Therapeutic analysis of high-dose-rate ^{192}Ir vaginal cuff brachytherapy for endometrial cancer using a cylindrical target volume model and varied cancer cell distributions

Hualin Zhang,^{a)} Eric D. Donnelly, and Jonathan B. Strauss

Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, Illinois 60611

Yujin Qi

Centre for Medical Radiation Physics, University of Wollongong, Wollongong, NSW 2522, Australia

(Received 18 May 2015; revised 3 December 2015; accepted for publication 12 December 2015; published 31 December 2015)

Purpose: To evaluate high-dose-rate (HDR) vaginal cuff brachytherapy (VCBT) in the treatment of endometrial cancer in a cylindrical target volume with either a varied or a constant cancer cell distributions using the linear quadratic (LQ) model.

Methods: A Monte Carlo (MC) technique was used to calculate the 3D dose distribution of HDR VCBT over a variety of cylinder diameters and treatment lengths. A treatment planning system (TPS) was used to make plans for the various cylinder diameters, treatment lengths, and prescriptions using the clinical protocol. The dwell times obtained from the TPS were fed into MC. The LQ model was used to evaluate the therapeutic outcome of two brachytherapy regimens prescribed either at 0.5 cm depth ($5.5 \text{ Gy} \times 4$ fractions) or at the vaginal mucosal surface ($8.8 \text{ Gy} \times 4$ fractions) for the treatment of endometrial cancer. An experimentally determined endometrial cancer cell distribution, which showed a varied and resembled a half-Gaussian distribution, was used in radiobiology modeling. The equivalent uniform dose (EUD) to cancer cells was calculated for each treatment scenario. The therapeutic ratio (TR) was defined by comparing VCBT with a uniform dose radiotherapy plan in term of normal cell survival at the same level of cancer cell killing. Calculations of clinical impact were run twice assuming two different types of cancer cell density distributions in the cylindrical target volume: (1) a half-Gaussian or (2) a uniform distribution.

Results: EUDs were weakly dependent on cylinder size, treatment length, and the prescription depth, but strongly dependent on the cancer cell distribution. TRs were strongly dependent on the cylinder size, treatment length, types of the cancer cell distributions, and the sensitivity of normal tissue. With a half-Gaussian distribution of cancer cells which populated at the vaginal mucosa the most, the EUDs were between $6.9 \text{ Gy} \times 4$ and $7.8 \text{ Gy} \times 4$, the TRs were in the range from $(5.0)^4$ to $(13.4)^4$ for the radiosensitive normal tissue depending on the cylinder size, treatment lengths, prescription depth, and dose as well. However, for a uniform cancer cell distribution, the EUDs were between $6.3 \text{ Gy} \times 4$ and $7.1 \text{ Gy} \times 4$, and the TRs were found to be between $(1.4)^4$ and $(1.7)^4$. For the uniformly interspersed cancer and radio-resistant normal cells, the TRs were less than 1. The two VCBT prescription regimens were found to be equivalent in terms of EUDs and TRs.

Conclusions: HDR VCBT strongly favors cylindrical target volume with the cancer cell distribution following its dosimetric trend. Assuming a half-Gaussian distribution of cancer cells, the HDR VCBT provides a considerable radiobiological advantage over the external beam radiotherapy (EBRT) in terms of sparing more normal tissues while maintaining the same level of cancer cell killing. But for the uniform cancer cell distribution and radio-resistant normal tissue, the radiobiology outcome of the HDR VCBT does not show an advantage over the EBRT. This study strongly suggests that radiation therapy design should consider the cancer cell distribution inside the target volume in addition to the shape of target. © 2016 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4939064>]

Key words: high-dose-rate ^{192}Ir source, brachytherapy, Monte Carlo, endometrial cancer, linear quadratic model

1. INTRODUCTION

The efficacy of intracavitary vaginal cuff brachytherapy (VCBT) alone has been demonstrated in both randomized and nonrandomized experiences and is increasingly used in

the adjuvant treatment of early stage endometrial cancer patients.^{1,2} For reasons of cost, convenience and safety, high-dose-rate (HDR) brachytherapy has replaced low-dose-rate (LDR) brachytherapy in this setting. Consequently, in the majority of radiation oncology departments, adjuvant vaginal cuff

HDR brachytherapy has become the standard of care for many patients with early stage endometrial cancer, either combined with external beam radiation or delivered as monotherapy.³ VCBT reduces the risk of recurrence at the vaginal cuff and is associated with significantly less toxicity when compared to whole pelvic external beam radiation therapy (EBRT).^{3,4}

Since the dose deposited by a HDR source decreases with distance, it would be particularly advantageous if the cancer cell population followed a similar distribution. Choo *et al.*⁵ demonstrated the distribution of lymphatic channels in the vaginal wall followed such a pattern. They found the percentage of lymphatics located within 1, 1–2, 2–3, 3–4 mm of the vaginal surface were 50.5%, 30.7%, 11.9%, and 6.9%, respectively. Thus, the distribution of lymphatic channels (a surrogate for cancer cell density) can be approximated as a half-Gaussian or a radial function. Consequently, the nonuniform dose distribution of HDR brachytherapy may be more favorable than a uniform dose distribution obtained with EBRT, given that the tissue with the largest tumor burden receives the highest dose.

The dosimetric characteristics and clinical efficacy of HDR VCBT have been well characterized; however, the therapeutic advantage of the nonuniform dose distribution of HDR VCBT has not been compared to the uniform dose radiotherapy of EBRT in light of assumptions concerning cancer cell distribution. To evaluate the cancer cell killing associated with varied cancer cell distributions, the dose at every point of target volume needs to be known. Clinical treatment planning system (TPS) can give differential or accumulative dose volume histograms (DVHs), but those DVHs lack of the dose location information, they can only be used for uniform cancer cell distribution, not for varied cancer cell distributions. Though theoretically, we could get doses and their location information anywhere in the target volume through a TPS or a spreadsheet using TG43 algorithm by entering numerous points of interest in the target volume, but this has been proven a challenge to reasonably populate so many points of interest in such an irregular shaped and high dose gradient target volume without missing some regions. Consequently, we used a Monte Carlo (MC) technique to calculate 3D dose distributions around the cylinder applicator using the dwell times obtained from the TPS plans, thus the varied cancer cell distribution can be directly applied to each point of target volume. In this study, the equivalent uniform dose (EUD) of HDR VCBT to cancer cell was obtained by calculating average cancer cell survival rate, and the therapeutic ratios (TRs) were evaluated by comparing the HDR VCBT with an assumed uniform dose EBRT on normal cell sparing at the same cancer cell kill, assuming either a half-Gaussian or uniform distribution of cancer cell density.

2. METHODS AND MATERIALS

2.A. MC simulations

Of the note, using the TPS or a spreadsheet with the TG-43 formalism readers can determine the doses at any points of a target volume, in principle, they should also be able to get the same accurate DVH results with location information. The

MC approach used in this study was simply to utilize a well-developed Fortran code for MC code to conveniently lay out the tally points across the target volume and analyze the dose results afterward.

A MC N-particle transport code (MCNP, Version 5, release 1.50)⁶ was used to calculate the doses in water around a HDR ¹⁹²Ir source (Nucletron, Elekta AB, Stockholm, Sweden). The source geometry of microSelectron V2 HDR ¹⁹²Ir and material densities was taken from the literature.⁷ The source was benchmarked through MC simulations by comparing AAPM TG-43 (American Association of Physicists in Medicine Task Group 43)⁸ parameters obtained from our calculation to those in the literature.^{7,9,10} The MCNP5 code considers photoelectric, coherent, Compton, and pair production interactions. Though some of the above interactions, such as coherent and pair production, are not the dominant process in the ¹⁹²Ir source energy range, all interaction types were turned on during the simulations. The photon transportation mode was used in all simulations, though the secondary electron dose was also scored. There are several tally types available in this code for dose calculation. In this study, the absorbed doses from photon and electron were calculated by F6 tally. The F6 tally calculates the average photon dose rate over a tally cell in (MeV/gm)/photon. The TG43U1 recommends using collision kerma to approximate absorbed dose for ¹²⁵I, ¹⁰³Pd, and ¹⁹²Ir brachytherapy sources due to the short range of the secondary electrons produced by interactions from photons emitted by the ¹²⁵I, ¹⁰³Pd, and ¹⁹²Ir nuclides. Since all materials involved are low-Z, the cylinder applicator was modeled as the water to keep consistent with the TPS which does not have a capability to consider inhomogeneity.

The photon interaction cross section file used in this study was the MCPLIB04 library distributed by the Radiation Shielding Information Computing Center (RSICC).¹¹ The energy spectrum of ¹⁹²Ir, which was taken from the NUDAT report¹² and recommended by AAPM and ESTRO,¹³ ranges from 61 keV to 1.19 MeV with corresponding intensities.

In all benchmarking calculations, the ¹⁹²Ir source was virtually placed at the center of spherical water phantom which is 15 cm in radius. Though the TG43 U1 recommends 5 cm of backscattering material for evaluating dose rate in a 15-cm radius liquid water sphere, the ¹⁹²Ir source photon energies are higher than those emitted from ¹²⁵I and ¹⁰³Pd energy, so the phantom size should be increased. However, in the previous study by Daskalov *et al.*, which contributed the widely used microSelectron ¹⁹²Ir HDR source TG43 data, a 15 cm-radius spherical phantom was used. Therefore, the 15-cm-radius spherical phantom was used in this study mainly for benchmarking ¹⁹²Ir source MC calculations. Considering a cylindrically symmetric source structure, circular torus cells (0.05 cm in transverse diameter) around the source longitudinal axis were employed as the tally cells to score the eligible events. For the single source radial dose function simulation, a series of concentric torus tally cells sitting on the source longitudinal axis and passing through the center of source (defined by active length) were created and used to score the doses at a range of 0.1–10 cm in the liquid water phantom. The same tally cells were used to calculate the air kerma by replacing the

liquid water phantom with the void space and tally cells with the dry air. In order to reduce the statistical error, the dose rates for deriving anisotropy functions at different distances were also simulated by a series of torus tally cells located at the plane perpendicular to the source axis. In the radial distance ranging from 0.5 to 10 cm, the anisotropy functions were tallied in torus tally cells from 0° to 180° in 5° intervals. The transverse diameters of tori ranged from 0.025 to 0.1 cm depending on which angles at which they were placed in order to avoid overlapping each other and overlimiting the events in the tori. Liquid water density used in the simulation was 0.998 g cm^{-3} . The composition and density of dry air were taken from the TG43U1 report.

During the source benchmarking with TG43U1 parameters, up to 2×10^8 source photon histories were processed for each set of in-water and in-air calculations. The elapsed time for each simulation was approximately 56 h in water, and 9 h in void space for air-kerma simulations. The statistical uncertainties were found to be less than 2% for all anisotropy tally points when the distance was smaller than 5 cm and/or the angle was greater than 10° . However, the uncertainty increased for larger distances and smaller angles. When the distance was 7 cm and/or the angle was less than 10° , the statistical uncertainty was about 9%. This is understandable because, when the distance is large and/or angle is at or close to 0° , the solid angle of this point to the source is very small, so very few photons and/or electrons will be able to enter this tally cell; thus, the statistical uncertainty would inevitably be large. The statistical uncertainty from air-kerma simulation was less than 0.3% at all tally points along the bisector axis. The statistical uncertainty for the dose rate constant was under 0.5%. The overall statistical uncertainty for the radial dose function tallies (distance from 0.5 to 10 cm) was less than 3%.

It should be noted that the source data used in the Oncentra TPS V3.4 are slightly different from the Daskalov's, mainly because of the modification of the source welding cable. We verified that the difference of dose calculation results is less than 2%.

In the ^{192}Ir HDR treatment simulation, the phantom size was increased to 25 cm in radius, in order to better accommodate the treatment length and reflect average patient's size. For calculating 3D dose and DVHs, a series of concentric-circular torus with radii ranging from the cylinder surface radius to the surface radius +0.5 cm at the step size of 0.1 cm and with the longitudinal extension up to 7 cm along the cylinder axis at the step size of 0.1 cm were used to form the tally cells. The radii of two minor axes of torus tally cells were carefully adjusted so that the surfaces will not touch each other; therefore, events will not be double counted.

The source locations (coordinates) obtained from the TPS (Oncentra, version 3.4, Elekta, Stockholm, Sweden) were used in MC calculations. The dwell times obtained from the TPS were fed into MC. By comparing the MC calculated doses with the TPS results for several known points in a single source and single dwell position setting at same dwell time, we first got a conversion factor between the contained and apparent activities, $1 \text{ Ci}_{\text{Apparent}} = 1.105 \text{ Ci}_{\text{contained}}$. This factor ($f = 1.105$) was then multiplied in all our MC simulation results of various

HDR VCBT treatments with multiple dwell points to get the comparable doses. Thus, the MC simulated dose distributions can be verified by the doses obtained from the TPS.

Every dwell position was run by MC separately; up to 426 tally cells were used in each simulation. MC simulation for individual dwell position took a history number of 3.0×10^6 , 9 h in a PC of 4-core 3.2 GHZ processor, 10 GB RAM, 500 GB hard drive. Using this history number is for balancing both the running time and statistical uncertainty. The statistical uncertainty was better than 3% for most tally points. But for the points on the cylinder central axis, the uncertainty could be up to 12% due to very small solid angle of all source positions. The dose distributions from all dwell positions were summed up to get the total dose distribution of the treatments of multiple dwell positions using dwell times obtained from the TPS; thus, the MC plan optimization approach is the same as the TPS. Although the calculation coverage length of each simulation was longer than the prescribed treatment length, the radiobiology modeling and DVH analysis just took the tally cells only within the prescribed treatment length.

2.B. Clinical treatment protocol and dose prescription

An Elekta HDR unit with an ^{192}Ir source was used for VCBT. The TPS was used to make vaginal cuff brachytherapy plans using cylinders with a range of diameters (2.5, 3.0, 3.5, 4.0 cm).

As per our clinical protocol and clinical guidelines, the two fractionation schemes tested for HDR VCBT were (1) 5.5 Gy prescribed to 0.5 cm depth times 4 fractions and (2) 8.8 Gy prescribed to the surface of the cylinder times 4 fractions.

In this study, the HDR VCBT plans were generated as follows: a set of reference points was created at the prescription depth for a list of source dwell positions. These "axis points" were used to normalize the prescription dose. Since our default step size is 0.5 cm, a 5-cm treatment length has 11 dwell points (Fig. 1). The most proximal dwell point was not used to create a corresponding reference point to avoid excessive extension of prescription isodose line. The cylindrical applicator (Elekta company, Stockholm, Sweden) used is composed by a combination of several discrete sections; the diameters of these sections decrease slightly at the junction regions to be identifiable on imaging. Using a nominal radius avoids these slight surface variations. The head of applicator is hemiellipsoidal; we used the measured radius at different in-head dwell points to account for this.

A volume of 0.5 cm thick cylinder shell named as PTV_Eval (see Fig. 1) was created by using TPS contouring tools for each treatment scenario. The DVHs of PTV_Eval, respectively, obtained from the TPS and MC were compared for verifying the MC results in calculating the treatment plan.

2.C. Cancer and normal cell population in vaginal wall

In most radiobiology modeling studies, uniform cancer cell distributions were often used.^{14–16} However, this assumption may be inaccurate. The magnetic resonance imaging (MRI) showed that the cancer cell density may vary in the

FIG. 1. Schematic diagram of HDR ^{192}Ir source treatment in vaginal cuff brachytherapy. More cancer cells are assumed to be located onto the vaginal surface in the half-Gaussian distribution, which are represented by the cancer cell density function $f_p(t)$. The evaluated treatment depth is 0.5 cm.

tumor volume. A biopsy study by Choo *et al.*⁵ reported that approximately 95% of vaginal lymphatic channels (a potential surrogate for cancer cell location) are located within a 3-mm depth from the vaginal surface and that the density of lymphatic channels decreases with the depth. The location and density of the vaginal lymphatics may be used as a surrogate of cancer cell distribution. Therefore, in one model, we assumed a half-Gaussian distribution to approximate the cancer cell population variation within 0.5 cm depth (Fig. 2). It should be noted that Choo's results were from the limited samples, so they may not represent the cancer cell density distributions of all endometrial cases, however although the real cancer cell density distribution may neither be radial nor half-Gaussian, considering the anatomic structure of vagina, a cylindrical target volume with a half-Gaussian cancer cell density distribution may be plausible. It should also be noted that we used a half-Gaussian distribution not only because this distribution can approximate a set of experimental data for endometrial cancer cell density variation along the depth but also because this distribution is easy to use and has long been used to describe the biological agent and molecular spreading, although it might not be true to represent the real case of endometrial cancer cell distributions particularly

FIG. 2. Experimentally determined vaginal wall cancer cell distribution and Gaussian fitting results (20% error bars were arbitrarily added in the experimental data for fitting). Normal cell distribution was also plotted. f_c and f_n are, respectively, the cancer and normal cell percentage functions.

after surgery. On this aspect, some researchers have estimated the impact of varied cancer cell density distribution to the nonuniform dose radiotherapy. Herskind *et al.*¹⁷ assumed three types of density distributions of recurrence-forming foci (aka cancer cells) to estimate the impact of nonuniform cancer cell distributions to the tumor control and recurrence rate in nonuniform dose radiotherapy delivered by the INTRABEAM (Carl Zeiss AG, Oberkochen, Germany) isotropic electronic source brachytherapy after surgery. Their study indicated that the different density distributions of recurrence-forming foci will result in different recurrence rates. Similar to the sphere of equivalence target volume model of Herskind *et al.*, our HDR VCBT target volume can be called as cylindrical equivalence target volume model. For the purpose of comparison, we also used a uniform cancer cell distribution throughout the vaginal wall in addition to the half-Gaussian along the depth. We applied these models of cell distributions to the calculations of cell survival fraction after radiotherapy. In addition, by changing assumptions of the density (percentage of cancer cells) at the surface, we also evaluated the impact of cancer cell density to the treatment outcome for the same cancer cell distribution.

We assumed that in any given small volume of target, the cells are either cancer or normal cells. If the percentage of cancer cells is p , then the percentage of normal cells is $1 - p$. Therefore, if the cancer cell density distribution is a half-Gaussian, the normal cell distribution will be a half-Gaussian as well (Fig. 2). If the cancer cell distribution is uniform, then the normal cell will also be uniform.

2.D. Radiobiology characteristics of HDR VCBT

The dose delivered to the vaginal cylindrical target volume PTV_Eval by HDR VCBT is nonuniform. The terms of EUD and TR developed for describing nonuniform dose EBRT (Refs. 18 and 19) were used in this study.

For the studied HDR VCBT, the survival fraction at the dose point $D(x, y, z)$ can be calculated by linear quadratic (LQ)

model,

$$SF(x, y, z) = e^{-(\alpha * D(x, y, z) + \beta * D(x, y, z)^2) * N}. \quad (1)$$

The tumor cells of endometrial cancers are usually adenocarcinoma cells. The linear quadratic model parameters (α and β) of radiobiological response for adenocarcinoma cells were taken from the literature,²⁰ $\alpha = 0.45 \text{ Gy}^{-1}$, $\beta = 0.039 \text{ Gy}^{-2}$, which are consistent with the data reported by Guerrero and Li.¹⁶ This study evaluated four fractions, $N = 4$. In the following, we first analyze single fraction and then expand to four fractions. In addition, the TPS and MC results indicated that most of PTV_Eval volume (95% or more) will get dose less than 9 Gy, so the LQ model is valid.

We assumed that normal cells were interspersed with cancer cells, but the density of cancer and normal cells varied with depth if a varied distribution was assumed. The average survival fraction of tumor or normal tissue in VCBT was calculated by²¹

$$\begin{aligned} \overline{SF}(\text{VCBT}) &= \frac{\int_V SF(x, y, z) * f_p(x, y, z) * dV}{\int_V f_p(x, y, z) * dV} \\ &= \frac{\int_V SF(x, y, z) * f_p(x, y, z) * dx * dy * dz}{\int_V f_p(x, y, z) * dx * dy * dz}. \end{aligned} \quad (2)$$

In the above equation, dV is the volume receiving dose $D(x, y, z)$, and $f_p(x, y, z)$ is the percentage of cancer (or normal if calculating normal cells) cells at that point (x, y, z) . V is the volume of 0.5 cm thick shell around the cylinder applicator with different treatment lengths, namely, PTV_Eval. The average cancer cell survival fraction in VCBT, $\overline{SF}(\text{VCBT})$ has an EUD, which is the equivalent uniform dose that would kill the same number of cancer cells across the tumor volume. The EUD can be obtained by solving the following equation:

$$\beta * (\text{EUD})^2 + \alpha * (\text{EUD}) + \ln(\overline{SF}(\text{VCBT})) = 0. \quad (3)$$

From the EUD, we could estimate the normal cell survival fraction $SF_{\text{normal}}(\text{EUD})$, if the normal cells included in the tumor volume were irradiated by one fraction of uniform dose radiotherapy at the dose of EUD instead of one fraction of VCBT. It should be noted that we relate the VCBT radiobiology modeling results to the same fraction number of EBRT just for showing a clearer relationship and better understanding of the underlying concept. We used an α/β ratio of normal tissue of 3.1.²² Both the radiosensitive [$SF(2 \text{ Gy}) = 0.3$, so $\alpha = 0.366 \text{ Gy}^{-1}$, $\beta = 0.118 \text{ Gy}^{-2}$] and radio-resistant [$SF(2 \text{ Gy}) = 0.7$, so $\alpha = 0.108 \text{ Gy}^{-1}$, $\beta = 0.0035 \text{ Gy}^{-2}$] normal tissues were used, because the radiosensitive normal cells were found to benefit the most from the nonuniform dose radiation, but the radio-resistant normal cells could not take advantage of nonuniform fields which have some relatively low dose zones for normal cell sparing.¹⁹

The TR is taken as a ratio of normal cell survival fractions of two regimens; this is based on the assumption that two regimens should have the same end point. The end point is the both regimens will kill same amount of cancer cells (same cancer cell SF), but two regimens may spare different amount of normal cells. Whichever sparing more normal cells is advantageous over another. The TR was calculated as

follows:²¹

$$\text{TR} = \frac{\overline{SF}_{\text{normal}}(\text{VCBT})}{\overline{SF}_{\text{normal}}(\text{EBRT})}. \quad (4)$$

A value of TR greater than 1 would suggest a survival advantage of normal tissue cells for VCBT as compared to uniform dose EBRT, at the same end point—both regimens (EBRT and VCBT) kill the same amount of cancer cells.

For four fractions of treatments, if we ignore the cell repopulation,

$$\text{TR4} = (\text{TR})^4 \quad (5)$$

$$\text{EUD4} = 4 * \text{EUD}. \quad (6)$$

TR4 and EUD4 are the therapeutic ratio and equivalent uniform dose for four fractions of the HDR VCBT, respectively. It should be noted that a course of multiple fractions of HDR VCBT is usually used for the radiation boost to vaginal cuff after a course of uniform dose EBRT with many fractions; the uniform dose EBRT was not used to treat PTV_Eval alone, it usually was used to treat the whole pelvis. The purpose of comparing four fractions of HDR VCBT with four fractions of uniform dose EBRT in the volume of PTV_Eval in this study was simply to estimate the normal cell sparing capability of HDR VCBT for the assumed cancer and normal cell distributions.

3. RESULTS

3.A. Benchmarking ¹⁹²Ir HDR source

The TG43 data of a microSelectron V2 ¹⁹²Ir HDR source were generated by MC.

The anisotropy functions were calculated at 0.5, 1.0, 3.0, and 5.0 cm of radial distance; they were found to be in good agreement with published data (Fig. 3), except for those at 0°–5° which are on or near the drive cable, a small difference was seen at smaller radial distance and smaller angle. Table I gives the calculated radial dose functions of microSelectron V2 ¹⁹²Ir source in a water phantom, compared with the published data. Our radial dose function is 2% higher than the work of Daskalov *et al.* at 7 cm and greater, 7% and 31% higher at 2 and 1 mm. The differences seen in the anisotropy functions and radial dose functions are due to different codes (MCPT vs MCNP5), different cross section files (DLC-99 vs MCPLIB04), different energy spectrums, and different geometry modeling methods used in both studies. It is reported that the low energy photon cross section data have been improved after DLC-99 was updated to MCLIB04 files,¹¹ the low energy photon dose will be larger than the old version. A recent study by Granero *et al.*⁹ with MCNP5 also confirmed that the radial dose function of microSelectron V2 ¹⁹²Ir HDR source is higher than the previously reported. The dose rate constant for ¹⁹²Ir source was $1.114 * (1\% \pm 0.033\%)$ (cGy/h)/U [compared to 1.108 (cGy/h)/U by Daskalov *et al.*], the difference is within 1%.

FIG. 3. A comparison of anisotropy functions of microSelectron V2 HDR ^{192}Ir at different radial distances between the MC calculated in this work and the literature (Ref. 7).

3.B. Dose distributions around the cylinder applicators

The 3D dose distribution for the cylinders with the diameter of 2.5, 3.0, 3.5, and 4.0 cm and treatment lengths of 3.0, 4.0, and 5 cm, at two types of prescription depths and doses, were individually calculated by MC.

TABLE I. MicroSelectron V2 ^{192}Ir HDR source radial dose function obtained by this work compared with a previous study by Daskalov *et al.* (Ref. 7) in a water phantom.

Distance r (cm)	$g(r)$		Ratio B/A
	A. By Daskalov	B. From this study	
0.10	1.004	1.316	1.311
0.20	1.000	1.069	1.069
0.30	1.001	1.013	1.012
0.50	1.000	0.994	0.994
1.00	1.000	1.000	1.000
1.50	1.003	0.994	0.991
2.00	1.007	0.998	0.991
2.50	1.008	1.001	0.993
3.00	1.008	1.003	0.995
4.00	1.004	0.999	0.995
5.00	0.995	0.997	1.002
6.00	0.981	0.990	1.009
7.00	0.964	0.982	1.019
8.00	0.940	0.968	1.030
9.00	0.913	0.950	1.041
10.00	0.882	0.932	1.057

Figure 4 exemplifies the evolution of dose distributions of different depths for a 5-cm treatment length when the diameter of cylinder applicator is changed from 2.5 to 4.0 cm. A dose of 5.5 Gy was prescribed at the 5 mm depth from the vaginal surface. It was found that the smallest cylinder (2.5 cm) had the largest surface doses as expected.

Figure 5 shows the dose distributions of the same cylinder applicators, but the dose of 8.8 Gy was prescribed at the vaginal surface. It was shown that the largest cylinder (4.0 cm) delivered the largest doses at 0.5 cm depth.

We also verified MC simulation quality by comparing the DVH curves of PTV_Eval. Figure 6 shows a comparison between the TPS predicted and MC calculated DVH curves of a case: a 3.0 cm-cylinder with 5.0 cm treatment length, 5.5 Gy prescribed at 0.5 cm depth. A good agreement was found for the dose covering the majority of target volume, but a noticeable difference was seen for the hot dose zone. The TPS and MC calculated PTV-Eval volumes were 31.23 and 30.52 cm³, respectively; the difference is only 2%. The difference of DVH curves will be explained in Sec. 4.

3.C. EUD and TR of HDR VCBT

Table II shows the EUDs and TRs obtained in the half-Gaussian cancer cell population, for the prescription doses of 5.5 Gy at 0.5 cm depth and 8.8 Gy at the surface, respectively. EUD is approximately 7 Gy for all lengths and diameters of cylinders when 5.5 Gy was prescribed at 0.5 cm depth and is approximately 7.5 Gy when 8.8 Gy was prescribed at

FIG. 4. Dose distributions of various cylinder applicators for the 5.5 Gy dose prescribed at the 5 mm depth. The treatment length is 5.0 cm. Each curve represents the dose of different depth from the surface.

the vaginal surface. The TR was found to be between 4.98 and 13.35 for the 5.5 Gy prescription regimen and between 8.07 and 12.60 for 8.8 Gy regimen in one fraction. Shorter treatment length and smaller cylinder size were found to have greater TRs. The average TR was only about 1.60 if the interspersed normal tissue is radio-resistant. The two dosing regimens yielded very similar results.

Considering the density of cancer cell at the vaginal surface could vary significantly, the impact of cancer cell percentage was also tested. When the cancer cell percentage at the vaginal surface was decreased from 55.6% to 0.1% at the same half-Gaussian cell distribution, EUDs were found to keep unchanged, but TRs decreased only 16% for both prescriptions.

Table III shows the EUDs and TRs for the situation if the cancer cells and normal cells were uniformly populated in

the cylindrical target volumes (the cancer and normal cell densities do not change with the depth). The EUDs were found about 11% smaller, but TRs were significantly smaller than that seen in half-Gaussian cell distributions. EUDs were about 6.5 Gy and TRs were only about 1.5. TR was found to be less than 1.0 if the interspersed normal cells were radioresistant.

If therapeutic ratios of four fractions of VCBT are calculated under the condition of ignoring cancer and normal cell repopulation, the TR4 would be very large in the half-Gaussian cancer cell distribution and the radiosensitive normal cells. However, for the uniform distribution of cancer cells and uniformly interspersed radio-resistant normal cells, TR4 would be much smaller than 1, only about 0.72, that means the EBRT would do a better job than HDR VCBT under such a circumstance.

FIG. 5. Dose distributions of various cylinder applicators for the 8.8 Gy dose prescribed at the cylinder surface. The treatment length is 5.0 cm. Each curve represents the dose of different depth from the surface.

In addition, a further testing found that in the uniform cancer cell distribution, the EUDs and TRs were the same for any percentage of cancer and normal cells in the target volume.

4. DISCUSSION

In this study, the 3D dose distribution of HDR VCBT was assessed over a variety of cylinder lengths and diameters, then an LQ model was used to estimate the TR of these regimens assuming cylindrical target volume with either a half-Gaussian distribution (our favored model based on experimental data) or a uniform distribution of cancer cells in the vaginal wall. Assuming a half-Gaussian distribution of cancer cells and radiosensitive normal tissue, the one-fraction TR for vaginal brachytherapy was very impressive, ranging from 5.0 to 13.4, compared to 1.4 to 1.8 for a uniform cancer cell distribution. The difference for four fractions of TRs is even more

remarkable, 625 to 33 242 vs 4 to 10.5. These findings may help to explain how relatively low dose vaginal brachytherapy appears remarkably effective at eliminating the rate of vaginal recurrence.²³

The effectiveness of nonuniform dose radiotherapy of EBRT for treating diverse tumors has been clinically identified,²⁴ although the radiobiologic response to the nonuniform radiation is still not well understood. All clinically reported cases using nonuniform dose radiotherapy were for large tumors, primarily because it is hard to generate desired nonuniform dose radiotherapy in a small tumor volume. One theory to explain the efficacy of nonuniform dose radiotherapy is when normal tissue cells are spared in the cold dose region, those underirradiated (spared) areas can serve as centers of regrowth of normal tissues. Radiobiological modeling revealed that the nonuniform dose radiotherapy leverages the superior repair capability of interspersed normal tissue cells to that of most cancer cells.¹⁹ Because of that the nonuniform

FIG. 6. A comparison of DVHs obtained, respectively, from the MC simulation and TPS for a case: 3 cm of diameter cylinder, 5 cm of treatment length, and 5.5 Gy was prescribed at the 0.5 cm depth from the cylinder surface.

field of radiation works like selective killing for acutely responding cancer cells. One can argue that a similar or better cancer cell killing rate can be achieved by using uniform dose radiotherapy with a large dose; however, nonuniform field radiotherapy has demonstrated improved radiation tolerance and response when compared with uniform field radiotherapy

for most tumors.^{24–27} HDR VCBT also has a varied dose distribution across the tumor target, so it possibly possesses similar therapeutic advantage to that seen in the external beam nonuniform dose radiotherapy [most known as spatially fractionated (grid) radiotherapy]. Additionally, assuming the distribution of cancer cells follows the dose variation, it may provide an even bigger therapeutic advantage than that seen in randomly modulated external beam nonuniform (grid) field, which does not take into account cancer cell distribution nor the normal cell distribution in its planning.

In HDR VCBT, the total dose deposition in target volume varies with depth and longitudinal position (Figs. 4 and 5), and the dose variation was somewhat greater when the prescription dose was at the 0.5 cm depth than when it was prescribed at the surface. For example, when using a 2.5 cm cylinder with 5 cm treatment length, the ratio between the surface dose and 0.5 cm depth dose at the tip of cylinder was 4.1 when the dose was prescribed at the 0.5 cm depth and 2.2 when the dose was prescribed at the cylinder surface. At the middle of cylinder, the ratio is about 1.5 for both prescription options. The treatments with 0.5 cm depth prescription showed larger dose modulation than that prescribed at the surface, even they both have a comparable EUD. Thus, the dose distribution seen with a prescription depth of 0.5 cm is more inhomogeneous and therefore may be preferable for inducing radiation response as reported in the clinical observation for the external

TABLE II. Single fraction EUDs and TR of HDR VCBT for different diameters and treatment lengths, when the density of cancer cells was distributed as a half-Gaussian function along the depth (see Fig. 2).

Cylinder diameter (cm)	5.5 Gy at 5 mm depth			8.8 Gy at surface		
	EUD (Gy)			EUD (Gy)		
	L = 3 cm	L = 4 cm	L = 5 cm	L = 3 cm	L = 4 cm	L = 5 cm
2.5	7.51	7.38	7.30	7.22	7.33	7.34
3.0	7.23	7.16	7.08	7.41	7.47	7.53
3.5	7.19	7.06	7.05	7.57	7.69	7.71
4.0	7.15	6.96	6.90	7.66	7.74	7.82
Average	7.27	7.14	7.08	7.47	7.56	7.60
For radiosensitive normal tissue [$\alpha/\beta = 3.1$, $SF(2\text{ Gy}) = 0.3$]						
Cylinder diameter (cm)	TR			TR		
	L = 3 cm	L = 4 cm	L = 5 cm	L = 3 cm	L = 4 cm	L = 5 cm
	L = 3 cm	L = 4 cm	L = 5 cm	L = 3 cm	L = 4 cm	L = 5 cm
2.5	13.35	10.74	9.42	12.60	11.90	11.51
3.0	9.82	8.20	7.20	11.03	10.39	9.94
3.5	8.31	6.81	6.01	10.42	9.80	9.13
4.0	7.12	5.80	4.98	9.67	8.66	8.07
Average	9.65	7.89	6.90	10.93	10.19	9.66
For radio-resistant normal tissue [$\alpha/\beta = 3.1$, $SF(2\text{ Gy}) = 0.7$]						
Cylinder diameter (cm)	TR			TR		
	L = 3 cm	L = 4 cm	L = 5 cm	L = 3 cm	L = 4 cm	L = 5 cm
	L = 3 cm	L = 4 cm	L = 5 cm	L = 3 cm	L = 4 cm	L = 5 cm
2.5	1.72	1.66	1.62	1.76	1.74	1.71
3.0	1.61	1.57	1.54	1.72	1.69	1.67
3.5	1.56	1.51	1.49	1.66	1.66	1.64
4.0	1.49	1.43	1.41	1.54	1.54	1.55
Average	1.60	1.54	1.52	1.67	1.66	1.64

TABLE III. Single fraction EUDs and TR of HDR VCBT for different cylinder diameters and treatment lengths, when the distribution of the cancer cells in vaginal wall was assumed to be uniform.

Cylinder diameter (cm)	5.5 Gy at 5 mm depth			8.8 Gy at surface		
	EUD (Gy)			EUD (Gy)		
	<i>L</i> = 3 cm	<i>L</i> = 4 cm	<i>L</i> = 5 cm	<i>L</i> = 3 cm	<i>L</i> = 4 cm	<i>L</i> = 5 cm
2.5	6.56	6.50	6.46	6.26	6.38	6.42
3.0	6.39	6.36	6.33	6.50	6.60	6.69
3.5	6.40	6.34	6.36	6.72	6.87	6.92
4.0	6.43	6.32	6.30	6.91	7.02	7.12
Average	6.45	6.38	6.36	6.60	6.72	6.79
For radiosensitive normal tissue [$\alpha/\beta = 3.1$, $SF(2\text{ Gy}) = 0.3$]						
Cylinder diameter (cm)	TR			TR		
	3 cm	4 cm	5 cm	3 cm	4 cm	5 cm
2.5	1.68	1.57	1.52	1.55	1.55	1.57
3.0	1.60	1.50	1.44	1.52	1.52	1.52
3.5	1.52	1.45	1.37	1.57	1.52	1.51
4.0	1.52	1.47	1.36	1.76	1.65	1.57
Average	1.58	1.50	1.42	1.60	1.56	1.54
For radio-resistant normal tissue [$\alpha/\beta = 3.1$, $SF(2\text{ Gy}) = 0.7$]						
Cylinder diameter (cm)	TR			TR		
	<i>L</i> = 3 cm	<i>L</i> = 4 cm	<i>L</i> = 5 cm	<i>L</i> = 3 cm	<i>L</i> = 4 cm	<i>L</i> = 5 cm
2.5	0.89	0.90	0.91	0.91	0.91	0.91
3.0	0.90	0.92	0.93	0.92	0.92	0.92
3.5	0.91	0.93	0.94	0.91	0.92	0.93
4.0	0.92	0.93	0.94	0.90	0.91	0.92
Average	0.91	0.92	0.93	0.91	0.92	0.92

beam spatially fractionated grid radiotherapy,²⁵ although on the other hand it may also risk possible vaginal side effects^{3,23} such as vaginal stenosis, since the applicator tip can receive a high dose.

The DVH comparison between the TPS and MC revealed some differences in hot dose regions. This is understandable if we look how the target volume was generated/used in the TPS and MC. When a cylinder was contoured in the TPS from axial views, because the cylinder is not parallel to the patient's axis due to patient's anatomic feature, the real cylinder surface cut should be ellipsoidal. But, the cylinder surface was contoured using circular shape with the nominal cylinder radius rather than actual ellipsoidal shape and size on each CT slice for convenience and the oblique image was ignored, thus the contoured cylinder will be tilted to its axis and the volume will be slightly larger. Consequently, this will cause the distance from the source to the contoured surface to be slightly shorter than the cylinder radius depending on the tilted angle of cylinder to patients axis, thus the hot dose volume was slightly exaggerated in the TPS as seen in the Fig. 6, comparing to the MC which used the ideal cylinder geometry and source locations in calculation.

The EUDs are 11% larger assuming a half-Gaussian cancer cell distribution than a uniform one (Tables II and III). This suggests that the HDR VCBT treats cylindrical target volume with half-Gaussian cancer cell distribution (or radial

decreasing cancer cell distribution) more effectively than that with uniform cancer cell distributions. Although the prescription dose is only 5.5 and 8.8 Gy, the TR of the HDR VCBT is impressive. With HDR VCBT (for example, in a case: the cylinder diameter was 2.5 cm, treatment length 3 cm, 5.5 Gy prescribed at 0.5 cm depth) and the assumed half-Gaussian distribution of the cancer cells, theoretically 13.35 times more normal cells can be spared (TR = 13.35) than using uniform dose radiotherapy with EBRT in the single fraction. The TR would be slightly lower (12.60) if 8.8 Gy was prescribed at the cylinder surface for the same treatment conditions. In addition, because a plan with a smaller cylinder and a shorter treatment length created larger percentage of hot and cold dose ratios in PTV_Eval, so the TR was greater (Table II).

The cancer cell distribution in this study was alternatively assumed to be uniform in addition to half-Gaussian. If the cancer cells were uniformly interspersed and their density stays constant across depth, EUDs of the 8.8 Gy regimens are close to that of the 5.5 Gy regimens for the same treatment length and cylinder size (within 10% difference) (Table III). HDR VCBT can on average spare about 1.50 times (TR ~ 1.5) of normal cells spared by the uniform dose EBRT in either regimens regardless of the cylinder size and treatment length. The TR of HDR VCBT is smaller than that seen in the external beam nonuniform dose (grid) radiotherapy (TR ~ 2.3), which has the nominal dose of 15 Gy, and EUD of 4.2 Gy.¹⁹ Apparently,

a uniform cancer cell density distribution does not fully take advantage of HDR source dose distribution, thus the TR is only slightly greater than 1.

The radio-resistant normal tissue apparently does not appreciate nonuniform radiotherapy. Same as found in the previous studies for cervical cancer¹⁹ and melanoma²¹ in grid field, the TR was less than 1.0 if the interspersed normal cells were radio-resistant and cancer cell distribution was uniform. This means the HDR VCBT itself does not show a benefit for sparing more normal cells in this scenario; the EBRT would be a better choice.

If the cancer and normal cell repopulations are ignored, the four fractions therapeutic ratios TR4 for the half-Gaussian cancer cell distribution and radiosensitive normal tissue would become very large, to 31 736 ($\sim 13.35^4$). For the uniform cancer cell distribution and uniformly interspersed radiosensitive normal cells, this number is only 4. That means the four fractions of HDR VCBT could possibly spare 31 736 times more normal cells than that of the EBRT at the same cancer cell killing. Actually, this huge TR would be compromised since the cell repopulation will likely happen during the course of 4 fractions (4 weeks) of treatments. In addition, if the cell repopulation does not happen, four fractions of HDR VCBT will become less attractive for the uniform distribution of cancer cells with uniformly interspersed radio-resistant normal cells, TR4 is only 0.7.

The theoretical results of HDR VCBT on sparing a huge amount of more normal cells than EBRT at the same cancer cell killing are supported by the clinical effectiveness and low toxicity demonstrated with vaginal cuff brachytherapy. As reported in the literature⁴ that vaginal recurrence after HDR VCBT is 1.6% comparing to 1.8% for EBRT, the local regional recurrence—defined as pelvic, vaginal or both, is 2.1% for HDR VCBT and 5.1% for EBRT. In HDR VCBT, no grade 3 and 4 complications were observed, the rate of grade 1 and 2 is 9% or less.^{4,28} Although it was also mentioned in those literatures that with contemporary surgical techniques, the incidence of vaginal cuff recurrence might be very small in low-risk endometrial cancer, even without any adjuvant therapy.

We found that cancer cell distribution significantly affects the calculated TRs. Therefore, it is reasonable to think the treatment outcome can be improved for known cancer cell density distribution by designing a dose distribution which produces the maximum TRs. Herskind *et al.* used three types of cancer cell distributions to evaluate breast cancer recurrence probability treated by nonuniform dose radiotherapy—INTRABEAM electronic brachytherapy source. Their study also indicated that different cancer cell distributions will result in different treatment outcomes.

It should be mentioned that the modern external beam radiation therapy (e.g., IMRT, VMAT, SBRT, and radiosurgery) can use more sources/beams of radiation in which each irradiates a sharply collimated portion of the tumor in order to achieve homogeneous or inhomogeneous if desired and highly conformal dose distributions with a steep gradient inside/outside the target volume; therefore, the dose conformity to the cancer cell distribution in addition to the tumor shape could be potentially achieved by using modern

external beam radiation therapy. This study shows that using a simple technique of HDR VCBT has easily attained the desired dose conformity for the assumed tumor shape and cancer cell distribution of endometrial cancer; thus, it is clinically advantageous. It is expected that the advantage of HDR VCBT can be further improved by using multiple channel cylinders to conform the complex tumor targets and cancer cell distributions.²⁹

HDR VCBT is one of the simplest HDR procedures, but HDR VCBT still incurs significant uncertainties.^{30,31} The uncertainties existed in this study include source strength (2%), treatment planning (3%), medium dosimetry corrections (1%), volume calculation (2%), and dose delivery including registration of applicator geometry to anatomy (5%), interfraction/intrafraction changes between images and dose delivery (5%), Monte Carlo dose calculation (3%), and cancer cell distribution (20%). We do not consider the uncertainty of LQ parameters (α and β). We assume all the uncertainty components are not correlated; thus, we can get the combined uncertainty of about 22% ($k = 1$) in the EUD and TR calculations.

A limitation of this study is the heavy reliance on the cancer cell distribution which was from limited experimental data and a simplified target volume. If the cancer cell distribution and target volume are not cylindrical, the results could be different. However, this model yields predictions of significant normal cell sparing that are consistent with the impressive results seen clinically, regarding both impressive cancer cell kill and very low normal tissue toxicity.

5. CONCLUSION

In conclusion, the MC technique can be used to help evaluate detailed radiobiology impact of a nonuniform dose radiotherapy; assuming a half-Gaussian distribution of cancer cells from the vaginal surface and a cylindrical target volume, HDR VCBT is found to have a significant therapeutic advantage over uniform dose EBRT. This study suggests that radiotherapy treatment design should also consider the cancer cell distribution inside the target volume in addition to the shape of tumor volume.

ACKNOWLEDGMENTS

The work was neither supported, funded, or sponsored by any extrainstitutional source nor are there any actual or potential conflicts of interest with the production or publication of this work. No author has any direct or indirect commercial financial incentive associated with publishing this paper.

^{a)}Author to whom correspondence should be addressed. Electronic mail: hualin.zhang@northwestern.edu; Telephone: (312) 926-0311; Fax: (312) 926-6374.

¹R. A. Nout, V. T. Smit, H. Putter, I. M. Jürgenliemk-Schulz, J. J. Jobsen, L. C. Lutgens, E. M. van der Steen-Banasik, J. W. Mens, A. Slot, M. C. Kroese, B. N. van Bunnigen, A. C. Ansink, W. L. van Putten, C. L. Creutzberg, and PORTEC Study Group, "Vaginal brachytherapy versus pelvic external beam

- radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial," *Lancet* **375**, 816–823 (2010).
- ²V. Diavolisits, A. Rademaker, J. Lurain, A. Hoekstra, J. Strauss, and W. Small, Jr., "Clinical outcomes in international federation of gynecology and obstetrics satge IA endometrial cancer with myometrial invasion treated with or without postoperative vaginal brachytherapy," *Int. J. Radiat. Oncol., Biol., Phys.* **84**, 415–419 (2012).
- ³A. Y. Bahng, A. Dagan, D. W. Bruner, and L. L. Lin, "Determination of prognostic factors for vaginal mucosal toxicity associated with intravaginal high-dose-rate brachytherapy in patients with endometrial cancer," *Int. J. Radiat. Oncol., Biol., Phys.* **82**, 667–673 (2012).
- ⁴W. Small, Jr., S. Beriwal, D. J. Demanes, K. E. Dusenbery, P. Eifel, B. Erickson, E. Jones, J. J. Rownd, J. F. De Los Santos, A. N. Viswanathan, and D. Gaffney, "American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy," *Brachytherapy* **11**, 58–67 (2012).
- ⁵J. J. Choo, J. Scudiere, P. Bitterman, A. Dickler, A. M. Gown, and T. W. Zusag, "Vaginal lymphatic channel location and its implication for intracavitary brachytherapy radiation treatment," *Brachytherapy* **4**, 236–240 (2005).
- ⁶MCNP X-5, MCNP-A General Monte Carlo N-Particle Transport Code Version 5, Los Alamos National Laboratory, Los Alamos, NM, 2003.
- ⁷G. M. Daskalov, E. Löffler, and J. F. Williamson, "Monte Carlo-aided dosimetry of a new highdose-rate brachytherapy source," *Med. Phys.* **25**, 2200–2208 (1998).
- ⁸M. J. Rivard, B. M. Coursey, L. A. DeWerd, W. F. Hanson, M. S. Huq, G. S. Ibbott, M. G. Mitch, R. Nath, and J. F. Williamson, "Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations," *Med. Phys.* **31**, 633–674 (2004).
- ⁹D. Granero, J. Vijande, F. Ballester, and M. J. Rivard, "Dosimetry revisited for the HDR ^{192}Ir brachytherapy source model mHDR-v2," *Med. Phys.* **38**, 487–494 (2011).
- ¹⁰F. J. Casado, S. García-Pareja, E. Cenizo, B. Mateo, C. Bodineau, and P. Galán, "Dosimetric characterization of an ^{192}Ir brachytherapy source with the Monte Carlo code PENELOPE," *Phys. Med.* **26**, 132–139 (2010).
- ¹¹C. W. Morgan, "Photo atomic data library MCPLIB04: A new atomic library based on data from ENDF/B-VI release 8," Report LA-UR-03-1019L-50400, Revision 5 (Los Alamos National Laboratory, Los Alamos, NM, 1997), Vol. 6.
- ¹²<http://www.nndc.bnl.gov/nudat2/>. NuDat 2.6, search and plot nuclear structure and decay data interactively, National Nuclear Data Center, Vol. 2012, Brookhaven National Laboratory, Brookhaven, NY, 2012, accessed on November 20, 2012.
- ¹³J. Perez-Calatayud, F. Ballester, R. K. Das, L. A. Dewerd, G. S. Ibbott, A. S. Meigooni, Z. Ouhib, M. J. Rivard, R. S. Sloboda, and J. F. Williamson, "Dose calculation for photon-emitting brachytherapy sources with average energy higher than 50 keV: Report of the AAPM and ESTRO," *Med. Phys.* **39**, 2904–2929 (2012).
- ¹⁴R. G. Dale and B. Jones, "The assessment of RBE effects using the concept of biologically effective dose," *Int. J. Radiat. Oncol., Biol., Phys.* **43**, 639–645 (1999).
- ¹⁵R. Zwicker, A. Meigooni, and M. Mohiuddin, "Therapeutic advantage of grid irradiation for large single fraction," *Int. J. Radiat. Oncol., Biol., Phys.* **58**, 1309–1315 (2003).
- ¹⁶M. Guerrero and X. A. Li, "Extending the linear quadratic model for large fraction doses pertinent to stereotactic radiotherapy," *Phys. Med. Biol.* **49**, 4825–4835 (2004).
- ¹⁷C. Herskind, J. Griebel, U. Kraus-Tiefenbacher, and F. Wenz, "Speher of equivalence—A novel target volume concept for intraoperative radiotherapy using low-energy x rays," *Int. J. Radiat. Oncol., Biol., Phys.* **72**, 1575–1581 (2008).
- ¹⁸A. Niemierko, "Reporting and analyzing dose distributions: A concept of equivalent uniform dose," *Med. Phys.* **24**, 103–110 (1997).
- ¹⁹H. Zhang, J. Z. Wang, N. Mayr, X. Kong, J. Yuan, N. Gupta, S. Lo, J. Grecula, J. Montebello, D. Martin, and W. Yuh, "Fractionated grid therapy in treating cervical cancers: Conventional fractionation or hypofractionation?," *Int. J. Radiat. Oncol., Biol., Phys.* **70**, 280–288 (2008).
- ²⁰E. P. Mailaise, B. Fetile, P. J. Daschanne, N. Chavaudra, and W. A. Brock, "Initial slope of radiation survival curves is characteristic of the origin of primary and established cultures of human tumor cells and fibroblasts," *Radiat. Res.* **111**, 319–333 (1987).
- ²¹H. Zhang, H. Zhong, R. Barth, M. Cao, and I. Das, "Impact of dose size in single fraction spatially fractionated megavoltage (grid) radiotherapy for melanoma," *Med. Phys.* **41**, 021727 (9pp.) (2014).
- ²²H. J. Withers *et al.*, "Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: Patterns of fractionation study of radiobiology," *Int. J. Radiat. Oncol., Biol., Phys.* **33**, 563–568 (1995).
- ²³B. Sorbe, B. Sorbe, A. Straumits, and L. Karlsson, "Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: A randomized study of two dose-per-fraction levels," *Int. J. Radiat. Oncol., Biol., Phys.* **62**, 1385–1389 (2005).
- ²⁴M. Mohiuddin, D. L. Curtis, W. T. Grizos, and L. Komarnicky, "Palliative treatment of advanced cancer using multiple nonconfluent pencil beam radiation," *Cancer* **66**, 114–118 (1990).
- ²⁵M. Mohiuddin, M. Fujita, W. F. Regine, A. S. Meigooni, G. S. Ibbott, and M. M. Ahmed, "High dose spatially fractionated radiation (grid): A new paradigm in the management of advanced cancers," *Int. J. Radiat. Oncol., Biol., Phys.* **45**, 721–727 (1999).
- ²⁶J. L. Huhn, W. F. Regine, J. P. Valentino, A. S. Meigooni, M. Kudrimoti, and M. Mohiuddin, "Spacially fractionated GRID radiation treatment of advanced neck disease associated with head and neck cancer," *Technol. Cancer Res. Treat.* **5**, 607–612 (2006).
- ²⁷G. Neuner *et al.*, "High dose spatially fractionated grid radiation therapy (SFGRT): A comparison of treatment outcomes with cerrobend vs. MLC SFGRT," *Int. J. Radiat. Oncol., Biol., Phys.* **82**, 1642–1649 (2012).
- ²⁸S. Nag, B. Erickson, S. Parikh, J. Fowler, N. Gupta, A. Martinez, and B. Thomadsen, "The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium," *Int. J. Radiat. Oncol., Biol., Phys.* **48**, 779–790 (2000).
- ²⁹H. S. Park, E. S. Ratner, L. Lucarelli, S. Polizzi, S. A. Higgins, and S. Damast, "Predictors of vaginal stenosis after intravaginal high-dose-rate brachytherapy for endometrial carcinoma," *Brachytherapy* **14**, 464–470 (2015).
- ³⁰L. A. DeWerd, G. S. Ibbott, A. S. Meigooni, M. G. Mitch, M. J. Rivard, K. E. Stump, B. R. Thomadsen, and J. L. Venselaar, "A dosimetric uncertainty analysis for photon-emitting brachytherapy sources: Report of AAPM Task Group No. 138 and GEC-ESTRO," *Med. Phys.* **38**, 782–801 (2011).
- ³¹C. Kirisits, M. J. Rivard, D. Baltas, F. Ballester, M. De Brabandere, R. van der Laarse, Y. Niatsetski, P. Papagiannis, T. P. Hellebust, J. Perez-Calatayud, K. Tanderup, J. L. Venselaar, and F. A. Siebert, "Review of clinical brachytherapy uncertainties: Analysis guidelines of GEC-ESTRO and the AAPM," *Radiother. Oncol.* **110**, 199–212 (2014).