in high risk patients. Survival graphics in whole group and patients with type I and II tumor are shown on Figure I and II. Age was independent risk factor both for low risk and high risk patients in multivariate analysis. Univariate and multivariate analysis are shown on table IV.

Table.I. Comparison of The Characteristics of patients ≥65 and <65 years of age

	<65 (n=689)	>65 (n=209)	p
Surgery type			0,137
TAH+BSO	91 (13,2)	23 (11)	
TAH+BSO+PLND	172 (25)	41 (19,6)	
TAH+BSO+PPLND	426 (61,8)	145 (69,4)	
FIGO stage			
I	579(84)	158 (75,6)	0,005
II	44 (6,4)	21 (10)	0,074
III / IV	66 (9,6)	30 (14,4)	0,050
Histologic type			<0,001
Type I	662 (96,1)	165 (78,9)	
Type II	38 (3,9)	44 (21,1)	
FIGO grade			
I	374 (54,3)	80 (38,3)	<0,001
II	238 (34,5)	67 (32,1)	0,506
III	77 (11,2)	62 (29,7)	<0,001
Cervical involvement			0,002
No	605 (87,8)	166 (79,4)	
Yes	84 (12,2)	43 (20,6)	
Depth of invasion			<0,001
Inner 1/2	445 (64,6)	81 (38,8)	
Outer 1/2	244 (35,4)	128 (61,2)	
Tumor diameter			
≤2 cm	272 (39,5)	58 (27,8)	
>2 cm	417 (60,5)	151 (72,2)	0,002
LVI			<0,001
No	569 (82,6)	140 (67)	
Yes	120 (17,4)	69 (33)	
Lymph node involvement			0,159
No	629 (91,3)	184 (88)	
Yes	60 (8,7)	25 (12)	
Radiation therapy			0,004
No	294 (42,7)	66 (31,6)	
Yes	395 (57,3)	143 (68,4)	
Chemotherapy			0,001
No	610 (88,5)	166 (79,4)	
Yes	79 (11,5)	43 (20,6)	
Relaps	28 (4,1)	17 (8,1)	0,018

TAH: Total Abdominal Hysterectomy, BSO: Bilateral Salpingooferectomy, PLND: Pelvic lymph node disection, PPLND: Pelvic and paraaortic lymph node disection, LVI: Lymphovascular invasion

Table II. Comparison of The Characteristics of Low Risk Patients ≥65 and <65 years of age

	<65 (n=612)	>65 (n=147)	p
Surgery type			0,350
TAH+BSO	87 (14,2)	17 (11,6)	
TAH+BSO+PLND	165 (27)	34 (23,1)	
TAH+BSO+PPLND	360 (58,8)	96 (65,3)	
FIGO Stage			
I	538 (87,9)	123 (83,7)	0,169
II	36 (5,9)	14 (9,5)	0,110
III / IV	38 (6,2)	10 (6,8)	0,791
FIGO grade			0,137
I	374 (82,4)	80 (54,4)	
II	238 (38,9)	67 (45,6)	
Cervical involvement			0,079
No	558 (91,2)	127 (86,4)	
Yes	54 (8,8)	20 (13,6)	
Depth of invasion			<0,001
Inner 1/2	423 (69,1)	66 (44,9)	
Outer 1/2	189 (30,9)	81 (55,1)	
Tumor diameter			0,004
≤2 cm	259 (42,3)	43 (29,3)	
>2 cm	353 (57,7)	104 (70,7)	
LVSI			0,038
No	539 (88,1)	120 (81,6)	
Yes	73 (11,9)	27 (18,4)	
Lymph node involvement			0,791
No	574 (93,8)	137 (93,2)	
Yes	38 (6,2)	10 (6,8)	
Radiation therapy			0,029
No	290 (47,4)	55 (37,4)	
Yes	322 (52,6)	92 (62,6)	
Chemotherapy			0,907
No	572 (93,5)	137 (93,2)	
Yes	40 (6,5)	10 (6,8)	

TAH: Total Abdominal Hysterectomy, BSO: Bilateral Salpingooferectomy, PLND: Pelvic lymph node disection, PPLND: Pelvic and paraaortic lymph node disection, LVI: Lymphovascular invasion

Table III. Comparison of The Characteristics of High Risk Patients ≥65 and <65 years of age

	<65 (n=77)	>65 (n=62)	p
Surgery type			
TAH+BSO	4 (5,2)	6 (9,7)	
TAH+BSO+PLND	7 (9,1)	7 (11,3)	
TAH+BSO+PPLND	66 (85,7)	49 (79)	0,255
FIGO stage			
I	41 (53,2)	27 (43,5)	0,706
II	8 (10,4)	7 (11,3)	0,865
III / IV	28 (36,4)	20 (32,3)	0,613
Cervical involvement			
No	47 (61)	39 (62,9)	
Yes	30 (39)	23 (37,1)	0,822
Depth of invasion			
Inner 1/2	22 (28,6)	15 (24,2)	
Outer 1/2	55 (71,4)	47 (75,8)	0,865
Tumor diameter			
≤2 cm	13 (16,9)	15 (24,2)	
>2 cm	64 (83,1)	47 (75,8)	0,285
LVI			
No	30 (39)	20 (32,3)	
Yes	47 (61)	42 (67,7)	0413
Lymph node involvement			
No	55 (71,4)	47 (75,8)	
Yes	22 (28,6)	15 (24,2)	0,562
Radiation therapy			
No	4 (5,2)	11 (17,7)	
Yes	73 (94,8)	51 (82,3)	0,026
Chemotherapy			
No	38 (49,4)	29 (46,8)	
Yes	39 (50,6)	33 (53,2)	0,762

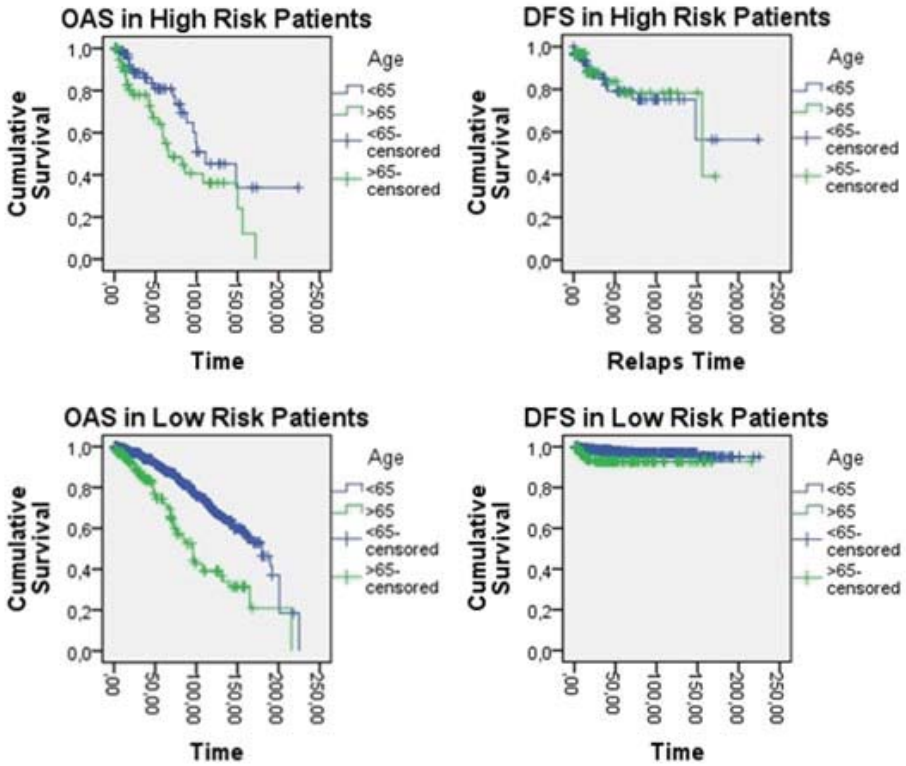
TAH: Total Abdominal Hysterectomy, BSO: Bilateral Salpingooferectomy, PLND: Pelvic lymph node disection, PPLND: Pelvic and paraaortic lymph node disection, LVI: Lymphovascular invasion

Table IV. Comparison Of Survival Characteristics

	<65 Years Old		≥65 Years Old		Log Rank p value
All Patients	Survival Ratio	M±SD	Survival Ratio	M±SD	
OAS	79	153±4	60	101±4	<0,001
DFS	95	212±2	91	189±7	0,004
Low Risk Group					
OAS	80	154±4	61	109±8	<0,001
DFS	97	217±2	93	201±4	0,01
High Risk Group					
OAS	75	130±14	56	87±10	0,02
DFS	83	161±16	87	134±11	0,85

OAS: Overall survival, DFS: Disease Free Survival, M±SD:Mean±standart deviation

Figure I. Overall and Disease Free Survival in High Risk and Low Risk Endometrial Cancer Patients



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DISCUSSION

We conducted this retrospective study of 898 women diagnosed with endometrial cancer and treated over an 19-year period. To our knowledge, this study represents one of the largest single-center series of patients with type 1 and 2 endometrial cancer to be reported in the literature.

Endometrial cancer in elderly women was reported to be more aggressive notably in all stages and histologies compared to youngers [14]. In the current study when we consider whole 898 patient, FIGO stage, tumor grade, cervical involvement, depth of invasion, tumor diameter, lymphovascular invasion, and adjuvant need for radiotherapy and chemotherapy were higher in elderly patients. Alhili et. al. also compared to the patients below and above 70 years of age and found significant differences between the groups in terms of perioperative morbidity, grade and stage of tumor, myometrial invasion and need for adjuvant therapy. Gayar et. al reported that elderly patients were found to have higher FIGO stages, grade of tumor and more frequently deeper myometrial invasion. But no significant difference was reported with respect to lymphovascular space invasion, number of lymph node dissected and adjuvant RT received [12]. In our study, there was no difference in numbers of lymph node dissected between age groups but radiotherapy and LVSI was higher in older patients compared to younger counterparts.

Park et. al. reported that patients over 65 years of age had significantly more serious and clear cell histology that was related to poorer prognosis[15]. Similarly in our study type II histologic type was more prevalent in older patients than youngers. Lachance et. al. also investigated the effect of age on endometrial cancer and found significant difference in terms of stage, grade, histologic type and perioperative morbidity in favor of elderly patients[16]. So these worse outcomes may be due to higher incidence of worse histologic subtypes among older patients. Our aim in this study is to investigate if age is still a prognostic factor when we consider the patients in different histologic types. To determine the effect of age on histologic subtypes we divided the patients according to histologic subtypes and compared each histologic subtype below and over 65 years.

Type I histology which is endometrioid adenocancer grade 1-2, is regarded to have better outcomes in endometrial carcinomas. Comparison of the patients with histologic subtype I according to age revealed bigger tumor diameter, more LVSI, depth of myometrial invasion and need for radiotherapy in elderly patients. But tumor grade, stage, number of lymph nodes dissected, lymph node metastasis and need for adjuvant chemotherapy were similar in older and younger patients with type I histologic subtype. Reason for more adjuvant radiotherapy treatment in similar tumor grade and stage is related with more LVSI and myometrial invasion seen in elderly patients. Also lower disease free survival in elderly patients with type I histology suggested a negative effect of age on patients with histologic type I tumor.

Surprisingly, there were no difference between older and younger patients with type II histology in comparison of operation time, hospitalization time, myometrial invasion, tumor diameter, LVSI, lymph node involvements and need for adjuvant chemotherapy. Only number of lymph nodes dissected was higher in youngers and need for adjuvant radiotherapy was higher in younger patients with type II histologic subtype.

Longer operation and hospitalization time was found in elderly patients in the whole group. Similarly De Marzi et al found longer hospital stay in older surgically treated endometrial cancer patients [17]. But when we look at specificly in type II high risk patients histology patients who had worse prognosis overall, there were no difference in operation time and hospital stay between elderly and younger counterparts, this is a new finding that there are no publications in this scope.

As seen above in the results section, worse pathologic characteristics in older patients with type I tumor and similar pathologic characteristics in older patients with type II histology that the effect of age may be more on low risk patients rather than high risk patients for tumor characteristics. Older patients have higher risk features higher adjuvant radiotherapy and chemotherapy are expected outcome as we reported in this paper. Type 1 and type 2 tumors show different outcomes in terms of

radiotherapy and chemotherapy. Higher radiotherapy rate was seen in women with older low risk patients in contrast the rate was higher in high risk younger patients. Hain et al found that older women were less likely to be treated with surgery, chemotherapy or radiation. This finding is totally inverse with our results and may be attributable to the cut off value for age is 75 in their study instead of 65 in our study [18]. Another study that have similar number of patients and age cut off that Alhili et al. also found no difference between older and younger women in terms of radiotherapy and chemotherapy [19]. So our finding that higher radiotherapy and higher chemotherapy rates differ from the literature.

Better survival outcomes seen in younger patients made us ask if older age had a negative effect on survival. Both in high and low risk patients older age was found to have a negative effect on overall survival. Alhili et. al reported that progression free survival was independent of age. [19] On the other hand, advanced age was reported to be a poor prognostic factor for survival characteristic for patients with endometrial carcinoma. Similarly age was reported to be an independent prognostic factor for survival in women with Type II endometrial carcinomas[20]. Our study supported this finding. Furthermore in both high risk and low risk group, older age was significantly associated with lower survival outcomes as an independent risk factor as seen in multivariate analysis.(Table IV).

The limitations of this study are its retrospective nature. Retrospective cohort studies are subjected to selection bias, recall bias, and unknown confounding variables, which may negatively impact the accuracy of the results. Moreover, during the 19-year study period, significant improvements in surgical techniques and adjuvant treatment may have also affected the results. Lastly, the data did not allow definitive and comparative analyses assessing the heterogeneity of the different adjuvant therapy regimens. Despite these limitations, a large number of patients with similar demographic characteristics were included in this study, and good follow-up data were available. Additionally, the surgeries were performed at a single institution, and the pathological slides were reviewed by experienced gynecologic pathologists. All of these factors most likely increased the validity of the results and mitigated the limitations.

CONCLUSION: Our study suggested that older age was a poor prognostic factor both for low risk and high risk endometrial cancer patients.

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