Original Article

The Prognostic Factors in Endometrial Cancers Treated with Radiotherapy: Retrospective Analysis

Radyoterapi Uygulanan Endometriyal Kanserlerinde Prognostik Faktörler: Retrospektif Analiz

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ABSTRACT

Introduction: Endometrial cancer is mostly diagnosed in the early stages and has a good prognosis. Surgery has main role in the treatment of patients with endometrial cancer and adjuvant radiotherapy (RT) is administered in certain risk groups. In this retrospective study, we analyzed the factors affecting the prognosis of patients with endometrial cancer who underwent RT.

Materials and methods: A total of 181 patients who were diagnosed with endometrial cancer were included in the study. Based on the prognostic factors, risk groups were recorded as low, intermediate, high-intermediate, high risk, and advanced/metastatic. Patients' overall survival (OS) was calculated using Kaplan– Meier method.

Results: Median age was 60 years (range, 28–82). The number of patients who received adjuvant RT alone, RT and chemotherapy, and chemotherapy alone were 77 (42.5%), 65 (36%), and 39 (21.5%), respectively. Median OS was 12.4 years (range, 0.1-21). Except for the advanced/metastatic risk group, OS was better in all the other risk groups who received RT alone ($p<0.001$).

Discussion: Risk groups (based on prognostic risk factors), p53, and treatment applied (RT alone) are the significant prognostic indicators for patients received adjuvant therapy in endometrial cancer. Adding adjuvant chemotherapy to RT adversely affects the prognosis.

Keywords: Chemotherapy, endometrial cancer, prognosis, radiotherapy

ÖZET

Giriş: Endometriyal kanser çoğunlukla erken evrelerde teşhis edilir ve iyi bir prognoza sahiptir. Endometriyal kanserli hastaların tedavisinde cerrahi tedavi temeldir ve belirli risk gruplarında adjuvan radyoterapi (RT) uygulanmaktadır. Bu retrospektif çalışmada, RT uygulanan endometriyal kanserli hastalada prognozu etkileyen faktörler inceledi.

Gereç ve yöntemler: Çalışmaya endometriyal kanser tanısı almış toplam 181 hasta dahil edildi. Prognostik faktörlere göre risk grupları düşük, orta, yüksek-orta, yüksek riskli ve ileri/metastatik olarak kaydedildi. Hastaların genel sağkalımı (GS), Kaplan-Meier yöntemi kullanılarak hesaplandı.

Bulgular: Ortanca yaş 60'tı (28-82). Tek başına adjuvan RT, RT ve kemoterapi ve tek başına kemoterapi alan hasta sayısı sırasıyla 77 (%42,5), 65 (%36) ve 39 (%21,5) idi. Ortanca GS 12.4 yıldı (0.1-21). İleri/metastatik risk grubu dışında diğer tüm risk gruplarında, tek başına RT alan hastalarda GS daha iyi bulundu ($p<0.001$).

Tartışma: Endometriyal kanserli hastalarda adjuvan tedavi alanlarda; risk grupları (prognostik risk faktörlerine göre), p53 ve uygulanan tedavi (yalnız RT) önemli prognostik göstergelerdir. RT'ye adjuvan kemoterapi eklenmesi prognozu olumsuz etkilemektedir.

Anahtar kelimeler: Endometriyal kanser, kemoterapi, prognoz, radyoterapi

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Introduction

Endometrial cancer is the most common gynecological cancer among women living in developed countries [1]. Most of the endometrial cancer patients are post-menopausal at the time of diagnosis, while the rate of disease in premenopausal period is only 25% [2]. Majority of the patients present with early-stage according to International Federation of Gynecology and Obstetrics (FIGO) at the time of diagnosis and survival time has been reported approximately 90% in these patients due to favorable prognosis [3]. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) (including regional lymph node dissection or not) is the definitive management for early-stage endometrial cancer, but not for locally advanced or metastatic disease.

Numerous previous studies have identified the important prognostic factors in endometrial carcinoma. These are tumor stage, patient age, histological type, tumor grade, deep myometrial invasion, and lymphovascular invasion [4,5]. Additionally, prognostic effects of p53 and ki67 on endometrial cancer have been shown by certain studies, however, it has not been established clear enough yet. [6,7]. Risk groups that have different prognoses have been identified based on the prognostic factors and adjuvant management is set according to this classification [4,5,8].

Adjuvant management of endometrial cancer includes radiotherapy (RT), chemotherapy and/or hormonal therapy in patients who have certain risk factors [9]. RT plays a significant role in the treatment of endometrial cancer and commonly administered in postoperative setting; however, definitive RT may be considered for patients who are medically inoperable or in case of local recurrence. Treatment decision with adjuvant RT is related to certain risk factors, such as higher tumor grade, deep myometrium invasion, and lymphovascular invasion [9]. In this retrospective study, we analyzed the risk factors affecting the prognosis of patients with endometrial cancer who received adjuvant therapy.

Patients and Methods

A total of 203 patients who were diagnosed with endometrial cancer and referred to the Department of Radiation Oncology between January 2010 and January 2020 were included in the retrospective study. Twenty-one patients were excluded from the study because of unavailable medical records. The study was approved by the local ethics committee (Date: 15.11.2022, Decision Number: 2022/289502) and conducted by principles of the Helsinki Declaration 2013.

Surgical procedure was TAH+BSO with or without pelvic and paraaortic lymph-adenectomy. Histopathology of the tumor, FIGO stage (2009), lymph node status, depth of myometrial invasion, tumor grade, lymphovascular invasion and metastatic sites were recorded. Risk groups according to these prognostic factors were recorded as in Table 1[8].

Percentage of cells presenting with positive nuclear staining was expressed as ki67 and p53 scores. Ki67 positivity was defined as positive ki67 staining in >40% of tumor cells and p53 positivity was defined as positive p53 staining in >25% of tumor cells [10].

Number of patients treated with adjuvant and definitive RT were 77 (42.5%) and three (1.7%), respectively. Consecutive chemo-therapy was administered to 36% (n=65) of the patients who received adjuvant RT. Simultaneous chemoradiotherapy was administered to one patient. Thirty-nine patients (21.5%) received chemotherapy alone. Radiation fields en-compassed tumor bed and regional nodes with a treatment dose of 45-50.4 Gy in adjuvant setting. Total dose was 70-75 Gy with brachytherapy in patients who underwent definitive treatment.

Table 1 Risk groups of endometrial carcinoma

Risk group	ESMO-ESGO-ESTRO consensus
Low risk	Endometrioid endometrial cancer, grade 1–2, <50% myometrial invasion, without lymphovascular space invasion
Low- intermediate risk	Endometrioid endometrial cancer, grade 1–2, ≥50% myometrial invasion, without lymphovascular space invasion
High- intermediate risk	Endometrioid endometrial cancer, grade 3, <50% myometrial invasion, any lymphovascular space invasion Endometrioid endometrial cancer, grade 1–2, with unequivocally lymphovascular space invasion, any myometrial invasion
High risk	Endometrioid endometrial cancer, grade 3, ≥50% myometrial invasion, any lymphovascular space invasion Stage II–III endometrioid endometrial cancer, no residual disease Stage I-III non-endometrioid endometrial cancer (serous, clear cell, or undifferentiated carcinosarcoma)
Advanced/metastatic	Stage III with residual disease and, stage IVa Stage IVb

ESGO, European Society of Gynecological Oncology
ESMO, European Society for Medical Oncology
ESTRO, European Society for Radiation Oncology

Overall survival (OS) was defined as the period (years) from the time of the patient's diagnosis until the last visit or death.

Statistical analysis

Statistical analyses were done using SPSS (Statistical Package for Social Sciences) for Windows 23.0 IBM SPSS Statistics, New York, USA). P value less than 0.05 was defined statistically significant. Data measurements were represented by the mean, median and range. Categorical data were expressed as frequency and percentage, and chi-square test was used for comparison between groups. Patients' OS was determined using Kaplan– Meier method. Multivariate Cox regression model was used to determine the independent prognostic predictors of survival with the variables which were statistically significant by univariate Cox regression model.

Results

Median age was 60 years (range, 28–82). The predominant histologic subtype was endometrioid adenocarcinoma in 69.1% of the patients. Median tumor size was 4.5 cm (range, 0.3-16). Lymphovascular invasion was detected in 39.2% of the patients and hormone receptor was positive in 64.6%. Most of the patients were with high risk disease (42.5%). p53 and Ki67 positivity were 32.5% and 67.8%, respectively. The clinico-pathologic characteristics of the patients receiving adjuvant therapy are shown in Table 2.

Advanced age (over 70 years) was associated with deep myometrial invasion (17.9% vs. 6.8%), advanced stage (42.9% vs. 18%), and higher rates of grade 2 and 3 tumors (78.4% vs. 57.3%) ($p<0.04$).

Non-endometrioid histology was associated with deep myometrial invasion (48.1% vs. 31.1%), advanced stage (42.6% vs. 12.9%), grade 3 tumor (50% vs. 25.6%), p53 positivity (53.3% vs. 7.9%), and hormone receptor negativity (29.3% vs. 2.2%) ($p<0.04$).

In addition, deep myometrial invasion was associated with lymph node involvement (29.1% vs. 9.4%), lymphovascular space invasion (55.6% vs. 26.5%), advanced stage (65.7% vs. 31.4%) and grade 3 tumor (40.5% vs. 16.7%) ($p<0.03$).

Table 2 The clinicopathologic characteristics of the patients

Characteristic	All patient % (n)	RT alone % (n)	CT+RT % (n)	CT alone % (n)
Histologic type				
Endometroid	69.1 (125)	55.2 (69)	31.2 (39)	13.6 (17)
Papillary serous	10 (18)	5.6 (1)	55.6 (10)	38.9 (7)
Carcinosarcoma	6.6 (12)	16.7 (2)	25 (3)	58.3 (7)
ESS	6.6 (12)	16.7 (2)	41.7 (5)	41.7 (5)
Other types	7.7 (14)	21.4 (3)	57.1 (8)	21.4 (3)
T stage				
T1a	19.9 (36)	52.8 (19)	30.6 (11)	16.7 (6)
T1b	38.7 (70)	51.4 (36)	35.7 (25)	12.9 (9)
T2	22.1 (40)	50 (20)	42.5 (17)	7.5 (3)
T3	7.7 (14)	14.3 (2)	50 (7)	35.7 (5)
T4	8.8 (16)	-	25 (4)	75 (12)
Unknown	2.8 (5)			
FIGO stage				
I	56.4 (102)	54.9 (56)	34.3 (35)	10.8 (11)
II	20.4 (37)	48.6 (18)	43.2 (16)	8.1 (3)
III	9.4 (17)	17.6 (3)	47.1 (8)	35.3 (6)
IV	12.2 (22)	-	27.3 (6)	72.7 (16)
Unknown	1.7 (3)			
Tumor grade				
I	11 (20)	55 (11)	35 (7)	10 (2)
II	44.8 (81)	56.8 (46)	33.3 (27)	9.9 (8)
III	23.2 (42)	33.3 (14)	40.5 (17)	26.2 (11)
Unknown	21 (38)			
LVI				
Positive	39.2 (71)	38 (27)	43.7 (31)	18.3 (13)
Negative	47.5 (86)	50 (43)	31.4 (27)	18.6 (16)
Unknown	13.3 (24)			
LN metastasis				
Positive	22.1 (40)	2.5 (1)	65 (26)	32.5 (13)
Negative	60.2 (109)	56.9 (62)	26.6 (29)	16.5 (18)
Unknown	17.7 (32)			
Risk categories				
Low	11 (20)	65 (13)	25 (5)	10 (2)
Low-intermediate	13.8 (25)	68 (17)	20 (5)	12 (3)
High-intermediate	19.3 (35)	42.9 (15)	51.4 (18)	5.7 (2)
High	42.5 (77)	41.6 (32)	39 (30)	19.5 (15)
Advanced/metastatic	12.2 (22)	-	31.8 (7)	68.2 (15)

ESS, Endometrial stromal sarcoma; *LN*, Lymph node; *LVI,* Lymph-vascular invasion; *CT*, Chemotherapy; *RT*, Radiotherapy

Ki67 positivity was correlated with advanced stage, grade 3 tumor, hormone receptor negativity, lymph node involvement, and paraaortic metastasis ($p<0.04$), and p53 positivity was correlated with non-endometroid histology, hormone receptor negativity, and advanced stage ($p<0.02$).

Locoregional recurrence and/or distant metastasis occurred in 50 patients (27.6%). Lymphatic recurrences were seen in abdominal paraaortic, pelvic and mediastinal nodal regions in 12 (6.6%), 6 (3.3%) and seven patients (3.9%), respectively. Vaginal recurrence was seen in only three patients (1.7%).

Median OS was 12.4 years (range, 0.1-21), and 5- and 10-year survival rates were 70.5% and 56.8%, respectively. Patients with high and advanced/metastatic risk had shorter OS (Figure 1). Except for the advanced/metastatic risk group, survival was better in the all of the other risk groups who received RT alone (Table 3).

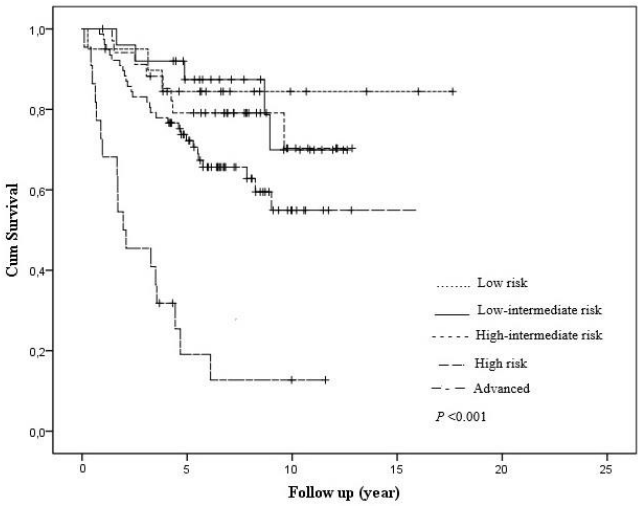

Figure 1. Overall survival by risk groups

Table 3. Median for Survival Time

				95% CI		
Risk group	Treatment	Time (year)	SE	Lower	Upper	*P value*
LIR	RT alone	16.5	1.5	13.3	19.8	0.004*
	RT-CT	9.5	1.7	6.1	12.5	
	CT	6.4	2.5	1.2	11.3	
HIR	RT alone	11.8	0.7	10.6	13.6	0.041*
	RT-CT	7.2	0.8	5.8	9.2	
	CT	5.6	1.3	3.4	7.8	
High risk	RT alone	12.5	0.4	10.8	13.2	0.042*
	RT-CT	6.7	0.7	5.7	8.4	
	CT	6.2	1.3	11.2	8.6	
Advanced	RT-CT	5	1.5	2	7.8	0.26
	CT	2.8	0.9	1.3	4.1	

HIR, High-intermediate risk; LIR, Low-intermediate risk; CT, Chemotherapy; RT, Radiotherapy; CI, Confidence interval; SE, Standard error
* P<0.05 was regarded statistically significant

Table 4 Cox regression analysis for prognosis

	Univariate			Multivariate		
Variable	HR	95%CI	P value	HR	95%CI	P Value
LNI (Yes vs No)	2.87	1.6-5.02	<0.001	0.77	0.39-1.49	0.44
Stage	1.97	1.6-2.4	<0.001	2.84	1.21-6.64	0.02*
PAND (Yes vs No)	2.14	1.25-3.65	0.006	0.54	0.12-2.49	0.43
PANM (Yes vs No)	2.6	1.3-5.2	0.007	1.07	0.20-5.70	0.94
Tumor size (≤4 cm vs >4 cm)	1.99	2.08-3.7	0.03	1.35	0.35-5.26	0.67
Age (≤70 vs >70)	1.05	1.02-1.08	0.04	0.65	0.10-4.25	0.66
P53 (≤25% vs >25%)	1.02	1.01-1.03	<0.001	0.16	0.05-0.53	0.003*
Ki67 (≤40% vs >40%)	3.18	1.44-7.02	0.004	0.41	0.08-1.95	0.26
Histology	1.3	1.12-1.5	0.001	0.84	0.44-1.62	0.60
Treatment	3.07	2.2-4.26	<0.001	4.39	1.65-11.70	0.003*
Risk groups	1.99	1.48-2.68	<0.001	0.29	0.11-0.79	0.02*

CI: Confidence interval; *HR*: Hazard Ratio; LNI, Lymph node involvement; PAND, Paraaortic node dissection; PANM, Paraaortic node metastasis
* *P<0.05* was regarded statistically significant

Prognosis was not found associated with lymphovascular space invasion (p= 0.08), extra-nodal spread (p= 0.6), and tumor grade (p= 0.2) by the univariate analysis. In the multivariate analysis, p53 (p= 0.003), tumor stage (p = 0.002), risk groups (p=0.02) and the treatment administered (adjuvant RT alone) (p<0.001) were significantly associated with prognosis. The results of univariate and multivariate analyses for prognosis are shown in Table 4.

Discussion

Endometrial cancer is predominantly diagnosed at earlier stages and has a good prognosis. Only 15–20% of the patients with endometrial cancer present with high-risk disease/distant metastases and poor prognosis. Surgery is the cornerstone of the endometrial cancer treatment and consists of TAH+BSO with or without pelvic and paraaortic lymphadenectomy [11]. Major factors affecting the prognosis of endometrial cancer have been established by previous studies and defined as age, tumor stage, histolopathology, tumor grade, deep myometrial invasion, and lymphovascular invasion [4,5]. After surgery, indications for adjuvant treatment are commonly related to these clinicopathological risk factors. In this study, factors affecting the prognosis of endometrial cancer were analyzed in patients received adjuvant therapy and it was found that tumor stage, and treatment applied (RT alone) were associated with prognosis in multivariate analysis.

Importance of RT in the adjuvant management of endometrial cancer was established by multiple studies. Recent studies have been concentrated upon the high-intermediate and high-risk diseases, whereas the adjuvant treatment in low-risk endometrial cancer is not indicated [8]. In our study, patients with high and high-intermediate risk diseases who received RT alone had a better prognosis than the patients who received chemotherapy with RT or chemotherapy alone. Addition of chemotherapy to RT also affected survival negatively in other risk groups except for the advanced/metastatic risk group.

The correlation between advanced age and poor prognosis is well established. The adverse impact of advanced age on worse progress of the disease is often explained by frequency of aggressive histology and advanced disease at diagnosis. Treatment with less aggressive regimens are another reason of the shorter survival in elderly patients [12]. In the present study, advanced stage, non-endometrioid histology and grade 2, 3 tumors were more frequent in patients over 70 years of age.

According to the FIGO annual report, serous and clear cell histologic types present with more advanced stages which explains the poorer survival in patients with non-endometrioid histology [13]. In our study, non-endometrioid histology was associated with higher rates of deep myometrial invasion and advanced stage resulting in shorter survival.

Myometrial invasion more than the half of the myometrial wall is defined as deep myometrial invasion which increases the risk of relapse and results in worse outcome [14]. In the present study, deep myometrial invasion was associated with non-endometrial types, advanced stage, lymphovascular invasion and higher grade. As a result, deep myometrial invasion and/or advanced stage were associated with poor survival.

Lymph node involvement has a potent impact on the outcome of the endometrial cancer which decreases the 5- year disease-free survival time to 65% to 70% alone. Presence of pelvic nodal metastases is an important indicator for the involvement of paraaortic nodes which decreases the 5-year disease-free survival rates to 30% [15]. In our study, whole patients with involved paraaortic nodes had

also involvement in pelvic nodes. However, prognosis was similar in patients who had only pelvic or pelvic plus paraaortic nodal involvements.

Increased ki67 or p53 expression in endometrial cancer was associated with more aggressive clinicopathological features and these markers were reported as indicators of poor prognosis [6,7]. In the present study, both markers were also associated with negative prognostic factors.

Prognosis of endometrial cancer is mainly affected by tumor grade which has a strong correlation with depth of myometrial invasion and metastasis to the lymph nodes. Grade 3 tumor for all stages has been reported to be an independent factor in predicting poor survival in the FIGO annual report [13]. Lympho-vascular invasion is also an important prognostic factor and indicates pelvic recurrence and distant metastasis which results in poor survival [16]. However, in our study, lymphovascular invasion and tumor grade was not associated with prognosis.

In univariate analysis, age, stage, histology, ki67, p53, pelvic or paraaortic nodal involvement, paraaortic lymphadenectomy, adjuvant RT alone, and risk groups were statistically associated with prognosis, however, only p53, stage, risk groups, and adjuvant RT alone were found statistically significant in multivariate analysis. Other prognostic factors, lymphovascular invasion and tumor grade, were not significantly associated with prognosis.

Conclusion

Tumor stage, p53, risk groups (based on prognostic risk factors), and RT alone are the most important prognostic indicators for patients received adjuvant therapy in the postoperative setting of endometrial cancer. Adding adjuvant chemotherapy to RT adversely affects the prognosis.

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