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Salvage high-dose-rate brachytherapy and external beam radiotherapy for isolated vaginal recurrences of endometrial cancer with no prior adjuvant therapy

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ABSTRACT

PURPOSE: To evaluate clinical outcomes for isolated vaginal recurrence of endometrial cancer without adjuvant therapy treated with salvage external beam radiation therapy (EBRT) and high-dose-rate CT-based inverse-planned brachytherapy.

METHODS AND MATERIALS: Thirty women were included in this retrospective study. Median time to first recurrence was 16.7 months, and median age at recurrence was 73 years. Initial grade was 1 or 2 in 19 patients (63%), and 2009 FIGO stage IA in 19 patients. All patients received pelvic EBRT in 1.8 Gy daily fractions to a total of 45 or 50.4 Gy. Interstitial brachytherapy was used in 27 patients (90%). The median total EQD2 dose was 68.3 Gy. Kaplan-Meier estimates of overall survival (OS), cause-specific survival (CSS), progression free survival (PFS), locoregional failure-free survival, and distant failure−free survival (DFFS) were calculated.

RESULTS: Median follow-up was 76.4 months for vital status and 57.7 months for disease status after salvage therapy. The 5-year OS, CSS, PFS, locoregional failure-free survival, and DFFS after salvage therapy were 77%, 83%, 75%, 87%, and 86%. Initial high-grade disease was prognostic for OS, CSS, and DFFS (5-year OS 95% vs. 29%, $p = 0.005$). Initial stage beyond IA was prognostic for CSS, PFS, and DFFS (5-year CSS 93% vs. 74%, $p = 0.025$).

CONCLUSIONS: Salvage EBRT and high-dose-rate brachytherapy resulted in a high rate of locoregional control. Initial high-grade and advanced stage disease were associated with greater distant failure and cancer-related mortality after salvage therapy.

Keywords: Endometrial neoplasms; Neoplasm recurrence; Local; Brachytherapy; Radiotherapy planning; Computer-assisted; Salvage therapy; Retrospective studies

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States and is increasing in incidence, with an estimated 60,000 cases in 2016 (1). Hysterectomy with salpingo-oophorectomy is the foundation of staging and therapy, and the majority of patients will present with disease confined to the uterine corpus. Yet despite initially localized disease, 10−15% of these patients will have pelvic recurrences without adjuvant therapy. Approximately 75% of these recurrences are isolated to the vaginal cuff (2−4). Randomized trials of adjuvant radiation therapy have identified patients at low absolute risk for recurrence, principally low-grade and low-stage tumors (2−4).

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Adjuvant therapy is often avoided in these lower-risk patients, with the option of salvage radiation in the event of recurrence.

Brachytherapy in conjunction with external beam radiation therapy (EBRT) has been used as salvage therapy in endometrial carcinoma for decades, especially in patients with no prior radiation. The inverse-square dose falloff of brachytherapy allows for high-target doses to control gross disease with relative sparing of adjacent normal tissues. The addition of EBRT to the pelvic lymph nodes reduces regional recurrence (5). Since 2000, the University of California San Francisco (UCSF) has performed high-dose-rate (HDR) brachytherapy using template-free (''freehand'') interstitial catheter placement under real-time transrectal ultrasonography guidance, as well as 3-dimensional image-based inverse planning. This allows for highly conformal plans adapted to individual anatomy (6).

Most data on the outcomes after salvage brachytherapy are limited to institutional series with fairly short follow-up times. Prior publications of patients with isolated vaginal recurrences treated with brachytherapy have reported long-term local control rates of approximately 60–75% (5, 7–9), although more recent series report higher local control with the use of image-guided brachytherapy (10, 11). Treatment techniques have continued to evolve, and there are few reports of endometrial carcinoma salvage using primarily interstitial, image-guided, and inverse-planned brachytherapy. The aims of the present study are to describe outcomes and identify prognostic factors with HDR brachytherapy and pelvic EBRT for isolated vaginal recurrences of endometrial carcinoma after surgery alone.

Methods and Materials

A single-institution clinical database was reviewed to identify women who received salvage EBRT and HDR brachytherapy for recurrent endometrial carcinoma after hysterectomy between 2000 and 2010. Inclusion criteria were histopathologically confirmed vaginal cuff recurrence with no evidence of distant or regional nodal recurrence by clinical exam and imaging, and no history of prior radiation (including vaginal brachytherapy) or systemic therapy for endometrial carcinoma received adjuvant to hysterectomy. Patients who underwent hysterectomy either with or without pelvic lymph node dissection were included. All data were collected and reviewed retrospectively. Stage of disease at initial surgery was recoded to match the International Federation of Gynecology and Obstetrics (FIGO) 2009 revised staging (12). Patient records were cross-referenced to the UCSF Cancer Registry to obtain information about second recurrences or changes to vital status recorded by other institutions.

All patients received salvage vaginal HDR brachytherapy at UCSF by a single-radiation oncologist (IH). Brachytherapy was performed using a vaginal cylinder with interstitial catheters. All patients received at least two transvaginal interstitial catheters to provide coverage of the vaginal apex. Additional transvaginal or transperineal interstitial catheters were added based on extent of disease determined on imaging (e.g., nodules beyond apex, periurethral disease, or $>$ 5 mm deep from vaginal cuff mucosa). Catheters were placed without templates under real-time transrectal ultrasonography guidance. Radio-opaque interstitial markers were also placed in the vaginal cuff apex. After implantation, a CT scan was obtained and 3-dimensional inverse planning-simulated annealing (IPSA; Oncentra Brachy, Elekta) was performed, as detailed previously (6). Planning CT scan as well as any available pretreatment PET or MRI imaging was used to define the target volume (gross disease plus distal vaginal cuff mucosa) and organs at risk (Fig. 1). Treatment goals were generally prescription dose to $\geq$90% of target volume, and 75% isodose volume (V75%) to less than 1 cc of any organ at risk (rectum, bladder, bowel). All patients were treated with a single implant. Radiation was delivered using an afterloaded ^{192}Ir source in fractions at least 6 h apart. EBRT was performed either at UCSF or an outside radiation oncology facility and was targeted to the vaginal cuff and pelvic lymph nodes. For evaluating dose as a prognostic factor for tumor outcome, EBRT, and brachytherapy prescription doses were converted to their equivalents in 2 Gy fractions (EQD2) using $\alpha/\beta = 10$ for tumor effects and $\alpha/\beta = 3$ for late effects (13).

Time to recurrence was defined as duration from initial surgery for endometrial cancer to histopathological confirmation of vaginal recurrence. Time to completion of radiation therapy was defined as duration from recurrence to completion of both EBRT and HDR brachytherapy. Outcome measures of vital status were overall survival (OS; freedom from death of any cause) and cause-specific survival (CSS; freedom from death due to endometrial cancer progression, censored at death from other cause). Second recurrences after salvage radiation were recorded as either ''locoregional'' (recurrence in the vaginal cuff or pelvic lymph nodes) or ''distant'', and disease status was established by documented clinical exam and imaging. Outcome measures of disease status were progression-free survival (PFS; freedom from any second recurrence, censored at death from any cause), locoregional failure-free survival (LFFS; freedom from locoregional recurrence, censored at distant failure or death from any cause), and distant failure-free survival (DFFS; freedom from distant recurrence, censored at locoregional failure or death from any cause).

Actuarial estimates of OS, CSS, PFS, LFFS, and DFFS were determined by the Kaplan-Meier method. Univariate Cox proportional hazard ratio models were used to identify clinical and treatment factors prognostic for outcomes. Multivariate analysis was precluded by the small number of events. Evaluated factors included initial FIGO grade of disease, initial FIGO stage, patient age at recurrence, time to recurrence, time to completion of radiation therapy,