ORIGINAL ARTICLE | KLİNİK ÇALIŞMA

Long-term results of adjuvant radiotherapy in stage I endometrial cancer

Evre I endometrium kanserinde adjuvan radyoterapi uzun dönem sonuçları

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OBJECTIVES

We aimed to analyze the treatment results and the acute and late side effects in patients with stage I endometrial carcinoma receiving adjuvant radiotherapy.

METHODS

Two hundred sixty-three patients with stage I endometrial adenocarcinoma, who were treated with postoperative radiotherapy between 1978 and 1998, were analyzed retrospectively. According to the 1988-FIGO staging system, the disease was stage IA in 19, stage IB in 128, and stage IC in 116 patients. One hundred and ninety-seven patients were treated with external and intracavitary irradiation, 45 patients with external radiotherapy and 21 patients with vaginal brachytherapy.

RESULTS

The 10-year local control, disease-free and actuarial survival rates were 96%, 93% and 95%, respectively. Fifty-five patients had late side effects. The late side effects were significantly higher in patients with acute toxicity and patients who were treated with external radiotherapy, followed by brachytherapy.

CONCLUSION

The decision of adjuvant therapy and choice of different treatment modalities in terms of a reduced risk of recurrence need to be weighed carefully against the treatment-related morbidity.

Key words: Endometrial cancer; stage I; postoperative radiotherapy; long-term results.

AMAÇ

Adjuvan radyoterapi uygulanan evre I endometrium kanserli olgularda erken ve geç dönem yan etkiler ile tedavi sonuçları değerlendirildi.

GEREÇ VE YÖNTEM

1978-1998 yılları arasında operasyon sonrası radyoterapi uygulanan 263 evre I endometrium kanser tanılı olgu retrospektif irdelendi. FIGO 1988 evrelemesine göre olguların 19'u evre IA, 128'i evre IB, 116'sı evre IC idi. Yüz doksan yedi olgu eksternal radyoterapi ve intrakaviter brakiterapi, 45 olgu eksternal pelvik radyoterapi ile tedavi edildi. Yirmi bir olguda ise sadece vajen kubbe ışınlaması yapıldı.

BULGULAR

On yıllık lokal kontrol, hastalıksız sağkalım, hastalığa bağlı sağkalım oranları sırasıyla %96, %93 ve %95 idi. Geç yan etki 55 olguda tespit edildi. Eksternal pelvik radyoterapi sonrasında vajinal brakiterapi ile tedavi edilen olgularda ve akut radyoterapi yan etki görülen olgularda anlamlı olarak daha fazla geç yan etki görüldü.

SONUÇ

Adjuvan tedavi kararında ve tedavide uygulanabilecek farklı modalitelerin seçiminde yineleme riskinin azaltılmasının yanında oluşabilecek yan etkiler de dikkate alınmalıdır.

Anahtar sözcükler: Endometrium kanseri; evre I; postoperatif radyoterapi; uzun dönem sonuçlar.

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Endometrial carcinoma is the most common gynecological cancer. About 80% of endometrial cancers are diagnosed at FIGO stage I (International Federation of Gynecology and Obstetrics) and have a favorable prognosis, with an overall survival of up to 90%.[1,2] Surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the main treatment. However, optimal adjuvant treatment of stage I endometrial carcinoma is currently in dispute despite published results from randomized trials.[3-8] Several postoperative treatment options such as surveillance, external radiotherapy and/or vaginal vault brachytherapy are currently promoted. Even, adjuvant chemotherapy is a current area of active investigation.[9-13]

During external pelvic radiation treatment of endometrial carcinoma, other pelvic organs receive a significant radiation dose, resulting in both acute side effects and late complications.[6,14] Although severe consequences are rare, patients may have treatment-related symptoms associated with bladder, bowel or genitalia sufficient to have a significant effect on quality of life over a 10-year period.[14-16] In addition, there is increasing recognition of the effect of persistent low-grade problems in women. As vagina is the most frequent site of recurrence, vaginal brachytherapy alone can be used with less treatment-related toxicity.[17]

The aim of this retrospective study was to assess the results of postoperative radiotherapy, patterns of failure and late complications in patients with stage I endometrial carcinoma who were treated before 1999.

Table 1

Patient characteristics

Characteristics	n	%
Age (years)		
31-39	10	3.8
40-49	31	11.8
50-59	118	44.8
60-69	93	35.4
70-79	10	3.8
83	1	0.4
Grade		
I	84	31.9
II	104	39.6
III	35	13.3
Unspecified	40	15.2
Pathological Stage		
IA	19	7.2
IB	128	48.7
IC	116	44.1
Treatment type		
ERT+VBT	197	74.9
ERT	45	17.1
VBT	21	8

ERT: External pelvic radiotherapy; VBT: Vaginal brachytherapy.

MATERIALS AND METHODS

Patient characteristics

Between 1978 and 1998, 263 patients with pathological stage I endometrial carcinoma who were treated with postoperative radiotherapy in our department, were retrospectively analyzed. Patients with only adenocarcinoma histology were taken to analyze. We haven't included patients treated after 1998; because we have changed our treatment protocol and our stage I A-IB, grade 1-2 endometrial cancer patients were included in a multicenter phase III randomized trial.[18]

Patients were evaluated with physical and pelvic examination, routine blood counts, blood chemistry profile including renal and hepatic function tests and chest X-ray. After the year 1989, most patients underwent abdominopelvic computerized tomography and/or pelvic magnetic resonance imaging. Patients were staged according to the FIGO 1988 pathologic staging. The patients who were treated before 1988, they were restaged according to FIGO 1988 staging. The patients' age ranged from 31 to 83 years, with a median of 57 years. The patient characteristics are summarized in Table 1.

Treatment

A simple hysterectomy was performed in 229 patients and 34 patients underwent radical hysterectomy. Peritoneal cytology was examined in 47 (17.9%) patients. All patients were evaluated according to indication of adjuvant radiotherapy. One hundred and ninety-seven (74.9%) patients were treated with external pelvic radiotherapy followed

by vaginal brachytherapy and 45 patients (17.1%) were treated with only external pelvic irradiation. Remaining 21 (8%) patients treated with vaginal cuff irradiation alone. Patients treated with both external and intracavitary radiotherapy, were initially treated with external pelvic irradiation.

In external pelvic radiotherapy, standard pelvic fields were used. The field borders extend from the L4-L5 interspace to the obturator foramen. Laterally, the fields extend 1.5 to 2.0 cm from the widest plane of the true pelvis. The radiotherapy technique consisted of an anterior and posterior pair in 195 (74.1%) patients, a four-field box technique (anteroposterior, posteroanterior, and two lateral fields) in 47 (17.9%) patients. During external irradiation, midline shielding was not used. The radiation dose was specified at the patient's midplane or at the isocentre of the fields. The total pelvic dose was median 50.4 Gy (45-54 Gy) with a daily dose of 1.8-2 Gy. In external pelvic irradiation, Co60 teletherapy device or 18 MV photons of linear accelerator were used.

Low-dose-rate radium source was used in intracavitary applications until the 1981; high-dose rate accelerated Curietron Co60 afterloading system has been used from that date on. Vaginal cuff HDR irradiation was performed in 215 (98.6%) patients. Each implant was performed at one week intervals. The vaginal cuff irradiation was performed with Fletcher-Suit HDR colpostats or vaginal cylinder. Patients treated with HDR brachytherapy each received three fractions of 8 Gy and the dose specified at 0.5 cm from the surface of the applicator.

Follow-up

During radiotherapy treatment, all patients were routinely reviewed once a week and patients underwent weekly blood tests. After the treatment, patients were seen monthly to assess acute reactions. Then, all patients were followed regularly with physical and pelvic examination every 3 months for 2 years, every 6 months between 3 and 5 years, and yearly thereafter. Chest X-rays, routine blood chemistry profiles were repeated in every 6 months. In the suspicious of the recurrence and/or metastases, other radiological examinations were required. Vaginal smears or biopsy samples were taken on indication. Loco-regional recurrences were confirmed by a biopsy sample. Acute and late toxic effects of radiotherapy were scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) acute and late morbidity criteria.

Prognostic factors and statistical methods

Pelvic and local control, disease free survival and actuarial survival rates were calculated using the Kaplan-Meier method. Differences between curves were compared by the long rank test. Survival was measured from the operation date. Variables were compared using student-t, Mann-Whitney-U or chi-square test according to the variable properties. Univarite and multivariate analysis of prognostic factors were performed using log-rank and Cox regression models, respectively. All reported p-values are based on two-sided tests with $p<0.005$ taken to be significant.

RESULTS

Survival and patterns of relapse

The median follow-up of all patients was 99 months (range: 12-311 months). Thirteen (%4.9) patients died of cancer, 22 patients (8.4%) died from intercurrent disease. Cardiovascular diseases were the most common cause of intercurrent death. In 3 patients, a metachronous breast cancer was the cause of death. The 5-year local control, disease-free and actuarial survival rates were 97%, 94% and 95%, respectively. The 10-year local control, disease-free and actuarial survival rates were 96%, 93% and 95%, respectively.

Of 263 patients, 17 (6.5%) had a relapse, and their clinical, pathologic, and treatment characteristics are shown in Table 2. Nine (3.4%) patients had failure in vaginal cuff following treatment. The median time to local progression was 20 months (range: 6-72 months). Among the 9 patients, 5 patients also developed distant metastasis and died of progressive disease. Four patients had a isolated vaginal cuff recurrence and 2 of them had not received brachytherapy. Two patients with isolated vaginal relapse died due to intercurrent disease

Table 2

Clinicopathologic features of 17 patients with treatment failure

No	Age	Stage	Grade	Surgery	Treatment	Site of relapse	Time interval (mo)	Outcome
1	57	IB	2	SH	VBT	Lung+Liver+VC	28	DoD
2	64	IB	2	SH	ERT+VBT	Lung+Pelvic LN+VC	13	DoD
3	56	IB	3	SH	ERT+VBT	Omentum+VC	20	DoD
4	65	IB	3	SH	ERT+VBT	Omentum	17	DoD
5	57	IC	–	SH	ERT+VBT	Lung	11	DoD
6	62	IC	1	SH	ERT+VBT	Omentum	28	DoD
7	55	IC	1	SH	ERT+VBT	Omentum	35	DoD
8	66	IC	2	RH	ERT+VBT	Lung	15	DoD
9	55	IC	2	SH	ERT+VBT	Lung+Pelvic LN+VC	33	DoD
10	62	IC	2	SH	ERT+VBT	Omentum+Lung+VC	6	DoD
11	67	IC	3	SH	ERT+VBT	Lung	15	DoD
12	60	IC	3	SH	ERT	Omentum+Lung	4	DoD
13	53	IC	3	SH	ERT	Omentum	9	DoD
14	55	IB	1	SH	ERT	VC	33	DoOD
15	57	IB	2	SH	ERT+VBT	VC	12	DoOD
16	60	IB	2	SH	ERT	VC	13	Alive, NED
17	62	IC	1	SH	ERT+VBT	VC	72	Alive, NED

RH: Radical hysterectomy; SH: Simple hysterectomy; VC: Vaginal cuff; LN: Lymph node; mo: Months; DoD: Died of disease; NED: No evidence of disease; DoOD: Died of other disease.

(cardiac, traffic accident). The other two patients were treated with chemotherapy and salvage surgery respectively and still alive at last follow-up. There was no isolated pelvic lymph node recurrence.

Distant metastasis was noted in 13 (4.9%) patients after median 21 months (range: 9-35 months). Among 13 patients, 9 of them had stage IC disease. The most common sites of distant relapse were the lung in 8 patients, omentum in 7 patients. All patients with omentum metastasis had received pelvic external radiotherapy and 5 of them had stage IC, 4 of them had grade 3 disease. All patients with metastases died with disease.

Univariate analysis

Prognostic factors that might influence local control, disease free survival and actuarial survival were subjected to univariate analysis. These factors included age (≥60 years vs. <60 years), grade, stage, myometrial invasion, treatment type, time to radiotherapy after surgery, external treatment time, duration between external and intracavitary irradiation. However, no factor significantly influences 10-year pelvic and local control, disease-free and actuarial survival rates.

Acute and late side effects

Among the 263 patients, acute radiation side effects were documented in 116 (44.1%) patients. The majority of patients developed acute grade 1 skin reactions (22%) and grade 1 gastrointestinal tract side effects (20.9%). Grade 3 gastrointestinal toxicity was detected in 2 patients and grade 3 skin reactions was seen in 3 (1.1%) patients and all of them treated with external radiotherapy with Co60 machine. Acute complications are shown in Table 3.

Fifty-five (20.9%) patients had late side effects. The median time to the development of late complications was 22 month (6-84 months). The most common late side effect was in the gastrointestinal tract (Table 4). There was one case of grade 3 radiation gastrointestinal tract toxicity. Grade 3 skin fibrosis developed in two patients, and both of them had received 54 Gy radiotherapy to the pelvic region with anterior-posterior fields. There was no significant relation between age, radiotherapy technique, type of surgery and the risk of late side

Table 3

Incidence of acute side effects

	Grade I n (%)	Grade II n (%)	Grade III n (%)	Grade IV n (%)
Gastrointestinal	55 (20.9)	29 (11)	2 (0.8)	–
Urinary	25 (9.5)	4 (1.5)	–	–
Skin	58 (22)	17 (6.5)	3 (1.1)	–
Hematological	2 (0.8)	9 (3.4)	–	–

Table 4

Incidence of late side effects

	Grade I n (%)	Grade II n (%)	Grade III n (%)	Grade IV n (%)
Gastrointestinal	23 (8.7)	18 (6.8)	1	–
Urinary	16 (6.1)	2 (0.8)	–	–
Skin and subcutaneous tissue	5 (1.9)	6 (2.3)	2 (0.8)	–

effects. However, as seen in Table 5, patients who were treated with external pelvic irradiation followed by vaginal brachytherapy had higher rates of late complications than patients being treated with external pelvic radiotherapy or vaginal brachytherapy alone (p=0.004) (Fig. 1). The other prognostic factor predisposing for the risk of late complications was the occurrence of acute radiotherapy side

Table 5

Association of patient and treatment variables with risk of late toxicity for patients treated with RT

	n	5-year complication rate (%)	p
Age			
<60 years	157	13	0.15
≥60 years	106	23	
Radiotherapy modality			
VBT	21	4	0.004
ERT	45	8	
ERT+VBT	197	23	
Type of external radiotherapy equipment			
Co 60	105	23	0.12
Linac	137	16	
Radiotherapy fields			
Anteroposterior	195	21	0.45
4-field box	47	17	
Acute toxicity			
Yes	116	30	0.0001
No	147	10	

ERT: External pelvic radiotherapy; VBT: Vaginal brachytherapy.

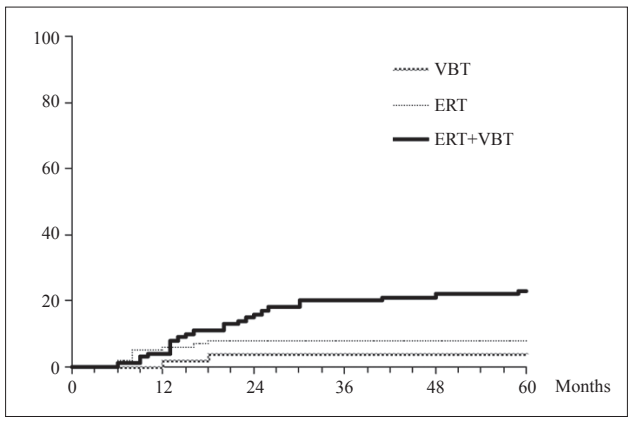

Fig. 1. Complication rate among different adjuvant treatment groups (p=0.004).
ERT: External pelvic radiotherapy; VBT: Vaginal brachytherapy.

effects. The 5-year late complication rate was lower in patients without acute radiotherapy toxicity, in contrast to in patients with acute radiotherapy toxicity (p=0.0001) (Table 5).

DISCUSSION

Surgery is the mainstay of the treatment of stage I endometrial carcinoma, consisting of a total abdominal hysterectomy with bilateral salpingo-oophorectomy and peritoneal washings. Nevertheless, extent and impact of pelvic and para-aortic lymphadenectomy or sampling is widely debated. Although determination of patients with nodal involvement has significant prognostic and therapeutic implications; most authors support evaluation of lymph nodes for patients with moderate and high-risk primary features, which are deep myometrial invasion, cervical or isthmus involvement, high-grade lesions, and capillary-space invasion. [19-21] Recently, a large randomized controlled trial, A Study in the Treatment of Endometrial Cancer (ASTEC), showed that systematic lymphadenectomy does not improve overall survival or disease specific survival.[22] Our study included patients who had complete surgical staging and those who did not. In this study, type of surgery did not significantly influence the rate of recurrence. Also, peritoneal cytology was examined in only 17.9% of our patients as peritoneal washing sampling has not been standard in these years. However, peritoneal cytology positivity or negativity no longer alter the staging in the 2008 FIGO and 2010 AJCC staging systems.

Numerous studies have demonstrated that age, depth of myometrial invasion, histology subtypes, histologic grade, cervical involvement, lymphovascular space involvement, nodal involvement can predict recurrence and survival in patients with endometrial cancer.[3,4,19,20,23-25] Although there are national and international variations in the definition of intermediate and high risk, based on these histopathological findings patients are classified into 3 risk groups (low, intermediate, or high) and adjuvant therapy can be modified on the basis of the estimated risk for recurrence. In our study, no factor significantly influences pelvic and local control, disease-free and actuarial survival rates. This might be due to most of (75%) our patients received pelvic radiotherapy followed by vaginal brachytherapy.

There have been controversies concerning the indications and types of adjuvant radiation therapy for stage I endometrial cancer. Recently, randomized studies (NHR, PORTEC 1 & 2, GOG 99, MRC, NCIC) regarding adjuvant radiotherapy for early-stage endometrial cancers were performed. [3-8,18] GOG 99 and PORTEC-1 trials compared pelvic external radiotherapy with no additional treatment after surgery. In these series, the locoregional recurrence rate was significantly lower in the pelvic irradiation group versus no adjuvant therapy group. Also, it has been shown that most locoregional recurrences were detected in the vaginal vault in the group receiving no additional treatment.[3,5] Medical Research Council (MRC) and the National Cancer Institute of Canada (NCIC) trial, 905 women with intermediate-risk or high-risk features were randomly assigned to immediate external radiotherapy or no radiotherapy until clinically indicated.[6] Brachytherapy was given to 50% of patients regardless of the EBRT allocation. However, the significant reduction in local recurrence would not justify its use as that may be reduced by brachytherapy. This pattern and the more favorable toxicity profile of vaginal brachytherapy suggest that brachytherapy alone may be a reasonable approach. For these reasons, many authors ad-

vocate radiation with vaginal brachytherapy alone. The randomized prospective study by Aalders et al.[4] compared vaginal brachytherapy to combination vaginal brachytherapy and external radiation therapy. This study showed the efficacy of pelvic external beam radiation therapy for patients who have >50% myometrial invasion or grade 3 cancers. However, the major criticism of the study is that the analysis was on patients who were surgically unstaged, and the study had a much higher incidence of stage I grade 3 cancers (34.4%) compared to that noted in most other surgical series (7% to 18%).[5,20,26] Beside this, GOG 99 trial showed us that nearly one-third of the pelvic failures in the surgery alone arm were in the lateral pelvis, and thus would not have been prevented with vaginal brachytherapy alone.[5] However, open-label, non-inferiority, randomized PORTEC-2 trial showed that vaginal brachytherapy is as effective as pelvic external beam radiotherapy, with fewer adverse effects in patients with endometrial carcinoma of high-intermediate risk.[7,17] Although, none of these above randomized studies showed a significant improvement in survival, adjuvant therapy spares these patients the psychological stress of recurrence and the morbidity of intensive treatment of relapse. Nevertheless, there is no evidence to support benefit from any form of adjuvant radiotherapy in low-risk patients.[18,20]

Clinical stage I disease has recently emerged in the form of a meta-analysis of five randomised trials of adjuvant radiotherapy.[27] The results indicate that there is no survival advantage for adjuvant radiotherapy in low risk and intermediate risk disease. Adjuvant radiotherapy is associated with side effects and worse overall survival in this group. As most pelvic recurrences can be cured with radiotherapy in radiation naive patients, the benefit of adjuvant radiotherapy in this group of women is outweighed by the risks.[28] In contrast, the meta-analysis showed a 10% survival advantage for adjuvant radiotherapy in high risk disease (IC grade 3).

The 5-year local control, disease-free and actuarial survival rates of 97%, 93% and 95%, respectively, for the stage I patients of our study are comparable with the results of previous reports. It has been confirmed that 68% to 100% of recurrences occur within the first 3 years of diagnosis.[29] In our series, 94% of locoregional or distant relapses were seen in first 3 years. Radiation therapy, either external alone or combined with vaginal brachytherapy, seems to lower the incidence of local recurrence, but allows the distant disease to manifest itself first especially in high-risk patients.[29] Although we were very successful in maintaining locoregional control, there was a 3% isolated and 4.9% overall distant failure rate. This is consistent with the literature where the risk of distant failure ranges from 4-12%[4,30-33] and the risk of isolated distant failure is 4-6%.[31] Peritoneal relapse within 5 years of simple hysterectomy occurred in 7 women and 5 of them had stage IC disease. So, recently randomized studies[9,13] for adjuvant systemic chemotherapies have therefore been developed in high risk patients since extrapelvic recurrence cannot be prevented by pelvic radiation, as reported by Creutzberg et al.[14] and other investigators.[4-6,30,34]

Since stage I endometrial cancer have an excellent outcome, many women with endometrial adenocarcinoma live for many years with the consequences of treatment related toxicity.[14,15,35,36] In the literature, late grade 1-2 radiation toxicity rate of 8-23% was reported after vaginal brachytherapy and 25-45% after pelvic radiotherapy followed by vaginal cuff irradiation.[32,36,37] It has been shown that the rate of gastrointestinal side effects was more severe and more frequent in the pelvic irradiation group after pelvic lymphadenectomy or lymph node sampling in both the PORTEC study[3,14] and the GOG study.[5] Similar to the literature, our complication rates are dose dependent and are higher for the combination of pelvic radiotherapy and vaginal brachytherapy than for pelvic radiotherapy or vaginal brachytherapy alone.[17,30,32,35,38,39] Although commonly used in the past, nowadays the combined use of both pelvic radiotherapy and vaginal brachytherapy has been used very rare cases since it simply increases the risk of toxicity, without improving pelvic control in stage I endometrial carcinoma.[39,40]

Postoperative brachytherapy alone is recommended to reduce the risk of vaginal cuff recurrence

with less toxicty in women with intermediate-risk disease in both retrospective and randomized studies.[7,17,21,26,38,41-44] Chadha et al.[41] reported success with vaginal brachytherapy alone and no grade 3 or 4 toxicity was detected. Fanning[21] designed a prospective evaluation of intermediate risk endometrial cancer treated with full lymphadenectomy and brachytherapy without pelvic radiotherapy. In this study, progression-free survival was 97% at a median follow-up of 4.4 years and with 6% major complication rate. Orr et al.[26] reported a 4% recurrence rate with minimal morbidity.

Treatment related factors that are related to the risk of complications are treatment volume, daily fractionation, radiotherapy technique.[15,20,37,39] We could not find significant relation between age, radiotherapy technique and equipment, type of surgery and the risk of late side effects. Furthermore, Creutzberg et al.[14] and Weiss et al.[45] found that; patients with acute side effects had a higher risk of late complications than patients without acute side effects. This observation was confirmed in our study: the presence of acute treatment-related symptoms was the important significant risk factor for late complications.

In conclusion, the benefit of adjuvant therapy in terms of a reduced risk of recurrence needs to be weighted carefully against the treatment related morbidity when deciding on treatment protocols for stage I endometrial carcinoma. Individual patient, the tumor characteristics should be considered. If administered, the least aggressive and modern radiotherapy approaches (conformal, intensity modulated radiotherapy-IMRT) should be used to reduce the rate of both acute and late side effects.

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