External radiation therapy for endometrial carcinoma: The University Hospital of Ioannina experience

E.E. Pakos, *M.D.*; **S.P. Gritzeli,** *M.D.*; **P.G. Tsekeris,** *M.D.*; **E.J. Pitouli,** *M.D.*; **M.E. Fintzou,** *M.D.*

Department of Radiation Therapy, University Hospital of Ioannina, University of Ioannina, Medical School, Ioannina (Greece)

Summary

Purpose of investigation: The aim of our study was to present the experience of our department in the treatment of endometrial cancer with postoperative external beam radiotherapy (EBRT) without intracavitary brachytherapy (BRT) and to evaluate the efficacy of such a method.

Methods: We retrospectively retrieved the medical records of all patients with endometrial cancer treated with surgery and EBRT alone (median dose 50.0 Gy). Thirty-one women (median age: 67 years) of all clinical stages were reviewed and analyzed for recurrences (local or metastases) and late post-radiation side-effects.

Results: Within a median follow-up of 17 months one patient developed local recurrence and four developed metastases. Overall survival was 97% and disease-free survival was 87%. Three women developed post-radiation colitis. No other treatment-related late side-effects were observed.

Conclusion: EBRT without BRT achieved an excellent local control in women with endometrial cancer although some of them were candidates for supplementary BRT.

Key words: Endometrial cancer; External radiotherapy.

Introduction

Endometrial carcinoma remains one of the most frequent gynecological malignancies occurring predominantly in postmenopausal women. Several prognostic factors have been reported to play a potential role regarding disease progression such as clinical stage, tumor grade, histological subtype, myometrial invasion, age, molecular markers and others [1-11]. The treatment is mainly surgical consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH & BSO), followed in most cases by postoperative radiotherapy. The role of radiotherapy in endometrial cancer is still a matter of controversy concerning the time that it should be performed (pre- or post-operatively), the combination of external beam radiotherapy (EBRT) with supplementary intracavitary brachytherapy (BRT) or not, the significance and efficacy of brachytherapy alone and the dose of radiation that should be given.

This retrospective study was undertaken to demonstrate the experience of our department in the treatment of patients with endometrial carcinoma managed with postoperative external beam irradiation without intracavitary brachytherapy. We also tried to evaluate the efficacy of such treatment in preventing recurrences regardless of disease stage.

Materials and Methods

We retrieved retrospectively the medical records of all patients with endometrial cancer treated between 1993 and 2002 with surgery and postoperative external beam irradiation alone without intracavitary brachytherapy at the Radiation Therapy Department of the Ioannina University Hospital. Thirty-one patients were reviewed. All were treated with total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), abdominopelvic exploration and peritoneal washings. Patients were classified according to the FIGO 1988 classification [12].

External beam radiotherapy was given postoperatively within a mean time of 67 days (range 33- 216 days). Irradiation was delivered by either a linear accelerator (6 MV), or a Cobalt-60 unit. Four parallel opposed fields – anteroposterior, posteroanterior, and two laterals – were used (box technique). All fields were treated every day. The daily dose was 1.8 to 2 Gy and the median total radiation dose was 50 Gy (range 40Gy – 57 Gy) (Figure 1). The mean number of fractions was 27 (range 20-33). No patient received intacavitary brachytherapy and one woman received chemotherapy (carboplatin) before irradiation. During irradiation patients were examined weekly for adverse treatment-related effects.

After the end of radiotherapy all patients were followed-up by the radiation therapy department on an outpatient basis. They were assessed every three months for the first two years, every six months for the third and fourth year and annually thereafter. Their evaluation included a history on treatment-related morbidity and other symptoms, a physical examination, blood count and biochemical measurements. A chest radiograph and computed tomography (CT) scans of the pelvis and abdomen were performed once a year. Vaginal smears were taken every six months and biopsy samples on indication. During follow-up women were estimated for late side-effects of radiotherapy, local recurrences (vaginal or pelvic), metastasis and death. Survival time, recurrences and side-effects were estimated from the day of diagnosis. All patients or their families were contacted by phone call if they had not responded to their last programmed visit and they were asked questions about their current condition.

Survival and disease-free survival proportions were calculated with the Kaplan-Meier method. Analyses were performed with SPSS 10.0 (SPSS Inc., Chicago, IL).

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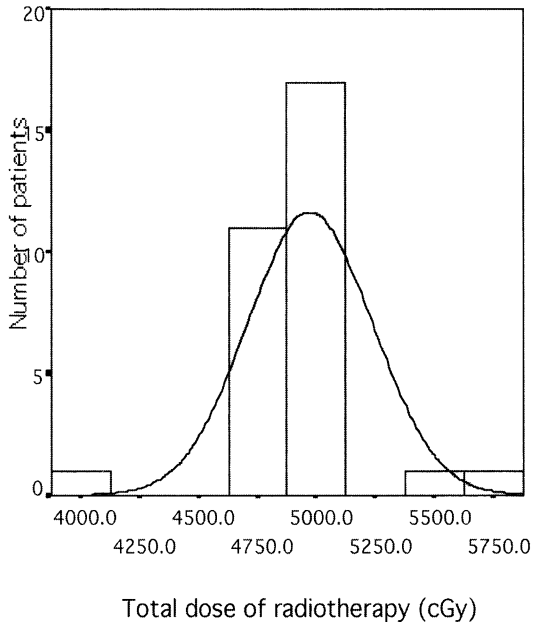

Figure 1. — Total dose of radiotherapy in 31 patients with endometrial carcinoma.

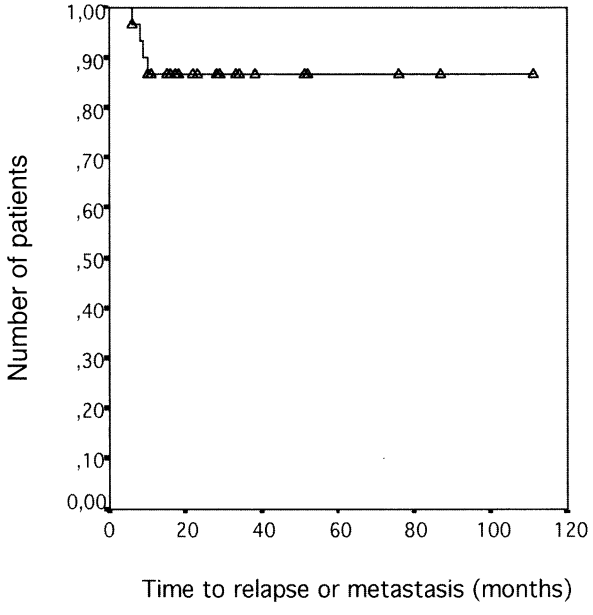

Figure 2. — Disease-free survival plot for 31 women included in the study. Triangles represent censorings.

Results

Thirty-one women with a variety of clinical stages were included in the study. No patient presented with metastatic disease at the initiation of radiotherapy. The median age of patients was 67 years (range 51- 76 years). Eighteen (58%) had Stage I endometrial cancer, four (13%) Stage II, eight (26%) Stage III, and in one case staging was unidentified. The most common histological subtype was endometrioid adenocarcinoma (22 women, 71%). The main patient characteristics are presented in Table 1. The median time of follow-up was 17 months (range 6-111 months), in which censoring was very common. All patients tolerated irradiation without interruption of their treatment. Acute side-effects (diarrhea, cystitis) developed in some patients and were managed with the appropriate medication.

Late radiation colitis proven by biopsy developed in three women (9.7%). All three responded to conservative management and required no surgical intervention or hospitalization. No other late side-effects were seen during follow-up. One patient developed local recurrence [3.23%, 95% Confidence Interval (CI) 0.1- 16.7%].

Distal metastases developed in four patients (12.9%, 95% CI 3.6-29.8%); two lung metastases, one liver metastasis and one abdominal carcinomatosis. Local recurrences and metastases occurred within the first two years all in patients with Stage III disease. The overall disease-free (DFS) (local recurrence or metastasis) survival was 87.1%, (95% CI 70.2%-96.3%) (Figure 2).

One woman with Stage III disease died at 12 months. The overall survival was 96.7%, (95% CI 83.3%-99.9%).

Discussion

The role of radiation therapy in endometrial cancer remains controversial despite the extension of its use in the last several years. The indications for radiotherapy, as well as the timing (external and/or brachytherapy), the dose and the time (pre- or postoperatively) have not been completely established yet, especially for Stage I disease. Some investigators recommend no treatment with radiation [13-15], whereas others support the usefulness of EBRT, either alone [16-18] in combination with BRT [19-22] according to the clinical sub-stage. The management of Stage I endometrial cancer requires the separation of patients into three groups of low, intermediate and high risk [22]. For Stages II and III disease postoperative EBRT combined with BRT seems to be the management choice [22].

Although the literature is dominated with a large number of studies examining the role of radiotherapy in endometrial cancer, only a few studies have focused on the role of external radiotherapy alone, without brachytherapy [16-18]. These studies have demonstrated the benefit of EBRT in the prevention of pelvic and vaginal cuff recurrences with restriction of the late side-effects of BRT, such as vaginal stenosis, chronic diarrhea, proctitis, sexual dysfunction and vault necrosis. Weis *et al.* [16] reported results of 61 women with endometrial cancer Stage Ic treated with adjuvant EBRT alone and no patient developed local recurrence within a median follow-up time of 69.5 months. The disease-free and overall survival, were 86.7% and 97.6%, respectively. Rush *et al.* [17] evaluated 87 patients with Stage I disease and noted no local recurrences, with a disease-free survival of 83% and a 5-year survival of 92%. Finally, Torrisi *et al.* [18] analyzed 46 women with Stage Ia-Ib disease and recorded three pelvic recurrences. In our study 18 patients with

Table 1. — *Characteristics of patients.*

Patient	Age	Histological Type	Grade	Stage	Type of RT	DD/TD	Follow-up
1.	63	Endometroid adenocarcinoma	–	IIIa	Linac	180/5040	12
2.	60	Endometroid adenocarcinoma	–	Ic	Linac	200/4000	28
3.	59	Endometroid adenocarcinoma	III	IIIb	Linac	180/5040	6
4.	51	Adenosquamous	I	IIa	Linac	200/4800	23
5.	71	Adenosquamous	II	IIIa	Linac	180/5040	9
6.	69	Endometroid adenocarcinoma	II	II	Linac	180/5040	10
7.	64	Endometroid adenocarcinoma	I	Ic	Linac	180/5020	16
8.	76	Endometroid adenocarcinoma	I	I	Linac	180/5000	29
9.	73	Endometroid adenocarcinoma	II	IIa	Linac	180/4860	11
10.	68	Endometroid adenocarcinoma	III	Ib	Alcyon	180/4860	76
11.	69	Papillary serous	II	Ic	Linac	180/4860	10
12.	52	Endometroid adenocarcinoma	II	Ic	Alcyon	180/5050	15
13.	70	Papillary serous	NR	Ic	Linac	200/4800	111
14.	65	Endometroid adenocarcinoma	I	Ic	Linac	180/4840	10
15.	71	Endometroid adenocarcinoma	II	Iib	Linac	180/5000	52
16.	65	Endometroid adenocarcinoma	II	Ic	Linac	200/5000	28
17.	51	Endometroid adenocarcinoma	III	Ic	Linac	180/5700	51
18.	55	Adenoacanthoma	NR	NR	Linac	180/4860	18
19.	67	Endometroid adenocarcinoma	II	Ic	Linac	180/5600	34
20.	73	Endometroid adenocarcinoma	II	Ic	Linac	180/5040	18
21.	73	Adenosquamous	I	Ic	Linac	180/5040	33
22.	62	Endometroid adenocarcinoma	II	Ic	Linac	180/4860	15
23	67	Endometroid adenocarcinoma	I	Ic	Linac	180/4860	11
24.	62	Adenosquamous	II	Ib	Linac	180/5040	22
25.	58	Endometroid adenocarcinoma	III	IIIa	Linac	200/5000	38
26.	67	Endometroid adenocarcinoma	III	IIIa	Linac	180/5040	7
27.	54	Endometroid adenocarcinoma	III	Ib	Linac	180/4860	17
28.	75	Adenoacanthoma	III	Ic	Linac	180/5040	17
29.	63	Endometroid adenocarcinoma	NR	IIIa	Alcyon	180/4860	15
30.	70	Endometroid adenocarcinoma	II	IIIb	Linac	200/5000	87
31.	67	Adenosquamous	III	IIIa	Linac	180/5040	10

NR: Not reported, RT: radiotherapy, Linac: linear accelerator, Alcyon: cobalt-60 unit, DD: daily radiation dose, TD: total radiation dose.

Stage I disease were included. No local recurrences or metastases were observed among them.

This study includes our experience since 1993, and our aim is not to demonstrate that in every case of endometrial carcinoma the appropriate treatment is postoperative external beam irradiation (EBRT) alone regardless of staging. A combination of EBRT and BRT should be given to a number of patients according to criteria such as infiltration of the lower uterine segment, vaginal involvement, positive or close surgical margins, capillary space involvement or unfavorable histology [22].

Some limitations of our study should be acknowledged. First of all there was a remarkable heterogeneity (dissimilarity) between our patients regarding stage of disease. Although some patients were candidates for supplementary intracavitary brachytherapy according to the previously presented indications [22], they refused the suggested supplementary treatment mainly due to their low social-economic and educational level. Secondly, despite the fact that we were all-inclusive our study was of limited sample size. Furthermore, the estimates that we obtained were unadjusted for parameters that may be related to endometrial cancer outcomes. Finally, although we tried to retrieve additional or missing information by calling patients or their families the median follow-up of patients was still short and censoring remained very common.

Given that a brachytherapy section is not available in the radiation therapy department of our hospital, which covers a large geographical area of our country, we present our data concerning patients with endometrial carcinoma treated postoperatively with EBRT alone, including a subgroup of patients that needed BRT. However, that was impossible to carry out due to several reasons.

The role of external beam radiotherapy without BRT in a group of patients with endometrial cancer should be examined by larger and randomized trials with a homogeneous population, adjusted for prognostic parameters. The short-term and the late side-effects of brachytherapy, along with the increase of treatment time, the cost and the hospitalization should be taken into serious consideration by future investigators.

Conclusion

The aim of our study was to report the experience of our department and to evaluate the efficacy of postoperative external beam radiotherapy, without intracavitary brachytherapy in women with endometrial carcinoma. External radiotherapy was proven to achieve an excellent local control of disease. With a median follow-up of 17 months (mean: 27 months) one patient out of 31 devel-

oped a local recurrence. The overall survival was 97% and the disease-free survival was 87%. Radiation colitis as a late side-effect was seen in three patients.

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Address reprint requests to:
E.E. PAKOS, M.D.
Neokoropoulo
Ioannina 45500 (Greece)