

# Brachytherapy for malignancies of the vagina in the 3D era

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## Abstract

Vaginal cancer is an uncommon malignancy and can be either recurrent or primary. In both cases, brachytherapy places a central role in the overall treatment course. Recent technological advances have led to more advanced brachytherapy techniques, which in turn have translated to improved outcomes for patients with malignancies of the vagina. The aim of this manuscript is to outline the incorporation of modern brachytherapy into the treatment of patients with vaginal cancer including patient selection along with the role of brachytherapy in conjunction with other treatment modalities, various brachytherapy techniques, treatment planning, dose fractionation schedules, and normal tissue tolerance.

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**Key words:** brachytherapy, intracavitary, interstitial, vaginal cancer.

## Purpose

Vaginal cancer, whether recurrent or primary, is a rare malignancy. There are 3,000-4,000 cases of primary vaginal cancer diagnosed each year in the United States [1,2]. As an uncommon disease, there are no published National Comprehensive Cancer Network (NCCN) guidelines. Radiotherapy, particularly brachytherapy, is fundamental in the treatment of both primary and recurrent vaginal cancers [3-8]. The complete treatment regimen for patients with vaginal cancer usually consists of brachytherapy (BT) in conjunction with external beam radiation therapy (EBRT), though in some instances can be either alone [9-11]. Recent national trends in utilization have shown an alarming decrease in BT boost in favor of other modalities, despite extensive published literature in support of BT, and relative scarceness of data supporting other modalities [12]. In this review, we aim to give an overview of the incorporation of modern BT into the treatment of vaginal cancer.

## Patient selection

### *External beam radiation*

The definitive management of both primary and recurrent vaginal cancer should include a course of EBRT in order to address potential micrometastatic nodal disease and to downsize the primary tumor prior to BT [13]. Some patients may be at low risk for nodal disease and could potentially be cured with BT alone (especially

those with small, superficial disease), though this cohort remains difficult to distinguish and has not been prospectively defined. Typically, 45-50.4 Gy is delivered in 25-28 fractions to the primary site including the entire vagina, the paravaginal area to the pelvic sidewalls, and the gross tumor volume with margin, as well as to the lymph nodes at risk including the distal common iliac, internal iliac, external iliac, obturator, presacral, and in cases of involvement of the distal third to half of the vagina, the inguinal nodes.

### *Chemotherapy*

The role of systemic therapy in the setting of primary vaginal cancer has not been prospectively evaluated. However, a recent analysis of the National Cancer Database demonstrated a trend for increased utilization of concurrent chemotherapy (nearly 60% in 2011 and 2012), and that concurrent chemotherapy was associated with an absolute 5-year survival benefit of 6.9% [14]. The survival benefit was seen in all stages, though to the greatest degree in stages II-IV. Extrapolating from the cervical cancer experience, chemotherapy is typically platinum-based [15,16]. The role of systemic therapy in the setting of recurrent tumors of the vagina is less clear, though this is the subject an ongoing study, GOG 238, which will hopefully help answer this question. Our institutional practice is to offer concurrent cisplatin for patients with bulky or high grade recurrences and for all patients with nodal recurrence.

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## Brachytherapy

Brachytherapy is indicated in nearly all patients with primary or recurrent vaginal cancer. The primary exception is patients who are medically unable to tolerate the BT procedure including any associated anesthesia. In order to deliver adequate dose to the target with high conformality and to limit dose to critical organs, numerous BT techniques have been developed. These include single-channel vaginal cylinder brachytherapy (SCVCB), multi-channel vaginal cylinder brachytherapy (MCVCB), and interstitial BT. The decision of which brachytherapy technique to employ is influenced by multiple factors, with tumor location, extent of disease, and response to EBRT as the main factors. Tumors can regress significantly with EBRT, making it important to evaluate extent of disease before and after EBRT. Modern three-dimensional conformal BT techniques have allowed for a growing emphasis on maintaining acceptable dosages to organs at risk (OAR).

## Imaging

In order to plan for BT, cross-sectional imaging is crucial. We strongly advocate for the use of Magnetic Resonance Imaging (MRI) whenever available, with both a pre-EBRT and post-EBRT diagnostic MRI. At our institution, we perform an MRI with vaginal gel for optimal distention of the vagina, which helps better visualize mucosal extent of disease (Figure 1).

## Brachytherapy techniques

### Single channel vaginal cylinder

The simplest form of vaginal BT is with a single-channel cylinder. This was the first type of intracavitary applicator to be widely adapted into the treatment of vaginal cancer, and historically was the most frequently used.



Fig. 1. Sagittal view T2 sequence MRI with vaginal gel, demonstrating the extent of tumor

The basic nature of SCVCB allow the dosimetric properties to be easily understood; however, at the same time limits the utility in the modern treatment of vaginal malignancies. Due to the single central channel, it is not possible to preferentially deliver dose to certain walls of the vagina while avoiding others, though by adjusting dwell times, plans can be created to dose distal and proximal portions of the vagina differently. The dose delivered to tissue falls off according to the inverse square law. Thus, when prescribing dose to a certain depth from the vaginal surface, tissue between the prescription point and the central source receives an exponentially higher dose the closer to the central source it is. This has important implications concerning cylinder size [17].

Commercially available vaginal cylinders range in diameter from 2 cm to 4 cm. When a smaller cylinder is used, the ratio of prescription depth to cylinder radius is greater. Following the inverse square law, this creates higher surface doses for smaller cylinders. For example, if a 2.5 cm cylinder were used with a prescription depth of 5 mm, the dose to the vaginal surface (tissue-cylinder interface) would be 196% of the prescription dose, whereas if a 3.5 cm cylinder were used with the same prescription depth of 5 mm, the vaginal surface dose would be reduced to 165% of the prescription dose. As such, when performing intracavitary BT, the largest cylinder, which the patient can comfortably accommodate should be used. This also helps prevent air gaps between the tissue and the cylinder, which are dosimetrically disadvantageous. An example of a SCVCB plan can be found in Figure 2.

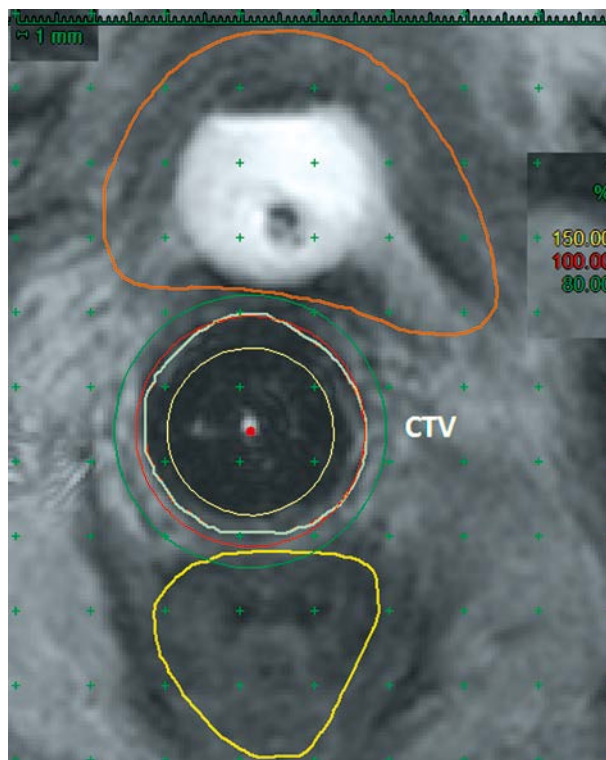


Fig. 2. Dosimetry of a single-channel vaginal cylinder with prescription dose of 45 Gy in 25 fractions of EBRT followed by 5 Gy x 5 fractions HDR brachytherapy with CTV  $D_{90} = 75.5$  Gy, Rectum  $D_{2cc} = 61.6$  Gy, Bladder  $D_{2cc} = 58.6$  Gy

Due to the inability to sculpt dose with a single central channel and concerns for associated dose to nearby OAR, SCVCB utilization in the modern era is primarily limited to instances where the entire circumference of the vagina is desired to receive the same dose, such as for adjuvant treatment of the vaginal cuff after hysterectomy for endometrial cancer or apical recurrences with residual disease thickness  $\leq 5$  mm [18]. In situations where dose to a particular region must be restricted, SCVCB with shielding can be employed. At our institution, SCVCB is not routinely used in the setting of vaginal cancer.

### Interstitial brachytherapy

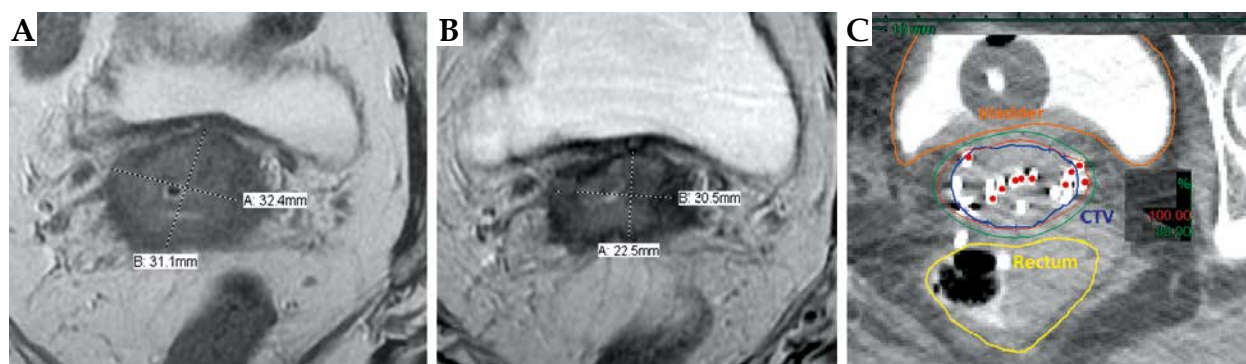
By placing needles directly in and around the tumor, numerous source dwell positions can be used and the source can be in closer proximity to the target. This allows for substantially better shaping of dose to fit an individual target. However, there is cost associated with this increased conformality as interstitial brachytherapy typically requires violation of tissue planes, anesthesia, prolonged immobilization, and hospitalization, and therefore has a higher likelihood of procedural morbidity than intracavitary BT.

The American Brachytherapy Society (ABS) guidelines recommend interstitial BT to be used for lesions greater than 5 mm in thickness after EBRT [19]. In order to achieve the best outcomes, a multidisciplinary approach involving gynecological oncology, radiation oncology, and radiology is recommended. Generally, patients should be taken to the operating room and placed under general anesthesia. An exam under anesthesia should be performed and information collected from this exam, as well as MRI of the pelvis pre- and post-EBRT should be used to plan needle placement. Gold fiducial markers can be placed at the proximal and distal end of residual disease, so that it can be identified on computed tomography (CT) scan for defining target volume. Generally, a perineal template should be used for needle placement, though for distal lesions one can place free hand needles under palpation and then anchor the needles to the perineum. Commercially available needles contain catheters made of titanium, stainless steel, or plastic. Plastic catheters have the advantage of being MRI compatible, though are not as

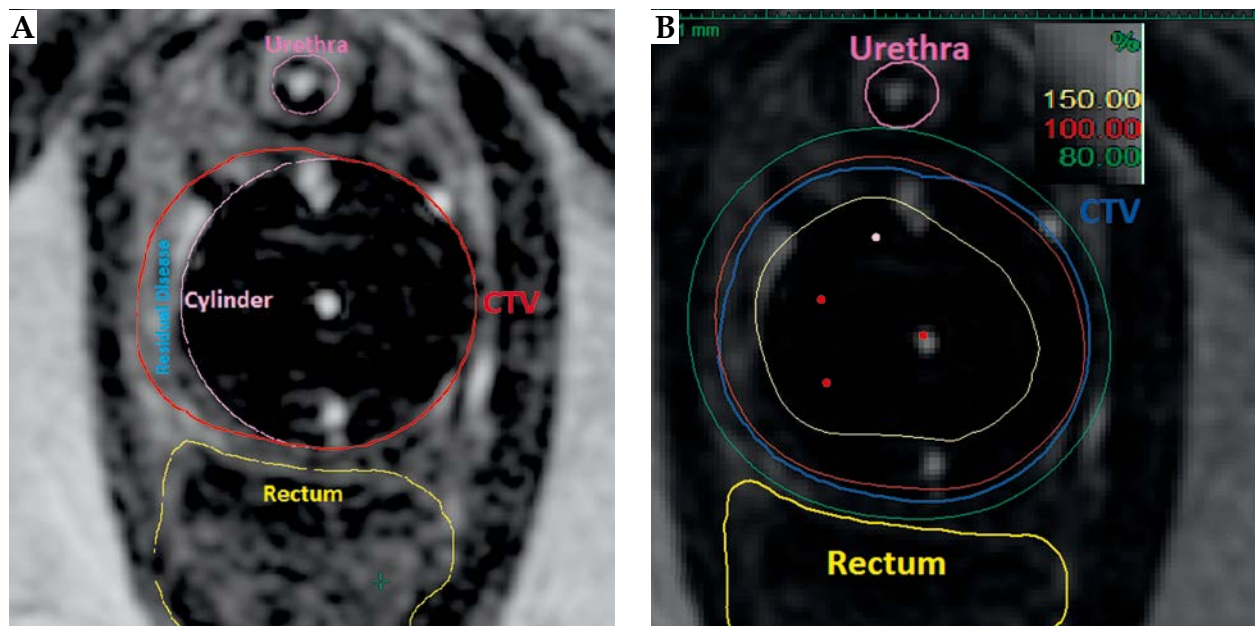
rigid and may be more prone to splaying. Our institutional preference is to use titanium catheters. Needles should be placed such that they extend approximately 5-10 mm beyond the tumor, provided this can be accomplished without perforating critical structures. Consideration for laparoscopic guidance is recommended in the setting of apically located lesions, especially if there is supravaginal extension or close proximity of small bowel loop or sigmoid to the tumor. Needles should be placed in a pattern such that there is approximately 10 mm between each and with attention to location of OAR to avoid perforation. Epidural anesthesia is utilized to control pain while the implant remains in place. A post-implant cross-sectional scan should be taken for dosimetric planning and needles adjusted under epidural for optimization of placement (CT scan should be utilized if stainless steel or titanium needles, as titanium is only compatible with MRI up to 0.3 tesla magnet, and MRI should be utilized with plastic needles). An example of an interstitial plan can be found in Figure 3. Even with sutured fixation of the template, interfraction variation in applicator placement is possible, and if displacement is suspected, repeat imaging should be performed with adjustment of catheters and/or dosimetry [20,21].

### Multichannel vaginal cylinder

In order to try and bridge the gap between the tolerability of SCVCB and the dosimetric advantages of interstitial brachytherapy, more modern brachytherapy applicators have been developed, with the most prominent being MCVCB. A typical multichannel vaginal cylinder has one central channel and 6-8 peripheral channels organized circumferentially around the central channel approximately 5 to 7 mm from the cylinder surface. These cylinders come in various sizes, with the most common being 3 and 3.5 cm in diameter. By utilizing multiple source positions in closer proximity to the target, MCVCB allows dose to be preferentially delivered to specific portions of the vagina. This translates into considerable advantages as compared to SCVCB as the target is able to be more adequately covered while simultaneously decreasing dose to OAR [22-24]. An example of a MCVCB plan can be found in Figure 4B. Still, there are limitations as to



**Fig. 3.** Dosimetry of an interstitial brachytherapy implant in a patient with adenocarcinoma and a poor response to EBRT with prescription dose of 45 Gy in 25 fractions of EBRT followed by 5.5 Gy  $\times$  5 HDR brachytherapy. A) Pre-EBRT MRI. B) Post-EBRT MRI. C) Interstitial Plan: CTV  $D_{90} = 82.1$  Gy, Rectum  $D_{2cc} = 60.0$  Gy, Bladder  $D_{2cc} = 58.6$  Gy



**Fig. 4.** Dosimetry of a multi-channel vaginal cylinder. **A)** Contouring. **B)** Plan with prescription dose of 45 Gy in 25 fractions EBRT and 5.5 Gy  $\times$  5 fractions HDR brachytherapy with CTV  $D_{90}$  = 79.8 Gy, Rectum  $D_{2cc}$  = 59.8 Gy, Bladder  $D_{2cc}$  = 54.1 Gy, Urethra  $D_{0.1cc}$  = 71.3 Gy

the size of lesions, which can be treated with MCVCB. As the thickness of the lesion increases so does the dose to the vaginal mucosa, and for lesions located away from the rectum, vaginal mucosal dose is typically the dose limiting structure. At our institution, we use a tumor thickness cut-off of approximately 5 mm for apically or posteriorly located lesions and 7 mm for other locations, provided dose constraints to other OAR are met. We recently published on a series of 41 patients, all of whom were treated with image-based high-dose-rate (HDR) MCVCB, and demonstrated excellent local-control and low toxicities, with an overall favorable comparison to historical results with SCVCB [25].

### Fractionation schedules

When discussing doses prescribed with vaginal brachytherapy, it is important to note the effects of dose per fraction and dose rate. One widely accepted way to standardize the dose prescribed is to calculate the biologically equivalent dose had the treatment been delivered with standard fractionation at 2 Gy per day (EQD2). An excellent resource for doing so is given by Nag *et al.* including instructions for a spreadsheet based dose calculator [26]. The ABS also provides a spreadsheet based EQD2 calculator ([https://www.american-brachytherapy.org/guidelines/LQ\\_spreadsheet.xls](https://www.american-brachytherapy.org/guidelines/LQ_spreadsheet.xls)). Historically, brachytherapy was delivered primarily with low-dose-rate (LDR) isotopes, however more recently HDR via remote afterloading has been the predominant modality [27-29]. The physics of afterloading HDR vaginal cylinder have been well described [30]. The advantages of HDR include the ability to customize dose after the implant by adjusting dwell times and weighting, shorter treatment time, which allows for more outpatient treat-

ment, better documentation, and a decreased exposure to radiation for health care workers [31].

There has not been a prospective trial comparing brachytherapy fractionation schedules and recommendations on dose are primarily based on single-institution reports and consensus guidelines. The typical prescription dose for vaginal malignancies is 70-80 Gy EQD2 including the contribution from the combination of EBRT and BT. Various fractionation schedules exist to deliver a dose in this range. At our institution, brachytherapy is predominately delivered in 5 fractions with a dose of 4.5-5.5 Gy per fraction after 45 Gy in 25 fractions of EBRT (EQD2 of 71.4-79.8 Gy). Another commonly used schedule is 3 Gy  $\times$  9-10 fractions (EQD2 of 73.5-76.8 Gy). The final decision on what dose to prescribe is dependent upon tumor location, response to EBRT, extent of residual disease, and critical organ dosimetry. Dose escalation up to 85 Gy may be appropriate for bulky tumors and/or those with poor response to EBRT as long as normal tissue dose constraints are respected.

### Treatment planning

Details of brachytherapy planning are beyond the scope of this review; however, collaboration with a physicist who has experience with gynecological brachytherapy is essential. In order to accurately calculate dose to OAR, it is imperative that both the target and OAR be contoured appropriately. Whenever possible, we recommend MRI imaging to be incorporated into treatment planning either by getting a pre-brachytherapy MRI scan or MRI scan with applicator in situ. Detailed recommendations for contouring have been given by both GEC-ESTRO, and the ABS [19,32]. At our institution, we define clinical target volume (CTV) for dose prescription

based on both pre and post EBRT imaging and clinical examination. We treat pre-EBRT involved length of vagina and include the entire circumference of vagina for that length. For the involved wall of the vagina, we include the entire thickness of vaginal wall plus residual disease seen on imaging, while for the uninvolved vaginal walls we contour only up to the mucosal surface (Figure 4A). Of note, it is critical to precisely contour the portion of the OAR in closest proximity to needles or applicator as this region is likely to be the dose-limiting region, and accuracy in determining absolute dose here will effectively help reduce the risk of side effects. At our institution, we aim for 90% of the target volume to be covered by at least 100% of the prescription dose ( $D_{90} \geq 100\%$ ). We try to limit hot spots by keeping the CTV volume to receive 150% of the prescription dose ( $V_{150}$ ) to less than 50% and the  $V_{200} < 15\text{-}20\%$ . We employ manual optimization for intracavitary BT, and a combination of manual and graphical optimization for interstitial BT.

If an odd number of fractions of interstitial BT are to be delivered, it is in the patient's best interest to attempt to place the implant in the morning, and have the first fraction planned and delivered by that afternoon in order

to minimize the period of immobilization and length of hospital stay.

### Tolerance of organs at risk

The primary toxicities associated with brachytherapy for vaginal cancer are related to the rectum, bladder, urethra, vaginal mucosa, and bowel. The tolerance of the rectum and bladder has been well defined with general agreement among single institution experiences and consensus guidelines, with recommended EQD2 to the most irradiated 2 cc ( $D_{2cc}$ ) for the bladder of less than 90 Gy and less than 70-75 Gy for the rectum [33-35]. These sources suggest that if these constraints are met, the rates of grade 2 or higher toxicities can be limited to less than 10%. The tolerance to the vaginal mucosa is not as well defined. To this point, ABS consensus guidelines avoid giving a precise constraint [19,35,36]. The upper portion of the vagina is thought to be more tolerant to radiation than the lower portion, likely due to the thinner rectovaginal septum and closer proximity to the urethra in the lower vagina [37]. In the modern, image-based era, a Japanese group found vaginal EQD2  $D_{2cc}$  of 145 Gy or

**Table 1.** Summary of local control and late toxicities for vaginal cancer patients treated with brachytherapy

Primary technique	First author (year of publication)	n	% recurrent/ % primary	Local control	Vaginal toxicity	Urinary toxicity	GI toxicity
EBRT + 2D LDR	Curran (1988) [42]	47	100/0	42% 5-yr	0%	0%	4%
EBRT + 2D LDR	Stock (1992) [43]	49	0/100	44% 2-yr	8%	4%	14%
EBRT + 2D LDR	Morgan (1993) [44]	34	100/0	85% 5-yr	12%	0%	0%
EBRT + 2D LDR	Sears (1994) [45]	45	100/0	54% 5-yr	0%	4%	16%
EBRT + 2D LDR	Chyle (1996) [46]	301	0/100	77% 5-yr	6%	4%	6%
EBRT + 2D LDR	Fine (1996) [47]	55	0/100	78% 5-yr	0%	0%	15%
EBRT + 2D LDR	Jereczek (2000) [48]	73	100/0	40% 5-yr	4%	4%	15%
EBRT + 2D LDR	Wylie (2000) [49]	58	100/0	65% 5-yr	NR	NR	NR
EBRT + 2D LDR	Jhingran (2003) [9]	91	100/0	75% 5-yr	0%	1%	11%
EBRT + 2D LDR	Lin (2005) [50]	50	100/0	72% 10-yr	0%	0%	10%
EBRT + 2D HDR	Pai (1997) [51]	20	100/0	74% 4-yr	5%	0%	5%
EBRT + 2D HDR	Mock (2003) [10]	86	0/100	NR (66% 5-yr DSS)	4%	1%	2%
EBRT + 2D HDR	Lieskovsky (2004) [52]	54	0/100	87% 4-yr	7%	2%	6%
EBRT + 2D HDR	Petignat (2006) [4]	22	100/0	100% 5-yr	50%	0%	18%
EBRT + 2D HDR	Sorbe (2013) [7]	25 <sup>#</sup>	100/0	92% 5-yr	19%	4%	35%
EBRT + 3D interstitial HDR	Dimopoulos (2012) [53]	13	0/100	92% 3-yr	15%	8%	0%
EBRT + 3D interstitial HDR	Beriwal (2012) [54]	30	43/57	79% 2-yr <sup>†</sup>	7%	0%	0%
EBRT + 3D HDR	Lee (2013) [55]	31 <sup>*</sup>	100/0	96% 2-yr	3%	0%	0%
IMRT + 3D MCVC HDR	Vargo (2015) [23]	41	76/24	93% 2-yr	0%	0%	4%

EBRT – external beam radiotherapy, LDR – low-dose-rate, HDR – high-dose-rate, IMRT – intensity modulated radiotherapy, 2D – 2-dimensional, 3D – 3-dimensional, MCVC – multichannel vaginal cylinder, GI – gastrointestinal

<sup>\*</sup>Excludes patients with prior pelvic radiotherapy. <sup>#</sup>Excludes patients treated with EBRT or brachytherapy alone. <sup>†</sup>Includes regional failures and patients with prior RT

higher predicted for increased risk of vaginal ulcer (23.5% versus 3.7%) [38]. On the contrary, the group from Vienna found no correlation of vaginal  $D_{2cc}$  with the incidence of vaginal side effects with mean vaginal EQD2  $D_{2cc}$  of 140 Gy and mean vaginal EQD2  $D_{0.1cc}$  of 750 Gy [39]. Both groups used the LENT/SOMA morbidity index, though, the Japanese group looked only at ulcer.

There is limited data to guide recommendations regarding urethral and small bowel dosimetry. A small series of patients with vaginal cancer treated with HDR brachytherapy suggested limiting the  $D_{0.1cc}$  to  $\leq$  prescription dose and avoiding any hot spot in the urethra, as those who had severe urethral toxicity had a mean equivalent dose to the urethra of 95 Gy versus 73 Gy for those without severe toxicity [40]. Dose to small bowel is difficult to quantify due to interfraction variability in position, and there is limited outcomes data relating to toxicity with gynecological brachytherapy, though, recommendations for increased reporting have been made [41]. At our institution, we attempt to limit small bowel dose by attempting to move bowel in close proximity to the target out of the way with bladder filling, keeping any hot spots out of the bowel, and limiting the EQD2 maximal point dose to 60-65 Gy.

## Discussion and conclusions

Incorporation of modern 3-dimensional imaging modalities into the brachytherapy regimen has resulted in a momentous step forward for vaginal cancer patients. Outcomes data suggest that image-based brachytherapy increases the therapeutic ratio by both increasing local control and decreasing morbidity (Table 1). Due to patient overlap with our interstitial and MCVCB series, we excluded our image-based brachytherapy salvage series from the table, though were able to demonstrate over 90% local control and low side effects in the purely salvage setting using a combination of interstitial and intracavitary techniques [8]. In the modern era, the use of 3D imaging is paramount due to the close proximity of critical organs, which is under assessed with 2D planning. The type of brachytherapy to use is a matter of tumor location, extent, and response to EBRT as well as the expertise available. However, in general, patients with proximally located tumors less than 5 mm in thickness, post-EBRT should be considered for MCVCB, while those with more extensive lesions or lesions in close proximity to OAR or the distal vagina should be considered for interstitial brachytherapy.

## Disclosure

Authors report no conflict of interest.

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