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CLINICAL INVESTIGATION **Endometrium**

DEFINITIVE RADIOTHERAPY IN THE MANAGEMENT OF ISOLATED VAGINAL RECURRENCES OF ENDOMETRIAL CANCER

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Purpose: The aim of our study was to assess prognostic factors and overall survival after salvage radiotherapy for patients who had endometrial carcinoma and who experienced an isolated vaginal recurrence.

Methods and Materials: We reviewed the records of 50 patients treated at our institution between 1967 and 2003 for an isolated vaginal recurrence of endometrial carcinoma. Initial treatment for endometrial carcinoma was definitive surgery in 49 patients and definitive radiotherapy in 1 patient. The median time from initial diagnosis of endometrial carcinoma to recurrence was 25 months (range, 4–179 months). Three patients (6%) received external-beam radiotherapy alone, 8 patients (16%) received brachytherapy only, and 39 patients (78%) received combined external-beam radiation therapy and brachytherapy. Median dose of radiation to the recurrence was 60 Gy (range, 16–85 Gy). Overall survival was calculated by the Kaplan-Meier method. Endpoints were measured from the date of diagnosis of the vaginal recurrence. Median follow-up of survivors after recurrence was 53 months (range, 8–159 months).

Results: The 5-year and 10-year disease-free and overall survivals were 68% and 55%, and 53% and 40%, respectively. On multivariate analysis, age ($p = 0.0242$), Grade 1 or 2 vs. Grade 3 tumor ($p = 0.002$), and size of recurrence ($p < 0.001$) were significant predictors of overall survival. All patients who had Grade 3 disease were dead by 3.6 years from the time of recurrence. Five patients experienced a Grade 3 or 4 complication.

Conclusions: Patients treated with radiotherapy for an isolated vaginal recurrence can be cured in over 50% the cases. Radiotherapy is well tolerated, with a low risk of complications. Factors predictive of overall survival include tumor grade, patient age at recurrence, and tumor size. © **2005 Elsevier Inc.**

Endometrial cancer, Recurrent, Radiotherapy.

INTRODUCTION

Endometrial carcinoma represents the most common gynecological malignancy in the United States. In 2004, an estimated 34,000 new cases occurred (1). Standard therapy for endometrial carcinoma is total abdominal hysterectomy, bilateral salphingo-oophorectomy with lymph node sampling. Factors that influence the selection of adjuvant treatment include age, depth of invasion, tumor grade, lymphovascular space invasion, histologic type, and lymph node status. Three randomized studies in patients who had intermediate-risk or high-risk features have demonstrated that postoperative radiotherapy reduces the risk of pelvic recurrence but with no clear benefit to overall survival (2–4). This risk reduction may be a result of the effective salvage methods for patients who experienced recurrence.

The purpose of this retrospective study is to analyze the outcome of patients who had isolated vaginal recurrences treated with radiotherapy at Washington University School of Medicine.

METHODS AND MATERIALS

The clinical records of patients treated with irradiation for recurrent endometrial carcinoma at the Department of Radiation Oncology at Washington University in St. Louis between 1967 and 2003 were reviewed. Patients who had pelvic or para-aortic lymph node metastases or any evidence of distant metastases were excluded from analysis. Fifty patients who received definitive radiotherapy for an isolated vaginal recurrence of endometrial carcinoma comprise our analysis. The Washington University Human Studies Committee approved this retrospective record review. The median age of patients at diagnosis was 69 years (range: 44–89 years). Patient and tumor characteristics at the time of initial treatment are listed in Table 1. Forty-nine patients underwent definitive surgery, with total abdominal hysterectomy and bilateral adnexectomy. No routine lymph node sampling was performed until after 1987. One patient received definitive radiotherapy to her pelvis to a dose of 4,600 cGy from ^{60}Co. Ten patients received radiotherapy (preoperative or postoperative) in addition to surgery as part of their initial management of endometrial carcinoma. Two

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Table 1. Patient and tumor characteristics at the time of primary treatment

Charateristics	*N*
Race/ethnicity	
Caucasian	49
Black	1
Histologic subtype	
Adenocarcinoma	46
Papillary (nonserous)	2
Papillary serous	1
Unknown	1
FIGO Stage	
I	33
II	9
III	6
Unknown	2
FIGO Grade	
Grade 1	16
Grade 2	22
Grade 3	12
Radiotherapy for primary	
None	39
Preoperative	3
Postoperative	7
Definitive	1
Site of recurrence	
Upper vagina	44
Distal vagina	6

Abbreviation: FIGO = Federation of Gynecology and Obstetrics.

patients received preoperative intracavitary radiotherapy, 1 patient received external-beam radiotherapy (EBRT) preoperatively, 2 patients received postoperative brachytherapy alone, 2 patients received postoperative EBRT, and 3 patients received a combination of EBRT and brachytherapy. Two patients received adjuvant chemotherapy. Six patients were recommended to have adjuvant radiotherapy but declined further treatment. These patients were felt to be at high risk for recurrence by their treating physicians. Additionally, 29 patients met the initial enrollment criteria for Gynecologic Oncology Group (GOG-99) (2). Nine patients had high intermediate-risk disease and 9 patients had low intermediate-risk disease. Risk classification was unknown for 11 patients.

Restaging evaluation

All patients underwent a complete medical evaluation at the time of their recurrence that included a thorough history and physical examination. The size of the vaginal recurrence was recorded on a tumor diagram. Vaginal recurrence was histologically confirmed by biopsy in each patient. All patients had chest radiography. Forty-four patients underwent CT scan of the abdomen and pelvis to rule out extravaginal disease. Thirteen patients received whole-body FDG-PET. Twenty patients were asymptomatic, and the diagnosis of recurrence was made by physical examination. In other patients, the most common symptom was vaginal bleeding (30 of 50 patients). Four patients developed pelvic/sciatic pain or constipation as a component of their initial symptoms. Median size of recurrent disease was 2.0 cm (range, 0–7 cm). Two patients did not have an estimate of the size of recurrence recorded. The recurrence was located in the upper vagina in 44 patients and the distal vagina in 6 patients. The site of recurrence for the 11 patients who received radiotherapy for any component of their treatment was distal vagina (2) and upper vagina (9).

Treatment of relapse

Two patients (4%) received EBRT alone, 8 patients (16%) received brachytherapy only, and 40 patients (80%) received combined EBRT and brachytherapy. The policy at Washington University for treatment of isolated vaginal recurrences of endometrial cancer has largely remained the same over the time period of this study. A combination of brachytherapy and EBRT was delivered if the patients had no previous history of radiotherapy. If patients had previously received EBRT, then brachytherapy alone was performed. EBRT was delivered via high-energy megavoltage photons (betatron, clinac 35, clinac 20, and 18 megavoltage photons). EBRT was delivered either in parallel opposed anteroposterior and posteroanterior fields or by use of a 4-field (box) technique. For 23 patients, central lead shielding was used for the last part of the EBRT. All fields were treated daily 5 days a week. EBRT was not delivered on days the patient received brachytherapy.

Brachytherapy was delivered by use of vaginal cylinders, ovoids, miralva applicator, or an interstitial implant. The isotopes used were either cesium or iridium for low-dose-rate brachytherapy and iridium for high-dose-rate brachytherapy. The choice of applicator for brachytherapy was determined by the depth of vaginal disease. For patients whose vaginal disease was at a dept of 5 mm or more, interstitial brachytherapy was used. The dose of radiotherapy delivered via a vaginal cylinder was prescribed to 5-mm depth.

Eight patients received brachytherapy only. Four patients had received initial postoperative EBRT, and 1 patient had previous pelvic EBRT for non-Hodgkin's lymphoma. One patient had previously received preoperative radiotherapy.

Median dose of radiation to the recurrence was 60 Gy (range, 16–85 Gy). Endpoints were measured from the time of first recurrence. Two patients received local excision before radiotherapy. Three patients received adjuvant hormonal therapy.

Follow-up

Patients were examined at 3-month intervals for the first 2 years after recurrence, at 6-month intervals for the next 3 years, and then yearly afterwards. Patients were censored at the time of death or last date of follow-up.

Statistical analysis

Time to recurrence was calculated from the date of surgery to the time of histologic confirmation of recurrence. Overall survival and disease-free survival were calculated by use of Kaplan-Meier estimates and calculated from the date of diagnosis of recurrence (5). The Cox regression model was used for multivariate analysis (6).

RESULTS

Median time from initial diagnosis to recurrence was 25 months (range, 4–179 months). Median age at the time of recurrence was 70 years (range, 45–90 years).

The overall 5-year and 10-year overall survival rates were 55% and 40%, respectively (Fig. 1). The disease-free survival rates at 5 and 10 years were 68% and 53%, respectively (Fig. 2). Thirteen patients developed a second recurrence in the pelvis: vaginal apex (9), distal vagina (3), and