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BRACHYTHERAPY

Brachytherapy 14 (2015) 464–470

Predictors of vaginal stenosis after intravaginal high-dose-rate brachytherapy for endometrial carcinoma

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ABSTRACT

PURPOSE: Intravaginal high-dose-rate brachytherapy is an effective adjuvant treatment for localized endometrial carcinoma. However, relatively little is known about risk factors of post-treatment vaginal stenosis (VS).

METHODS AND MATERIALS: We included patients treated with brachytherapy for endometrial carcinoma from September 2011 to January 2014 with at least 3 months of followup. Patients who received external beam radiation therapy were excluded. VS was prospectively graded at each followup visit per Common Terminology Criteria for Adverse Events, version 4.03. χ^2 and t test analyses were used to assess the association of VS with various patient, tumor, treatment, and post-treatment factors. Multivariable logistic regression analysis was used to identify independent predictors of VS Grade $\geq$1 and $\geq$2.

RESULTS: All 101 patients were disease free at last followup. Mean followup was 12.9 months (range, 3–34). Highest VS grades were zero in 67%, one in 26%, two in 6%, and three in 1%. Borderline significant variables associated with Grade $\geq$1 VS included vagina length, proportion of vagina treated, and total dose. Dilator use was significantly associated with Grade $\geq$2. Multivariable analysis revealed that proportion of vagina treated >60% (odds ratio [OR], 3.48; $p = 0.009$) and total dose >14 Gy (OR, 4.27; $p = 0.015$) were independent predictors of Grade $\geq$1 VS, and lack of consistent dilator use was an independent predictor of Grade $\geq$2 VS (OR, 5.60; $p = 0.047$).

CONCLUSIONS: Patients treated with a higher total dose to a larger proportion of the vagina were more likely to develop Grade $\geq$1 VS. Consistent dilator use may also be protective against Grade $\geq$2 VS.

Keywords: Vaginal stenosis; Endometrial cancer; Brachytherapy; High-dose-rate; Toxicity

Introduction

Intravaginal high-dose-rate (HDR) brachytherapy (BT) is an effective and widely used adjuvant treatment for localized endometrial carcinoma. The postoperative radiation therapy in endometrial cancer (PORTEC)-2 randomized clinical trial established the efficacy of this treatment modality in improving local control after total abdominal hysterectomy/bilateral salpingo-oophrectomy, as well as decreased bowel and bladder toxicities compared with pelvic external beam radiation therapy (EBRT) (1).

However, one significant late effect described for this treatment is vaginal stenosis (VS) or the narrowing and shortening of the vaginal vault thought to result from a combination of adhesions and circumferential fibrosis in the upper vaginal tissue. The incidence of VS resulting from BT is highly variable, with some estimates as high as 50–60% (2–6). In the PORTEC-2 trial, the incidence of Grade 1–2 vaginal mucosal atrophy was approximately 35%, although specific rates of VS were not reported (1). VS can interfere with physical examinations and affect sexual functioning and quality of life, which can lead to patients fearing the prospect of BT (7–9).

Received 24 December 2014; received in revised form 27 January 2015; accepted 3 March 2015.

Conflicts of interest: There are no relevant conflicts of interest for this article.

Previous presentation: This research was presented in part as an oral presentation at the 56th Annual Meeting of the American Society for Radiation Oncology (September 14–17, 2014).

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2015.03.001

Despite the high prevalence, however, relatively little is known about risk factors of post-treatment VS. Previous single-institution studies from Fox Chase Cancer Center and the University of Pennsylvania have shown that age, tumor stage, dose, shorter active length, and dilator use may be associated with vaginal toxicity (10, 11). Dose–fractionation scheme has also been associated with vaginal toxicity in prospective studies conducted in Sweden (12, 13).

The aim of this study was to further investigate clinical and dosimetric predictors of VS among a cohort of endometrial cancer patients treated with HDR BT at our institution.

Methods and materials

In this institutional review board–approved study, we analyzed a cohort of endometrial cancer patients who completed treatment with adjuvant HDR iridium-192 BT without EBRT from September 2011 to January 2014 at Yale-New Haven Hospital. They were eligible for the study if they had no evidence of disease with at least 3 months of followup through October 2014. Patients were excluded if they did not tolerate at least a 2.3-cm cylinder ($n = 1$) or did not complete treatment within 3 months ($n = 1$). The default dose–fractionation scheme was 21 Gy in three fractions every 1–2 weeks for patients using 3.0-cm cylinders. However, for those with smaller cylinders, the dose was adjusted to 18 Gy in three fractions to decrease mucosal toxicity, based on the well-published experience of Memorial Sloan Kettering Cancer Center (14). For certain patients with serous or clear cell histology receiving chemotherapy, dose was adjusted to 14 Gy in two fractions, based on our long-standing institutional experience at Yale, dating back to the early 1990s (15, 16). Baseline posthysterectomy vaginal length from the apex to introitus was systematically measured at the time of initial consultation with a custom rigid cylinder with 14 cm length, similar to the validated method used by Bruner *et al.* (10).

For patients with an average posthysterectomy vaginal length of 8–9 cm, active treatment length (defined as the distance between the most proximal and distal activated dwell positions, see Fig. 1) was tailored to 4 cm for the lowest risk patients, 5 cm for the intermediate-risk patients (>50% myometrial invasion or Stage II or higher disease), and 6 cm for the highest risk patients (Grade 3, or serous/clear cell histologies). For patients with short (<8 cm) or long (>9 cm) vaginal length, alteration of the aforementioned schema was considered on a case-by-case basis. Active treatment length was not altered based on the presence or the absence of lymphovascular space involvement.

All patients were educated by nursing staff and provided written instruction to perform vaginal dilation with a rigid dilator three times per week for 10-min sessions, beginning 2 weeks after completion of BT. Consistent dilator use was defined as patient-reported utilization at least two times per week for at least 1 year or the longest period of followup. Every patient was followed up with radiation oncology at 3–6 months post-BT, then annually. VS was prospectively graded at each followup visit per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 criteria for vaginal stricture (1: asymptomatic, mild vaginal narrowing/shortening; 2: vaginal narrowing/shortening not interfering with physical examination; 3: vaginal narrowing/shortening interfering with use of tampons, sexual activity, or physical examination). Interim followup every 3 months with cytology every 3–6 months was performed by gynecologic oncology to assess disease status.

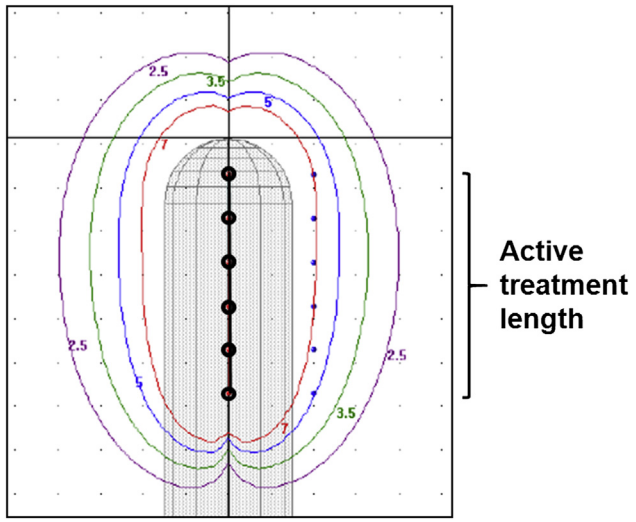

Fig. 1. Active treatment length was defined as the distance between the most proximal and distal activated dwell positions in the cylinder's central channel. In this example (exaggerated for illustration), there are six active dwell positions separated by 1 cm, for an active treatment length of 5 cm.

Data on potential predictors of at least Grade 1 VS were collected, with reference values based on median splits or clinical utility. Patient factors included age and body mass index. Tumor factors included stage and histology. Treatment factors included total prescription dose, fraction size, cylinder width, posthysterectomy vaginal length, active treatment length, proportion of vagina treated, hysterectomy approach (open vs. robotic), and receipt of chemotherapy. Post-treatment factors included dilator use and sexual activity. Univariable analyses were performed with the χ^2 test for categorical variables and t test for continuous variables for VS Grade ≥1 and ≥2. Multivariable logistic regression analysis was performed to calculate adjusted odds ratios (ORs) for any independent predictors of VS Grade ≥1 and ≥2.

Results

A total of 101 patients were included, all of whom were disease free at last followup. Among them, 79% had Stage I