ORIGINAL ARTICLE

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Radiotherapy for Pelvic Recurrence after Radical Hysterectomy for Cervical Cancer

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Purpose: To evaluate outcomes in patients treated with irradiation for recurrent cervical cancer after hysterectomy.

Methods: This is a retrospective chart review of 36 patients initially treated with a radical hysterectomy and lymph node dissection who developed a pelvic recurrence and were subsequently treated with irradiation. None received chemotherapy.

Results: The overall 5- and 10-year survivals were 74% and 50%, respectively. Ten patients developed recurrent disease after irradiation. The sites of failure in these 10 patients were pelvis only in two, pelvis and distant metastases in five, and distant metastases only in three. Severe complications occurred in four patients. One patient developed a hip fracture, one developed a bowel obstruction requiring a colostomy, and two developed fistulae.

Conclusion: Pelvic irradiation and brachytherapy resulted in a 74% overall 5-year survival. Distant metastases were the most common site of failure. Systemic chemotherapy should be considered as adjunctive therapy for these patients.

Key words: cervical cancer, pelvic recurrence, radical hysterectomy

INTRODUCTION

THE INCIDENCE OF A PELVIC RECURRENCE AFTER A radical hysterectomy and lymph node dissection varies depending upon patient-specific risk factors. Even in the absence of these poor prognostic factors such as large tumor size, deep stromal invasion by tumor, lymphovascular space involvement, positive margins, positive parametrial invasion, and positive pelvic lymph nodes, a small percentage of patients will develop a pelvic recurrence of their disease. These recurrences are most often detected when the patient presents with symptoms of a recurrence.[1] Because these recurrences are symptomatic they tend to be large in size and, therefore, irradiation is usually the treatment of choice rather than surgery. Survival rates in patients with pelvic recurrences of cervical cancer after a radical hysterectomy that are treated with irradiation alone range from 6% to 77%.[2] The purpose of this study was to ascertain the treatment results in patients treated at the Mallinckrodt Institute of Radiology with irradiation for recurrent cervical cancer after hysterectomy.

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PATIENTS AND METHODS

Patient characteristics

This study is a retrospective review of 36 patients with the diagnosis of recurrent cervical cancer after a radical hysterectomy and lymph node dissection. This study was approved by the Institutional Review Board, and informed consent was obtained from each subject. Recurrent tumor was confined to the pelvis. Patients were treated with irradiation alone between 1953 and 1996.

Patients were evaluated by a medical history and a physical examination. Routine blood counts and chemistry profiles were performed. All patients had a chest x-ray. An intravenous urogram was obtained in the majority of patients. Patients not undergoing an intravenous urogram underwent a CT scan of the abdomen and pelvis with intravenous contrast material. Most patients had a barium enema. All patients had a pelvic examination under anesthesia. Patients with urinary and gastrointestinal symptoms had a cystoscopy and a procto-sigmoidoscopy performed. Recurrent carcino-

ma of the cervix was histologically confirmed in all patients. Tumor was confined to the vaginal apex and immediately adjacent tissues in 33 patients. Pelvic sidewall recurrences occurred in three.

Patient age ranged from 24 to 58 years (mean, 32 years). The histology of the recurrent tumor was squamous cell carcinoma in 32 and adenocarcinoma in four. The median time to recurrence after the hysterectomy was 2.6 years.

All patients were followed for a minimum of 5 years after irradiation. The mean follow-up of patients alive at the time of last follow-up was 15.6 years (range, 5 to 25 years).

Radiation therapy

Patients were treated with a combination of external irradiation and brachytherapy. External irradiation was delivered to the pelvis with high energy photons. In the early years of the study, 22 MV photons (Betatron) were utilized, and, later, 18-25 MV photons from linear accelerators were used. Pelvic fields were treated with parallel-opposed anterior-posterior fields. The pelvic field extended from the L4-L5 intervertebral space superiorly, to encompass the common iliac lymph nodes, to the lower border of the ischial tuberosities, or 4 cm below the distal vaginal disease. The lateral border of the pelvic field was 1 cm lateral to the widest diameter of the pelvis.

Brachytherapy was administered with either Fletcher-Suit afterloading applicators, interstitial Cs-137 needles, or afterloading interstitial Ir-192 needles.

Irradiation doses

Fractionation of the external irradiation was 1.8 Gy midplane tumor dose daily, 5 fractions per week, to the pelvis. Doses to the pelvis ranged from 50.1 Gy to 60.4 Gy (median, 57.6 Gy). Most patients underwent additional low-dose-rate brachytherapy for an additional tumor dose of 10.0 Gy to 30.0 Gy (median, 20 Gy). Brachytherapy tumor dose was defined as the minimum irradiation dose covering the clinical tumor volume with a 0.5 cm margin.

External pelvic irradiation only was administered to the three patients with pelvic sidewall recurrences. The remaining 33 patients with vaginal apex recurrences were treated with external pelvic irradiation and brachytherapy.

Response evaluation

Patients were evaluated for toxicity and tumor response weekly and at the completion of radiation therapy. Patients were evaluated periodically as follows: monthly for 3 months; every 3 months until 12 months; every 4 months during the second year; every 6 months in years 3, 4, and 5; and yearly thereafter.

Chronic radiation toxicity, later than 90 days after completion of therapy, were documented according to the following criteria: 3 for severe symptoms requiring frequent medication; 4 for severe and persistent symptoms requiring surgical intervention; and 5 for treatment-related death.

Statistical methods

Local tumor control, overall survival, cause-specific survival, patterns of relapse, and toxicity were the major endpoints of this study. Survival time was measured from the date of the start of radiation therapy. The Kaplan-Meier (product limit) method was used to derive the estimates of survival.[3]

RESULTS

The overall survival estimates at 5, 10, and 25 years were 74%, 50%, and 35%, respectively. The median overall survival was 9.5 years (Fig. 1). The 5- and 10-year cause-specific survival estimates were 74% and 71%, respectively (Fig. 2). The median time to the development of recurrent disease after irradiation was 2.75 years (range, 1 to 5.5 years).

The status of the patients at the time of last follow-up was as follows: alive and no evidence of disease, 16; dead of disease, 10; and dead of intercurrent disease, 10. The sites of failure for the 10 patients who developed recurrent disease after irradiation were pelvis only in two, pelvis and distant metastases in five, and distant metastases only in three. Pelvic failures without distant metastases occurred in 20% of those who failed. The overall pelvic failure rate was 70% of those who failed. Thirty percent of the failures were distant metastases only and 80% of those who failed had distant metastases with or without pelvic failure. The most common sites of distant metastases were lung, liver, and bone. Central and peripheral recurrences were not analyzed separately because only three patients had pelvic sidewall failures.

No patient died as a complication of treatment. Severe, grade 4 toxicity occurred in four patients. Three patients were treated with external pelvic irradiation alone. One of these patients developed a hip fracture thought to be due to irradiation of the groins and another one developed a bowel obstruction requiring a colostomy. Thirty-three patients received combined external pelvic irradiation and brachytherapy. In this combined therapy group, two patients developed recto-vaginal fistulae requiring surgical repair.

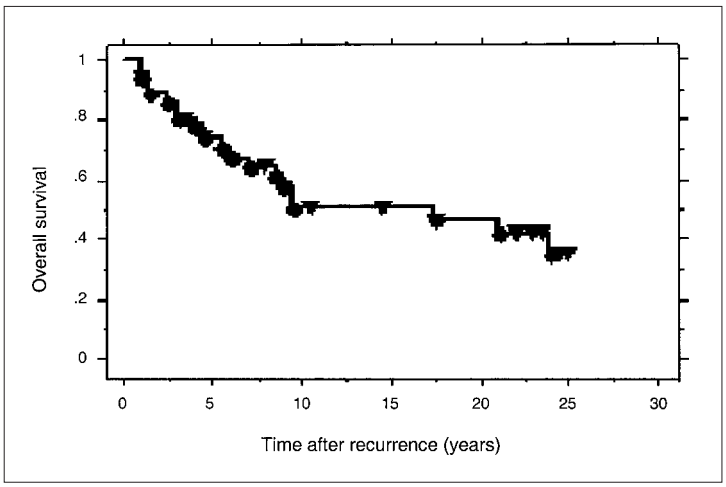

Fig. 1. Overall survival after recurrence.

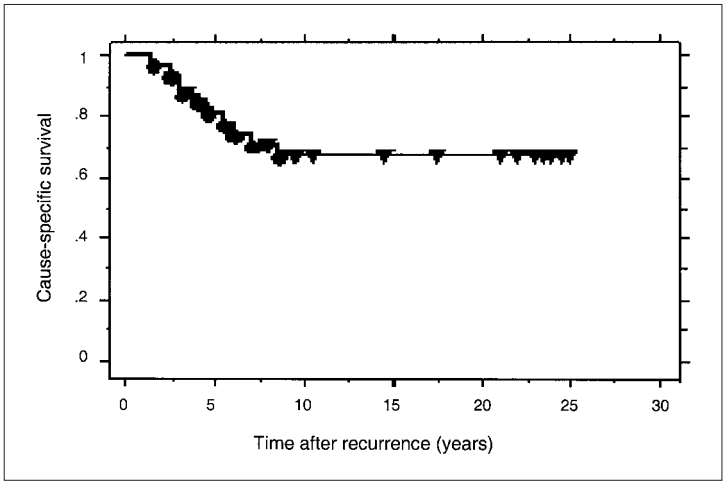

Fig. 2. Cause-specific survival after recurrence.

DISCUSSION

The patients reported in this retrospective study were treated over a period of several years, and the criteria for the routine administration of immediate postoperative pelvic irradiation were constantly changing. Initially these criteria included only patients with 2 or more positive pelvic lymph nodes, but at present it includes those with negative pelvic lymph nodes but large tumor size, deep stromal invasion by tumor, and lymphovascular space invasion as evaluated by Sedlis and colleagues,[4] and those with positive lymph nodes.[5] It is thought by some investigators that the prognosis of primary uterine cervical cancer is worse if the histology of the tumor is adenocarcinoma as compared with squamous cell carcinoma. It was not possible to evaluate this prognostic factor in our group of patients with recurrent cervical cancer since only 11% of our patients had the adenocarcinoma histology. These changing criteria have undoubtedly lead to changing patterns of failure after surgery for these patients, but these patterns were not evident in this retrospective study.

Patients that develop recurrent cervical cancer after the initial surgical therapy may present with recurrent disease in the pelvis, distant metastatic disease, or pelvic and distant disease. If cervical cancer recurs outside of the pelvis, then essentially no patients are cured of their recurrent disease.[6] This current report addresses only patients with recurrent tumor that was clinically confined to the pelvis and treated with curative intent. The cause-specific survival rate in this report was 74% at 5 years and declined to 71% at 25 years. These survival rates are similar to those reported by others for patients treated with irradiation alone.[7-11]

As with primary carcinoma of the cervix, the ability of irradiation to control the tumor in the pelvis is a

function of tumor size.[7] Tumor size was not specified in all patients in this current report but ranged from <1 cm to 15 cm in diameter. Patients with large tumors received external pelvic irradiation first, in order to shrink the mass, and then received brachytherapy. Of the 10 patients who failed treatment, 70% had a component of pelvic failure. Location of the recurrent disease within the pelvis is also of prognostic significance.[8] Ijaz and colleagues[8] noted that patients with a central recurrence in the vagina had a better outcome than patients who had a pelvic recurrence that involved the pelvic sidewall. An additional prognostic factor noted by Finan and associates[9] was the recurrence interval from initial surgery. These investigators found that the risk of death from recurrence increased 19-fold if the recurrence occurred immediately after surgery as compared to a delayed recurrence.

Distant metastasis, as a component of treatment failure, occurred in 80% of the patients who developed recurrent disease. This high rate of failure with distant metastases has been noted by other investigators.[10-12] None of the patients in this study were treated with concurrent irradiation and chemotherapy. Rose and associates[13] and Morris and colleagues[14] have reported a decreased incidence of distant metastases in patients with primary advanced cervical cancer when treated with irradiation and concurrent chemotherapy. It is therefore logical to assume that patients with a pelvic recurrence after radical hysterectomy and lymph node dissection would benefit from the addition of concurrent chemotherapy to their pelvic irradiation.

Patients with pelvic recurrences of cervical cancer after radical hysterectomy and lymph node dissection have a poor prognosis. Patterns of failure indicate a very high rate of distant metastases. It is currently recommended that patients with recurrent cervical cancer be evaluated by a total-body FDG-PET scan to determine their disease extent. Patients with disease isolated to the pelvis should be treated with external pelvic irradiation to the pelvis to about 50.4 Gy and an interstitial brachytherapy procedure (one or two) to boost the total tumor dose to about 75 Gy to 85 Gy (low-dose-rate). High-dose-rate brachytherapy, with adjustments in total dose, may also be utilized. Patients may benefit from the use of concurrent cisplatin-based chemotherapy. Hopefully, with improvements in three-dimensional external irradiation treatment planning and the use of image-guided interstitial brachytherapy techniques, pelvic control of tumor can be improved. Long-term follow-up is warranted.

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