Postoperative radiotherapy in intermediate and high-risk Stage I endometrial cancer: analysis of prognostic factors and survival

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Summary

Purpose: Patients with Stage IA Grade (G) III, Stage IB GII-III and Stage IC GI-II-III endometrial cancer who received postoperative adjuvant radiotherapy were evaluated in terms of local control, disease-free and overall survival rates and prognostic factors. *Materials and Methods:* Four hundred and three patients with Stage I endometrial cancer treated with radiotherapy from January 1990 to December 2003 at Ege University Faculty of Medicine Department of Radiation Oncology were reviewed retrospectively. According to our radiotherapy protocol patients with Stage IB G2 disease (149 patients) received only external radiotherapy and the remaining (254 patients) received both external radiotherapy and intracavitary brachytherapy. *Results:* Median age of the patients was 58 (range: 37-83). Nine patients (2.2%) had Stage IA, 196 (48.6%) had Stage IB and 198 (49.1%) had Stage IC disease. Histologic grade was 1 in 52 (12.9%) patients, 2 in 268 (66.5%) patients and 3 in 83 (20.6%) patients. Seventy-one (17.7%) patients had lymphovascular space invasion. Five-year locoregional relapse-free, distant-free, disease-free survival (DFS) and overall survival (OS) were 98.2%, 92.8%, 91.8% and 87.7%, respectively. In multivariate analysis, myometrial invasion and lymphovascular invasion were predictive factors for DFS and for OS prognostic factors were histologic type, myometrial invasion, and histologic grade. During radiotherapy 47.9% of the patients developed acute morbidity and 26.3% developed late morbidity, vaginal stenosis being the most frequent late morbidity. *Conclusion:* Postoperative adjuvant radiotherapy provides high locoregional control rates with acceptable toxicity in selected patients with Stage I endometrial carcinoma.

Key words: Intermediate and high risk stage I endometrial cancer; Radiotherapy; Prognostic factors.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract, and it is the fourth most frequently diagnosed cancer in women. It was estimated that during 2006, 41,200 new cases and 7,350 deaths would be attributed to endometrial cancer in the United States [1]. The estimate was that 72% of women diagnosed with endometrial cancer would have locally confined disease [2]. Widely accepted management of endometrial cancer consists of total hysterectomy, removal of the remaining adnexal structures, and appropriate surgical staging in patients considered at risk for extrauterine disease [3-5]. In the adjuvant setting prognostic factors like FIGO stage, histopathology and grade, myometrial invasion, status of pelvic lymph nodes, lymphovascular invasion and performance status of the patients have an important role in the treatment choices [2-24]. If risk factors are present, that is, myometrial invasion is 50% or more of the myometrial width and/or grade 2 or 3 histology, pelvic radiotherapy is indicated to reduce the risk of pelvic failure [6]. In the recent published data, postoperative pelvic radiotherapy reduced vaginal and pelvic recurrences from 15% to 0-3%, however survival was not improved [5, 11, 12, 19]. Women with low-risk histopathologic features [grade 1 or 2, < 50% myometrial invasion) do not routinely receive adjuvant radiotherapy (RT) since the risk of recurrence is lower than 5% with or without surgical staging [6]. For "intermediate or high risk" subgroup patients, randomized studies have reported significantly less pelvic and vaginal recurrences with postoperative RT compared to surgery alone [7, 10, 16]. Based on these data, our institutions have developed and maintained a standardized policy for adjuvant RT based on certain disease characteristics. The intent of this retrospective analysis was to evaluate disease outcomes in women with early-stage (FIGO Stage IA to IC) endometrial cancer treated at Ege University. Clinical and pathologic factors were evaluated for potential prognostic significance.

Patients and Methods

Between October 1990 and December 2003 patients were included in this retrospective study at the Ege University Medical School Department of Radiation Oncology. The initial evaluation included chest radiography, CT scan of the abdomen, a complete blood count and biochemistry. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) with (n = 148) or without (n = 255) bilateral pelvic lymph node dissection. In the patient group with lymph node dissection, the median number of lymph nodes removed was 19 with a range of three to 76. Patients were staged according to the 1988 FIGO staging system [25].

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According to the protocol of Ege University, women with grade 1 or 2, and < 50% myometrial invasion do not receive adjuvant radiotherapy and all patients with Stage I, grade 2 and IA grade 3 disease are treated with postoperative external-beam RT alone. The rest of Stage 1 patients receive postoperative external-beam RT and vaginal brachytherapy. Adjuvant RT was administered as external-beam RT only in 149 (36.9%) patients or combined with vaginal brachytherapy in 254 (63.1%) patients. Patient characteristics are given in Table 1.

External-beam RT was delivered using a linear accelerator with 6 MV photons with a daily dose of irradiation of 1.8 Gy. Patients were treated with a combination of the 4-field box or AP-PA technique of irradiation and high-dose rate intracavitary brachytherapy. The irradiation volumes were designed to include the primary tumor and the locoregional lymph nodes. The superior border of the AP-PA fields was placed at the L5-S1 interspace. The inferior border of the AP-PA fields was placed at the bottom of the obturator foramina. The lateral margins of the AP-PA fields were placed 2 cm laterally to the bony pelvis. The anterior margin of the lateral fields was placed at the pubic symphysis. The lateral fields had the same cephalocaudal extent as the AP-PA fields. The posterior margin of the lateral fields was individually designed using custom made blocks to cover the posterior part of the sacrum and posterior portion of the rectum. Vaginal brachytherapy was performed by using microselectron "high-dose rate" (HDR) Ir-192 equipment. Between 1990 and 2000, 9.25 Gy in one fraction was delivered to point 0.5-0.9 cm depth, from 2000 till 2003 a dose of 6.5 Gy in two fractions and after 2003, a dose of 3 x 6 Gy has been delivered. Median total radiation therapy duration was 49 days (range: 31-120 days).

Table 1. — *Patient and pathological characteristics of 403 patients with Stage 1 endometrial cancer.*

Characteristics	Patients (No.)	(%)
Age		
< 60	240	59.5
≥ 60	163	40.5
Median age (yrs)	57 (range: 37-83)	
Median BMI (kg/m^2)	29.6 (range: 26.3-51.1)	
Menopausal		
Premenopausal	86	21.3
Postmenopausal	327	77.7
Hypertension	77	19.1
Diabetes mellitus	94	23.3
Nulliparous	51	12.7
Operation		
TAH+BSO	255	63.3
TAH+BSO+LD	148	36.7
FIGO Stage I		
IA	9	2.3
IB	196	48.6
IC	198	49.1
Histolopathology		
Adenocarcinoma	356	88.3
Adenosquamous carcinoma	21	5.2
Clear cell carcinoma	20	5
Papillary serous carcinoma	6	1.5
Histologic grade		
1	52	12.9
2	265	65.8
3	86	21.3
Lymphovascular invasion		
No	332	82.4
Yes	71	17.6
Extension to isthmus		
No	391	97
Yes	12	3
Length of radiotherapy		
≥ 8 weeks	95	23.6
< 8 weeks	308	76.4

After completion of the whole treatment, patients were evaluated every three months by history taking, gynecological examinations, and blood counts. Toxicity was assessed using by RTOG-EORTC early and late radiation morbidity criteria [26]. The French-Italian glossary was used for grading vaginal side-effects [27]. Toxicity was recorded at each visit.

Statistical analysis

Overall survival (OS) was calculated from the time of diagnosis to death or date of last follow-up. Disease-free survival (DFS) was calculated from the time of diagnosis to relapse or death from any cause. All statistical analyses were performed by the software program SPSS 13.0. OS, DFS, and pelvic local control were calculated according to the actuarial method of Kaplan and Meier. Risk of failure was determined by Cox multiple regression analysis. Histologic type, histologic grade, myometrial invasion, patient age, extension to isthmus, body mass index (BMI), lymphovascular space invasion (LVSI), overall radiation treatment time, and operation type were the variable factors analyzed for actuarial overall survival and actuarial local control. Statistical significance was considered with p-values of less than 0.05.

Results

Descriptive statistics

The median age of the 403 patients was 57 (range: 37-83) and median BMI was 29.6 kg/m^2 (range: 26.3-51.1 kg/m^2). Two hundred and ninety-nine patients (77.7%) were postmenopausal. Comorbid conditions in the patients were as follows: 77 (19.1%) with hypertension, 94 (23.3%) with diabetes mellitus, 17 (4.1%) with secondary malignancies. Histologically 88.3% were adenocarcinoma, 5.2% adenosquamous carcinoma, 5% clear-cell carcinoma and 1.5% serous papillary carcinoma. Six of the Stage IA patients' histopathology was other than adencarcinoma. Distribution of the patients according to stage and grade were as follows: nine patients IA grade 3, 149 patients IB grade 2, 47 patients IB grade 3, 52 patients IC grade 1, 116 patients IC grade 2, 30 patients IC grade 3. Lymphovascular invasion was positive in 71 patients (17.6%). Pathological characteristics of the tumors and surgical stages are shown in Table 2.

Median follow-up was 96 months (range: 12-262 months). We observed locoregional relapse in four patients, distant metastases in 26 patients and simultaneous recurrence at both locoregional relapse and distant metastases in four patients. Distribution of distant metastases was as follows: lung 13 (3.2%), bone two (0.5%), paraaortic lymph nodes six (1.5%), supraclavicular lymph nodes one (0.2%), liver one (0.2%), brain one (0.2%) and multiple six (1.5%). Five-year locoregional relapse-free, distant free, DFS and OS were 98.2%, 92.8%, 91.8% and 87.7%, respectively.

Prognostic factors

According to univariate analyses prognostic factors influencing DFS were histologic type (p = 0.004), myometrial invasion (p = 0.001), LVSI (p = 0.04), while the prognostic factor affecting local recurrence-free survival was histologic type (p = 0.025). According to multivariate analyses the prognostic factor influencing DFS was myometrial invasion (p = 0.001) and LVSI (p = 0.033). Prognostic factors related with OS in multivariate analyses were: myometrial invasion (p = 0.011), histologic type (p = 0.026), and histologic grade (p = 0.005). Univariate and multivariate analyses for locoregional relapse-free, distant-free, DFS and OS are shown in Tables 2, 3, 4, 5, respectively.

Side-effects

Treatment was generally well tolerated. There were no treatment-related deaths. Only one patient experienced grade 3 diarrhea. The most frequently observed acute side-effects related to radiotherapy were diarrhea (22.2%), cystitis (21.3%) and radiodermatitis (16.1%). One hundred and ninety-three patients developed toxicity due to radiotherapy. According to the RTOG/EORTC late radiation morbidity scoring scheme guidelines, of the patients, 31 had vaginal stenosis, 26 cystitis, seven urinary incontinence, two proctitis, 23 grade 1-2 vaginal atrophy and two had fistulas. Treatment-related acute and late side-effects are listed in Table 6.

Discussion

Long-term life expectancy is very high in endometrial carcinoma because most patients are diagnosed in early stages. There are lots of retrospective studies which have evaluated the effect of postoperative radiotherapy in local and systemic disease control. In these studies, radiotherapy increases pelvic control but it has no effect on survival, especially in high-risk patients [18, 19]. In low-risk patients (Stage IA G1-2, Stage IB G1) the rates of vaginal recurrence were below 5% with surgery and additional therapy was not recommended. In intermediate-risk patients (Stage IB G2-3, Stage IC, Stage IIA-B) addition of radiotherapy decreased pelvic failure rates from 15% to 0-3% [7, 16]. In the last few years two large studies investigated the role of postoperative radiotherapy. In 1999, the GOG (Gynecological Oncology Group) randomized 390 endometrium cancer patients to 50.4 radiotherapy vs observation. Although most of the patients were in the low-risk group such as Stage IB and grade 1-2, progression-free survival rates were 96% in the radiotherapy arm versus 88% in the control arm (p = 0.004), however the survival difference did not reach significance [16]. In the PORTEC trial 715 patients in the intermediate-risk group were randomized to pelvic radiotherapy and control arms. Five-year locoregional recurrence rates were 4% in the radiotherapy arm and 14% in the control arm (p < 0.001), and 5-year survival rates were 81% and 84%, respectively (p = 0.31) [7]. In a third trial by Aalders *et al.* they randomized 540 clinically Stage I

Table 2. — *Univariate and multivariate analyses for prognostic factors influencing disease-free survival.*

Factor	5 years	Univariate (p value)	Multivariate (p value)
Age			
≤ 60	90.9	0.540	
> 60	93.6		
Operation type			
TAH+BSO	93	0.267	
TAH+BSO+LD	89.3		
FIGO stage			
IA	87.5		
IB	97.9	0.001	0.001
IC	86		
Histopathology	100		
Adenocarcinoma	92.9	0.004	0.10
Other pathological types	82.5		
Histologic grade			
1	91.7		
2	92.2	0.247	
3	90.7		
Lymphovascular invasion			
No	93.2	0.04	0.033
Yes	85.1		
Overall radiation treatment time			
≤ 8 weeks	93.1		
> 8 weeks	87.3	0.158	
BMI (kg/m²)			
≤ 30	91		
> 30	95.6	0.540	
Extension to isthmus			
Yes	83.3		
No	92.3	0.282	

Table 3. — *Univariate and multivariate analyses for prognostic factors influencing overall survival.*

Factor	5 years	Univariate (p value)	Multivariate (p value)
Age			
≤ 60	85.3	1.85	
> 60	86		
Operation type			
TAH+BSO	88.5	0.012	0.170
TAH+BSO+LD	83.9		
FIGO stage			
IA	87.5		
IB	94.1	0.017	0.011
IC	81.7		
Histopathology			
Adenocarcinoma	88.9	0.005	0.026
Other pathological types	76.6		
Histologic grade			
1	94		
2	89.2	0.02	0.005
3	78		
Lymphovascular invasion			
No	88.5	0.012	0.170
Yes	83.9		
Overall radiation treatment time			
≤ 8 weeks	89.7		
> 8 weeks	81.1	0.021	0.134
BMI (kg/m²)			
≤ 30	85.3		
> 30	89.1	0.637	
Extension to isthmus			
Yes	83.3		
No	87.9	0.995	

Table 4. — *Univariate and multivariate analyses for prognostic factors influencing loco regional relapse-free survival.*

Factor	5 years	Univariate (p value)	Multivariate (p value)
Age			
≤ 60	98.1	0.628	
> 60	98.4		
Operation type			
TAH+BSO	99.2	0.073	
TAH+BSO+LD	96.1		
FIGO stage			
IA	100		
IB	99.5	0.312	
IC	96.8		
Histopathology			
Adenocarcinoma	98.6	0.025	0.045
Other pathological types	92.1		
Histologic grade			
1	97.9		
2	98.5	0.915	
3	97.2		
Lymphovascular invasion			
No	100	0.195	
Yes	97.2		
Overall radiation treatment time			
≤ 8 weeks	98.3		
> 8 weeks	98.9	0.48	
BMI (kg/m²)			
≤ 30	100		
> 30	99.1	0.628	
Extension to isthmus			
Yes	98.1		
No	100	0.61	

Table 5. — *Univariate and multivariate analyses for prognostic factors influencing distant metastasis-free survival.*

Factor	5 years	Univariate (p value)	Multivariate (p value)
Age			
≤ 60	91.6	0.239	
> 60	95.1		
Operation type			
TAH+BSO	93.7	0.358	
TAH+BSO+LD	90.8		
FIGO stage			
IA	87.5		
IB	98.4	0.01	0.003
IC	87.5		
Histopathology			
Adenocarcinoma	93.4	0.04	0.09
Other pathological types	87.1		
Histologic grade			
1	93.7		
2	92.9	0.737	
3	91.8		
Lymphovascular invasion			
No	94.4	0.001	0.06
Yes	85.2		
Overall radiation treatment time			
≤ 8 weeks	94.4		
> 8 weeks	87.3	0.058	
BMI (kg/m²)			
≤ 30	91		
> 30	95.6	0.538	
Extension to isthmus			
Yes	83.3		
No	93.1	0.246	

Table 6. — *List of treatment related acute and late side-effects according to RTOG/EORTC morbidity criteria.*

	Number of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Acute side-effects				
Diarrhea	26 (6.5)	62 (15.5)	1 (0.2)	–
Cystitis	38 (9.4)	52 (12.9)	–	–
Radiodermatitis	34 (8.4)	31 (7.7)	–	–
Leucopenia	14 (3.5)	–	–	–
Nausea and vomiting	6 (1.5)	–	–	–
Proctitis	12 (3)	47 (11.7)	–	–
Late side-effects				
Genitourinary tract	29 (7.2)	5 (5)	2 (0.4)	–
Gastrointestinal tract	10 (2.5)	7 (1.7)	2 (0.5)	–
Vaginal stenosis*	23 (5.7)	9 (2.2)	31 (7.7)	–

* Graded according to the French-Italian glossary.

patients after hysterectomy and vaginal brachytherapy to receive pelvic radiotherapy or no further treatment. The local control rate was 2% with vaginal brachytherapy and pelvic radiotherapy versus 6.9% with vaginal brachytherapy alone [10]. All these results reveal that postoperative radiotherapy has an impact on locoregional control in intermediate-risk groups of patients but this benefit does not reflect overall survival. In the present study intermediate-risk patient locoregional recurrence rates were 2% and 5-year overall survival 87.7%, in accord with other reports [7, 10].

Radiotherapy is used in the treatment of endometrial carcinoma, especially in patients with poor prognostic factors, and many published series have tried to identify prognostic factors for local recurrence and distant metastases [9, 17, 24]. The degree of histopathologic differentiation is generally considered to be one of the most sensitive predicting factors of tumor spread [4]. Histological degree, myometrial invasion depth and presence of intraperitoneal metastases have been clearly defined as poor prognostics. In 1991, the GOG revealed that there was tendency for deep myometrial invasion and subsequently a higher rate of pelvic and paraaortic lymph node involvement [17]. Touboul *et al.* analyzed 437 operable endometrium carcinoma cases and concluded that there is a correlation between grade and myometrial invasion [4]. In multivariate analysis, myometrial invasion ($p = 0.011$) and grade ($p = 0.005$) were confirmed to be significant prognostic factors. Survival rates for Stage IA, IB, IC were 87.5%, 94.1%, 81.7%, respectively. In that study, lower survival rates for Stage I patients were due to poor histopathology (6 of the 9 Stage IA patients had serous papillary and clear cell carcinoma histopathology).

As in our series, many authors have also found that each histopathology subtype has a different biologic behavior and adenocarcinoma has a better prognosis than adenosquamous, clear cell, and serous papillary subtypes. Recurrence rates were higher in these groups [17, 23, 24]. After multivariate analyses, histopathological subtypes other than adenocarcinoma have an independent impact on locoregional relapse-free survival and OS ($p = 0.004$).

Lymphovascular space invasion is defined as an independent risk factor for locoregional or systemic recur-

rence and a common sign of tumors with deep myometrial penetration and cervical invasion. It is related to the high regional and intraabdominal failure rates. According to Alders *et al.*, the death rate increases from 4% to 27% in the presence of LVSI (p = 0.01) [10]. In the current study the presence of LVSI had an adverse effect on overall, disease-free and distant metastasis-free survival. Extension to the isthmus and/or cervix has often been cited as a prognostic factor for outcome. In the literature, when univariate analysis is applied, extension to the isthmus and/or cervix effectively influences DFS. However, after multivariate analysis it is not independently significant because it is thought that these results are influenced mainly by tumor stage [4]. In the present study there was no statistical significance for extension to the isthmus and/or cervix on DFS.

The impact of age on survival remains uncertain. According to the PORTEC trial the most important prognostic factors that affected locoregional control were age and radiotherapy. The locoregional recurrence rate for patients under 60 years was 4%, and 10% for patients over 60 years (p = 0.02), and in multivariate analyses locoregional recurrence rates were three times higher in patients over 60 years (p = 0.003) [7], however, in several other series (including the present), age did not influence survival rate [4].

In past years it was shown that overall radiation time in patients with intact cancer is an important prognostic factor for OS [28, 29]. The impact of overall radiation time was questioned in two retrospective studies and no influence was found [30, 31]. Different from the literature, prolongation of overall radiotherapy treatment time in our study was found to be an adverse prognostic factor on OS in univariate analysis.

Obesity is a known risk factor for endometrial cancer due to the excess endogenous estrogen found in adipose tissue. Anderson *et al.* found that time to recurrence increased significantly (p = 0.014) and recurrence rates decreased (not significant) as BMI increased [32]. Also pathologically, patients with a BMI > 40 were more likely to have endometriod histology, lower stage disease, expression of HER-2/neu and lower grade tumors than women with a BMI of < 30 [33-35]. Obesity is associated with OS in cancer of the uterus. However, because of the association of obesity with confounding variables like age, stage and grade, obesity does not appear to be an independent predictor of survival in women with endometrial carcinoma [33]. In the present study because of the low number of patients with a BMI of < 25 or > 40, the relationship between obesity and survival was not defined statistically.

Because of long-term life expectancy in endometrium carcinoma, the best tumor control with minimal morbidity should be obtained. The benefit of lymphadenectomy is unclear; firstly lymphadenectomy increases complication rates and the risk of lymph node metastases is below 10% for Stage I carcinomas except Stage IC grade 3 [7, 8, 24]. However the most important benefit of lymphadenectomy is to select patients with high-risk pelvic recurrence or accurate staging [36]. A significantly higher 5-year OS rate was seen in patients who had not had lymphadenectomy performed compared to those undergoing lymphadenectomy (88.5% vs 83.9%; p = 0.012). In the first group, more than 40% of the patients were Stage IB G2 and in the second group only 40% of the patients were Stage IB G2. This statistical significance on the OS could be associated with distribution of the patients with Stage IB G2.

In the reported literature severe complication rates were low. Grade 3 and 4 late toxicity rates were published after TAH-BSO with external radiotherapy from 2% to 6%, after surgery followed by ERT with VBT from 4% to 13% and after ERT and surgery including lymphadenectomy from 7% to 18% [37]. Grade 1-2 late toxicities were about 20% and the most frequent were diarrhea, increasing motility of intestines and abdominal cramps. Urinary complications such as polyuria, minor incontinence and cystitis episodes were seen less frequently [15]. In a GOG study, hematological, gastrointestinal, genitourinary and cutaneous toxicities rates were higher in the pelvic radiotherapy arm compared to the observation arm (p < 0.001); two patient deaths were related to gastrointestinal toxicity. In the radiotherapy arm GI and genitourinary toxicity were reported in 68% and 30% of patients, respectively [16]. In the PORTEC study, during radiotherapy 63% of the patients were treated with medication or dietary aids or both, for treatment-related symptoms. In the present study, 48% of the patients were treated for acute side-effects. Mild and moderate vaginal stenosis is the most commonly noted late side-effect after radiotherapy [38-40]. Sorbe *et al.* reported 15% of vaginal stenosis with only HDR brachytherapy [38]. In the present study, we observed 22.2% of gastrointestinal and 21.3% of genitourinary toxicity. The most common late side-effect was vaginal stenosis (7.7%). The overall late toxicity rate was 25.7% and no RTOG grade 4 complication was recorded.

In conclusion, our analysis showed a relatively good prognosis in endometrial cancer patients treated with external RT and vaginal brachytherapy. Postoperative treatment increases the risk of late radiation side effects. To reduce the side-effects, the role of vaginal brachytherapy alone or the addition of vaginal brachytherapy to external pelvic RT needs to be clarified through well designed randomized trials using modern radiotherapy techniques. Future work is needed to define the role of radiotherapy in a subgroup of Stage I patients. We conclude that postoperative adjuvant RT provides high locoregional control rates with acceptable toxicity in selected patients with Stage I endometrial carcinoma.

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