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Original Article

Prognostic role of hormone status in endometrium cancer

Endometrium kanserinde hormon reseptörlerinin prognostik önemi

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ABSTRACT

Aim: Endometrial carcinoma (EC) is the most common female reproductive system cancer in Europe and fifth leading reason of death in female cancer in worldwide. Hormone receptors are the main modulator of endometrium functions. Aim of present study was to evaluate prognostic indicator Estrogen receptors (ER) and progesterone receptor (PR) in patients at FIGO stage 3 EC.

Material and Methods: This study was designed as retrospective one institution analysis. ER status and PR status was enrolled from medical records of patients. Primary endpoint of this study was effect of hormone status to the disease-free survival (DFS) and overall survival (OS).

Results: Present study enrolled 133 patients from January 2015 to October 2021. ER and hormone positivity were statistically significant in OS analysis (HR: 1.40 p:0.005 and HR:2.173 p: 0.047). PR status was significant statistically in DFS but insignificant in OS survival analysis (HR: 1.80 p:0.09 and HR: 1.72, p: 0.062 respectively). The median DFS and OS were 58 months (51-64) and 129 months (88-169) patients with ER positive tumor respectively (p<0.0001), whereas 19 months (17-20) and 28 months (23-32) patients with ER negative tumor (p<0.000).

Conclusion: ER positivity was with better DFS and OS and was significantly good prognostic indicator in patients with FIGO stage 3. ER positivity may be used to stratify patients in FIGO stage 3 and close follow-up may be needed in patients in ER negative.

Keywords: Endometrial carcinoma, estrogen receptors, progesterone receptor, FIGO stage 3

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Öz

Amaç: Endometrium kanseri (EK) kadın üreme sisteminde Avrupa'da en sık beşinci sırada yer alan ve ölüme sebep olan kanserdir. Hormon reseptörleri (HR) endometrium fizyolojisinde ana modülatörlerindendir. Bu çalışmanın amacı Östrojen reseptörü (ÖR) ve progesterone reseptörünün (PR) opera olan FIGO ever 3 EK olgularında prognostik önemini belirlemektir.

Gereç ve Yöntemler: Bu çalışma tek merkezli retrospektif bir çalışma olarak tasarlandı. ÖR ve PR durumları hasta kayıtlarından incelendi. Çalışmanın birinci sonlanım noktası hormon reseptör durumlarının hastalıksız sağ kalım (HSK) ve genel sağ kalım (GSK) olan etkilerini incelemekti.

Bulgular: Mevcut çalışmada Ocak 2015 ile Ekim 2021 arasında 113 hasta tarandı. ÖR pozitifliği GSK analizi arasında istatistiki bir anlamlılık görüldü. (HR: 1.40 p:0.005 ve HR:2.173 p: 0.047). PR pozitiflik durumu HSK için anlamlı iken GSK arasında istatistiki bir anlamlılığa ulaşamadı. (HR: 1.80 p:0.09 ve HR: 1.72, p: 0.062 sırasıyla). ÖR pozitif hastalarında ortanca HSK ve GSK sırasıyla 58 ay (51-64) ve 129 ay (88-169) olarak görülürken (p<0.0001), ÖR negatif hastalarda sırasıyla 19 ay (17-20) ve 28 ay (23-32) olarak gözlemlendi (p<0.000).

Sonuç: ÖR pozitif FIGO evre 3 hastaların hem HSK hem de GSK'ları daha iyi olması ÖR' nün iyi bir prognostik gösterge olduğunu göstermektedir. FIGO evre 3'teki hastaları sınıflandırmak için ÖR pozitifliği kullanılabilir ve ÖR negatif olan hastalarda yakın takip gerekebilir.

Anahtar Kelimeler: Endometrium kanseri, östrojen reseptörü, progesteron reseptörü, FIGO evre 3, hastalıksız sağ kalım, genel sağ kalım

Introduction

Endometrial carcinoma (EC) is the most common female reproductive system cancer in Europe and fifth leading reason of death in female cancer in worldwide (1). EC consists of two major histological type, endometrioid endometrial cancer and non-endometrioid endometrial cancer. Endometrium cancer is %90 of all types(2). EC mostly diagnosed at early stages however main problem is average 20% of patients' relapses(3). Especially in International Federation of Gynecology and Obstetrics (FIGO) stage 3 an increase of relapses with 5 years is nearly 40% to 70% (4). In metastatic stages expected overall survival is about 12 months therefore predictive and prognostic indicators are important to evaluate the disease especially to follow-up in the beginning of treatment (5).

Hormone receptors are the main modulator of endometrium functions. Estrogen receptors (ER) activate endometrium proliferation whereas progesterone receptor (PR) inhibits and balance proliferation of endometrium(6). Disarrangement of balance of hormone receptors might cause several types of malignancies. These malignancies might be in uterus or other part of body such as, endometrium cancers, over cancers, prostate cancers, or breast cancers (7-9).

ER and PR positivity are with increased survival rates in EC in many studies due to higher respond rates hormone therapies are choice of treatment in metastatic lines (10, 11). However, some outcomes of trials showed insignificant results with hormone positivity in EC(12, 13). Therefore, results are conflicting, and the possible predictive role of ER and PR is still undefined in EC.

Aim of present study was to evaluate prognostic indicator of ER and PR in patients at FIGO stage 3 EC that underwent optimal surgical operations and received adjuvant therapies.

Material and Methods

Study population

This study was designed as retrospective one institution analysis. Patients diagnosed as EC from January 2015 to October 2021 were enrolled the study. Depending on medical records of patients diagnosed EC, underwent optimal surgical operation, staged as FIGO 3 were included. Patients <18 years old, diagnosed non-adenocarcinoma histology, had metastatic disease, not optimally surgical resected and had secondary malignancies were excluded. Age, body mass index (BMI), estrogen receptor (ER) status, progesterone receptor (PR) status was enrolled from medical records of patients. Primary endpoint of this study was effect of hormone status to the disease-free survival (DFS) and overall survival (OS).

The ethics committee of Institutional Review Board of Medeniyet University approved this study (reference ID: 2021/0047).

Treatment procedure

All patients diagnosed endometrial adenocarcinoma and underwent optimal surgical resection; total abdominal hysterectomy, bilateral salpingo-oophorectomy, and selective bilateral pelvic and para-aortic lymphadenectomy. After surgical

procedures all patients received adjuvant treatment including adjuvant chemotherapy and radiotherapy as guidelines recommended. Adjuvant chemotherapy was carboplatin AUC (4-5) plus paclitaxel (175mg/m2) for six-four cycles at three-week intervals and adjuvant radiotherapy dose was 25.5 Gy for whole abdomen, 45 Gy for whole pelvis and 45 Gy for extended field.

Statistical analysis

Quantitative variables were performed by Mann-Whitney U test and qualitative variables were by chi square analysis. Survival curves were calculated using the Kaplan-Meier method and analyzed with the log-rank test. Disease Free Survival (DFS) was defined from the date of EC diagnosis to the time of proven recurrence. Overall Survival (OS) was determined from the date of diagnosis until the last follow-up or death. Univariate and multivariate Cox regression analyses were used to examine independent factors for determining DFS and OS. Confidence interval was accepted as, 95%and significant differences were considered significant when p was less than 0.05. All statistical analyses were performed with SPSS statistical software (version 24.0, SPSS Inc., Chicago, IL).

Results

Patient characteristics

Present study enrolled 133 patients from January 2015 to October 2021 with median age of 57 (26–84). Median BMI is 27.3 (14.5–40.4). Eighty-four (63.2%) patients were with ER positive and forty-nine (36.8%) were negative. Fifty-eight (43.6%) patients' tumors were PR negative whereas seventy-five had (56.4%) positive. In the evaluation of both hormone receptors (ER and/or PR), the number of patients who were positive was eighty-six (64.7%) and negative was forty-seven (35.3%). Cycles of adjuvant chemotherapy was 6 (3-8). All patients received adjuvant radiotherapy without any interruption. Characteristics of patients included study were detailed in Table 1.

Table.1 Patient's characteristics	
Median Age	57 (26–84)
BMI	27.3 (14.5–40.4)
ER Negative Positive	49 (36.8%) 84(63.2%)
PR Negative Positive	58 (43.6%) 75 (56.4%)
Hormone Positive (ER and/or PR) Negative Positive	47 (35.3%) 86 (64.7%)
Cycles of treatment (n)	6 (3–8)

Univariate and Multivariate and Survival Analysis

In univariate analysis of study, age at diagnosis, BMI, ER, PR and hormone status were significant parameters for both DFS and OS. All parameters were statistical significance. Only number of cycles of treatment was not significant for DFS and OS (p:0.949 and p:0.975 respectively). All parameters summarized in Table 2. Multivariate analysis showed ER, PR and hormone receptor positivity (ER and/or PR) found to be independent risk factor for DFS (HR: 0.003p:0.009, HR: 1.80 p:0.09 and HR:0.232 p: 0.05, respectively). However, ER and hormone positivity were statistically significant in OS analysis (HR: 1.40 p:0.005 and HR:2.173 p: 0.047). PR status was insignificant statistically in both DFS and OS survival analysis (HR: 1.80 p:0.09 and HR: 1.72, p: 0.062 respectively); detailed in Table 3.

Table 2: Univariate Analysis for PFS and OS

	PFS			OS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at diagnosis	0.042	0.047–0.853	0.007	0.002	0.190–0.939	0.016
BMI	0.054	0.117–1.912	0.016	0.062	0.074–1.33	0.047
ER	0.055	0.050–0.076	0.000	0.002	0.935–1.013	0.000
PR	0.034	0.092–1.077	0.000	0.038	0.929–1.058	0.000
Hormone Positive (ER and/or PR)	0.015	0.075–2.102	0.000	0.029	0.077–0104	0.000
Cycles of treatment (n)	0.206	0.006-2.065	0.949	0.162	0.094-1.112	0.975

Table3: Multivariate analysis of PFS and OS

	PFS			OS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at diagnosis	0.980	0.947–1.013	0.229	1.026	0.993-1.061	0.123
BMI	2.149	0.857–5.390	0.103	0.274	0.142–0.527	0.399
ER	0.003	0.006-1.042	0.009	1.40	0.147-0.876	0.005
PR	1.80	0.07-3.159	0.09	1.72	0.91-3.57	0.062
Hormone Positive (ER and/or PR)	0.232	0.041-1.052	0.05	2.173	0.996-4.706	0.047

The median DFS and OS were 58 months (51-64) and 129 months (88-169) patients with ER positive tumor respectively (p<0.0001), whereas 19 months (17-20) and 28 months (23-32) patients with ER negative tumor (p<0.000) (Figure 1 and Figure 2). ER status found to be positive factor for survival analysis with statistically significance.

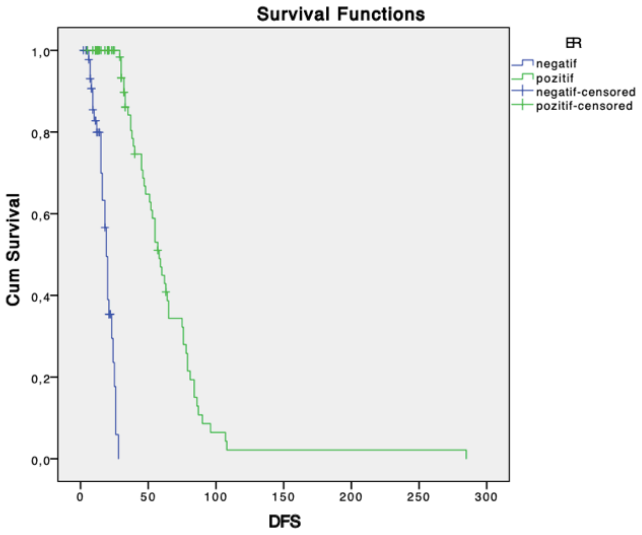

Figure 1: Kaplan–Meier curve of disease free survival patients with ER positive

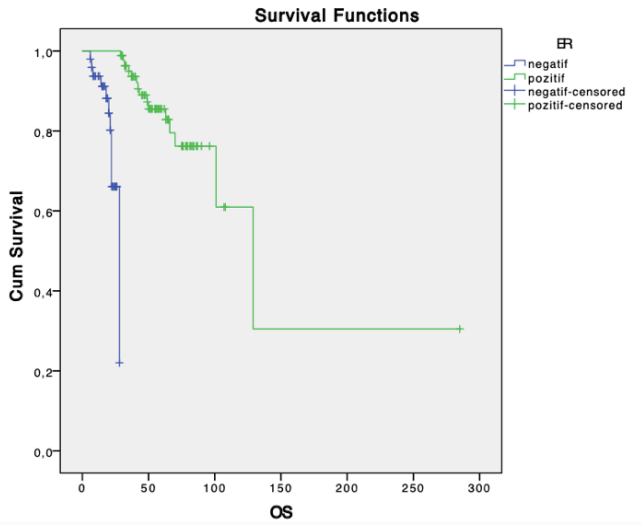

Figure 2: Kaplan–Meier curve of overall survival patients with ER positive

Discussion

Present study showed that hormone positivity especially ER positive status is independent good prognostic factor in FIGO stage 3 EC. Patients with ER positive tumors, had extended disease free survival and overall survival time. PR positivity had good responses in univariate analysis whereas multivariate analysis results did not reach significance (p:0.062). Hormone positivity tumors were (ER and/or PR) also with better survival rates and found to be good prognostic factor with statistically significance (p:0.047).

ER and PR are nuclear receptors that effect on endometrium in all cycles of menstrual cycle. ER controls estrogen, that is affecting on endometrium proliferation(14). In the middle of cycle PR controls progesterone and inhibits the action of estrogen and difference the endometrium for implantation. If estrogen is not balanced with progesterone than hyperplasia and in the continuation, carcinogenesis starts (6). Importance of hormone receptors were investigated in many studies, especially early stages of EC. Gehrig PA. et al (15) studied predictor value of ER in FIGO stage 1 EC. Patients with ER negative had increased recurrence and worse survival rates (p< 0.05) , so that ER negativity was defined as independent risk factor for EC in FIGO stage 1. Suthipintawong C. et al. (16) investigated prognostic role of ER in 65 cases and followed up 60 months. ER was positive 76.9% of patients and had lower grade and low stage at diagnosis. At the follow up patients had lower recurrence rates especially in early stages and ER positivity found to be prognostic indicator in EC. Similarly, Guan J. and colleagues (17) observed both ER and PR importance in early grade of EC in 903 patients independent of FIGO stages. Patients with ER positive at diagnosis found earlier stages and lower grades. ER negativity resulted shorter DFS and OS in FIGO stage 2-4 and ER positivity was defined as good prognostic factor for EC in grade 1 and 2 in all FIGO stages. Present study focused on patients with FIGO stage 3 and searched ER and PR positive status as prognostic value in EC. In univariate analysis ER, PR and HR positivity was correlated with extended survival rate whereas in multivariate analysis ER and HR were found to be independent prognostic indicators for both DFS and OS (p: 0.005, p: 0.047 respectively).

Klein W. et. al (18) investigated prognostic factor of ER and PR in 309 operated EC in all stages. Patients diagnosed as FIGO stage 1 with ER and PR positive were better survival data tan negative group whereas in FIGO stage 2-4 only PR was demonstrated positive survival affect, ER was resulted insignificant in multivariate analysis. But in this analysis authors mentioned about ER subunits might affect this uncorrelations. Gonzalez-Rodilla I. et al. (19) studied e-cadherin as prognostic marker in EC. The found e-cadherin as strong prognostic marker in all FIGO stages correlated with ER but PR was not correlated in FIGO stage 3 and 4. These results were similar to our study, we found ER as a prognostic indicator in FIGO stage 3 but PR could not reach significance. Voss M.A. and colleagues

(13) studied CD151 as predictive and prognostic in all FIGO stages in EC. In multivariate analysis patients with CD151 was effective in survival bur ER, PR were not prognostic for survival. Our study differently demonstrated ER as prognostic novel for survival in multivariate analysis whereas PR was not statistically significance. Bu this study contained all types of EC, endometrioid endometrial cancer and non-endometrioid endometrial cancer. In sub-analysis patients with endometroid adenocarcinoma in FIGO stage 3 and 4, ER positivity was good prognostic value similarly to present study.

Present study had some limitations. Firstly, this study was designed as retrospectively with small number. Although, operations were defined as optimal surgical procedures and no residual disease was seen, operations were not performed from same surgent.

Conclusion

Based the results of present study, ER positivity was with better DFS and OS and was significantly good prognostic indicator in patients with FIGO stage 3. ER positivity may be used to stratify patients in FIGO stage 3 and close follow-up may be needed in patients in ER negative.

Ethics approval

This study was approved by the local ethics committee of Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (approval number: 49109414-604.02).

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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