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Endometrial Kanserde Radyoterapinin Rolü

The Role of the Radiotherapy in Endometrial Cancer

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ÖZET

Endometriyal kanser, batı ülkelerinde en sık görülen jinekolojik kanserdir ve endometriyal kanser insidansı, artan mortalite oranlarıyla birlikte son birkaç on yılda artmıştır. Endometrial kanserli hastaların tedavisinde cerrahi tedavi baş rolü oynamakta ve bazı klinikopatolojik risk faktörlerinde adjuvan tedavi gerekmektedir. Bu çalışmada endometrial kanserli hastalarda risk gruplarına göre adjuvan radyoterapinin (RT) genel sağkalım (GSK) ve hastalıksız sağkalım (HSK) üzerine etkisi retrospektif olarak değerlendirildi. Çalışmaya endometriyal kanser tanısı almış toplam 512 hasta dahil edildi. Prognostik faktörlere göre risk grupları düşük, orta, yüksek-orta, yüksek riskli ve ileri/metastatik olarak kaydedildi. Hastaların GSK ve HSK'ı Kaplan-Meier yöntemi kullanılarak hesaplandı. Ortanca yaş 58'di (aralık, 28-82). Düşük risk grubu, düşük-orta risk, yüksek-orta risk, yüksek risk ve ileri risk grubuna sahip hasta sayısı sırasıyla 139 (%28), 84 (%16.9), 50 (%10.1), 182 (%36.6) ve 42 (%8.5) olarak bulundu. Medyan GSK ve HSK sırasıyla 14.1 yıl (0.1-20.7 aralığında) ve 1.3 yıl (0.7-11.2 aralığında) idi. İleri/metastatik risk grubu dışındaki tüm risk gruplarında tek başına RT alan hastalarda GSK ve HSK daha iyi bulundu ($p<0,001$). Günümüzde düşük riskli endometriyum kanseri olan hastalar için artık adjuvan tedavi önerilmemektedir. Yüksek riskli hastalarda adjuvan tedavi gerekli olmakla birlikte önceki çalışmaların aksine bu çalışmada adjuvan RT'ye kemoterapi eklenmesi prognozu kötü etkilemiştir.

Anahtar Kelimeler: Endometriyal kanser, prognoz, radyoterapi

ABSTRACT

Endometrial cancer is the most common gynecological cancer in western countries and endometrial cancer incidence has been increased in the last few decades with increased mortality rates. Surgery has main role in the treatment of patients with endometrial cancer and adjuvant management is required in certain clinicopathological risk factors. In this study, the effect of adjuvant radiation therapy (RT) on overall survival (OS) and disease-free survival (DFS) according to risk groups in patients with endometrial cancer was evaluated retrospectively. A total of 512 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' OS and DFS were calculated using Kaplan– Meier method. Median age was 58 years (range, 28–82). The number of patients who had low risk group, low-intermediate risk, high-intermediate risk, high-risk and advanced risk were 139 (28%), 84 (16.9%), 50 (10.1%), 182 (36.6%) and 42 (8.5%), respectively. Median OS and DFS were 14.1 years (range, 0.1-20.7) and 1.3 years (range, 0.7-11.2), respectively. OS and DFS were found to be better in patients who received RT alone in all

risk groups except the advanced/metastatic risk group ($p<0.001$). Currently, adjuvant therapy is no longer recommended for patients with low-risk endometrial cancer. Although adjuvant treatment is required in high- risk patients, in contrast to previous studies, the addition of chemotherapy to adjuvant RT, poor effect on prognosis in this study.

Keywords: Endometrial cancer, prognosis, radiotherapy

1. INTRODUCTION

Endometrial cancer is the most common gynecological cancer in western countries and fourth most common cancer among women. Endometrial cancer incidence has been increased in the last few decades with increased mortality rates (Raffone et al., 2019). The primary treatment of endometrial cancer is surgery, consisting of a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO) with or without pelvic and paraaortic lymphadenectomy. After surgery, additional treatment is indicated in presence of certain clinical and pathological factors, such as age, grade, histological type, tumor volume, tumor stage, depth of myometrial invasion, presence of lymphovascular space invasion and lower uterine segment or cervical glandular involvement. Risk groups (low, intermediate, high-intermediate, and high) are defined based on these prognostic factors and each group has different prognosis and treatment indication (Creutzberg et al., 2000; Keys et al., 2004; Colombo et al., 2016; Lybeert et al., 1998).

Radiotherapy (RT) plays a significant role in the adjuvant management of endometrial cancer; however, definitive RT may be considered only for patients who are medically inoperable or in case of local recurrence (Lybeert et al., 19985). Adjuvant management of endometrial cancer also includes chemotherapy and/or hormonal therapy.

Many studies have analyzed the role of RT in the adjuvant treatment of endometrial cancer. The prognosis is extremely good in low risk early stage disease, whereas the recurrence rate may vary among the risk groups. However, adjuvant RT in early stage disease is controversial due to treatment related side effects such as diarrhea and intestinal obstruction (Creutzberg et al., 2000; Keys et al., 2004). Therefore, in recent years, studies have focused on the utilization of adjuvant RT in high-intermediate risk and high-risk patients (Colombo et al., 2016). In this study, the effect of adjuvant RT on survival and disease-free survival (DFS) according to risk groups in patients with endometrial cancer was evaluated retrospectively.

2. MATERIAL AND METHOD

A total of 643 patients who were diagnosed with endometrial cancer and referred to the Oncology Hospital between January 2010 and January 2020 were included in the study. One hundred thirty-one patients were excluded from the study because of unavailable medical records. The retrospective study was approved by the local ethics board and conducted by principles of the Helsinki Declaration 2013.

Surgical procedure was TAH BSO with or without pelvic and paraaortic lymphadenectomy. Tumor histology, depth of myometrial invasion, FIGO stage (2009), grade, lymph node status, lymphovascular space invasion, and metastatic sites were recorded. Based on these prognostic factors, risk groups (Table 1) were recorded as low, intermediate, high-intermediate, high- risk, and advanced/metastatic (Colombo et al., 2016).

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	

While 112 (29.2%) patients did not receive adjuvant therapy, 108 (30.8%) patients received RT alone, 83 (26%) received RT and chemotherapy, and 51 (14%) received chemotherapy alone. Radiation fields encompassed tumor bed and regional nodes with a treatment dose of 45-50.4 Gy in adjuvant setting. In eligible patients, the total dose was completed to 70-75 Gy with brachytherapy. While the most commonly used adjuvant chemotherapy regimen was carboplatin/paclitaxel,

carboplatin/docetaxel was preferred in metastatic disease.

Overall survival (OS) was defined as the period (years) from the time of the diagnosis until the last visit or death. DFS was defined as the period (years) from the time of diagnosis until a local relapse or metastasis. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows 23.0 IBM SPSS Statistics, New York, USA). Frequency of distributions between subgroups for categorical variables were compared using $\chi 2$ test. Patients' OS and DFS were calculated using Kaplan– Meier method. Log-rank test was used to determine the significance of the differences in survival. The results were accepted statistically significant when p value was less than 0.05.

3. RESULTS AND DISCUSSION

Median age was 58 years (28–82). The predominant histologic subtype was endometrioid adenocarcinoma in 399 patients (77.9%). Median tumor size was 3.5 cm (0.3-16). Tumor grade was I and II in 347 patients (81.5%). Majority of the patients had stage I disease 337 (66.6%). Lymphovascular space invasion was detected in 140 patients (31%). Most of the patients were with high- risk disease (37%, n=185). The clinicopathologic characteristics of the patients are shown in Table 2.

Median OS and DFS were 14.1 years (range, 0.1-20.7) and 1.3 years (range, 0.7-11.2), respectively. During this period, recurrent disease developed in 87 patients (17%); the most common site of recurrence was abdomen (39%) (Table 3), while vaginal recurrence occurred in 11.5% (not shown here). Recurrence rates were found to be 38%, 10.3%, 20.7 % and 31% in patients who did not receive

Table 2. The clinicopathologic characteristics of the adjuvant managements

Characteristic	Follow up % (n)	RT alone % (n)	CT+RT % (n)	CT alone % (n)	Total % (n)
Age					
>70	7.7 (12)	13.4 (24)	14.3 (16)	14.1 (9)	12 (61)
<70	92.3 (143)	86.6 (155)	85.7 (96)	85.9 (55)	88 (449)
Histologic type					
Endometroid	90.3 (140)	89.4 (160)	60.7 (68)	48.4 (31)	78.2 (399)
Papillary serous	1.9 (3)	0.6 (1)	15.2 (17)	17.2 (11)	6.3 (32)
Non endometroid	6.5 (10)	8.9 (16)	18.8 (21)	28.1 (18)	12.7 (65)
ESS	1.3 (2)	1.1 (2)	5.4 (6)	6.3 (4)	2.8 (14)
FIGO stage					
I	96.1 (148)	76.6 (137)	33.1 (37)	25.5 (15)	66.9 (337)
II	3.9 (6)	20.7 (37)	11.6 (13)	3.4 (2)	11.5 (58)
III	-	2.8 (5)	44.6 (50)	16.9 (10)	12.8 (65)
IV	-	-	10.7 (12)	54.2 (32)	8.8 (44)
Tumor grade					
I	47.4 (65)	14.1 (23)	13.3 (12)	11.1 (4)	24.4 (104)
II	51.8 (71)	67.5 (110)	51.1 (46)	44.4 (16)	57 (243)
III	0.7 (1)	18.4 (30)	35.6 (32)	44.4 (16)	18.6 (79)
LVI					
Positive	10.8 (15)	32.1 (53)	54 (54)	38.3 (18)	31 (140)
Negative	89.2 (124)	67.9 (112)	46 (48)	61.7 (29)	69 (311)
LN metastasis					
Positive	4.8 (6)	1.3 (2)	51.6 (49)	56.9 (29)	18 (76)
Negative	95.2 (120)	98.7 (149)	48.4 (46)	43.1 (22)	82 (347)
Risk categories					
Low	62.1 (95)	21.5 (38)	-	10.2 (6)	28.1 (139)
Low-intermediate	20.9 (32)	24.9 (44)	3.8 (4)	6.8 (4)	16.9 (84)
High-intermediate	9.8 (15)	15.8 (28)	9.4 (10)	1.7 (1)	10.9 (54)
High	7.2 (11)	37.9 (67)	77.4 (82)	27.1 (16)	35.5 (176)
Advanced/metastatic	-	-	9.4 (10)	54.2 (32)	8.6 (42)

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

adjuvant therapy, received RT alone, RT and chemotherapy, and only chemotherapy, respectively ($p<0.001$). Vaginal recurrence was more common in the group that did not receive adjuvant RT (28% vs 5%) ($p<0.004$).

Patients with high and advanced/metastatic risk disease had shorter OS and DFS irrespective of adjuvant treatment received ($p<0.002$). When the patients who received adjuvant RT were compared to those who did not receive adjuvant therapy, there was not a statistical difference between OS and DFS regardless of risk groups ($p>0.06$). However, DFS (Fig. 1) and OS (Fig. 2) were found to be shorter in patients who underwent adjuvant chemotherapy alone or received combined chemotherapy and RT ($p<0.001$).

DFS and OS were not statistically different in low-risk patients who received adjuvant therapy.

Median OS in low-intermediate risk patients were found to be 15.3, 12.4, 7.2 and 6.8 years in patients who did not receive adjuvant therapy, received RT alone, RT and chemotherapy, and only chemotherapy, respectively ($p=0.006$). While DFS was statistically significant in high-int risk patients who received RT ($p<0.02$), OS was not found statistically significant ($p>0.7$). OS of the patients who received adjuvant treatment according to risk groups are shown in the Fig.3.

Table 3. Relapse areas by risk categories

Relapse areas	Low % (n)	Low-int. % (n)	High-int. % (n)	High %(n)	Advanced % (n)	Total % (n)
Abdominal	66.7 (8)	28.6 (4)	33.3 (2)	36.4 (12)	6 (35.3)	39 (32)
Pelvic	33.3 (4)	28.6 (4)	50 (3)	24.2 (8)	35.3 (6)	30.5 (25)
Mediastinal	-	28.6 (4)	16.7 (1)	9.1 (3)	-	9.8 (8)
Other	-	14.3 (2)	-	30.3 (10)	29.4 (5)	20.7 (17)
Total	100 (12)	100 (14)	100 (6)	100 (33)	100 (17)	100 (82)

Most of the patients with endometrial cancer are diagnosed at early stage, and surgery (with or without adjuvant therapy) is the main treatment modality in medically operable patients. After surgery, presence of certain clinical and pathologic factors including patient age, tumor grade, tumor stage and lymphovascular space invasion play major role in decision for adjuvant RT. Risk groups were defined to determine the adjuvant RT based on these clinicopathological factors. Importance of RT in the adjuvant management of endometrial cancer was established by multiple studies.

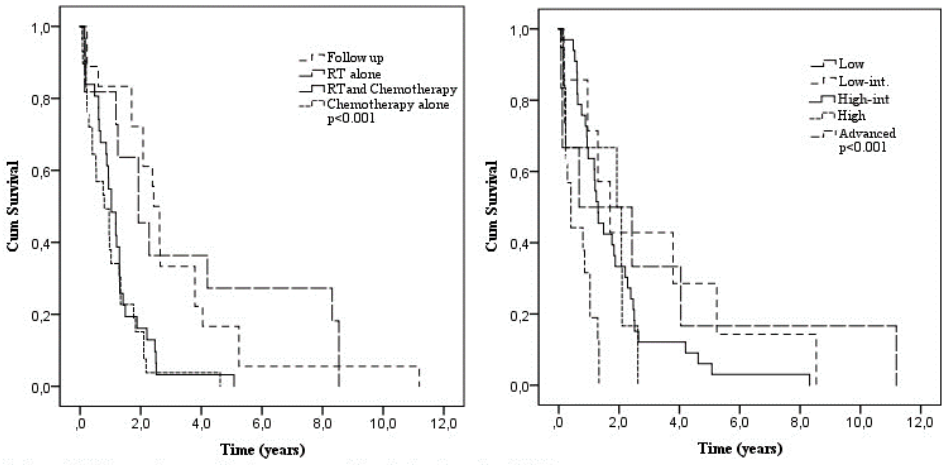

Figure 1. Disease-free survival curve according to treatment and risk groups

Recent studies have been concentrated upon the high-intermediate and high-risk diseases, whereas adjuvant treatment in low-risk endometrial cancer is not currently indicated (Colombo et al., 2016). 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 prognosis negatively in other risk groups except for the advanced/metastatic risk group.

Several studies have shown that adjuvant RT reduces locoregional recurrence but has no impact on OS in patients with endometrial cancer. However, applying adjuvant RT in the treatment of early-stage disease is controversial due to treatment related gastrointestinal side effects and lymphedema (Creutzberg et al., 2000; Keys et al., 2004). Efficacy of adjuvant pelvic RT was compared with no treatment in the prospective, randomized postoperative radiation therapy in endometrial carci¬noma trial (PORTEC-1).

Locoregional recurrence rate was reported as 5.8% in RT arm and 15.5% in no treatment arm at 15 years ($p < 0.001$). The most fre¬quent site of recurrence was vagina in 75% patients who underwent surgery alone (Scholten et al., 2005), however, vaginal brachytherapy alone is effective treatment to obtain vaginal control avoiding adjuvant RT-related complications (Reboux et al., 2019). In this study, there was no difference between OS and DFS in low risk patients with endometrial cancer when comparing those who did not receive adjuvant therapy with those who received adjuvant RT alone, while DFS (pelvic control) was statistically significant in patients who received adjuvant RT alone in low-intermediate risk patients ($p<0.02$). However, OS was found to be lower in low-intermediate risk patients who added chemotherapy to RT ($p=0.006$) (Fig. 3).

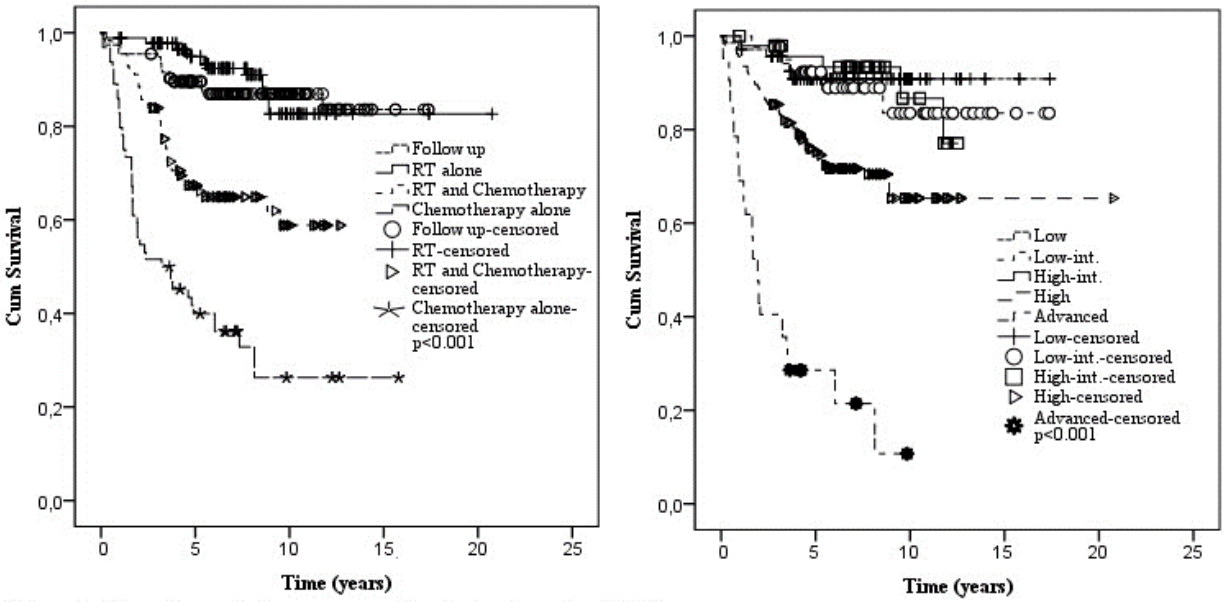

Figure 2. Overall survival curve according to treatment and risk groups

Approximately 20% of patients with endometrial cancer have an increased risk of distant metastasis and disease-related death at the time of diagnosis, and therefore, they are classified as high- risk disease. This comprises a heterogeneous group of histological types, grades and stages, and this heterogeneity of the high- risk patient population results in variations of adjuvant treatment strategies (Colombo et al., 2016). Higher risk of recurrence in the high-intermediate risk group, adjuvant

brachytherapy can be recommended to decrease vaginal recurrence. In presence of lymphovascular space invasion and/or stage II disease, pelvic RT can be considered to reduce the risk of regional nodal relapse (Concin et al., 2021). In two older studies, DFS and OS was not different between adjuvant chemotherapy alone and RT alone (Maggi et al., 2006; Susumu et al., 2008). In the Nordic Society of Gynecologic Oncology/European Organization for the Research and Treatment of Cancer and PORTEC-3 trials, the combination chemotherapy and RT seemed to provide better DFS and OS outcomes respectively compared to RT alone (Hogberg et al., 2010; de Boer et al., 2018). In the Gynecologic Oncology Group-249 trial DFS or OS was not found improved from 3 cycles of chemotherapy with brachytherapy compared to RT alone (Randall et al., 2019). In this study, while DFS was statistically better in high-risk and high-intermediate risk patients receiving RT than patients with no adjuvant treatment, OS was better only in high-risk patients. Unlike previous studies, it was observed that the addition of chemotherapy to RT had a poor effect on DFS and OS in these patients in this study. Although the reason for this difference is unclear, it may be due to the content of risk groups or the compliance of the patients to chemotherapy.

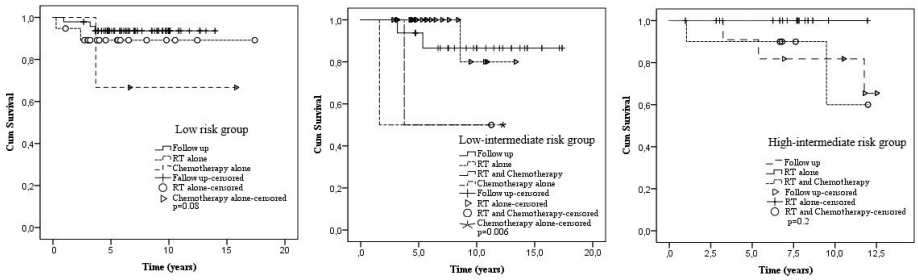

Figure 3. Overall survival curves of the patients who received adjuvant treatment according to risk groups

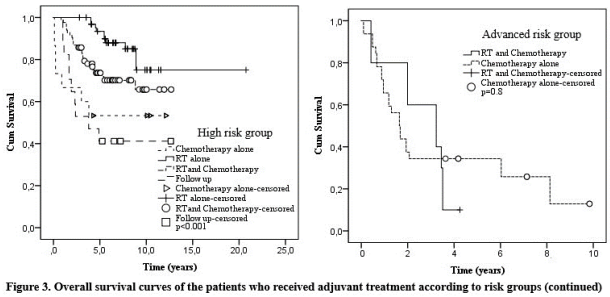

Figure 3. Overall survival curves of the patients who received adjuvant treatment according to risk groups (continued)

There is a consensus that patients with documented advanced/metastatic disease are at increased risk for recurrence and need adjuvant treatment; however, the optimal form of adjuvant treatment has yet to be determined. For advanced/metastatic disease, chemotherapy forms the mainstay of treatment and can be combined with RT (Hogberg et al., 2008; Koh et al., 2001; Secord et al., 2013). In this study, DFS and OS were similar in patients receiving chemotherapy alone compared to patients receiving sequential or simultaneous RT and chemotherapy. Although chemotherapy alone can benefit this patient group, symptomatic patients may benefit from palliative RT.

4. CONCLUSION

Adjuvant treatment for patients with endometrial cancer has become increasingly risk-based using clinicopathologic risk factors. Currently, adjuvant therapy is no longer recommended for patients with low-risk endometrial cancer. Although adjuvant treatment is required in high- risk patients, in contrast to previous studies, the addition of chemotherapy to adjuvant RT, poor effect on survival in this study. However, chemotherapy alone is sufficient in metastatic disease, RT may be required in symptomatic patients.

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