CLINICAL INVESTIGATION

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

LILIE L. LIN, M.D.,* PERRY W. GRIGSBY, M.D., M.B.A.,†‡ MATTHEW A. POWELL, M.D.,†‡ AND DAVID G. Mutch, M.D.†‡

*Department of Radiation Oncology, Washington University Medical School, St. Louis, MO; the †Alvin J. Siteman Cancer Center, St. Louis, MO; and ‡Division Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University Medical School, St. Louis, MO

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.

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 salpingo-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 60Co. Ten patients received radiotherapy (preoperative or postoperative) in addition to surgery as part of their initial management of endometrial carcinoma. Two

Reprint requests to: Perry W. Grigsby, M.D., Radiation Oncology Department, Washington University Medical School, Box 8224, 4921 Parkview Place, St. Louis, MO 63110. Tel: (314) 362-8502; Fax: (314) 747-9557; E-mail: pgrigsby@wustl.edu

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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.

### 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 depth 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

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pelvic lymph nodes and vaginal cuff (1). One patient had simultaneous distant metastases and vaginal apex failure. Six patients had distant metastases as the first site of failure; lung and liver were the most common sites. Twenty-five patients were dead at last follow-up. Twelve patients died of disease. Six patients died of intercurrent illnesses; 2 patients had evidence of endometrial cancer at the time of their death. Two patients died of a second primary cancer. The cause of death was unable to be determined for 5 patients. All had no evidence of disease at last follow-up.

The mean length of follow-up from the date of initial diagnosis of recurrence of endometrial cancer was 4.9 years (range, 0.70–22.5 years). For the 25 patients who were alive at last follow-up, the mean duration of follow-up was 5.3 years (0.70–13.3 years).

Prognostic factors

On multivariate analysis, factors predictive of overall survival included grade of the primary lesion, age at recurrence, and size of recurrence. Patients who had initial Grade 3 disease had a worse outcome compared with patients who had initial Grade 1 or Grade 2 disease ($p = 0.002$). The relationship between grade and overall survival can be seen in Fig. 3. Factors that did not influence overall survival included total dose of radiotherapy, type of treatment delivered, and time to recurrence. A number of factors, such as size of recurrence, time to recurrence, patient age, dose, and grade of primary lesion, were examined as potential prognostic factors for local control; however, none were significant.

DISCUSSION

Survival rates after vaginal relapses after salvage radiotherapy have been reported in the literature to range between 25% and 68% (7–10). A previous report from our institution concluded that patients who had extravaginal disease were unable to be salvaged with radiotherapy alone and are excluded from this analysis (11). Similar results have been reported elsewhere (4). The majority of recurrences regardless of initial site occur during the first 3 years from the time of original treatment (7, 8, 11).

Several factors have been previously reported to correlate with overall survival. These factors include size of recurrent tumor, grade, dose of radiotherapy, and time to recurrence. High tumor grade has been reported to correlate with poor

![Fig. 1. Kaplan-Meier curve of overall survival for 50 patients treated with radiotherapy for vaginal recurrence of endometrial cancer.](image1)

Complications

Five late Grade 3 or 4 gastrointestinal complications occurred. All 5 patients had small-bowel obstruction. Three patients required partial small-bowel resection. Two patients were managed without surgical intervention. All 5 patients received tumor doses less than 75 Gy. One patient previously received a preoperative intracavitary radiotherapy implant. Two patients are alive without evidence of disease and 2 patients have died after a subsequent recurrence. No late Grade 3 or 4 genitourinary complications resulted from treatment.

![Fig. 2. Kaplan-Meier curve of disease-free survival for 50 patients treated with recurrent endometrial cancer.](image2)

![Fig. 3. Kaplan-Meier curve of overall survival for 50 patients treated for recurrent endometrial cancer stratified by grade of primary lesion.](image3)
outcome (7, 12, 13). Hart et al. (12), in a review of 26 patients treated with definitive radiotherapy for isolated vaginal relapses, found that moderate to poor differentiation correlated with poor overall survival. Jhingran et al. (7) reported in a similar cohort that patients who had Grade 3 lesions had poorer overall survival compared with patients who had Grade 1 or 2 lesions, as was seen in our study. In a surgicopathologic staging study conducted by the Gynecologic Oncology Group of 895 patients who had clinical Stage I or II endometrial carcinoma, Grade 3 tumors was the single most important predictor of recurrence (13). In our analysis, initial grade of the tumor was significantly predictive of overall survival; no patients survived beyond 3.6 years with Grade 3 tumors. Patients who had Grade 2 tumors had an outcome similar to patients who had Grade 1 tumors. This observation is consistent with what has been reported by others (14, 15).

Time to local recurrence has also been reported to be a significant predictor of overall survival, with a better prognosis for late recurrences (16, 17). Most studies have reported recurrences within the first 3 years after initial diagnosis. Sears et al. (16) reported actuarial survival rates of 40% and 70% for patients who relapsed less than 1 year and more than 1 year, respectively, from time of diagnosis. We did not find time to recurrence to be predictive of overall survival.

Local control of tumor has also been reported to be related to size of recurrence (9, 18). Greven and Olds (18) reported size to be the most important prognostic factor for local control. Wylie et al. (9) also reported actuarial survival rates of 40% and 70% for patients who relapsed less than 1 year and more than 1 year, respectively, from time of diagnosis. We did not find size to be predictive of overall survival.

Several groups have reported the influence of dose to the tumor on overall survival and pelvic-control results. Wylie et al. (9) found that disease bulk greater than 2 cm resulted in worse local control, but had no influence on overall survival. In our study, overall survival was significantly worse for patients who had disease greater than 2 cm; however, local control was independent of size.

Curran et al. (19) reported that patients who received 60 Gy or more had a significantly improved overall survival and pelvic-control results. Wylie et al. (9) also reported a trend toward improved local control at doses greater than 80 Gy (p = 0.07). Jhingran et al. (7) also found that doses of 80 Gy or more had higher local control rates. The median dose of radiation in our study was 60 Gy. No statistically significant difference occurred in local control or overall survival for patients with respect to dose in our series (p = 0.42).

Five-year disease-free survival in our study was 68%, with local control of disease in 37 of 50 patients. This outcome is similar to what has been reported by Jhingran et al. (7). They found local control at 5 years to be 75%. We found no factors that were prognostic of local control in our study. This observation may be a result of the few pelvic or vaginal failures that were seen.

Two recent reported randomized studies have addressed the role of adjuvant radiotherapy in intermediate-risk patients (2, 3). A Phase III study by GOG-99 randomized patients to receive pelvic EBRT or observation (2) after surgery. Overall survival estimates at 48 months for patients in the observation arm was 86% vs. 92% in the radiotherapy arm (p = 0.55). However, a statistically significant difference occurred in cumulative incidence of recurrence: 2% for radiotherapy arm vs. 12% for the observation arm (p = 0.007). Similar results were previously reported by the PORTEC study group: a 5-year locoregional recurrence rate of 14% in the no-adjuvant-treatment group vs. 4% in the pelvic-radiotherapy group (20). Despite the higher locoregional control rate, no survival difference was reported. The absence of a survival difference in these studies is likely related to the rate of successful salvage after relapse. In a follow-up report, the PORTEC study group analyzed the rates of local control and survival after relapse (3). The majority of recurrences occurred in the vaginal vault and could be salvaged by radiotherapy, surgery, or both, with the 3-year actuarial survival rate after vaginal relapse at 73%. In our analysis, 29 patients that would have met initial criteria for GOG-99, and at least 9 of those patients would have criteria for high intermediate-risk disease. Initial adjuvant radiotherapy for these patients may possibly have prevented subsequent local recurrence. Our current treatment policy at Washington University is to deliver adjuvant radiotherapy to patients who have high intermediate-risk endometrial cancer.

CONCLUSIONS

Patients who have isolated vaginal recurrences of endometrial cancer can be salvaged with radiotherapy with a low risk of complications, especially patients who have Grade 1 or 2 disease, small tumors, and younger age. Histologic grade has been reported by several studies to be important to overall survival but not necessarily significant for local control. Identifying patients at higher risk for a second recurrence or distant metastases may be important in the determination of their treatment.

REFERENCES


