RESEARCH ARTICLE

# Evaluation of Treatment Outcomes of Early-Stage Endometrial Cancer Radiotherapy: A Single Center Experience

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## Abstract

**Background: Postoperative adjuvant radiotherapy (RT) in the management of early stage endometrial cancer (EC) is still controversial. Here we report our institutional experience with patients who received postoperative RT for stage I-II EC over a period of 35 years and assess potential predictors of local recurrence (LR), distant metastasis (DM), and overall survival (OS). Materials and Methods: A total of 188 patients undergoing postoperative RT for stage IA-II EC between 1977 and 2012 were evaluated. Some 96 received median 46 Gy whole pelvic radiotherapy (WPRT) (range: 40-60 Gy), 37 were given WPRT with vaginal cuff therapy (VCT), and 55 received only VCT either with brachytherapy (BT) or stereotactic body radiotherapy (SBRT). Chemotherapy was given to 5 patients with uterine papillary serous carcinoma (UPSC). Logistic regression analysis was used to assess the effect of clinicopathological factors on LR, DM, and OS. Results: Median follow-up time was 11 years (range: 1-35 years). At the time of analysis, 34 patients were not alive. Of the 15 patients with LR, 7 (46.7%) recurred in the vaginal stump, 5 (33.3%) in the pelvic region, and 3 (20%) in the paraaortic nodal region, while 12 had distant metastasis. UPSC histology (p=0.027), sole VCT (p=0.041), high histologic grade (p=0.034), and age ≥ 71 (p=0.04) were poor prognostic factors on univariate analysis. Conclusions: In our patients receiving radiotherapy for early-stage EC, grade III disease and age ≥ 71 were associated with shorter OS whereas UPSC histology was an independent predictor for both LR and DM.**

**Keywords:** Endometrial cancer - whole pelvic radiotherapy - vaginal cuff therapy - prognosis

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## Introduction

Endometrial cancer (EC) is the most common gynecologic cancer and the fourth most common cancer in females. Despite its high incidence, it is only the seventh cancer-related mortality cause thanks to early diagnosis and treatment (Polyzos et al., 2006; Beyzadeoglu et al., 2010). Some subgroup of patients with early stage EC may have a higher likelihood for progression or recurrence. To address the issue of adjuvant treatment for early stage EC, multiple risk classification strategies have been proposed. Radiotherapy constitutes the most commonly utilized adjuvant therapeutic modality for these patients (Tangjitgamol et al., 2010; Zighelboim et al., 2011).

Addition of postoperative RT showed an increase in local control (LC), with no significant effect on the management of these patients, thus, high-risk patients should particularly be considered for postoperative RT (Aalders et al., 1980; Creutzberg et al., 2000; Krusun et al., 2014).

In this retrospective study, we assessed the outcomes of 188 patients with early stage EC who underwent postoperative RT over a period of 35 years. We aimed to analyze the prognostic and clinicopathological factors for LR, DM, and OS.

## Materials and Methods

Between January 1977 and September 2012, 188 patients were treated with postoperative RT for pathological stage I-II EC at the Department of Radiation Oncology, Gulhane Military Medical Academy. Median follow-up time was 11 years (range: 1-35 years). Type of surgery was total abdominal histerectomy, bilateral salpingooopherectomy (TAH+BSO) and pelvic lymph node dissection (PLND) in 122 patients (64.9%), TAH + BSO and pelvic-paraaortic lymph node dissection (PPLND) in 66 patients (35.1%).

Our institutional policy is to use postoperative RT for stage IB, II disease according to FIGO 2008 staging and for stage IA in case of grade 3 disease, age >60 years, and poor hystogical type or LVSI. For the 188 patients in our study, whole pelvic RT (WPRT) was used in 96 patients (51%), WPRT + vaginal cuff therapy (VCT) in 37 patients (19.7%), and only VCT in 55 patients (29.3%). Co-60 teletherapy device was used in the period between

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1977 and 1997, and linear accelerator (LINAC) with 6-18 MV photons was used between 1997 and 2012 to deliver WPRT for a median dose of 46 Gy (range: 40-60 Gy) at 1.8-2 Gy daily fractions over 4 to 7 weeks. Before 2007, WPRT was delivered using opposed anteroposterior-posteroanterior 2 fields, and with 3D conformal radiation therapy using 4-field box technique afterwards. No patients in our study received paraaortic RT.

For VCT, radium implants were used between 1977 and 1988 for 6 patients at a dose of 3000-3600 mgE/h preoperatively, Co-60 HDR with vaginal cylinders was used between 1989 and 2004 for 37 patients at a median total dose of 15 Gy (range: 15-20 Gy) in 3 fractions given weekly. Ir-192 HDR brachytherapy was used between 2004 and 2012 for 26 patients at a median total dose of 18 Gy in 3 fractions given weekly. Stereotactic Body Radiation Therapy (SBRT) was used in 23 patients for VCT at a median total dose of 18 Gy in 3 fractions given weekly and SBRT technique was reported in our previous study (Demiral et al., 2013). All patients with UPSC histology received chemotherapy.

Follow-up visits after RT including physical examination, gynecological examination, vaginal smear, blood chemistry, chest radiogram, abdominal ultrasonography, and pelvic magnetic resonance imaging (MRI) was scheduled for every patient at 3-month intervals in the first year, at 4-month intervals for the second year, at 6-month intervals in 3-5 years, and yearly thereafter.

**Table 1. Clinico-Pathological Characteristics of Patients with EC Diagnosis**

| Characteristics | n |
|---|---|
| Histology | |
| Endometrial adenocarcinoma | 183 (97.4%) |
| Papillary serous carcinoma | 5 (2.6%) |
| Grade | |
| Grade 1 | 41 (21.8%) |
| Grade 2 | 112 (59.6%) |
| Grade 3 | 35 (18.6%) |
| Stage | |
| IA | 39 (20.7%) |
| IB | 99 (52.7%) |
| II | 50 (26.6%) |
| Radiotherapy | |
| WPRT | 96 (51%) |
| WPRT+VCT | 37 (19.7%) |
| VCT | 55 (29.3%) |
| Surgery | |
| TAH+BSO + Pelvic LND | 122 (64.9%) |
| TAH+BSO + Pelvic-Paraaortic LND | 66 (35.1%) |
| Age (years) | |
| ≤50 | 27 (14.4%) |
| 51-60 | 80 (42.6%) |
| 61-70 | 62 (32.9%) |
| ≥71 | 19 (10.1%) |

*Statistical methods*

Statistical Package for the Social Sciences, version 17.0 (SPSS, Inc., Chicago, IL) software was used in data analysis. Number, percentage, median, minimum and maximum values were used in description of data. OS was calculated from the time of surgery till death or last follow-up visit. Effect of each specific factor on LR, DM, and OS was assessed with univariate analysis whereas multivariate analysis was used in determining the main predictors of LR, DM, and OS. Logistic regression model was used in assessing the effect of clinicopathological factors on LR, DM, and OS. Hazard ratio and 95% confidence interval (CI) was used in predicting relative risks of death, relapse, and metastatic progression. Level of significance was set at $p<0.05$.

## Results

Patient characteristics are shown in Table 1. Median age was 58 years (range: 42-83 years). 183 patients (97.3%) had type 1 EC, whereas 5 patients (2.7%) had UPSC. Stage grouping of patients according to FIGO 2008 staging was; stage IA in 39 patients (20.7%), stage IB in 99 patients (52.6%), and stage II in 50 patients (26.6%).

**Table 2. LR, DM, Death and OS Rates**

| | Total number | LR 15 pts | DM 12 pts | Dead 34 pts | Alive-OS 154 pts |
|---|---|---|---|---|---|
| Diagnosis | | | | | |
| EC | 183 | 13 (7.1%) | 10 (5.4%) | 32 (17.4%) | 151 (82.6%) |
| UPSC | 5 | 2 (40%) | 2 (40%) | 2 (40%) | 3 (60%) |
| Grade | | | | | |
| Grade 1 | 41 | 3 (7.3%) | 1 (2.4%) | 4 (9.7%) | 37 (90.3%) |
| Grade 2 | 112 | 6 (5.3%) | 7 (6.2%) | 22 (19.6%) | 90 (80.4%) |
| Grade 3 | 35 | 6 (17%) | 4 (11.4%) | 8 (22.8%) | 27 (77.2%) |
| Stage | | | | | |
| IA | 39 | 2 (5%) | 1 (2.5%) | 6 (15.3%) | 33 (84.7%) |
| IB | 99 | 7 (7%) | 6 (6%) | 19 (19.2%) | 80 (80.8%) |
| II | 50 | 6 (12%) | 5 (10%) | 9 (18%) | 41 (82%) |
| RT | | | | | |
| WPRT | 96 | 7 (7.3%) | 4 (4.1%) | 19 (19.8%) | 77 (80.2%) |
| WPRT + VCT | 37 | 3 (8%) | 3 (8.1%) | 4 (10.8%) | 33 (89.2%) |
| VCT | 55 | 5 (9%) | 5 (9%) | 11 (20%) | 44 (80%) |
| Surgery | | | | | |
| TAH+BSO + PLND | 122 | 11 (9%) | 8 (6.5%) | 24 (19.6%) | 98 (80.4%) |
| TAH+BSO + PPLND | 66 | 4 (6%) | 4 (6%) | 10 (15.1%) | 56 (84.9%) |
| Age (years) | | | | | |
| ≤50 | 27 | 2 (7.4%) | 1 (3.7%) | 2 (7.4%) | 25 (92.6%) |
| 51-60 | 80 | 7 (8.7%) | 5 (6.2%) | 14 (17.5%) | 66 (82.5%) |
| 61-70 | 62 | 4 (6.4%) | 4 (6.4%) | 12 (19.3%) | 50 (80.7%) |
| ≥71 | 19 | 2 (10.5%) | 2 (10.5%) | 6 (31.5%) | 13 (68.5%) |

Pts: PatientsEC: Endometrial adenocarcinomaUPSC: Uterin papillary serous carcinoma

**Table 3. Logistic Regression Analysis of Factors Associated with LR, DM and OS**

| Characteristics | | Univariate HR | Univariate 95% CI of HR | Univariate P value | Multivariate HR | Multivariate 95% CI of HR | Multivariate P value |
|---|---|---|---|---|---|---|---|
| Stage | | | | | | | |
| IA | LR | * | | | | | |
| IB | LR | * | | | | | |
| II | LR | 8.718 | 1.336-56.904 | 0.027 | | | |
| Diagnosis | | | | | | | |
| EC | LR | * | | | * | | |
| UPSC | LR | 4.207 | 1.451-39.233 | 0.02 | 8.156 | 1.583-44.463 | 0.024 |
| EC | DM | * | | | * | | |
| UPSC | DM | 11.533 | 1.726-77.061 | 0.018 | 4.102 | 1.342-23.452 | 0.012 |
| RT | | | | | | | |
| WPRT | DM | * | | | | | |
| WPRT + VCT | DM | * | | | | | |
| VCT | DM | 6.528 | 1.08-39.469 | 0.041 | | | |
| Grade | | | | | | | |
| I | OS | * | | | | | |
| II | OS | * | | | | | |
| III | OS | 5.019 | 1.126-22.371 | 0.034 | | | |
| Age | | | | | | | |
| ≤50 | OS | * | | | | | |
| 51-60 | OS | * | | | | | |
| 61-70 | OS | * | | | | | |
| ≥71 | OS | 5.898 | 1.986-35.268 | 0.04 | | | |

* Not Significant, HR: Hazard Ratio, CI: Confidence Interval, LR: Local recurrence, DM: Distanst metastasis, OS: Overall survival, EC: Endometrial adenocarcinoma, UPSC: Uterin papillary serous carcinoma, RT: Radiotherapy, WPRT: Whole pelvic radiotherapy, VCT: Vaginal cuff therapy.

At the time of analysis, 154 of the 188 patients (82%) were alive and 34 patients (18%) were dead. Fifteen patients (7.9%) had LR and 12 patients (6.4%) had DM.

Of the 15 patients with LR, 7 patients (46%) recurred in the vaginal stump, 5 patients (33.3%) recurred in the pelvic region, and 3 patients (20%) recurred at paraaortic nodal region. Out of the 12 patients with DM, metastatic site was the lung in 6 patients (50%), the liver in 2 patients (16.7%), and multiple metastasis in 4 patients (33.3%). Two patients (1%) had both LR and DM synchronously. LR, DM, and OS rates are shown in Table 2.

Univariate analysis revealed that patients with UPSC histology (p=0.02, Hazard Ratio (HR), 4.207; 95% confidence interval [CI], 1.451-39.233) and stage II disease (p=0.027, HR, 8.718; 95% [CI], 1.336-56,904) had a significantly higher risk of LR whereas patients with UPSC histology (p=0.018, HR, 11.533; 95% [CI], 1.726-77.061) and VCT application only (p=0.041, HR, 6.528; 95% [CI], 1.08-39,469) had a significantly higher risk of DM.

Grade III disease (p=0.034, HR, 5.019; 95% [CI], 1.126-22.371) and age ≥71 (p=0.04, HR, 5.898; 95% [CI], 1.986-35.268) were associated with shorter OS in univariate analysis. Multivariate analysis revealed that UPSC was an independent predictor for both LR (p=0.024, HR, 8.156; 95% [CI], 1.583-44.463) and DM (p=0.012, HR, 4.102; 95% [CI], 1.342-23.452).

Statistical analysis revealed that patients with UPSC histology had a 8.7-fold increased risk of LR, 11.5-fold increased risk of DM, and a 3.1-fold increased risk of death. Grade 3 disease was associated with a 2.6-fold increased risk of LR, 5.1-fold increased risk of DM, and a 2.7-fold increased risk of death. Stage II disease was associated with a 2.5-fold increased risk of LR, and 4.2-fold increased risk of DM, and a 1.2-fold increased risk of death.

Patients with LR had a 3-fold increased risk of death (p=0.001, HR, 6.462; 95% [CI], 2.158-19.342) while patients with DM had a 4-fold increased risk of death (p=0.001, HR, 7.726; 95% confidence interval [CI], 2.284-26.134).

## Discussion

A high potential of cure is achievable in endometrial cancers (EC) confined to the uterus ( Balasubramaniam et al., 2013; Setakornnukul et al., 2014). Surgery may only provide cure for early stage EC with a 5-year OS rate of 80% (Cecere et al., 2013). However, recurrence rates range between 20% and 30% within 5 years following surgery alone. Adjuvant treatment for early stage EC is offered in patients with independent risk factors of grade, age, and stage. RT decreases the rates of LR, increases the rates of progression-free survival, but does not affect OS (Cecere et al., 2013). A retrospective study with 883 patients receiving postoperative RT for stage I-II EC revealed a relapse rate of 10.6% (47 patients had LR, 38 patients had DM) in 9 years of median follow-up (Scotti et al., 2010). Univariate analysis showed diagnosis, stage, and histologic type to be significant prognostic factors whereas multivariate analysis revealed histologic type to be an independent predictor for relapse in that study (Scotti et al., 2010). In our study, 15 patients out of total 188 (7.9%) had LR, and 12 patients (6.4%) had DM.

UPSC accounts for 2.9% of all uterine cancers and has a significantly worse prognosis compared to other histological types (Jaishuen et al., 2014). In a retrospective study, postoperative combined treatment with chemotherapy and radiation therapy improved relapse-free survival in patients with UPSC (Al Husaini et al., 2012). A study by Fader et al. (2013) reported high recurrence rates (0%-80%) in UPSC with cancer-related deaths even in the early stages (stage I-II) and noted that these high rates could be decreased by the

use of chemotherapy and radiotherapy. In a recent study, 37 patients with stage I-II UPSC or Clear Cell (CC) histology received HDR BT and adjuvant chemotherapy (Townamchai et al., 2013). At a mean follow-up time of 24.8 months, 4 patients (2UPSC, 2 CC) relapsed, with an overall 2-year LC and OS rates of 96.8% and 100%, respectively (Townamchai et al. 2013). In our study, UPSC histology or stage II disease status increased the risk of LR whilst USPC histology alone or sole VCT increased the risk of DM. UPSC was also found to be an independent predictor for LR and DM.

In Zusterzeel et al.'s (2008) study of 295 moderate or high-risk stage I-II EC patients, 34 patients (11.5%) had recurrence (20 locoregional, 14 distant recurrence). Multivariate analysis showed age over 60 years to be an unfavorable prognostic factor for recurrence. In a study with 45 patients having stage I EC, 16 patients developed recurrence after postoperative RT and a minimum follow-up of 3 years has revealed 3-year survival rate to be 42% and papillary carcinoma histology a predictor of recurrence (Vavra et al., 1991).

PORTEC study randomized 715 patients with stage IC, grade 1 or 2, and stage IB, grade 2 or 3 EC to postop pelvic RT or sole surgery arms (Creutzberg et al., 2000). The 5-year locoregional relapse rate was 1-3% with a DM rate of 3% to 7% for grade 1 and 2 tumors, and 20% for stage IB ,grade 3 tumors. OS rates were 83-85% for grade 1-2, and 74% for stage IB, grade 3 tumors (Creutzberg et al., 2000). In another study by Creutzberg et al. (2004), stage IC-grade III tumors excluded in PORTEC study were assessed and; DM and OS of the total 104 patients were noted to be 31% and 58%, respectively. Multivariate analysis revealed grade III disease to be the most important prognostic factor for relapse and death (Creutzberg et al., 2004). In our study, grade III disease and age ≥71 were associated with shorter OS. Patients with LR had a 3-fold increased risk of death whilst patients with DM had a 4-fold increased risk of death. Major limitations of our study include its retrospective design and the limited number of patients, particularly for the subgroup of patients with UPSC.

In conclusion; grade III disease and age ≥71 were associated with shorter OS whereas UPSC histology was an independent predictor for both LR and DM in our patients receiving radiotherapy for early-stage EC, which is consistent with the related literature.

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