

Scientific Article

Toxicity and Efficacy After Adjuvant Vaginal Brachytherapy Using 30 Gy in 6 Fractions for Stages I and II Endometrial Cancer



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Abstract

Purpose: This study aimed to evaluate outcomes and toxicity in patients with endometrial cancer per our institutional adjuvant vaginal cuff brachytherapy (VBT) fractionation scheme.

Methods and Materials: We identified women with International Federation of Gynecology and Oncology stages I and II endometrial cancer who underwent surgical staging and adjuvant high-dose-rate VBT without external beam radiation. All patients received 30 Gy in 6 fractions to the upper one-third of the vagina, prescribed to a depth of 5 mm and delivered twice weekly. Toxicities were prospectively elicited at each follow up, and rates of recurrence and survival were retrospectively assessed.

Results: We identified 247 eligible patients treated between 1992 and 2018 with a median follow up of 5.8 years (range, 0.1-24.7 years). Most patients had stage I disease (52% stage IA; 37% stage IB), and 11% of patients were stage II. Deep myometrial invasion was predictive of local recurrence ($P = .002$). The 5-year rates of local recurrence, regional recurrence, and distant metastases were 5%, 5%, and 7%, respectively. Five-year overall and disease-free survival were 91% and 83%, respectively. The most common grade 1 toxicities were acute fatigue (11% crude rate), urinary frequency (11%), chronic (>6 months) urinary frequency (13%), urinary incontinence (13%), and vaginal stenosis (21%). There were few grade 2 toxicities (all <5%) and no grade 3 to 5 toxicities.

Conclusions: The adjuvant VBT fractionation scheme of 30 Gy in 6 fractions results in low rates of toxicity, with no grade ≥ 3 adverse events, and local control rates comparable with those from other published series using different fractionation schemes.

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Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 65,620 new cases in 2020.¹ International Federation of Gynecology and Oncology (FIGO) stages I to II disease constitute two-thirds of new diagnoses, and are treated with a total hysterectomy with bilateral salpingo-oophorectomy,

Disclosures: none

Research data are stored in an institutional repository, and will be shared upon request to the corresponding author.

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surgical staging, and lymph node assessment, followed by risk-adapted adjuvant therapy.² Patients with high-intermediate risk (HIR) factors (deep myometrial invasion; grade 3 disease; presence of lymphovascular space; and age >50, >60, or >70 depending on other risk factors) receive adjuvant radiation therapy to improve local control.^{3,4} Specifically, adjuvant vaginal brachytherapy (VBT) is preferred because this method provides equivalent local control with improved toxicity compared with external beam radiation therapy (EBRT).⁴ For HIR patients, VBT results in a 1.8% rate of vaginal recurrence, but substantially lower rates of gastrointestinal toxicity.⁴

The American Brachytherapy Society (ABS) published guidelines regarding the technical aspects of VBT.⁵ In the most recent version of the ABS guidelines, published early 2019, several acceptable dose-fractionation schedules are outlined.⁶ Three fractions of 7 Gy prescribed to a depth of 5 mm is commonly used, because this was the fractionation scheme used in the PORTEC-2 study. However, subsequent studies using different dose-fractionation schedules showed similar local control.⁷ The ABS guidelines caution that schedules using higher doses per fraction and fewer fractions may result in increased toxicity, although data on the rate of toxicity associated with specific VBT fractionation schemes is lacking.^{6,8}

Before the publication of the ABS guidelines on fractionation choices, we adopted the fractionation scheme of 6 fractions of 5 Gy, prescribed to a depth of 5 mm from the vaginal surface (biologically equivalent dose [BED]₁₀: 45 Gy; equivalent total dose in 2-Gy fractions [EQD2]₁₀: 37.5 Gy). This fractionation was selected with the goal of delivering an adequate radiation dose to reduce local recurrence (LR) while also limiting the dose per fraction to minimize toxicity. We previously published our 2-year recurrence and 4-year survival outcomes, which showed very favorable local control with this fractionation.⁹ Herein, we report on acute and chronic toxicity outcomes associated with this fractionation, as well as long-term clinical outcomes.

Methods and Materials

In this retrospective study, we identified all patients with FIGO stages I to II endometrial cancer treated with adjuvant VBT at our institution for whom a minimum of 6 months of follow-up data were available. For the purpose of this study, our goal was to evaluate clinical outcomes and toxicity for patients treated with 30 Gy in 6 fractions. Therefore, only patients who received a dose of 30 Gy delivered in 6 fractions were included. Patients who received adjuvant EBRT or alternative VBT doses were excluded. However, this dose fractionation has been our institutional standard since the early 1990s (before the publication of randomized trials that used other dose fractionation schemes). Therefore, a majority of the

patients treated with VBT alone at our institution were treated with this fractionation. Overall, we identified a total of 359 women with early stage endometrial cancer, of whom 247 patients met our criteria of treatment with VBT to 30 Gy in 6 fractions. This study was approved by our institutional review board.

All patients underwent surgical staging with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, with or without pelvic and/or para-aortic lymph node assessment and/or peritoneal cytology. Surgical staging was completed either openly, laparoscopically, or robotically because standards regarding surgical approach changed over time at our institution. The decision to administer chemotherapy was based on individual patient risk factors, such as high-risk histology (eg, clear cell, serous, or carcinosarcoma), tumor grade, and/or lymphovascular space invasion (LVSI).

After surgical staging, all patients received high-dose-rate (HDR) VBT with an Iridium-192 source using a vaginal cylinder. Treatment was initiated after the vaginal cuff healed completely, no sooner than 4 weeks after surgery. All patients received 30 Gy in 6 fractions twice weekly, prescribed to a depth of 5 mm from the vaginal surface. The target included the upper third of the vagina, consisting of a length of 4 cm in 87% of patients. The BED₁₀ for this fractionation is 45 Gy, with EQD2₁₀ of 37.5 Gy, both at a depth of 5 mm.

Baseline patient characteristics, treatment details, and follow-up information were retrospectively collected. A typical patient follow-up schedule consisted of visits at 3-month intervals for the initial 2 years, then every 6 months for the next 3 years, alternating between radiation and gynecologic oncologists. Patients followed up annually after 5 years with their gynecologic oncologist, but did not routinely continue to have follow up in the radiation oncology department beyond 5 years. Pelvic examinations (speculum and bimanual) were performed at the time of each follow-up visit, and an assessment of vaginal stenosis was performed at that time. Vaginal length was not routinely recorded. Surveillance imaging was not routinely performed, but ordered at the discretion of the treating physician. Of note, patients were encouraged to use a vaginal dilator after their VBT treatments to help prevent and minimize vaginal stenosis. Specifically, patients were provided with a dilator and asked to use this 3 times per week for a duration of 10 minutes per use, beginning 2 weeks after completion of the VBT and continuing for a minimum of 1 year. Subsequently, patients were encouraged to continue dilator use indefinitely at a frequency of at least once per week.

For the toxicity analysis, rates of genitourinary, gastrointestinal, and gynecologic toxicities were prospectively elicited at each follow-up appointment in the radiation oncology department, and entered into a database beginning in 2010. Toxicity was graded according to the Common Terminology Criteria for Adverse

Events, version 4.0. Acute toxicity was defined as symptoms ≤ 6 months after VBT and chronic toxicity as > 6 months after VBT. If prospective toxicity data were unavailable for a given patient (ie, if a patient was lost to follow up in the radiation oncology clinic but continued to follow up with their gynecologic oncologist, or for patients seen in our department before 2010), toxicity data were retrospectively collected from information available in the follow-up notes.

The following clinical outcomes were analyzed: LR, regional recurrence (RR), distant metastasis (DM), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS). For the purpose of this study, LR was defined as vaginal recurrence and RR as nonvaginal pelvic recurrence. Any occurrences of LR, RR, or DM were recorded, even if not the first recurrence. For DFS, events were defined as the first incidence of recurrence (either LR, RR, or DM) or death due to any cause. Patients still alive were censored as of the date of last follow up. Clinical outcomes were analyzed using Kaplan–Meier estimates.

VBT is offered with the intent to improve local control; thus, we performed a univariable analysis (UVA) to identify the prognostic impact of baseline patient characteristics on LR. The following covariates were included in our analysis: age at the time of diagnosis, tumor grade, presence of LVSI, depth of invasion ($< 50\%$ or $\geq 50\%$ invasion), pathologic T stage, overall pathologic stage, time to brachytherapy (≤ 60 or > 60 days), surgical lymph node evaluation, and the use of adjuvant chemotherapy. Cox proportional hazard modeling was used for the UVA. *P*-values $< .05$ were considered significant.

Results

Patient and disease characteristics

We identified 247 patients with early stage disease who received 30 Gy in 6 fractions to a depth of 5 mm between 1992 and 2018. The median follow-up time was 5.8 years (range, 0.2–24.7 years). Patient and tumor characteristics are listed in [Table 1](#). The majority of patients (80%) in this study received HDR VBT as a monotherapy; however, 50 patients (20%) also received adjuvant chemotherapy, consisting primarily of 6 cycles of carboplatin and paclitaxel ([Table 1](#)). Forty-eight of 50 patients who received chemotherapy had either stage II disease (10%), a high-risk histology (72%), LVSI (38%), and/or a combination of grade 3 disease and deep myometrial invasion (22%). The remaining 2 patients were a 70-year-old woman with grade 3 disease (stage IA) and a 52-year-old woman with 60% myometrial invasion (grade 1, stage IB).

A total of 79 patients with either stage II disease (26 patients, 11%) or high-risk disease (defined as high-risk histology and/or combined grade 3 disease and deep

myometrial invasion; present in 53 patients, 21%) were included in this study. Of these patients, 46 were included in the above subset that received both VBT and chemotherapy. The remaining 33 patients were deemed appropriate candidates for HDR VBT as a monotherapy based on the best data and guidelines available at the time when these patients were treated. Of the remaining patients, 112 (45%) were deemed to have HIR factors per the PORTEC-2 and/or GOG-99 study criteria.^{3,4} Specifically, 83 patients met the criteria for the PORTEC-2 study, 74 met the criteria for the GOG-99 study, and 47 met the criteria for both studies. The remaining 56 patients (23%) did not meet the criteria for high-risk or HIR disease, although 7 patients had LVSI.

Clinical outcomes

Recurrences were as follows: 11 patients (crude rate: 4.5%) experienced LR (vaginal recurrence) with a mean time to recurrence of 1.4 years (range, 0.5–3.9 years), 9 patients experienced recurrence within the radiation treatment field, and 2 patients experienced an out-of-field recurrence at the distal vagina (both patients had an endometrioid histology, and 1 patient had LVSI but the other did not). For both patients, the proximal 4 cm of the vagina (corresponding to the upper third of the vagina) had been targeted at the time of their initial VBT treatments. Seven patients experienced isolated LR and were successfully salvaged (5 patients remain alive and free of disease, 2 patients died of other causes with no evidence of disease at the time of death), 3 patients died of progressive disease, and 1 patient remains alive with progressive disease.

On UVA of the baseline patient characteristics on LR, only depth of myometrial invasion (assessed as a categorical variable, $< 50\%$ or $\geq 50\%$ invasion), tumor stage, and overall FIGO stage were significant predictors of LR (hazard ratios: 0.06, 0.06, and 0.05, respectively; *P* = .002, .003, and .003, respectively; [Suppl. Table 1](#)). Histology, tumor grade, presence of LVSI, age at the time of diagnosis, lymph node evaluation status (whether or not pelvic lymph nodes were evaluated surgically), time from surgery to VBT (≤ 60 or > 60 days), and use of adjuvant chemotherapy were not significant predictors of LR. We examined the depth of myometrial invasion, tumor stage, and overall FIGO stage of all 11 patients who experienced LR, and all 11 patients had deep myometrial invasion ($\geq 50\%$). Therefore, all 11 patients had a tumor stage (and overall FIGO stage, which was equivalent to tumor stage) of IB or greater. Nine patients were stage IB, and 2 patients were stage II. When patients were stratified by risk factors (no risk factors, HIR or high risk, or stage II disease, as defined above), the rate of LR did not significantly differ ([Fig. E1](#); *P* = .24). The 5-year rate of LR was 8.4% for HIR patients, 2.4% for high-risk patients, and 4.4% for stage II patients.

Table 1 Baseline characteristics of patients and tumors (N = 247)

Age, y median (range)	65 (31-89)
Follow up, y median (range)	5.8 (0.2-24.7)
Tumor size, cm median (range)	4.0 (0.3-15)
Histology, n (%)	
Serous	31 (13%)
Carcinosarcoma	8 (3%)
Clear cell	3 (1%)
Endometrioid	196 (80%)
Mixed	9 (4%)
Grade, n (%)	
I	93 (38%)
II	80 (33%)
III	60 (25%)
N/A	13 (5%)
Unknown	1 (1%)
FIGO T stage, n (%)	
1a	129 (52%)
1b	92 (37%)
2	26 (11%)
FIGO stage, n (%)	
IA	128 (52%)
IB	92 (37%)
II	26 (11%)
Lymphovascular space invasion, n (%)	
Yes	79 (32%)
No	157 (64%)
Unknown	11 (4%)
Pelvic lymph nodes assessed surgically, n (%)	
Yes	209 (85%)
No	38 (15%)
Risk stratification, n (%)	26 (11%)
Stage II	53 (21%)
High risk	112 (45%)
High-intermediate risk	85 (34%)
PORTEC-2 criteria, n (%)	75 (30%)
GOG-99 criteria	48 (19%)
Both	56 (23%)
Criteria for HR/HIR not met	
Chemotherapy, n (%)	
Yes	50 (20%)
No	119 (48%)
Unknown	78 (32%)
Vaginal cuff treatment length, n (%)	
4 cm	215 (87%)
5 cm	12 (5%)
>5 cm	10 (4%)
Unknown	10 (4%)

Abbreviations: FIGO = International Federation of Gynecology and Oncology.

The 5-year Kaplan–Meier estimates of LR and RR (nonvaginal pelvic recurrence) were 5% and 5%, respectively. The 5-year rate of distant metastases was 7%. The 5-year DFS was 83%, CSS was 96%, and OS was 91% (Table 2).

Toxicity

Acute and chronic toxicity data were available for 206 and 178 patients, respectively (Tables 3 and 4). There were no grade ≥ 3 acute or chronic toxicities. Grade 2

Table 2 Clinical outcomes for 2- and 5-year survival and recurrence

	2 years, %	5 years, %
Overall survival	97.8	90.9
Cancer-specific survival	98.7	96.2
Disease-free survival	91.3	82.6
Local recurrence	4.0	5.1
Regional recurrence	3.0	4.6
Distant metastasis	3.5	6.9

acute and chronic toxicities were minimal. The most common grade 1 acute toxicities were fatigue (11%), urinary frequency (11%), and vaginal discharge (9%). All others were <8%. The most common grade 2 acute toxicities were urinary incontinence (3%) and vaginal dryness (2%). The most common grade 1 chronic toxicities were urinary frequency (13%), urinary incontinence (13%), and vaginal stenosis (21%). The most common grade 2 toxicities were vaginal dryness (4%), urinary incontinence (3%), and vaginal stenosis (3%).

Discussion

Our data show that the 30 Gy in 6 fractions dose-fractionation schedule for HDR VBT results in acceptable local control and minimal acute and chronic toxicity. Our

5-year LR rate of 5% compares favorably with the 5-year vaginal recurrence rate of 1.8% reported in the PORTEC-2 study, particularly because the PORTEC-2 study evaluated women with HIR disease treated with HDR VBT monotherapy, whereas 32% of patients included in our study had high-risk or stage II disease.⁴ Likewise, our finding that deep myometrial invasion predicts for LR is in line with modern staging and risk-stratification criteria.^{3,4}

We calculated the 5-year LR rates for HIR, high-risk, and stage II patients (8.4%, 2.4%, and 4.4%, respectively), and found no significant difference in LR rates by risk group. However, caution should be used when comparing the outcomes of these risk groups, because the majority of high-risk and stage II patients received adjuvant chemotherapy (58% of these groups compared with 20% of our entire cohort). Additionally, our 5-year LR rate of 8.4% for HIR patients is higher than the rate reported in the PORTEC-2 study; however, differences in baseline patient characteristics (eg, possibly the percentage of patients with substantial LVSI) in our analysis and the PORTEC-2 study might explain this.

As previously mentioned, the PORTEC-2 study established VBT as the treatment of choice for patients with HIR endometrial cancer owing to a lower rate of grade 1 to 2 gastrointestinal toxicity (53.8% after EBRT vs 12.6% after VBT),⁴ and additional studies confirmed this.¹⁰ A systematic review found that VBT is very well tolerated, with <20.6% of patients experiencing grade 1 or 2 acute vaginal toxicity and <2% grade 3 to 4

Table 3 Acute radiation toxicities (patients with available data, N = 206)

	None, n (%)	Grade 1, n (%)	Grade 2, n (%)
General			
Fatigue	184 (89)	22 (11)	0 (0)
Weight loss	206 (100)	0 (0)	0 (0)
Anorexia	206 (100)	0 (0)	0 (0)
Gastrointestinal			
Nausea	204 (99)	2 (1)	0 (0)
Vomiting	205 (99.5)	1 (0.5)	0 (0)
Diarrhea	192 (93)	13 (6.5)	1 (0.5)
Constipation	198 (96)	8 (4)	0 (0)
Small bowel/colon obstruction	206 (100)	0 (0)	0 (0)
Rectal pain	206 (100)	0 (0)	0 (0)
Genitourinary			
Urinary tract pain/dysuria	204 (99)	2 (1)	0 (0)
Urinary incontinence	192 (93)	8 (4)	6 (3)
Hematuria	206 (100)	0 (0)	0 (0)
Frequency/urgency	184 (89)	22 (11)	0 (0)
Pelvic pain	200 (97)	6 (3)	0 (0)
Vaginal			
Vaginal infection/vaginitis	204 (99)	1 (0.5)	1 (0.5)
Vaginal stenosis/stricture	200 (97)	5 (2.5)	1 (0.5)
Vaginal dryness	200 (97)	2 (1)	4 (2)
Vaginal discharge	186 (90.5)	19 (9)	1 (0.5)
Female genital tract fistula	206 (100)	0 (0)	0 (0)

Table 4 Chronic radiation toxicities (patients with available data, N = 178)

	None, n (%)	Grade 1, n (%)	Grade 2, n (%)
General			
Fatigue	162 (91)	15 (8)	1 (1)
Weight loss	175 (98)	3 (2)	0 (0)
Anorexia	177 (99)	1 (1)	0 (0)
Gastrointestinal			
Nausea	177 (99)	1 (1)	0 (0)
Vomiting	177 (99)	1 (1)	0 (0)
Diarrhea	164 (92)	11 (6)	3 (2)
Constipation	169 (95)	9 (5)	0 (0)
Small bowel/colon obstruction	178 (100)	0 (0)	0 (0)
Rectal pain	173 (97)	4 (2%)	1 (1)
Genitourinary			
Urinary tract pain/dysuria	172 (96)	5 (3)	1 (1)
Urinary incontinence	149 (84)	24 (13)	5 (3)
Hematuria	174 (98)	4 (2)	0 (0)
Frequency/urgency	152 (85)	23 (13)	3 (2)
Pelvic pain	168 (94)	10 (6)	0 (0)
Vaginal			
Vaginal infection/vaginitis	174 (98)	4 (2)	0 (0)
Vaginal stenosis/stricture	135 (75)	37 (21)	5 (3)
Vaginal dryness	163 (92)	7 (4)	8 (4)
Vaginal discharge	162 (91)	15 (8)	1 (1)
Female genital tract fistula	177 (99)	1 (1)	0 (0)
Other			
Lymphedema	170 (95)	8 (5)	0 (0)
Renal disorder	178 (100)	0 (0)	0 (0)

toxicity.⁸ In comparison, we report <10% rates of acute vaginal toxicity and no grade ≥ 3 toxicity.

In the absence of randomized data, a direct comparison of the rates of toxicity after various doses of VBT is difficult. There is limited data regarding dosimetric predictors of acute and late vaginal toxicity. One study found that doses >68 Gy EQD₂₃ to 2cc of the vagina was associated with a 20.5% rate of grade 2 toxicity,¹¹ and several studies have shown that the bladder point dose does not correlate with urinary toxicity.^{12,13} Multiple studies have evaluated the impact of altering fractionation and timing on toxicity. Several single institution experiences investigating the use of condensed fractionation schedules, including daily fractions, have shown acceptably low rates of acute and late toxicity.^{14,15} Furthermore, various risk factors known to impact rates of toxicity after VBT (eg, cylinder size, vaginal treatment length, and rates of vaginal dilator use)¹⁶⁻²¹ are difficult to control for across studies, which further limits a direct comparison of our outcomes to those of other retrospective reports of toxicity after other doses.

The recent ABS Task Group Report on fractionation choices for gynecologic HDR VBT recommends several dose fractionations, but does not recommend any one scheme over another.⁶ In fact, the report highlights the lack of evidence supporting one fractionation over another, and comments that various institutions have published acceptable outcomes with several regimens. No

randomized trials comparing the regimens recommended by the ABS Task Group have been conducted, and a limited number of single-institution, retrospective studies have compared dose-fractionation regimens, either alone or in combination with EBRT, showing no significant differences in local control or toxicity.^{10,22,23} Specifically, Sorbe et al. compared 15 or 30 Gy, each derived in 6 fractions and prescribed to a depth of 5 mm, and showed that local control and overall rates of vaginal, genitourinary, and gastrointestinal toxicities did not statistically differ.¹⁰ However, in the 30-Gy arm, there were significantly higher rates of vaginal shortening as measured by colpometry.

The 2019 ABS Task Group publication outlines the EQD₂₁₀ for several of the dose-fractionation schemes,⁶ and we have listed those in comparison with our own in Table 5. The total EQD₂₁₀ at a depth of 5 mm ranges from 15.62 to 31.25 Gy for other doses, while our dose has a higher EQD₂₁₀ (37.5 Gy). We also listed the EQD₂₃ for each fractionation, and showed that ours is higher (48 Gy at a depth of 5 mm, 103.3 Gy at the surface) compared with other doses (16.5-42 Gy at a depth of 5 mm, 33.6-92.4 Gy at the surface). Despite this higher equivalent dose, we report low rates of toxicity after 30 Gy in 6 fractions prescribed to a depth of 5 mm. Further work is needed to determine whether this higher dose may result in superior local control for a subset of patients with certain risk factors. The idea of further risk stratification is in

Table 5 Vaginal cuff brachytherapy dose-fractionation schemes with corresponding EQD_{2,10} for 3-cm diameter cylinder, adapted from American Brachytherapy Society guidelines⁶

Cylinder dose	Prescription depth	Total surface EQD _{2,10} (Gy)	Total surface EQD _{2,3} (Gy)	Total 5-mm depth EQD _{2,10} (Gy)	Total 5-mm depth EQD _{2,3} (Gy)
7 Gy × 3	5 mm	57.75	92.4	29.75	42
5.5 Gy × 4	5 mm	54.23	81.43	28.42	37.4
7.5 Gy × 5	Surface	54.69	78.75	29.6	37.44
5 Gy × 5	5 mm	58.92	86.11	31.25	40
6 Gy × 5	Surface	40	54	22.59	26.91
2.5 Gy × 6	5 mm	28	33.6	15.62	16.5
5 Gy × 6*	5 mm	70.7	103.3	37.5	48

Abbreviations: EQD2 = equivalent total dose in 2-Gy fractions.

* Dose-fractionation scheme used at our institution.

line with current trends in early stage endometrial cancer. For instance, the ongoing PORTEC-4a trial randomizes women with HIR endometrial cancer to VBT or molecular profile-directed therapy, with observation, VBT, or EBRT depending on molecular risk factors.²⁴

Overall, there are minimal data regarding the comparison of various dose-fractionation schemes for adjuvant HDR VBT, and the recent ABS Task Group Report on fractionation choices notes that multiple different fractionations are equally acceptable. However, the PORTEC-2 fractionation of 7 Gy × 3 fractions prescribed to a depth of 5 mm is used most commonly.⁶ In our analysis, 30 Gy in 6 fractions, which has a higher equivalent dose than other more commonly used dose fractionations, was associated with comparable rates of low toxicity. Future work is needed to determine whether patients with certain risk factors will benefit from this escalated dose. At this time, under what circumstances a dose of 30 Gy in 6 fractions offers any benefit to offset the additional fractions required compared with other shorter, more commonly used dose fractionations is unclear. However, we believe that this regimen may be useful in select cases where dose escalation is desirable.

This study has several limitations. First, data were gathered retrospectively; therefore, some factors with the potential to affect toxicity outcomes may not have been uniformly applied. For instance, vaginal dilators are routinely offered to patients in our clinical practice and their use is encouraged at the time of follow up, but patient compliance was not consistently recorded. Detailed information regarding vaginal dilator use would have strengthened our paper given that consistent dilator use is associated with lower rates of vaginal stenosis. Similarly, we were unable to report rates of sexual activity at baseline and follow up because these data were not routinely recorded. In addition, a more detailed comparison of the clinical outcomes and toxicities reported in this review with prior reports in the literature is beyond the scope of this study.

Also, our median follow-up time was 5.8 years, which limits conclusions regarding longer-term toxicity, which is due in part to the fact that many patients were lost to follow up after 5 years. Furthermore, toxicity data were prospectively collected for the majority of patients included in this study, but toxicity data were retrospectively collected from information available in follow-up notes for some patients for whom prospective data were not available. This limits the strength of our toxicity data. Additionally, surgical approaches were not uniform. Laparoscopic and robotic surgical staging became standard at our institution in 2006; therefore, this analysis includes outcomes of patients who received a mix of open, laparoscopic, and robotic surgery. Laparoscopic and robotic methods have similar immediate outcomes, but further work is required to investigate how surgical approaches may influence toxicity outcomes in our patient population.²⁵ Finally, further analysis to investigate the presence

of LVSI as a risk factor in this population is planned, because the presence of LVSI is a known poor prognostic indicator for recurrence and survival.²⁶

Conclusions

This study shows that the dose-fractionation schedule of 30 Gy in 6 fractions results in acceptable clinical outcomes with minimal toxicity, and is comparable to the recommended dose-fractionation schedules in the ABS guidelines. This dose fractionation has a higher equivalent dose than other more commonly used doses, but was associated with comparable rates of low toxicity. Future work is needed to better define whether certain patients may benefit from this escalated dose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.adro.2021.100773](https://doi.org/10.1016/j.adro.2021.100773).

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