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Brachytherapy ■ (2015) ■

BRACHYTHERAPY

Vaginal brachytherapy for early-stage carcinosarcoma of the uterus

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ABSTRACT

OBJECTIVE: Uterine carcinosarcoma (CS) is an aggressive malignancy and the optimal adjuvant treatment is not well-established. We report outcomes with vaginal brachytherapy (VB) for women with early-stage CS.

METHODS AND MATERIALS: A multi-institutional retrospective study of Stage I-II CS treated with hysterectomy, surgical staging, and adjuvant high-dose-rate VB without external-beam pelvic radiotherapy was performed. Rates of vaginal control, pelvic control, locoregional control, disease-free survival, and overall survival were determined using the Kaplan-Meier method.

RESULTS: 33 patients were identified. Prescribed VB dose was 21 Gy in three fractions (n = 15 [45%]) or 24 Gy in six fractions (n = 18 [55%]). Eighteen patients (55%) received chemotherapy. Median followup was 2.0 years. Twenty-seven patients (82%) underwent pelvic lymphadenectomy, 5 (15%) had nodal sampling, and 1 (3%) had no lymph node assessment. Relapse occurred in 11 patients (33%), all of whom had lymph node evaluation. Locoregional relapse was a component of failure in 6 patients (18%), of whom 3 (9%) failed in the pelvis alone. Three patients (9%) had simultaneous distant and locoregional relapse (two vaginal, one pelvic). Five additional patients (15%) had distant relapse. Six of the 11 patients (55%) with disease recurrence received chemotherapy. Two-year vaginal control and pelvic control were 94% and 87%. Two-year locoregional control, disease-free survival, and overall survival were 81%, 66%, and 79%.

CONCLUSIONS: Despite having early-stage disease and treatment with VB, patients in this series had relatively high rates of local and distant relapse. Patients who undergo lymphadenectomy and VB remain at risk for relapse. Novel treatment strategies are needed.

Keywords: Carcinosarcoma; Radiation therapy; Uterine cancer

Introduction

Uterine carcinosarcoma (CS) is a rare and aggressive uterine malignancy, accounting for fewer than 5% of uterine cancers (1). Formerly termed *malignant mixed Müllerian tumor*, CS is defined by its biphasic composition, with both epithelial and stromal malignant components (1). Historically, CS was considered a type of uterine sarcoma; however, mounting molecular, pathologic, and clinical evidence suggests that it is likely a monoclonal metaplastic carcinoma, with the carcinomatous component giving rise to the sarcomatous component and largely determining the biologic behavior of the tumor (2,3). In keeping with this evidence, the seventh edition of the American Joint Committee on Cancer staging manual, which stages sarcomas and carcinomas differently, states that CS shall be staged per the carcinoma rules (4).

CS has more aggressive behavior and portends a poorer prognosis than other uterine carcinomas, even when compared with Grade 3 adenocarcinomas, papillary serous carcinoma, and clear cell carcinoma (5). Five-year overall survival (OS) for CS is poor, reported as 25–55% (5–8), due in part to the frequency of the advanced stage of disease

Received 10 November 2014; received in revised form 7 January 2015; accepted 12 February 2015.

Conflict of interest: None.

Presented at the American Brachytherapy Society Annual Meeting, San Diego, CA, April 3–5, 2014.

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2015.02.194

at diagnosis. Five-year OS for patients with Stage I-II CS is commonly reported in the range of 55−74% (8−10). CS is associated with both lymphatic dissemination and distant metastasis. Surgical extirpation of disease, via hysterectomy and bilateral salpingo-oophorectomy (BSO), is the cornerstone of treatment for CS, as with other uterine malignancies.

The utility of vaginal brachytherapy (VB) after complete surgical staging for women with uterine-confined disease has not been defined. Consequently, decisions regarding the addition of adjuvant radiotherapy for women with early-stage disease are based on conclusions extrapolated from data from other uterine malignancies and are likely to vary greatly between oncologists. In women with Stage I endometrioid adenocarcinoma with high-intermediate risk factors, VB and pelvic radiotherapy (PRT) have been shown to result in equivalent survival (11). Recent reports also suggest excellent outcomes with VB in patients with early-stage uterine papillary serous and clear cell carcinoma (12,13). Thus, in patients with surgically staged CS confined to the uterus (Stage I), adjuvant treatment with VB as the sole radiotherapeutic modality is a consideration; however, to our knowledge, outcomes with this approach have not been previously reported. Herein, we report multi-institutional outcomes with VB for early-stage CS, to investigate whether VB is sufficient adjuvant radiotherapy for this aggressive malignancy.

Materials and methods

Patient selection

With approval from the institutional review boards of the participating institutions, a multi-institutional retrospective review of patients treated with adjuvant high-dose-rate VB after hysterectomy and BSO for CS from January 1, 2000 through December 31, 2013 was performed. Patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 (4) Stage I-II disease, confined to the uterus and cervical stroma, were included. Women receiving PRT were excluded.

Surgical management

After diagnosis via endometrial sampling, all patients were staged with axial imaging of the chest, abdomen, and pelvis. Patients then underwent total hysterectomy and BSO via an open abdominal procedure or a laparoscopic or robotic-assisted approach. Surgical staging with omental sampling (biopsy or omentectomy), peritoneal washings, and/or pelvic and para-aortic lymph node sampling or dissection was performed. Lymphadenectomy was defined as removal of 10 or more lymph nodes from bilateral nodal basins (pelvic and para-aortic basins were considered separately); removal of 1 to 9 was considered lymph node sampling.

Adjuvant therapy

Receipt of adjuvant chemotherapy was based on patient and tumor characteristics, at the discretion of the treating medical or gynecologic oncologist. Timing of chemotherapy (before, concurrent with, or after VB) was provider-dependent. When delivered, chemotherapy was most commonly carboplatin and paclitaxel.

All patients received outpatient high-dose-rate VB in a dedicated brachytherapy suite. On Day 1 of treatment, patients were placed in the dorsal lithotomy position and examined, with special attention paid to the integrity of the vaginal cuff. The vagina was serially dilated and the distance from the apex to the vaginal introitus noted. After placement of the largest tolerable applicator, the level of the introitus was marked with a radiopaque wire on the applicator, and a CT scan was obtained to document positioning of the applicator and for treatment planning.

Fractionation pattern and prescription details differed between the two participating institutions. At Mayo Clinic ($n = 15$), patients received a total dose of 21 Gy in three fractions, delivered every other day with multichannel cylinders ranging from 3 to 4 cm in diameter. A dose of 7 Gy per fraction was prescribed to a volume spanning 5 mm cephalad to the applicator down to 1 cm proximal to the vaginal introitus, and to a depth of 7 mm lateral to the upper aspect of the applicator, tapering down to the surface caudally. Dwell times were determined from a library of plans in the Varian Brachytherapy Planning System (Varian, Inc, Palo Alto, CA), with a source step size of 0.5 cm. Volumetric doses to nearby critical structures were calculated after treatment. For subsequent fractions, orthogonal images were obtained and treatment was delivered using the same plan, with appropriate decay modifications.

At Brigham and Women's Hospital/Dana-Farber Cancer Institute ($n = 18$), patients received a total dose of 24 Gy, delivered in six twice-weekly fractions with a single-channel cylinder. Treatment was delivered to the full vaginal length, determined clinically, minus 1 cm to avoid scatter to the labial tissues. Optimization dose points were placed at a fixed distance from the central catheter, equal to the radius of the vaginal cylinder. The dwell times were automatically optimized in the Oncentra Brachy Planning System (Nucletron/Elekta, Stockholm, Sweden) so that the average dose to the dose points was equal to 4 Gy, with a dwell time dose gradient of 0.5. The source step size was 0.5 cm. CT imaging on the first fraction was used to evaluate the length of the vagina and to confirm that the clinically obtained measurement equaled that seen on CT, with the inferior extent of vaginal tissue approximated as a horizontal line between the bottom of the symphysis and the anal region.

Followup

Followup consisted of history and physical examination, including pelvic examination, every 3 months for 2 years,