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The Design of a New Vaginal Applicator for Direction Modulated Brachytherapy (DMBT) Using GEANT4 Monte Carlo Simulation Code

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The Design of a New Vaginal Applicator for Direction Modulated Brachytherapy (DMBT) Using GEANT4 Monte Carlo Simulation Code

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

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Abstract

THE DESIGN OF A NEW VAGINAL APPLICATOR FOR DIRECTION MODULATED BRACHYTHERAPY (DMBT) USING GEANT4 MONTE CARLO SIMULATION CODE

By Moeen Meftahi, MS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, at Virginia Commonwealth University.

Virginia Commonwealth University, 2020
Advisor: William Y. Song, Ph.D.
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Purpose: Anisotropy of the ^{192}Ir source causes a lack of dose coverage at the apex in HDR vaginal cylinder brachytherapy (VC BT). In this study, we took advantage of the GEANT4 Monte Carlo (MC) simulation code to design a new DMBT vaginal applicator so that it maintains the dose coverage of the current vaginal cylinder at periphery everywhere while improving the apex coverage. In addition, since current treatment planning systems (TPS) considers the whole environment as water according to TG43 formalism, based on the capability of the MC in the calculation of dose in the material, the effect of inhomogeneity of the vaginal cylinder in the dose coverage was investigated.

Methods: The new DMBT vaginal applicator was designed to be a 30 mm diameter, single lumen vaginal cylinder, made of polyphenylsulfone (PPSU) plastic. The central part of the applicator, which includes the lumen, was considered to be a detachable 8 mm diameter tandem rod. In order to provide directional modulation, a tungsten rod similar to the dimensions of the detachable tandem was added to the simulation. The applicator works in two steps. First, we get a typical dose distribution based on the planning system using the applicator with a detachable polyetheretherketone (PEEK) plastic tandem in place. Second, the detachable tandem is replaced

with a tungsten tandem to compensate for the lack of coverage at the apex utilizing a directional radiation beam generated. The same source dwell positioning is used for both steps, while the dwell time for the second step is a small fraction of the first step. Furthermore, in order to assess the effect of VC inhomogeneity, a separate simulation with the same dwell time and position based on TG43 model was performed and the results were compared. The MATLAB software was used for data analysis.

Results: The analysis showed that the new applicator can address the lack of coverage at the apex due to anisotropy (~2 mm), while simultaneously preventing from overdosing the periphery. Also, the analysis of the data indicated that there is a reduction of dose at the surface of the cylinder (~7.3%) at the periphery, in comparison to TG43 model.

Conclusion: This new DMBT concept design can be considered as a possible solution for the lack of apex coverage due to anisotropy as there is a subset of patients who experience recurrences after brachytherapy, frequently in the vaginal apex. Further, based on the VC heterogeneity analysis, the reduction of the dose at the surface of the cylinder indicates that prescribing the dose to VC surface involves additional level of uncertainty.

Key: Vaginal Cylinder, DMBT, Brachytherapy, Inhomogeneity

Background

Endometrial carcinoma is the most common gynecologic malignancy in the united states. It constitutes 6% of female cancers, and accounts for 3% of all cancer deaths in women. The incidence of endometrial cancer has been steadily increasing in the U.S. and worldwide over the past several decades. The standard treatment for endometrial cancer is a total abdominal hysterectomy with bilateral salpingo-oophorectomy with or without lymph node dissection. Adjuvant external beam radiation therapy (EBRT) and/or brachytherapy (BT) are integral component in the adjuvant therapy of select patients and the radiation is a major component in the management of inoperable or recurrent endometrial cancers (Alban et al., 2020; Demiral, 2017; Small et al., 2012).

The recent clinical trial (PORTEC-2) compared vaginal BT with EBRT in early-stage postoperative endometrial cancer patients. The study suggested that vaginal BT is equivalent to EBRT in preventing local vaginal recurrences and distant metastases (Nout et al., 2010). Vaginal brachytherapy is also associated with significantly less toxicity when compared to whole pelvic EBRT (Petereit et al., 1999; Zhang et al., 2016). In addition, High dose-rate (HDR) brachytherapy is advantageous in that you can achieve a highly conformal dose to the target under image guidance in an outpatient setting (Zhou et al., 2017). Nonetheless, intracavitary BT is best reserved for tumors less than 5 mm in thickness (Leung et al., 2019).

Following surgery, the vaginal canal for most patients is roughly cylindrical, and the American Brachytherapy Society (ABS) recommends a properly sized, single-channel vaginal cylinder applicator (VC) for BT treatment. The VC is the most common applicator used for high-dose-rate (HDR) BT and is ideal for patients with a narrow vagina. The region, including the vaginal cuff, accounts for about 75% of recurrences in endometrial cancer patients. Therefore, vaginal cuff BT is recommended to decrease the risk of recurrence without adding the toxicities associated with pelvic radiotherapy (Guy et al., 2019; Kim et al., 2018). Besides the simplicity, there are a few limiting factors in the application of VCBT that can result in underdosing the target, in particular, at the apex.

In one study, it is shown that the presence of air gaps around the cylinder can potentially reduce mucosal dose. They took advantage of post-insertion CT to detect air gaps for 22 patients and

concluded more than two-third of the patients presented air gaps, in particular at the apex (Sapienza et al., 2019). Hassouna et al. (Hassouna et al., 2014) has also retrospectively assessed the presence of air gap in VCBT. Most of the cases they studied had air gap at periphery, indicating the reduction of dose coverage at target. A shortage of the coverage has been studied by another group through MRI-based evaluation of vaginal cuff, as well. They figured that suture material may be restricting access to the vaginal apex and reduce the dose coverage noticeably at vaginal cuff, resulting in underdosing of at-risk vaginal mucosa (Chapman et al., 2016).

Kim *et al.*(Kim et al., 2018) studied two different Varian's VC applicators with the same diameter, but different top thickness. They showed there is a relatively high loss of coverage at the apex for the applicator with the thicker top. Another issue involves the significant dose gradients outside of the cylinders and the variability of the dose falloff relative with the cylinder size and dose specification point. The effect of the same prescription dose can be significantly different in two cylinders, for example, 2.3- cm and 3.5-cm diameter, and dramatically different if prescribed to the cylinder surface vs. 5-mm depth. Thus regardless of treatment regimens, the way that physicians prescribe the dose can have different clinical outcomes (Ager et al., 2019; Guy et al., 2019).

Anisotropy of the source is also an important factor that affects the dose coverage at the apex. The dose distribution produced by the HDR ^{192}Ir source is inherently anisotropic due to self-absorption by the high-density source core, oblique filtration by the source capsule and asymmetric geometry of the source capsule (Sharma et al., 2004), which prevents it from having a uniform dose coverage at the apex. This phenomenon more commonly affects single-channel applicators, as these are the most widely used vaginal applicators. Although it can be modified using multichannel applicators through inverse planning to some extent, this modification can cause loss of coverage at the other part of the apex (Bahadur et al., 2014; Sabater et al., 2017).

Further, the effect of VC inhomogeneity in treatment planning can affect the dose coverage, depending on the material, the density, the size, and, the design of the applicator. The current standard of practice for brachytherapy absorbed dose calculations relies on the AAPM Task Group 43 TG43 formalism. The dosimetry parameters used in TG- 43 are obtained for a single BT source located at the center of a fixed-volume, homogeneous, liquid-water phantom. As a

result, this method cannot consider the effect of patients' body shape and the presence of materials other than water, such as VCs (Abe et al., 2018; Mikell et al., 2012; Rivard et al., 2004, 2009).

In this research, we aim to find a novel solution to remedy the anisotropy of the source for a single channel VC applicator, so that it does not affect the integrity of dose distribution of a typical VC while eradicating the anisotropy effect. To do this, we benefit from the concept of direction modulated brachytherapy (DMBT), which has been used for the design of other applicators such as cervical, and rectal applicators by other researchers (Bellezzo et al., 2018; Safigholi et al., 2017). The DMBT applicators utilize a shielded part embedded into them in order to focus the radiation in a specific direction, while cut the radiation drastically in other directions simultaneously. Therefore, we design a novel DMBT vaginal cylinder applicator using the general-purpose GEANT4 Monte Carlo (MC) Simulation code to address the anisotropy of the source. MC simulation, as gold standard for dosimetry, has been utilized for modeling of the brachytherapy sources and evaluation of model-based dose calculation algorithms, considering the effect of inhomogeneity on dose calculation, and dose calculation near the source by other researchers (Ababneh et al., 2014; Facundo Ballester et al., 2015; Rodrigues et al., 2008). It can also account for the limitations related to TG43 with better accuracy for absorbed dose calculations (Mikell & Mourtada, 2010); therefore, as a second goal, we will assess the effect of inhomogeneity of VC in the dose coverage and its possible impact on the clinical outcome.

Material and Method

The GEANT4 MC simulation code, toolkit 10.05 was used for the simulation. A typical Varian Gamma Med Plus source was modeled as described in the literature (Figure 1) (Perez-Calatayud et al., 2012). The extension of cable was modeled to be 50 mm. Because of the symmetry, 2D data acquisition was performed, such that the source and the extension of the cable were placed across the Y axis. The ^{192}Ir was defined based on all its significant gamma-ray and x-ray radiations (Ababneh et al., 2014; Chu et al., 1999; *X-ray and Gamma-ray Decay Data Standards for Detector Calibration and Other Applications*, 2005).
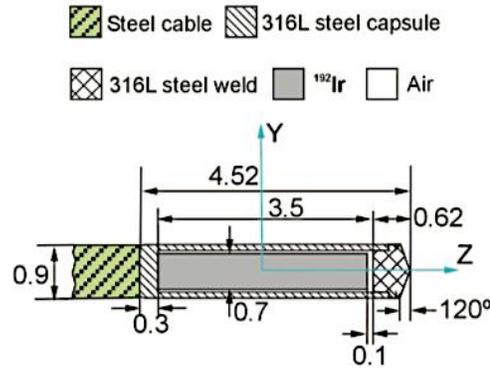
Figure 1. a typical structure for Varian HDR source, Gamma Med Plus

Calculation of the Dose Rate Constant

At the first step, Air Kerma Strength (S_k) was calculated. For this purpose, the source was placed at the center of a 6*6*6 m^3 box, filled with air and gridded into voxels with a 5 mm length side. Up to $2 * 10^{10}$ histories were performed (F. Ballester et al., 1997).

At the next step, the source was located at the center of a water phantom 30*30*30 cc, gridded into voxels with a length side of 0.5 mm. Up to $5 * 10^9$ histories were performed. As pointed out by Williamson (Williamson JF, 1995), air-kerma estimation was found to be well described by the linear equation $k_{air}/G = S_k + b*y$. The slope b describes the increase in k_{air}/G due to buildup of scatter in the air and the intercept is an estimate of the ratio of the air-kerma rate in free space and the geometry factor.

Design of the applicator

The new DMBT vaginal applicator was designed to be a 30 mm diameter, single lumen VC, made of PPSU plastic (currently used in Varian's VC applicators) , with a density of 1.29 g/cm^3 (Sigma-Aldrich, n.d.). The central part of the applicator which includes the lumen was considered to be a detachable 8 mm diameter tandem rod. In order to provide directional modulation, a tungsten rod similar to the dimensions of the detachable tandem was added to simulation. The applicator works in two steps. First, we get a typical dose distribution based on the planning system using the applicator with a detachable PEEK (currently used in Varian's VC applicators) tandem, with a density of 1.3 g/cm^3, in place. Second, the detachable tandem is

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replaced with a tungsten tandem, with a density of 19.3 g/cm^3, to compensate for lack of coverage at the apex utilizing directional radiation beam generated. The same source dwell positioning is used for both steps, fed from Varian's TPS, while the dwell time for the second step is equivalent to three quarter of one fraction of the first step (five fractions). For both steps, the applicator is placed at a water phantom 30*30*30 cc, gridded into voxels with a side length of 1 mm. In addition, because the dwell time and positions were fed from a TG43-based TPS (Table 1), the source was placed at the same condition into a water phantom in order to assess the effect of the VC inhomogeneity in comparison to TG43 model. The treatment length for this plan was 5 cm, while prescribing to 5 mm depth. Up to 10^9 histories were performed for each dwell position. Furthermore, The MATLAB software was used for data analysis.

DP (mm)	DT (s)
70	132.8
65	110.7
60	105.7
40	19
35	105.9
30	106.2
25	106.2

Table 1, The data obtained from a TG43 TPS. Dwell Positions (DP) across the Y Axis and the Dwell Time (DT) of the source were used for performing the GEANT4 MC simulations.

Results

The simulated source and the new designed applicator are shown in Figure 2.
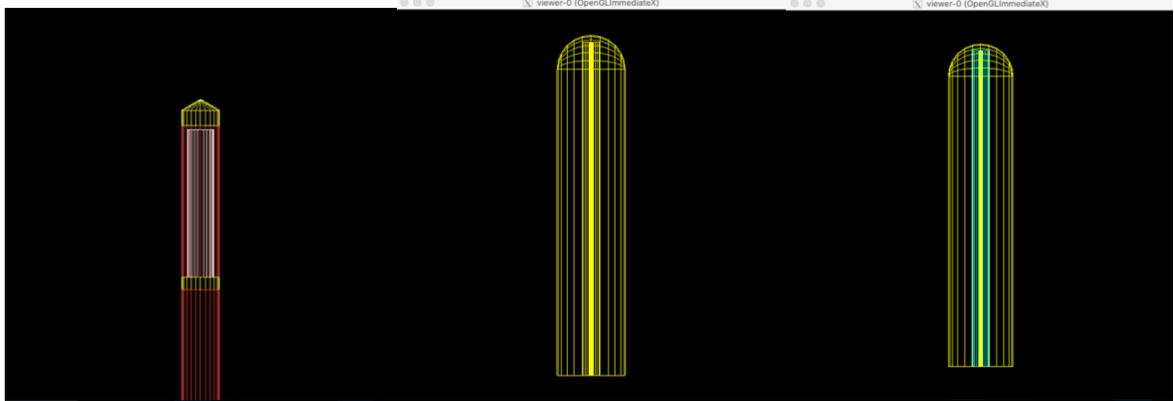
Figure 2, the source and the two-step applicator, designed using GEANT4 MC simulation code. The left, the simulated source. The middle, the applicator with the PEEK tandem. The right, the applicator with the Tungsten tandem. (the images are not in scale)

The dose rate constant for Gamma Med Plus calculated from the linear fit was obtained to be 1.122 cGy.h^{-1}.U^{-1} that is in a good agreement with the consensus data of 1.117 cGy.h^{-1}U^{-1}, with relative error less than 0.5% (F. Ballester et al., 2001; Perez-Calatayud et al., 2012).
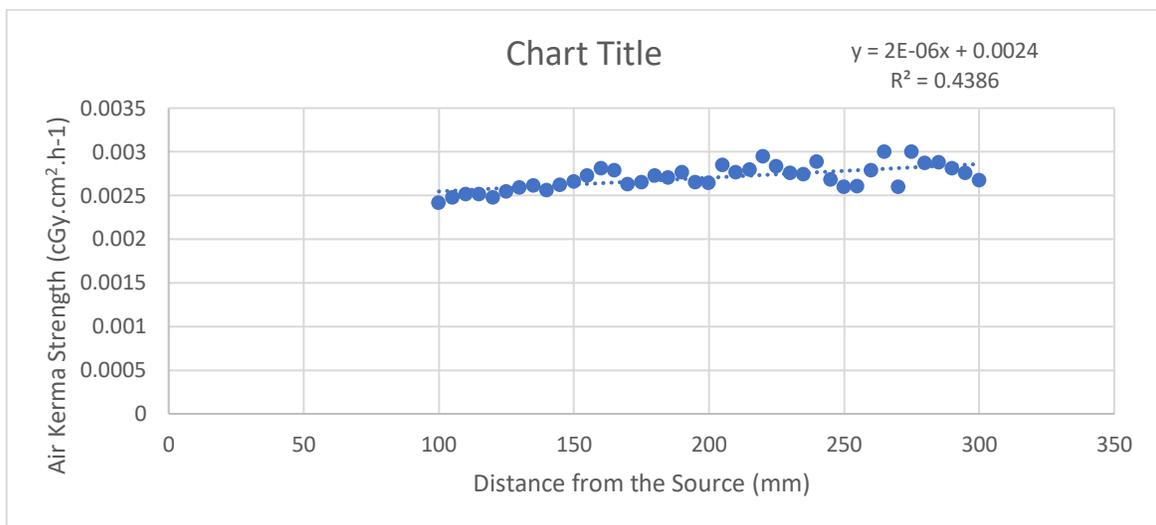
Figure 3, the linear fit for calculation of the air kerma strength

A typical dose distribution of the Gamma Med Plus source in the water phantom is given in Figure 4.
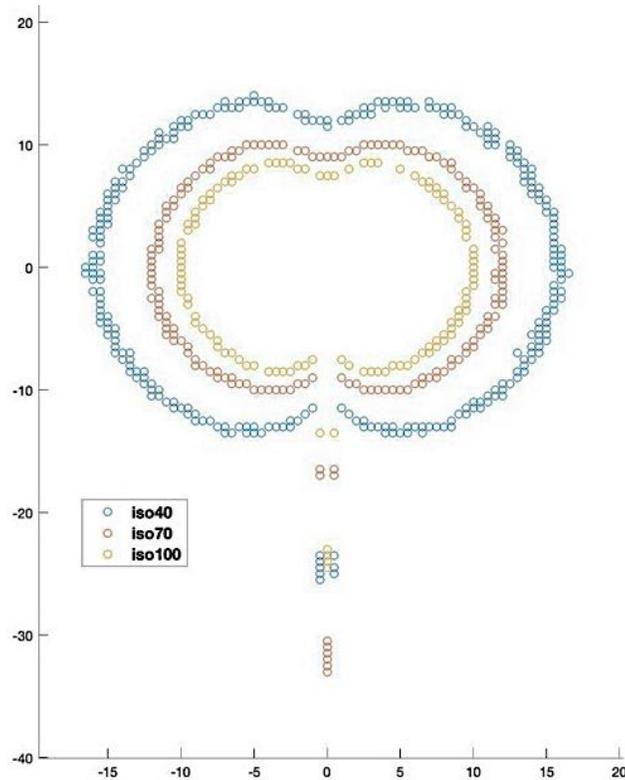
Figure 4, the dose distribution (%) of Gamma Med Plus Source is a water phantom normalized to the dose value at the point (10,0)

The results from positioning of the source in the VC applicator with PEEK tandem in place, and those from TG43 is given in the Figure 5. The prescription dose line is shown in <u>red</u>. As mentioned, the TG43 model does not account for the inhomogeneity of the VC, assuming all the environment as water as opposed to the MC calculations. Based on the results, the dose distribution inside the cylinder (-15 mm < x < 15 mm) is noticeably different from TG43 Model, so that unlike TG43 Model, the isodose lines 6000 cGy and 4500 cGy cover a larger area inside the VC applicator.
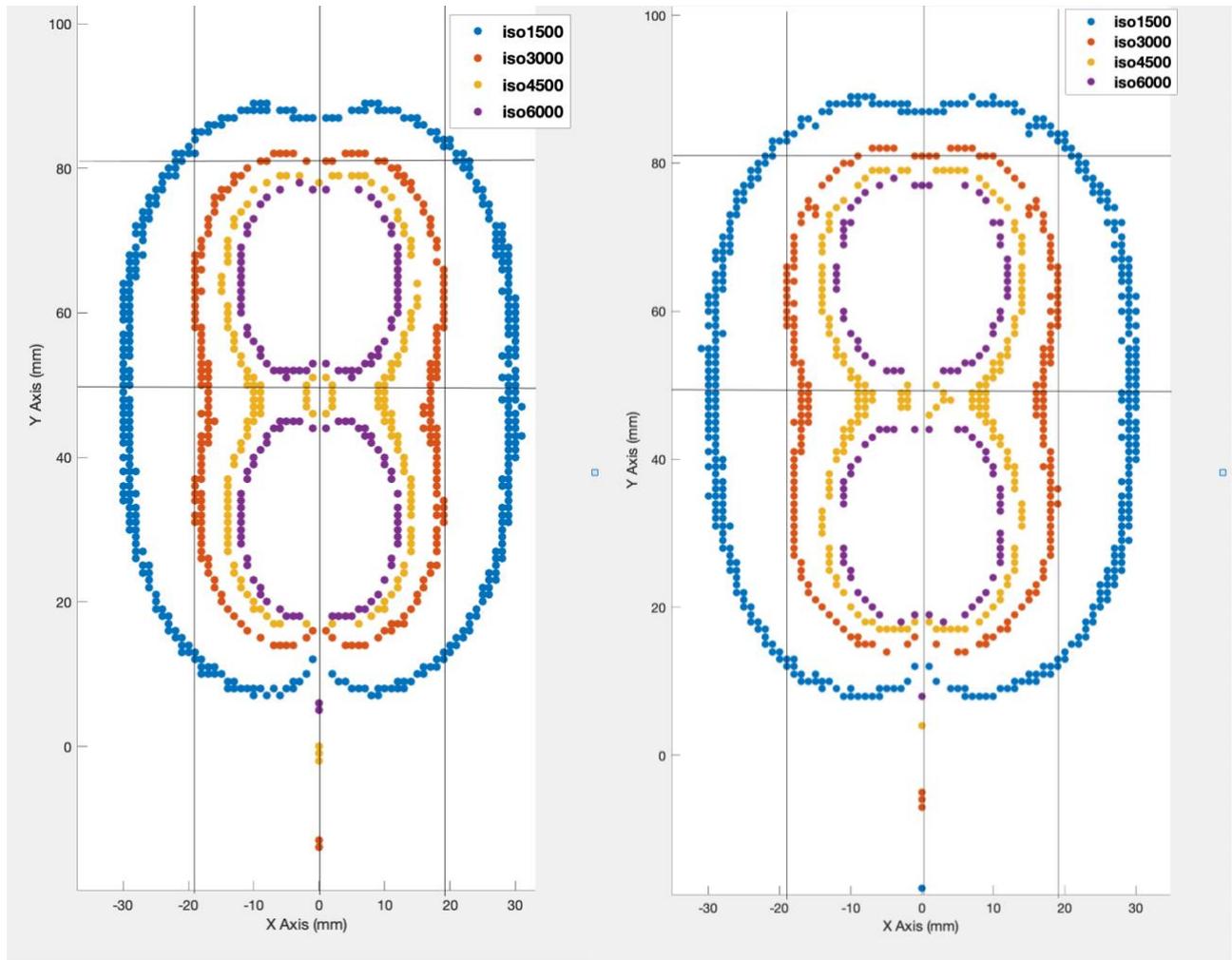
Figure 5, isodose lines (cGy) obtained from GEANT4 MC simulations for TG43 model, considering all the environment as water (Left), and for a 30 mm diameter cylinder, considering the inhomogeneity of the VC applicator (Right). The Prescription dose line is shown in red.

In addition, the isodose lines slightly shrink at the periphery beyond the VC surface, indicating a reduction in the dose coverage. In further investigation, a point by point dose analysis at the boundary of the applicator and water phantom was also performed across the horizontal line y= 50 mm with an interval of 1 mm. The dose values are given in the Table 2. Because the point x=15 mm is located right at the boundary of the applicator and water phantom, the dose at this point was extrapolated using the data values x < 15 mm.

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	x (mm)	11	12	13	14	15	16	17	18	19	20
TG43	Dose (cGy)	4250.81	4041.24	3754.78	3601.63	3364.25	3192.67	3079.86	2815.44	2710.27	2540.59
VC*	Dose (cGy)	3959.28	3741.48	3587.04	3276.63	3118.30	3103.05	2925.12	2763.68	2658.72	2466.86

* Vaginal Cylinder

Table 2, Dose per Point at y=50 mm obtained from GEANT4 MC simulations, for TG43 Model (without considering the effect of VC heterogeneity) as well as a 30 mm diameter VC applicator (with considering the effect of VC heterogeneity)

Comparing the data at the surface of the cylinder (x = 15 mm) indicates that there is a reduction of 7.3% in dose at the boundary for the VC compared to TG43 (3118.30 vs 3364.25 cGy), resulting in a cold spot at the surface.

For better analysis, the dose data for the applicator were also categorized into 2 groups and an exponential function was fitted for each set of data, as given.

$$y = 7967.6e^{-0.057x}$$
$$R^2 = 0.9897$$
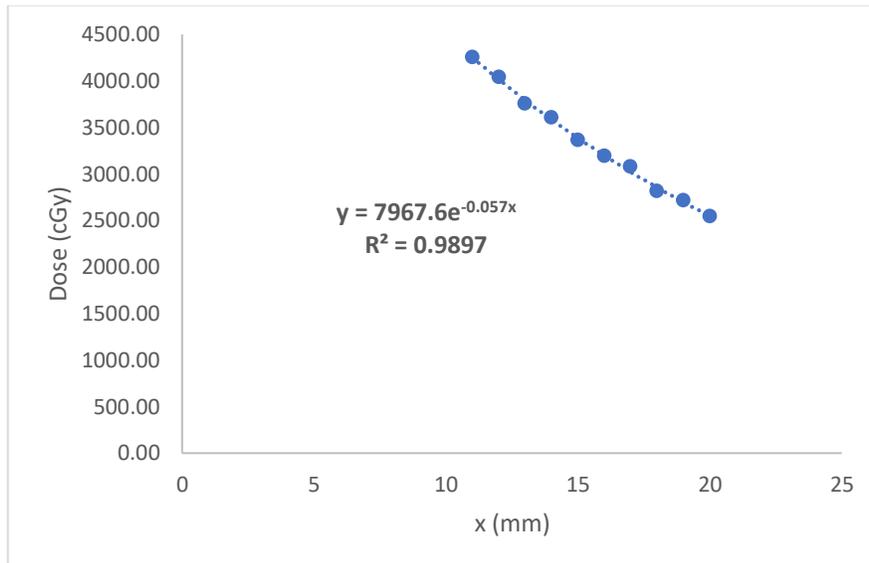
Figure 6, Dose per Point at y=50 mm for the TG43 model
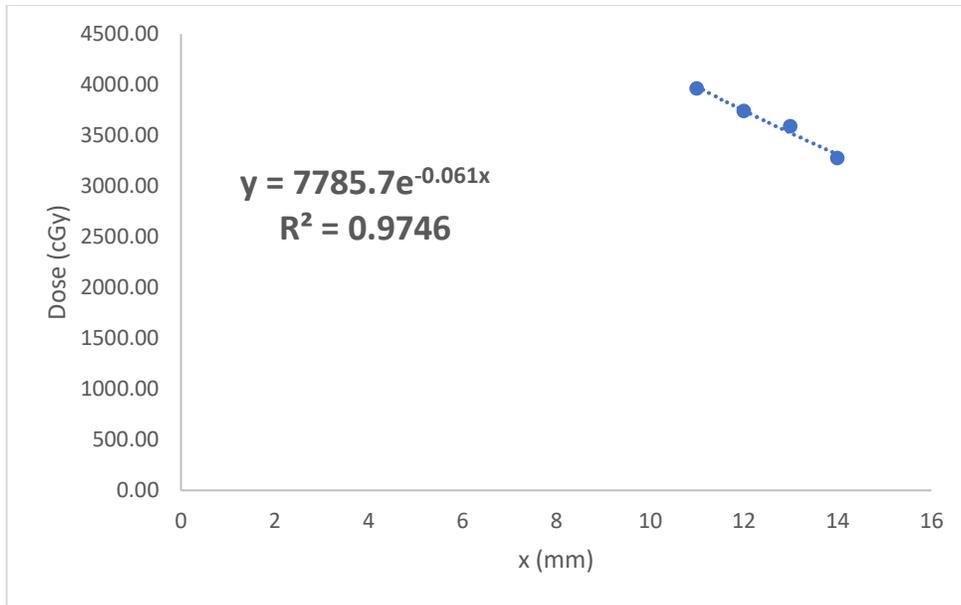
Figure 7, Dose per Point at y=50mm & x < 15 mm for a 30 mm diameter Applicator
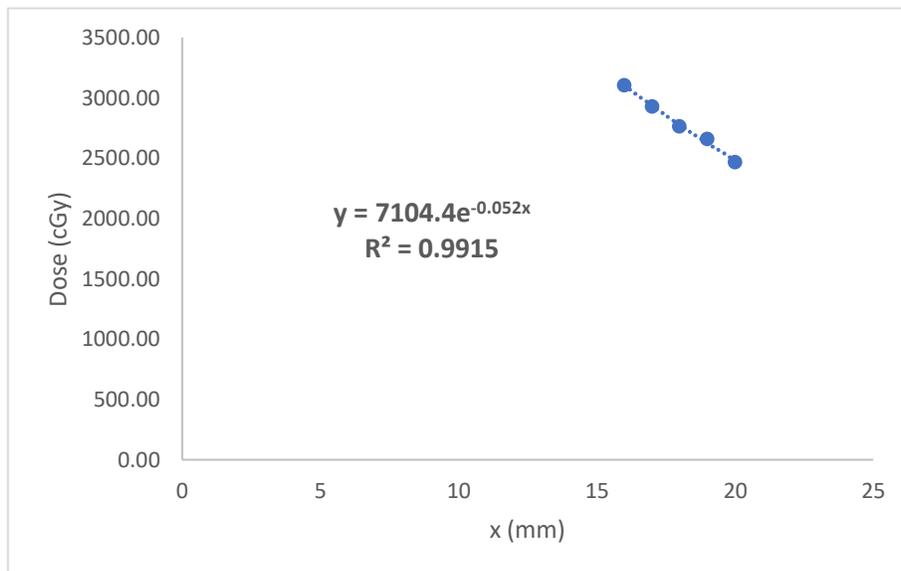

Figure 8, Dose per Point at y=50mm & x > 15 mm for a 30 mm diameter Applicator

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As depicted, the attenuation coefficient of the radiation in the water phantom is 0.057 mm^{-1}. However, when the applicator is in place, the radiation gets attenuated with the coefficients of 0.061 mm^{-1} inside the applicator, and 0.052 mm^{-1} outside the applicator in the water phantom. The multiplication factor for attenuation in the applicator is about 2.3% less than that in the water phantom, as well.

The coverage at the apex looks pretty similar in both models at the prescription isodose line (red lines). However, the same type of analysis is given across the horizontal line x=0. The dose values are shown in the Table 3.

	y (mm)	74	75	76	77	78	79	80	81	82	83
TG43	Dose (cGy)	14581.54	9986.77	7281.08	5632.91	4610.98	3769.89	3154.48	2762.90	2371.04	2123.75
VC*	Dose (cGy)	14719.43	9639.88	7270.68	5955.89	4773.11	3973.22	3380.43	2951.93	2569.11	2283.10

* Vaginal Cylinder

Table 3, Dose per Point at x=0 mm obtained from GEANT4 MC simulations, for TG43 Model (without considering the effect of VC heterogeneity) as well as a 30 mm diameter VC applicator (with considering the effect of VC heterogeneity)

The boundary at the apex is located at y = 76.5 mm. Comparing the dose values at y = 76 mm in the two models indicates similar results near the apex surface of the applicator (7281.08 vs 7270.68 cGy). However, according to the Table 3 there is an average increase of 5% in dose values beyond the boundary (y = 76.5 mm) across the line in the water phantom.

Furthermore, the results from the two-step DMBT applicator is shown in Figure 9. The prescription dose line is shown in red. According to the results, this novel DMBT applicator can remove the anisotropy dip at the apex and lift up the prescription isodose line up to 2 mm

without overdosing the other periphery surfaces, i.e., only 3-4 % increase in dose at those surfaces.
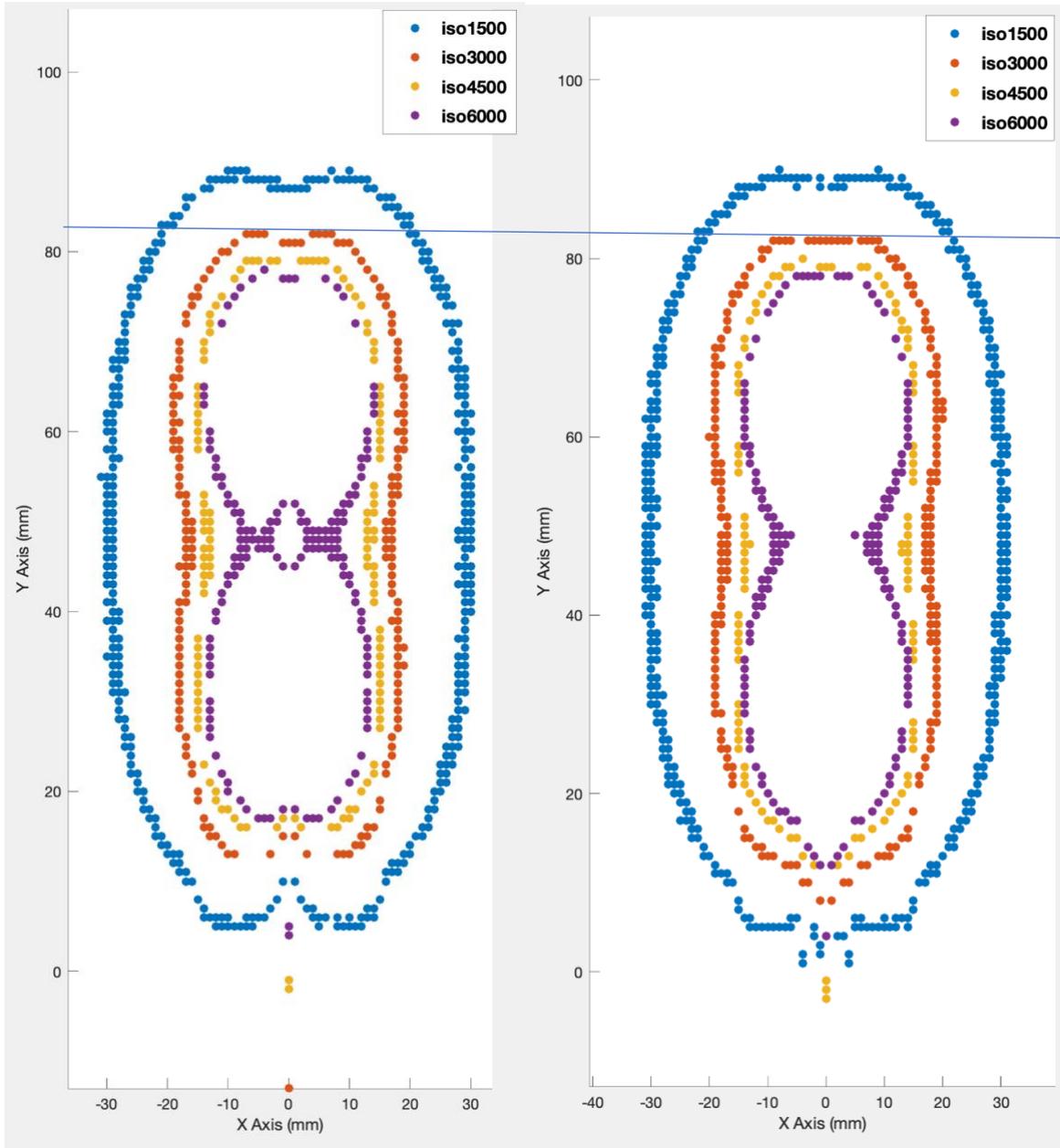
Figure 9, isodose lines (cGy) obtained from GEANT4 MC simulations considering heterogeneities, for a 30 mm diameter applicator. Left, with the Peek tandem in place. Right, with the Tungsten tandem in place. The Prescription dose line is shown in red.

Discussion and Conclusion

It is important to generate a radiation dose distribution that best and uniformly conforms to the vaginal cuff region as it is the most common place for post-treatment recurrence, through optimization during treatment planning. The most recent ABS recommendations (released in 2012 (Small et al., 2012)), define optimization as the manipulation of the HDR BT dwell positions, dwell times, or both. The ABS recommends using an optimization line at the upper apex or at vaginal cuff as well as the lateral sides of the applicator to avoid unacceptably high doses to the vaginal apex and any overlying portions of the small bowel. Delivering radiation dose to the vaginal cuff area that receives uniform prescription dose (Rx) as much as possible is desired. At minimum, considerable cold spots should be avoided during the planning process as the risk of recurrence at the vaginal cuff site is approximately 70% [9,10]. Due to the nature of the source construction, however, the anisotropy of the source will cause underdosage in the apex area even after the optimization.

A novel single-channel DMBT vaginal applicator is proposed in this research to address the anisotropy underdosage effect. Based on the results, this applicator can be a possible solution to compensate for the lack of coverage at the apex due to anisotropy of the source. With the same dwell positions, the dwell times of the source for this compensation was obtained to be a small fraction of the total treatment time, i.e., adding few minutes extra to the overall treatment time. There is a subset of patients who experience recurrence of the disease at the vaginal apex after vaginal BT. Considering an optimization line as ABS recommends and using the new introduced DMBT applicator can assure the sufficient coverage of vaginal apex, without overdosing the lateral periphery. In addition, the new design can be utilized for minimizing of the underdose effect of the frequent air gaps due to the presence of restricting suture materials at the cuff through the optimization processes.

The impact of the cylinder applicator heterogeneity was also investigated in this research. It was shown the inhomogeneity of the cylinder (i.e., density being greater than water) could cause the creation of cold spot at the surface of the cylinder at the periphery. The main reason for this phenomenon is the higher density of the VC than water (1.29 g/cm^3), which causes gamma and x rays with lower energies to have more interactions inside the applicator as opposed to when

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TG43 model is assumed with water everywhere. As a result, the applicator has more absorbed dose in shallower depth in comparison to when the water is in place. This clarifies why at the same depth inside the VC including the surface, there is less dose compared to TG43 model. In addition, radiation gets hardened slightly after passing through the higher density applicator, which explains the difference among the attenuation coefficients found. The magnitude of cold spots is strongly dependent on the size of the cylinder for the same plan (with larger the cylinder, e.g., 35 mm, the bigger the effect), since such determines the level of the beam hardening and requires further MC simulation studies to characterize.

The magnitude of anisotropy at the apex is slightly different in the two dose calculation models, as well. This is because of the presence of the lumen at the center of the VC applicator. Since the channel is not filled with the applicator material (but rather with air), there is no major interaction and therefore attenuation inside it. Consequently, the dose increases at the apex of the applicator as opposed to the TG43 model predictions. Moreover, the magnitude of the anisotropy dip can vary depending on the cylinder top thickness, the material, and the density of the applicator, which needs further MC simulation studies to characterize.

In conclusion, the novel DMBT cylinder design proposed in this thesis work is a potential solution to remedy the underdosage at the vaginal apex due to source anisotropy. Such design may be of clinical benefit. Also, the VC heterogeneity analysis of this research based on MC simulation calculations indicates that prescribing to the VC surface suffers from extra level of uncertainty because of the dose reduction at the surface (i.e., cold spots), which should be considered in treatment planning.

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