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ORIGINAL ARTICLE

Extended duration of dilator use beyond 1 year may reduce vaginal stenosis after intravaginal high-dose-rate brachytherapy

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Abstract

Background Vaginal dilators (VD) are recommended following vaginal or pelvic radiotherapy for patients with endometrial carcinoma (EC) to prevent vaginal stenosis (VS). The time course of VS is not fully understood and the optimal duration of VD use is unknown.

Methods We reviewed 243 stage IA–II EC patients who received adjuvant brachytherapy (BT) at an academic tertiary referral center. Patients were instructed to use their VD three times per week for at least 1-year duration. The primary outcome was development of grade ≥ 1 VS using CTCAEv4 criteria during the follow-up period. The log-rank test and multivariable Cox proportional hazards modeling were used to evaluate the effect of VD use (noncompliance vs. standard compliance [up to 1 year] vs. extended compliance [over 1 year]) on VS.

Results The median follow-up was 15.2 months over the 5-year study period. At 15 months, the incidence of VS was 38.8% for noncompliant patients, 33.5% for those with standard compliance, and 21.4% for those with extended compliance (median time to grade ≥ 1 VS was 17.5 months, 26.7 months, and not yet reached for these groups, respectively). On multivariable Cox regression analysis, extended compliance remained a significant predictor of reduced VS risk when compared to both noncompliance (HR 0.38, 95% CI 0.18–0.80, $p = 0.012$) and standard compliance (HR 0.43, 95% CI 0.20–0.89, $p = 0.023$).

Conclusions The risk of VS persists beyond 1 year after BT. Extended VD compliance beyond 1 year may mitigate this risk.

Keywords Vaginal stenosis · Intravaginal brachytherapy · High-dose-rate · Vaginal dilators · Endometrial cancer

Introduction

Vaginal stenosis (VS) is a sub-acute-to-late toxicity resulting from brachytherapy (BT) or external beam radiotherapy (EBRT) for pelvic malignancies [8, 23]. It is characterized by narrowing or shortening of the vaginal vault and loss of elasticity thought to occur due to collagen deposition and elastosis (aggregated and entangled elastin fibers) in the irradiated vaginal tissue [14]. In the most severe form, VS interferes with pelvic examination necessary for cancer surveillance and leads to sexual dysfunction which can negatively affect patient quality of life [32]. To mitigate the risk of VS, regular home vaginal dilator (VD) use is recommended after completing radiotherapy (RT), with multiple observational studies correlating VD use with reduced risk of VS [3, 11, 20, 26, 33, 34].

Although the time course of VS is not fully understood, studies across disease sites have demonstrated that the risk appears to increase over time with the most significant rise apparent within the first 2–5 years post-RT [11, 18, 31]. There are no prospective or randomized studies examining the required duration of preventative VD use to reduce VS. Recent practice guidelines suggest as few as 9–12-month duration after pelvic RT [5] and yet others suggest 5 years or

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indefinitely [35]. Canadian consensus nursing guidelines suggest at least 1-year duration [1], while a survey of US radiation oncologists showed that > 70% recommended duration over 1 year [16]. Whether 1-year duration is sufficient or longer time is necessary is not known. This uncertainty is reflected in considerable variation in practice among practitioners in both the USA [16] and abroad [19].

To further our understanding of the prophylactic effects of VD use following RT, we conducted a review of VD practices and compliance among endometrial cancer (EC) patients who received adjuvant BT at our institution. We examined whether there was an association between duration of preventative VD use and the incidence of VS over time.

Materials and methods

Patient cohort

Following approval by the institutional review board, we examined the records of 304 consecutive patients who underwent adjuvant vaginal BT without EBRT for International Federation of Gynecologic and Obstetrics (FIGO) stage I–II EC at our academic tertiary referral center between September 2011 and December 2015. Follow-up data was collected through October 2016. Sixty-one patients were excluded due to lack of follow-up in the radiation oncology clinic, leaving 243 patients with follow-up data for analysis. All patients had undergone total hysterectomy, bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node evaluation and peritoneal cytology as indicated. Adjuvant BT with or without chemotherapy was recommended based on risk factors for recurrence.

Patients were examined and prepared to start BT in a manner previously described [27]. Each patient was fitted with a vaginal cylinder selected from custom-fabricated diameter sizes of 2.0, 2.3, 2.6, and 3.0 cm. BT was delivered using a high-dose-rate (HDR) ^{192}Ir source by a single-channel vaginal cylinder to a prescription point 5 mm from the cylinder surface. The standard dose-fractionation prescribed was 18–21 Gy in 3 weekly or bi-weekly fractions. A minority of patients received an alternative lower dose BT schedule either due to unusual vaginal anatomy or the specifications of a particular combined BT/chemotherapy protocol (i.e., 14 Gy in two fractions) [10]. Active treatment length varied from 3 to 6 cm. All patients were treated from a library of template plans, with each source dwell position separated by 1 cm. Planning was based on calculations in a homogeneous phantom without heterogeneity correction and was performed in Eclipse BrachyVision 3D treatment planning system version 13.6 (Varian Medical Systems Inc.).

Provision of VD

Each patient was provided a plastic cylindrical VD with a diameter matched to her BT cylinder diameter, with the goal of preserving her baseline vaginal capacity post treatment. Both verbal and written instructions for VD use were provided by a specially trained nurse, typically following the second BT fraction. Education was reinforced by the radiation oncologist after the final BT session. Patients were instructed to insert the VD in the vagina at a frequency of three times per week, for a total of 10 minutes per session, for at least 1 year in duration. This institutional practice is within range of recommendations suggested by published practice guidelines [22, 35]. Patients were instructed to break apart adhesions and to focus on maintaining vaginal capacity to ease pelvic examination in the future and improve sexual health outcomes. Graduated VD sets were not provided, though oftentimes patients were provided with two sizes, with instruction to work towards finding comfort with the larger of the two. Water-based lubricant was provided along with the VD. Personal moisturizers were not provided but were recommended during the follow-up period for those who expressed discomfort or dryness with VD use or intercourse.

VD compliance

The degree of patient compliance with VD use was determined during the interview at each scheduled follow-up in the radiation oncology clinic. Patients were typically seen 3–6 months after their final BT fraction and then yearly thereafter. At each visit, the physician completed a template document detailing whether the patient was using her VD and specifically how many times per week, along with other questions regarding vaginal dryness, use of lubricant and/or moisturizer, frequency of sexual intercourse, and dyspareunia (i.e., pain with intercourse; graded 0 (none), 1 (mild), 2 (moderate), or 3 (severe)).

The date of each follow-up visit and VD use frequency were recorded in the database. The longest duration of follow-up in the radiation oncology clinic was noted; patients who continued using the VD at least two times per week for more than 1 year (> 365 days) were coded as having "extended compliance," while those who used the VD a minimum of two times per week for up to 1 year (≤ 365 days) were defined as having "standard compliance." Patients who reported use of the VD < 2 times per week or who did not use their VD were coded as "noncompliant." Among patients with one follow-up visit at 3–6 months after their final BT fraction and no visits thereafter (or last follow-up occurring at < 12 months), those who were complaint were coded as having "standard compliance" since their follow-up was insufficient to qualify them for "extended compliance." VD compliance was coded independently of reported sexual intercourse. All patients were

included regardless of length of follow-up assuming they had at least one.

Outcomes

The primary outcome of the study was the development of grade ≥ 1 VS as assessed by physical examination at any follow-up in the radiation oncology clinic after determining VD compliance. Toxicity was graded prospectively at each follow-up visit using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (grade 1: asymptomatic, mild vaginal shortening/narrowing; grade 2: vaginal shortening/narrowing not interfering with physical examination; grade 3: shortening/narrowing interfering with use of tampons, sexual activity, or physical examination). The Kaplan-Meier method was used to estimate VS over time, with patients censored at last follow-up or at time of first diagnosis of VS. Clinicopathologic and treatment data were abstracted for each patient and included age, body mass index (BMI), race, gravidity, reported sexual activity at any follow-up (defined as regular penetrative vaginal intercourse), tumor stage, grade, histology, receipt of chemotherapy, baseline (pre-BT) vaginal length, cylinder size, dose, active treatment length, and percent vaginal length treated. Percent vaginal length treated was defined as the ratio of the distance between the most proximal and distal dwell positions in the cylinder's central channel and the vaginal length measured on baseline vaginal exam. Dose was analyzed as a binary variable of standard dose (18–21 Gy) and low dose (14 Gy). The log-rank test and multivariable Cox proportional hazards modeling were used to evaluate the effect of VD use on the primary outcome. To determine factors associated with VD compliance, the chi-squared tests and multivariable logistic regression modeling were used. Covariates with $p < 0.15$ on univariable analysis or those felt to be clinically relevant were included in multivariable analyses. Variables were tested for multicollinearity before inclusion in the multivariable model by deriving the variance inflation factor (< 5 indicated low likelihood of multicollinearity). Two-sided p values were considered significant if $p < 0.05$. IBM SPSS statistics version 22 (SPSS, Armonk, NY) was used for statistical analysis.

Results

VD compliance and risk of VS

Table 1 shows baseline patient characteristics for the entire cohort. The median age was 65 years (range, 43–94) and the majority (67.5%) were not sexually active. The majority (84.8%) received a dose of 18–21 Gy in three fractions. The median follow-up time was 15.2 months (range, 1.9–38.1), 108 patients (44.4%) had at least 1 year of follow-up, and 20 patients (8.2%) had 2 years or more of follow-up. Concerning VD use, 98 (40.3%) were noncompliant, 97 (39.9%) had standard compliance, and 48 (19.8%) had extended compliance.

For the entire cohort, the incidence (1 minus survival) of VS grade ≥ 1 at 12 months was 28%, and at 24 months was 44% (Fig. 1a). Among the 74 patients with recorded VS, 62 had grade 1 (83.8%), 11 had grade 2 (14.9%), and only 1 (1.3%) had grade 3 toxicity. Of all grade ≥ 2 VS, 7/12 (58.3%) cases were noted in noncompliant patients. Grade ≥ 2 VS was not observed among those with extended compliance.

On univariable analysis, extended VD use compared with standard/noncompliant groups had a significant association with reduced likelihood of VS incidence (log-rank, $p = 0.005$, Fig. 1b). The median time to VS was 17.5 months for noncompliant patients, 26.7 months for standard compliance, and was not yet reached for extended compliance. At 15 months, the incidence of VS was 38.8% for noncompliance, 33.5% for standard compliance, and 21.4% for extended compliance. The 24-month estimates were 61.2%, 50.5%, and 21.1%, respectively, though endpoint evaluation at 24 months was limited by the small number of patients followed to this timepoint (20 patients). Other significant predictors of development of VS (Table 1) included G0 gravidity ($p = 0.001$), lack of sexual intercourse ($p = 0.002$), and smaller cylinder size ($p = 0.001$), with a trend for greater vaginal percent length treated ($p = 0.101$).

On multivariable Cox regression analysis (Table 2), after adjusting for other significant variables impacting incidence of VS, extended compliance remained a significant predictor of freedom from VS when compared to both noncompliance (HR 0.38, 95% CI 0.18–0.80, $p = 0.012$) and to standard compliance (HR 0.43, 95% CI 0.20–0.89, $p = 0.023$).

Sensitivity analysis performed on a cohort of the 108 patients with at least 1 year of follow-up showed that the above findings on univariable and multivariable analysis remained significant in regard to VD compliance.

Frequency of VD use among compliant patients

When analysis was restricted to those exhibiting only standard or extended compliance (100% of these patients used their VD 2 or more times per week by definition), 78.8% (115/146) of patients reported VD use three or more times per week, and 11.0% (16/146) reported use four or more times per week. There was no difference in median time to grade ≥ 1 VS based on frequency of VD use.

Predictors of extended compliance

To test for factors associated with extended compliance, we looked at patient and treatment characteristics, as well as post-treatment behavioral factors and symptoms thought to influence a patient's compliance. On univariable analysis (Table 3),

Table 1 Patient and treatment characteristics, univariable comparison of covariates by development of vaginal stenosis over time

Variable	Categories	$N = 243$	Median time to grade ≥ 1 VS	95% CI	p value (log-rank)
Age	< 60 years	69 (28.4%)	28.0 months	21.3–34.7	0.206
	≥ 60 years	174 (71.6%)	26.7 months	14.0–39.4	
Body mass index	Normal	46 (19.0%)	38.1 months	NA	0.647
	Overweight	57 (23.5%)	28.0 months	15.8–40.1	
	Obese	85 (35.0%)	27.0 months	12.3–41.7	
	Morbidly obese	54 (22.2%)	26.7 months	16.2–37.2	
Race	Caucasian	202 (83.1%)	27.0 months	19.7–34.3	0.816
	Other	41 (16.9%)	Not reached	NA	
Gravidity	Nulligravid	40 (16.5%)	8.8 months	5.2–12.4	0.001
	Parous	203 (83.5%)	31.8 months	NA	
Sexually active*	Yes	79 (32.5%)	Not reached	NA	0.002
	No	164 (67.5%)	18.5 months	15.5–21.4	
Cylinder size	2 or 2.3 cm	39 (16.0%)	9.9 months	6.6–19.2	0.001
	2.6	78 (32.1%)	20.7 months	15.2–26.3	
	3 cm	126 (51.9%)	28.0 months	25.8–30.1	
Baseline vaginal length	< 8 cm	116 (47.7%)	27.0 months	20.3–33.6	0.891
	≥ 8 cm	127 (52.3%)	28.0 months	18.0–38.0	
Histological FIGO grade	Grade 1	178 (73.3%)	31.8 months	NA	0.415
	Grade 2	55 (22.6%)	27.0 months	22.4–31.6	
	Grade 3	10 (4.1%)	19.4 months	11.7–27.1	
Endometrioid histology	Yes	183 (75.3%)	19.4 months	NA	0.464
	No	60 (24.7%)	28.0 months	26.1–29.9	
Radiation dose-fractionation	Standard dose	206 (84.8%)	26.7 months	18.4–35.0	0.159
	Low dose	37 (15.2%)	Not reached	NA	
Receipt of chemotherapy	Yes	78 (32.1%)	38.1 months	NA	0.376
	No	165 (67.9%)	27.0 months	21.3–32.7	
Vaginal percent length treated	> 60%	134 (55.1%)	18.5 months	NA	0.101
	≤ 60%	103 (42.4%)	28.0 months	26.1–29.8	
Vaginal dilator compliance	Noncompliant	97 (39.9%)	17.5 months	14.3–20.8	0.019
	Standard compliance	98 (40.3%)	26.7 months	15.2–38.2	
	Extended compliance	48 (19.8%)	Not reached	NA	
Vaginal dilator compliance	Extended compliance	48 (19.8%)	Not reached	NA	0.005
	Other	195 (80.2%)	19.4 months	16.2–22.5	
Frequency of dilator use	> 2 times per week	115 (47.3%)	27.0 months	20.4–33.6	0.642
	≤ 2 times per week	128 (52.7%)	38.1 months	NA	

FIGO International Federation of Gynecologic and Obstetrics

*The term sexual activity specifically referred to having penetrative sexual intercourse

significant factors included lack of receipt of chemotherapy ($p = 0.037$), moisturizer use ($p = 0.10$), and frequency of VD use more than two times per week ($p < 0.001$). On multivariable logistic regression, patients most likely to have extended compliance tended to use their VD more than twice per week (OR 6.81, 95% CI 2.96–15.37, $p < 0.001$), use vaginal moisturizers (OR 4.39, 95% CI 1.50–12.82, $p = 0.007$), and had not received chemotherapy (OR 2.77, 95% CI 1.09–7.05, $p = 0.032$).

VD toxicity

Only seven patients (2.9%) reported any toxicity with VD use resulting in the recommendation that they discontinue. Five patients experienced bleeding/pain/ulceration, one had an episode where the VD became temporarily lodged during use, and one patient experienced a grade 3 traumatic dehiscence requiring surgical repair.

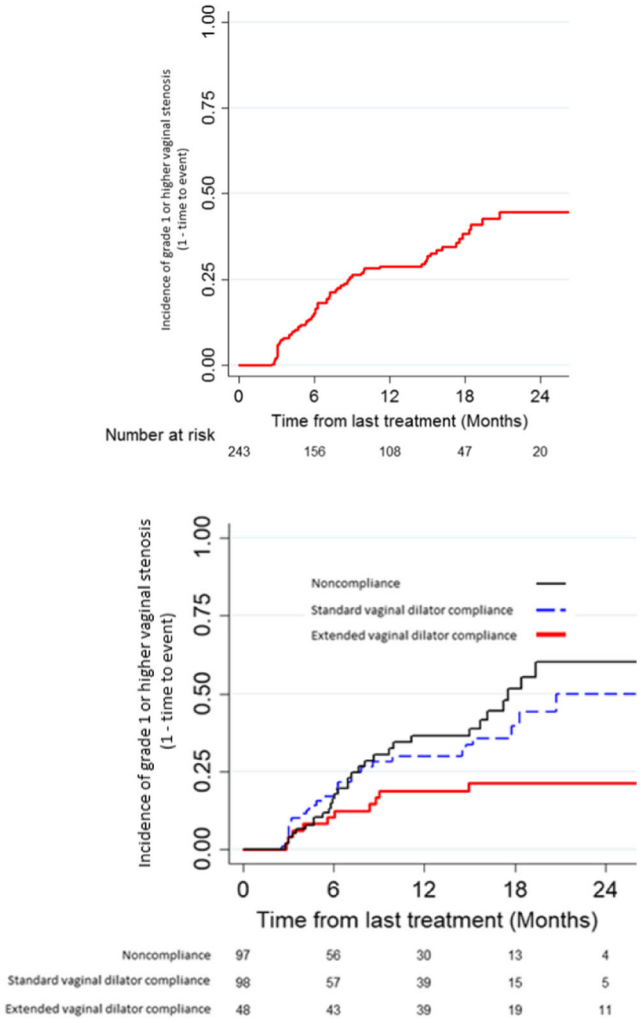

Fig. 1 **a** Inverse Kaplan-Meier showing grade ≥ 1 vaginal stenosis (N = 243). **b** Inverse Kaplan-Meier showing grade ≥ 1 vaginal stenosis by dilator compliance (N = 243)

Discussion

In the present study of early stage EC patients who underwent adjuvant BT, we found that the incidence of grade ≥ 1 VS increases over time and continues beyond 1 year, with an estimated incidence of 28% at 12 months, 32% at 15 months, and 44% at 24 months. The practice of continued VD use over an extended time period (beyond 1 year) was associated with a lower risk of VS in this cohort, both compared to patients with suboptimal VD compliance (HR 0.38), and also compared with patients who practiced "standard" VD compliance of two to three times per week for up to 12 months (HR 0.43). This is the first study to report the actuarial incidence of VS over time in patients undergoing BT for EC in relation to preventative VD utilization.

The time course for the development of VS following pelvic/vaginal radiotherapy has been documented in several prior studies, and may include early changes which occur on or shortly after treatment, as well as late effects which evolve over several years [18, 25, 28, 31]. The largest prospective experience reporting the actuarial risk of VS comes from the EMBRACE study and included 630 patients treated for locally advanced cervical cancer (CC). At a median follow-up of 24 months, the 2-year actuarial estimate for VS grade ≥ 2 was 21% [18]. Longer follow-up from this study is eagerly anticipated to understand the full time course of VS. A large, retrospective study of 374 CC patients from the University of Wisconsin with slightly longer follow-up time (median follow-up of 35.5 months), also looked at actuarial estimates of VS in CC patients [11]. These authors found the steepest rise in incidence in the first 5 years following RT, and estimated a 5-year rate of severe (grade ≥ 3) VS of 42%, with a subsequent continuous risk of only 2.3% per year beyond 5 years.

Table 2 Multivariable Cox regression analysis for hazard of developing grade ≥ 1 vaginal stenosis

Variable	Hazard ratio	95% confidence interval	p value
Gravidity			0.076
Nulliparous vs parous	1.70	0.95–3.04	
Sexually active*			0.004
No vs yes	2.48	1.34–4.57	
Cylinder size			0.009
2 or 2.3 cm vs 3 cm	2.04	1.01–4.10	0.046
2.6 cm vs 3 cm	0.73	0.39–1.37	0.731
Radiation dose-fractionation			0.489
Low dose vs high dose	0.49	0.20–1.19	
Vaginal percent length treated			0.030
> 60% vs ≤ 60%	1.78	1.06–3.00	
Vaginal dilator compliance			0.035
Extended compliance vs standard compliance	0.43	0.20–0.89	0.023
Extended compliance vs noncompliance	0.38	0.18–0.80	0.012

*The term sexual activity specifically referred to having penetrative sexual intercourse

Table 3 Predictors of extended dilator compliance

Variable	Categories	Extended compliance	Standard or noncompliance	Univariable *p* value	Multivariable *p* value	Multivariable OR, (95% CI)
Age	< 60 years	31 (64.6%)	143 (73.3%)	0.283		
	≥ 60 years	17 (35.4%)	52 (26.7%)			
Body mass index	Normal	14 (29.2%)	32 (16.5%)	0.246		
	Overweight	9 (18.8%)	48 (24.7%)			
	Obese	15 (31.3%)	70 (36.1%)			
	Morbidly obese	10 (20.8%)	44 (22.7%)			
Race	Caucasian	42 (87.5%)	160 (82.1%)	0.518		
	Other	6 (12.5%)	35 (17.9%)			
Gravidity	Nulligravid	6 (12.5%)	34 (17.4%)	0.517		
	Parous	42 (87.5%)	161 (82.6%)			
Sexually active**	Yes	17 (35.4%)	62 (31.8%)	0.731		
	No	31 (64.6%)	133 (68.2%)			
Lubricant use	Yes	32 (66.7%)	148 (75.9%)	0.201		
	No	16 (33.3%)	47 (24.1%)			
Moisturizer use	Yes	9 (18.8%)	12 (6.2%)	0.010	0.007	4.39, (1.50–12.82)
	No	39 (81.3%)	183 (93.8%)			
Vaginal dryness	Yes	15 (31.3%)	58 (29.7%)	0.861		
	No	33 (68.8%)	137 (70.3%)			
Dyspareunia	Yes	7 (14.6%)	18 (9.2%)	0.291		
	No	41 (85.4%)	177 (90.8%)			
Cylinder size	2 or 2.3 cm	9 (18.8%)	30 (15.4%)	0.670		
	2.6	13 (27.1%)	65 (33.3%)			
	3 cm	26 (54.2%)	100 (51.3%)			
Baseline vaginal length	< 8 cm	25 (52.1%)	102 (52.3%)	1.000		
	≥ 8 cm	23 (47.9%)	93 (47.7%)			
Histological FIGO grade	Grade 1	7 (14.6%)	39 (20.0%)	0.207		
	Grade 2	27 (56.3%)	82 (42.1%)			
	Grade 3	14 (29.2%)	74 (37.9%)			
Endometrioid histology	Yes	41 (85.4%)	142 (72.8%)	0.092	*	
	No	7 (14.6%)	53 (27.2%)			
Radiation dose-fractionation	Standard dose	44 (91.7%)	162 (83.1%)	0.179	*	
	Low dose	4 (8.3%)	33 (16.9%)			
Receipt of chemotherapy	Yes	9 (18.8%)	69 (35.4%)	0.037		
	No	39 (81.3%)	126 (64.6%)		0.032	2.77, (1.09–7.05)
Vaginal percent length treated	> 60%	31 (67.4%)	103 (53.9%)	0.135	*	
	≤ 60%	15 (32.6%)	88 (46.1%)			
Dilator frequency > 2 times per week	Yes	39 (81.3%)	76 (39.0%)	< 0.001	< 0.001	6.81, (2.96–15.37)
	No	9 (18.8%)	119 (61.0%)			

FIGO International Federation of Gynecologic and Obstetrics

*Variable included in multivariable analysis but not statistically significant

**The term sexual activity specifically referred to having penetrative sexual intercourse

In contrast to CC, the treatment of EC with adjuvant RT utilizes significantly lower dose, treats a more limited volume/thickness of vagina, and oftentimes does not include pelvic EBRT or chemotherapy. Further, the population of patients is older, post-hysterectomy, and less likely to be sexually active. As such, the actuarial risk and severity of VS over time in EC patients is likely to differ significantly as well. As a basis for comparison, the postoperative radiation therapy for endometrial cancer (PORTEC)-2 randomized trial reported the 3-year incidence of grade 1–2 vaginal mucosal atrophy at 35% (only

11% grade ≥ 2) [24]. A retrospective study by Onsrud et al. reported on rates of VS over time in 217 early stage EC patients followed for a minimum of 4 years and found rates of grade 1–2 VS of 18–34%, with the steepest rise occurring in the first 24 months, with little increase in incidence after that [25]. Taken together, these studies of both CC and EC populations illustrate the importance of looking at VS as a time-dependent actuarial rather than crude outcome, and also illustrate that VS severity and time course will differ across disease sites and treatments.

To mitigate the risk of VS, VD can be used preventatively after pelvic or vaginal RT. While there is no randomized data demonstrating the superiority of preventative VD therapy compared to therapeutic (after VS has been diagnosed) [34] after RT, multiple retrospective reports across disease sites have suggested an association between preventative VD use with lower risk of VS [3, 11, 20, 26, 33]. Indeed, a recent survey suggests that a majority of practicing US radiation oncologists recommend preventative VD use for patients with pelvic malignancies, however, with considerable variation in recommended frequency and duration [16]. A consensus statement from the Netherlands recommends starting dilation around 4 weeks after treatment, performing dilation two to three times a week for 1 to 3 minutes, and continuing dilation for 9 to 12 months for gynecologic cancer patients [5]. However, evidence supporting optimal duration of VD use is lacking. The largest study to examine the extent of VD compliance is the University of Wisconsin [11] study by Gondi et al. of CC patients. After completing treatment, patients were told to use their VD ≥ 2 times per week for the first 2 years (then at least monthly thereafter) and were defined as having high compliance if this was followed. At 3 years, the incidence of grade 3 VS was 20.2% for patients receiving RT alone and 35.1% for concurrent chemoradiation. The degree of VD compliance was associated with a dose-response-like association between probability of VS over time and degree of compliance, with high compliance patients having the lowest incidence at 15.6%. In EC, while several studies have demonstrated a benefit to VD use [3], no prior reports have analyzed the risk of VS over time with regard to duration of VD use. Our findings that VD use beyond 1 year may be beneficial in EC patients receiving BT is thus novel and practice informing. However, the full duration of optimal use remains unknown. Controlled, prospective study of this topic would be needed to build upon these results.

The majority of patients in our cohort followed at least the standard recommendation for VD compliance (60%), but some patients (~ 20%) were extremely compliant for unclear reasons; this practice of extended VD use beyond 12 months appeared to benefit them. We found several additional behavioral factors which correlated with superior compliance, as defined as VD use beyond 12 months, including increased frequency of VD use (greater than two times per week) and routine use of vaginal moisturizers (such as vitamin E, Replens, or hyalonuric acid). We hypothesize that patients who use VD more often and also use moisturizers might have an improved experience with the VD and therefore are willing to use it longer. In addition, we found that patients not receiving chemotherapy were more likely to use the VD for longer periods of time. Chemotherapy has been shown previously to predict for non-adherence with VD, likely due to increased complexity of the overall treatment course [20]. Despite their reduced compliance, we did not observe an increased risk of VS in our patients who received chemotherapy; this may be due to our institutional practice of prescribing reduced dose BT for these patients [10].

Conversely, despite enthusiastic teaching, verbal and written instruction, and close follow-up, a significant proportion of our patients were noncompliant with VD recommendations (use < 2 times per week). Barriers to VD adherence have been reported to be primarily related to lack of time, social embarrassment, anxiety, and uncertainty about proper use [4, 6, 7]. In our cohort, since all patients were instructed to begin VD therapy prior to development of vaginal adhesions, pain (experienced in only 5/243 patients) or vaginal adhesions were not common causes of noncompliance. While randomized trials exploring the efficacy of psycho-educational/enhanced education programs have shown mixed results [12, 15, 21, 29], we recommend careful counseling during patient interviews explaining the importance of VD use by defining its dual role in their future health and providing positive feedback during routine follow-up examination. Additionally, the use of lubricants, vaginal moisturizers, and an appropriately sized VD should be encouraged. Although one patient in our cohort experienced a traumatic vaginal cuff dehiscence associated with VD use, this was an unusual singular event and was attributed to this specific patient's confusion concerning the purpose of the VD. In a study examining 510 surgical patients experiencing 21 vaginal cuff dehiscence events after hysterectomy, trachelectomy, or upper vaginectomy, only one case was due to VD use after BT [17]. Vaginal cuff dehiscence with vaginal cylinder placement prior to BT (shortly after surgery) is also described in the literature, but even in this high-risk time frame, the event is limited to small case reports [2, 9]. Based on this unanticipated event, which occurred very early in our study period, we systematically adjusted our institutional teaching practice to include patient specific, personalized instructions on the expected depth of VD placement based on her physical vaginal measurements. We caution each patient with the instruction to never force placement. Since implementing the above, no further events have occurred.

The strengths of our study include a large cohort of patients treated with homogeneous therapies who were evaluated for the primary outcome in a consistent manner, with meticulous and prospective recording of even mild (grade 1) vaginal toxicity. In regard to study limitations, the lack of randomization

in this review prevents determination of a cause and effect relationship. Although a validated measure, the CTCAE may be limited as a toxicity endpoint for recording VS in that this primary outcome measure is physician determined toxicity primarily based on physical examination. As such, we did not account for patient-reported measures and thus the relevance of this finding to patient quality of life is not clear. Future studies might consider examining the impact of VD use on a patient-reported outcome of VS, such as the one used in a recent study from Memorial Sloan Kettering, which defined the efficacy of VD use as the ability to maintain or return to pre-RT baseline size with the dilator in place 10 minutes [20]. Further, our primary outcome of grade ≥ 1 VS also fails to differentiate grade 1 from grade 2 VS—two degrees of toxicity with potentially different clinical implications. Without patient reporting via daily journal entry, our assessment of VD compliance at discrete time-points (with relatively long interval) may not fully represent their true practice in terms of frequency and duration of use. Additionally, the cut-off of 365 days was based on variations in guidelines, and there likely exists heterogeneity within groups, given the retrospective and non-randomized nature of this study. The follow-up interval was not long enough to define the full duration of VS risk, and further study is needed to determine if indefinite VD use is beneficial. Although our sensitivity analysis failed to show obvious bias due to inclusion of patients with shorter than 12-month duration of follow-up, the possibility exists that the VD compliance variable was influenced by the duration of available follow-up. Long-term follow-up (ideally, with a 5-year endpoint) would be worthwhile to validate the robustness of our findings. Lastly, the findings in this study are directly applicable only to patients receiving vaginal cylinder BT at standard adjuvant doses for EC. It is unknown whether these findings could be extrapolated to patients with other types of cancer or receiving different therapies, such as EBRT. A pelvic RT cohort would ideally be analyzed separately as such patients were specifically excluded from the present study. Although dose is a known predictor of VS [18, 26, 30], our study was underpowered to examine the effect of dose, with only 15% of patients receiving a low-dose regimen. How alternative BT schedules which deliver significantly lower vaginal mucosal dose (such as 6 Gy × 5 fractions prescribed at the surface [13]) impact recommendations for VD use is an important topic for further study.

Conclusions

Prospective research investigating the optimal duration of VD use following RT is lacking. Our findings suggest that for patients receiving adjuvant BT for EC, there may be a benefit to an extended duration of preventative VD use beyond 1 year. Further research is needed to develop essential evidence-based guidelines to improve patient-centered care, and might include prospective and longitudinal patient-centered endpoints, patient diary recording of VD practice, examination of outcomes over longer follow-up periods out to 5 years, and consideration of randomization of VD use over different lengths of time.

Compliance with ethical standards

Conflict of interest Henry Park received honoraria from Varian Medical Systems, Inc. and Rad Onc Questions, LLC. All other authors have no financial relationships to disclose. This project did not require funding. We have full control of all primary data and agree to allow the journal to review our data if requested. It has been submitted along with the manuscript as a SPSS data file.

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