Three-dimension anatomy-based planning optimization for high dose rate vaginal vault brachytherapy

Yasir A. Bahadur, FRCPC, ABR, Ashraf H. Hassouna, MSc, MD, Camelia T. Constantinescu, MSc, PhD, Adly F. Naga, BSc, MSc, Noor M. Ghasal, BSc, Mohamed E. Elsayed, MSc, MD.

ABSTRACT

الأهداف : عمل مقارنة بين التقدير الأمثل للتخطيط المعاكس الثلاثي الأبعاد وطرق التخطيط التقليدية الثنائية أثناء المعالجة الإشعاعية الموضعية الكثيفة ذات الجرعات العالية لقبو المهبل .

الطريقة : أُجريت هذه الدراسة في وحدة العلاج الإشعاعي، مستشفى جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من يوليو 2010م إلى أكتوبر 2011م. شملت هذه الدراسة الموضعية 26 مريضة مصابة بسرطان بطانة الرحم واللاتي عولجن بحزم العلاج الإشعاعي وتبع ذلك المعالجة الإشعاعية الموضعية الكثيفة ذات الجرعات العالية لقبو المهبل . ولقد قمنا بتحليل مُنسج أحجام الجرعات لثلاثة برتوكولات لوصف الجرعات وذلك لكل جزء من أجزاء المعالجة الإشعاعية الموضعية الكثيفة وهي كالتالي : 0.5 سم من قمة أسطوانة العلاج، و0.5 سم من السطح الخارجي الجانبي لاسطوانة العلاج، والتخطيط المعاكس .

النتائج : أظهر تحليل مُنسج أحجام الجرعات اختلافاً كبيراً من الناحية الإحصائية (p<0.001) بين طرق تخطيط العلاج الثلاثة وذلك فيما يخص مقدار تغطية الجرعات لأحجام المواضع السريرية المستهدفة : 26.7%±5.4% مقابل 48.5%±6.7% مقابل 68.6%±7.5%. وكانت جرعات أحجام 2 سم³ للأعضاء المعرضة للخطر كالتالي (p<0.001) : المستقيم : 4.6±1.1 مقابل 2.8±0.5 مقابل 3.3±0.5 جراي، والجوف السيني الصغير للزند : 1.4±0.8 مقابل 0.7±0.3 مقابل 0.9±0.5 جراي، والمثانة : 3.7±1.0 مقابل 2.3±0.5 مقابل 7±0.6. جراي .

خاتمة : أظهرت هذه الدراسة بأن للتخطيط المعاكس الثلاثي الأبعاد القدرة على موازنة تغطية الجرعات للمواضع المستهدفة وتجنيب الأعضاء المعرضة للخطر. وفيما يخص التخطيط المعاكس الثلاثي الأبعاد أثناء المعالجة الإشعاعية الموضعية الكثيفة ذات الجرعات العالية لقبو المهبل فإن استخدام الأشعة الطبقية فحسب للجزء الأول من العلاج يعد سهلاً، كما أن تأثير قياس الجرعات يعد محدوداً.

Objectives: To retrospectively compare 3-dimension (3D)-inverse planning optimization with 2 conventional planning methods in vaginal vault high-dose-rate brachytherapy.

Methods: We randomly selected 26 patients with endometrium cancer, treated with external beam radiotherapy followed by intracavitary high-dose-rate brachytherapy. The study was carried out in the Radiotherapy Unit of King Abdulaziz University Hospital, Jeddah, Saudi Arabia between July 2010 and October 2011. For each brachytherapy fraction, dose-volume-histograms were analyzed for 3 different dose prescription protocols: 0.5 cm from the applicator's tip, 0.5 cm along the applicator's surface, and inverse planning.

Results: Dose-volume-histogram analysis showed a significant difference ($p<0.001$) between the 3 treatment planning methods regarding clinical-target-volume prescribed dose coverage: 26.7%±5.4% versus 48.5%±6.7% versus 68.6%±7.5%. The doses received by the volumes of 2 cm³ of organs-at-risk were ($p<0.001$): rectum: 4.6±1.1 Gy versus 2.8±0.5 Gy versus 3.3±0.5 Gy; sigmoid: 1.4±0.8 Gy versus 0.7±0.3 Gy versus 0.9±0.5 Gy; and bladder: 3.7±1.0 Gy versus 2.3±0.5 Gy, versus 2.7±0.6 Gy.

Conclusion: Three-dimension inverse planning provides the ability to balance the target dose coverage against the sparing of organs at risk. For vaginal vault high-dose-rate inverse planning brachytherapy, the use of a CT scan only for the first fraction of treatment is feasible, and the dosimetric impact is minimal.

High dose rate brachytherapy (HDR BT) was introduced by O'Connell et al[1] in the 1960s, and its use in endometrial carcinoma treatment was first reported in the 1970s by Joslin et al.[2] Late radiation reactions after HDR brachytherapy are serious concerns, especially when the patients are young and sexually active. The risk of late reaction depends on the dose received by the nearby critical organs (bladder and rectum). Dose optimization is an old concept in brachytherapy practice, but just recently became a topic for extensive study, due to technological advances in both treatment planning systems and 3-dimension (3D) imaging possibilities, as CT and magnetic resonance. In 2000, the American Brachytherapy Society (ABS) reported the recommendations on HDR BT for post-operative endometrial carcinoma treatment, establishing dose prescription, and optimization guidelines, as well as dose fractionation schedules.[3] Although it was expected to influence the clinical outcome, yet to date there is no consensus regarding the dose prescription or optimization for these treatments. In clinical practice, a brachytherapy treatment plan is usually manually optimized, by either geometric or dose-point optimization methods, based on the location of the active dwells, but failing to use anatomical information. Recently, several anatomy-based inverse planning algorithms have been developed, driven by prescribed dose constraints on anatomic volumes.

The purpose of this study is to retrospectively compare 3D inverse planning optimization versus 2 conventional treatment planning methods, using various dosimetric indices in post-operative intracavitary HDR brachytherapy planning for endometrial carcinoma. This comparison is made by analyzing dose distributions to target and organs at risk (OARs) volumes. We have also looked if there is any patterns of loading the cylindrical vaginal applicator, resulting in an optimal fulfill of all dose constraints in the particular case of an inverse planning optimization methods.

Methods. We are reporting the analyzed data of 26 patients with carcinoma of the endometrium, randomly selected and identified as candidates for vaginal vault brachytherapy according to our current treatment practice. The patients were treated in the Radiotherapy Unit of King Abdulaziz University Hospital, Jeddah, Saudi Arabia between July 2010 and October 2011. All patients had post-operative external beam radiotherapy (45 Gy in 25 fractions, one fraction per day, 5 times per week) to the whole pelvis, using 4r-fields CT-based planning, followed by HDR brachytherapy (12 Gy in 3 fractions, one fraction per week). Brachytherapy was performed with cylindrical vaginal applicators of various diameters (2, 2.6, 3, and 3.5 cm), and to help delineating the bladder and rectum, a 20 cc of contrast media (diluted urographine) is injected into the bladder and 35 cc into the rectum. Computerized tomography images were acquired using a Siemens Somatom Emotion CT scanner, with 2 mm slice intervals from the iliac crest to the ischial tuberosities, without intravenous contrast.

Target and OARs delineation. The clinical target volume (CTV) and the OARs volumes have been delineated on axial CT images for each patient and each brachytherapy fraction prospectively, at the time of each treatment planning, and reviewed retrospectively by one radiation oncologist, for the purpose of this study. The CTV was nominally a 5 mm expansion of the applicator surface along 5 cm length measured from the top of the applicator dome. Organ at risk volumes included the bladder, rectum, and sigmoid. The outer wall of the rectum was contoured from the rectosigmoid junction until 1 cm above the anal verge, the outer wall of the sigmoid was contoured from the rectosigmoid junction until the level of the sacral promontory and the outer wall of the bladder was contoured to the urethra. Computerized-tomography-based planning was performed in Varian Brachyvision planning system, version 8.9.15 (Varian Medical Systems, Palo Alto/CA, USA), for a brachytherapy remote after loader Varian HDR VariSource iX (Varian Medical Systems, Palo Alto, CA, USA). The dose calculation algorithm is based on the TG-43 formalism, as recommended by the American Association of Physicists in Medicine (AAPM).[4]

For each patient and each brachytherapy fraction, 3 treatment plans were considered, and dose distributions were calculated according to 3 different dose prescription protocols, as following: (a) 0.5 cm from the applicator tip calculation protocol is a conventional treatment planning method, prescribing the dose at 0.5 cm from the top of the applicator dome and using one dwell position at the tip of the applicator. This was our current dose prescription methods. (b) 0.5 cm along the applicator surface is used as an alternative conventional planning method, prescribing the dose at 0.5 cm along the applicator surface and using 9 dwell positions; the dwell times for the first and last dwell positions are 5 times higher than the rest of the dwell times. (c) Inverse planning after the volumes of interest are contoured, dose constraints are set, and an inverse planning algorithm is run to calculate the optimal dwell times that fulfill the dose constraints.

The dose constraints used in our study were: for CTV: 95% of the volume to receive 4 Gy and 100%

of the volume to receive 3.8 Gy (95% of the prescribed dose, as a minimum); for rectum and sigmoid: 2 cc of the volume to receive maximum 2.8 Gy (70% of the prescribed dose); and for bladder: 2 cc of the volume to receive maximum 3.2 Gy (80% of the prescribed dose).

All dose constraints were set to have the same priority. Dose distributions and dose-volume histograms from these plans were analyzed, and all plans were evaluated using the following indices: the dose covering 100% of volume ($D_{100\%}$) and the dose covering 95% of volume ($D_{95\%}$) for clinical target volume. For OARs, the doses received by the volumes of $1\,cm^3$ (D_{1cc}), $2\,cm^3$ (D_{2cc}), and $5\,cm^3$ (D_{5cc}), the volumes receiving 70% of prescription dose ($V_{70\%}$) were evaluated for both rectum and sigmoid, and the volume receiving 80% of prescription dose ($V_{80\%}$) was evaluated for bladder.

The statistical analysis was performed using the Wilcoxon matched pairs test and an in-house software; a p value of <0.05 was considered significant.

Additional consideration has been given to the inverse plans, in order to identify a possible pattern of loading of the cylindrical vaginal applicator. The dwell times normalized to the radioactive source activity and the values of the total reference air kerma (TRAK) for the inverse plans of all 3 fractions for each patient have been compared. The study was reviewed and approved by the Institutional Review Board.

Results. Dose distributions and dose-volume histograms were generated for the clinical target volume and organs at risk for all patients and all dose prescription protocols.

Figures 1 and 2 show a comparative example of conventional (0.5 cm from the applicator's tip and 0.5 cm along the applicator's surface) and 3D inverse plans, for a representative patient. The comparison is performed with respect to the dose distribution (**Figures 1a-1c**) and dose-volume histogram (**Figures 2a-2c**).

Dose-volume histogram analysis showed significant difference (*p*<0.001) regarding CTV prescription dose coverage among the 3 dose prescription protocols: average 26.7%±5.4% (95% CI: 25.5%-28%) if prescribing the dose at 0.5 cm from the applicator tip versus 48.5%±6.7% (95% CI: 46.9%-50%) for a prescribed dose at 0.5 cm along the applicator surface versus 68.6%±7.5% (95% CI: 66.9%-70.4%) if inverse planning was used. Ninety-five percent of the prescribed dose covered approximately 35.8%±6.9% (95% CI: 34.2%-37.4%), 83.4%±7.7% (95% CI: 81.7%-85.2%), and 106.7%±2.5% (95% CI: 106.1%-107.3%)of the clinical target volume for the planning methods analyzed (**Table 1**). For the organs at risk considered in this study, prescribing the dose at 0.5 cm along the applicator surface method provided the best sparing (*p*<0.001).
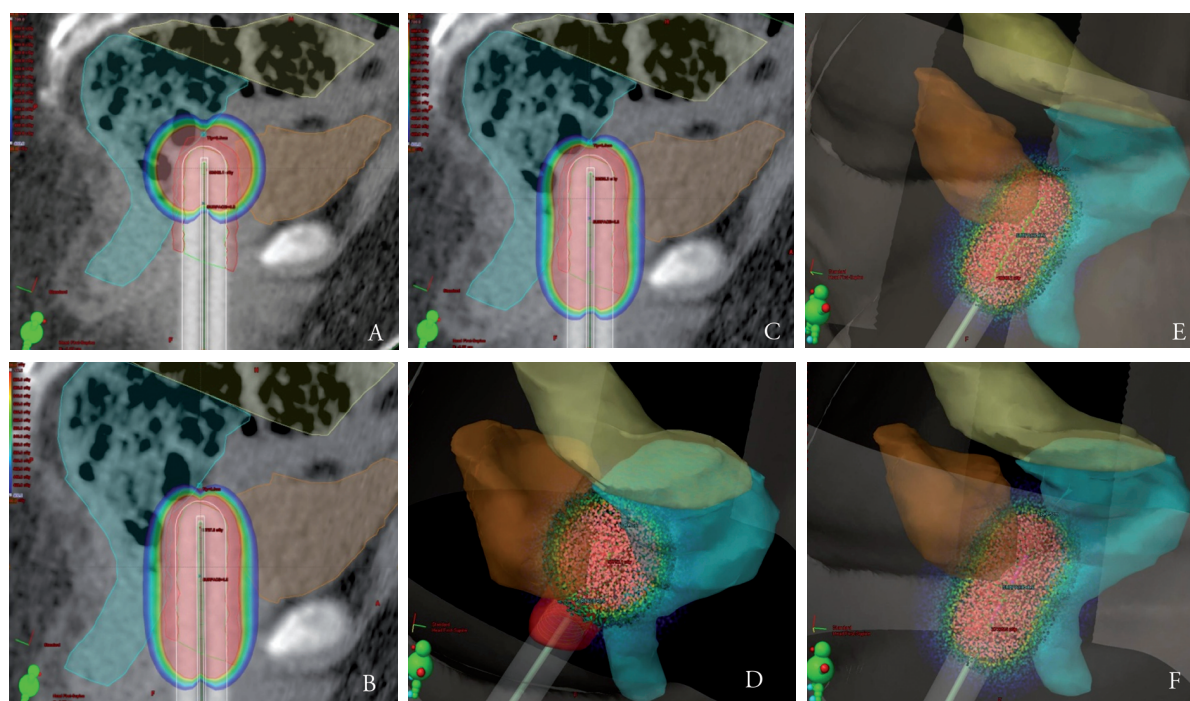

Figure 1 - Dose distribution for **A & B**) conventional, **C**) 3D inverse plans in sagittal, and **D**) 3D views

For D$_{2cc}$ of rectum, an average of 4.6±1.1 Gy (95% CI: 4.4 cGy to 4.9 cGy) resulted for a prescribed dose at 0.5 cm along the applicator's surface versus 2.8±0.5 Gy (95% CI: 2.8 cGy to 3.0 cGy) for prescribing the dose at 0.5 cm from the applicator's tip, and 3.3±0.5 Gy (95% CI: 3.2 cGy to 3.5 cGy) for inverse planning method. The average rectal volumes receiving 70% of prescription dose (V$_{70\%}$) were respectively 10.4±6.2 cc (95% CI: 9.0cc to 11.8cc), 3.1±2.5 cc (95% CI: 2.5 cc to 3.6 cc), and 5.9 ± 3.7 cc (95% CI: 5.0 cc to 6.7 cc) for the 3 planning methods investigated.
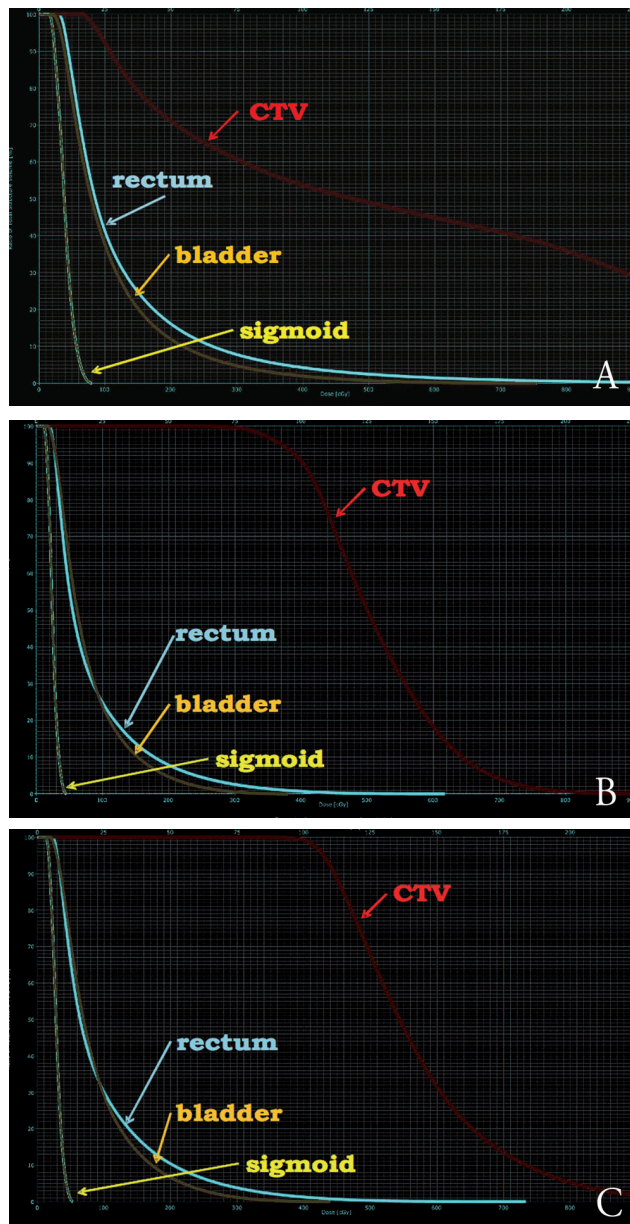
Figure 2 - Dose-volume histograms for **A & B**) conventional and **C**) 3D inverse plans.

For D$_{2cc}$ of sigmoid, an average of 1.4±0.8 Gy (95% CI: 1.2 cGy to 1.6 cGy) resulted for a prescribed dose at 0.5 cm along the applicator's surface versus 0.7 ± 0.3 Gy (95% CI: 0.6 cGy to 0.9 cGy) for prescribing the dose at 0.5 cm from the applicator's tip and 0.9 ± 0.5 Gy (95% CI: 0.8 cGy to 1.1 cGy) for inverse planning method. The average sigmoid volumes receiving 70% of prescription dose (V$_{70\%}$) were: 0.4±1.0 cc (95% CI: 0.2 cc to 0.7 cc), 0 cc (95% CI: 0.0 cc to 0.1 cc), and 0.0±0.2 cc (95% CI: 0.0 cc to 0.1 cc) for the 3 planning methods investigated.

For D$_{2cc}$ of bladder, an average of 3.7±1.0 Gy (95% CI: 3.5 cGy to 4.0 cGy) resulted for a prescribed dose at 0.5 cm along the applicator's surface versus 2.3±0.5 Gy (95% CI: 2.2 cGy to 2.4 cGy) for prescribing the dose at 0.5 cm from the applicator's tip and 2.7 ± 0.6 Gy (95% CI: 2.6 cGy to 2.9 cGy) for inverse planning method. The average bladder volumes receiving 80% of prescription dose (V$_{80\%}$) were: 5.1 ± 4.8 cc (95% CI: 4.0 cc to 6.2 cc), 0.3 ± 0.6 cc (95% CI: 0.2 cc to 0.4 cc), and 1.3 ± 1.7 cc (95% CI: 0.9 cc to 1.7 cc).

The values of the total reference air kerma (TRAK) and dwell times normalized to the radioactive source activity for the inverse plans of all 3e fractions for each patient have been compared, as an attempt to evaluate the pattern of loading of the cylindrical vaginal applicator. The TRAK showed a strong dependence with the size of the applicator used, and ranged from 0.17 to 0.18 cGym2 for 2 cm diameter applicator, from 0.20 to 0.23 cGym2 for 2.6 cm diameter, from 0.24 to 0.28 cGym2 for 3 cm diameter, and from 0.28 to 0.29 cGym2 for 3.5 cm diameter (**Figure 3**).

For a given applicator diameter, the TRAK varied from patient to patient within the ranges mentioned above, as a result of the dose distribution optimization process. However, for a selected patient, the TRAK was relatively constant from fraction to fraction. We could identify a patient related loading pattern of the vaginal applicator (**Figure 4**), and observe that this pattern is as strong as the standard deviation of TRAK is small.

Discussion. Brachytherapy has been a standard component of therapy for carcinoma of the endometrium for over 100 years. As the use of anatomy-based treatment planning for HDR brachytherapy becomes more widely used, a systematic method of dose optimization is important for quality assurance, reproducibility, and respect of the clinical issues. As yet, there is insufficient data regarding the normalization and optimization rules in vaginal cuff brachytherapy. In practice, different types of target dose prescription are used, while the normalization is based on reference points. Following

Table 1 - Comparison of dose optimization methods in high dose rate (HDR) vaginal vault brachytherapy.

| Methods	HDR	0.5 cm from tip (a) Mean±SD	0.5 cm along surface (b) Mean±SD	Inverse planning (c) Mean±SD	P-value (a-b)	P-value (a-c)	P-value (b-c)
Clinical target volume	$D_{100\%}$ (%)	26.7±5.4	48.5±6.7	68.6±7.5	0.0004	0.0001	0.0005
	$D_{95\%}$ (%)	35.8±6.9	83.4±7.7	106.7±2.5	0.0003	0.0001	0.0005
	D_{1cc} (Gy)	5.3±1.3	3.1±0.5	3.7±0.5	0.0003	0.0006	0.0009
Rectum	D_{2cc} (Gy)	4.6±1.1	2.8±0.5	3.3±0.5	0.0003	0.0006	0.0008
	D_{5cc} (Gy)	3.6±0.9	2.3±0.5	2.8±0.5	0.0003	0.0006	0.0009
	$V_{70\%}$ (cc)	10.4±6.2	3.1±2.5	5.9±3.7	0.0001	0.0005	0.0007
	D_{1cc} (Gy)	1.7±1.3	0.8±0.4	1.0±0.6	0.0003	0.0005	0.0007
	D_{2cc} (Gy)	1.4±0.8	0.7±0.3	0.9±0.5	0.0002	0.0004	0.0009
Sigmoid	D_{5cc} (Gy)	1.1±0.6	0.6±0.3	0.8±0.4	0.0002	0.0006	0.0009
	$V_{70\%}$ (cc)	0.4±1.0	0.0±0.0	0.0±0.2	0.0001	0.0001	0.001
	D_{1cc} (Gy)	4.1±1.2	2.5±0.5	3.0±0.6	0.0003	0.0006	0.0009
	D_{2cc} (Gy)	3.7±1.0	2.3±0.5	2.7±0.6	0.0004	0.0007	0.0009
Bladder	D_{5cc} (Gy)	2.9±0.9	2.0±0.4	2.3±0.6	0.0003	0.0007	0.0009
	$V_{80\%}$ (cc)	5.1±4.8	0.3±0.6	1.3±1.7	0.0001	0.0001	0.0007
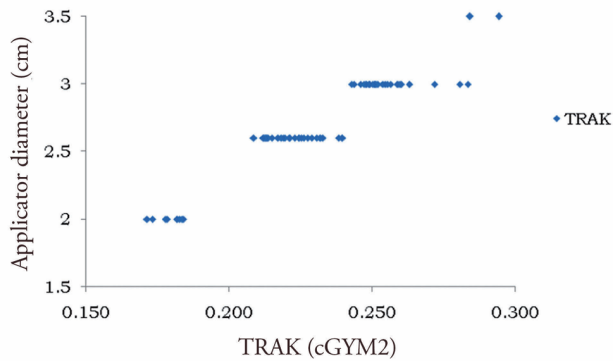
Figure 3 - Dependence of total reference air kerma (TRAK) with the applicator's diameter.

the recommendations of the American Brachytherapy Society HDR BT in endometrial cancer,[3] some centers have investigated various dose optimization methods, mainly applicator related and failing to use the patient anatomical information.[5-8]

Adapting a HDR vaginal brachytherapy plan to patient specific anatomy using cylindrical applicators is limited. Recent studies described attempts of anatomically optimized post-operative vaginal cuff HDR brachytherapy,[9-18] but with contradicting results. While Symon et al[9] shown that individual fraction optimization is important, in order to minimize doses to critical structures, other investigators[10,19,20] stated that the small inter-fraction variation in doses to the bladder and rectum do not support treatment planning and reporting doses to the OARs beyond the first fraction. In 2006, Small[14] concluded that the need for
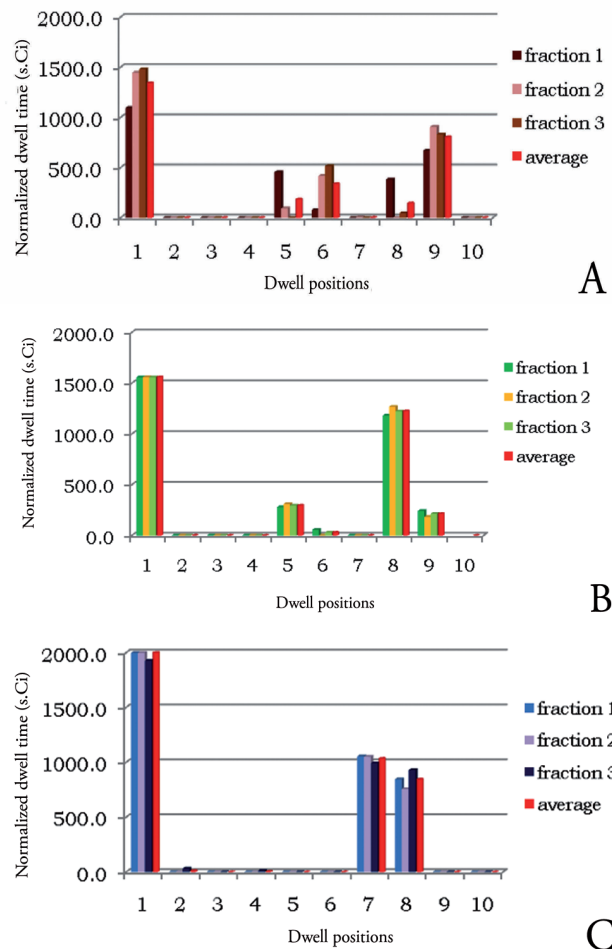

Figure 4 - The dwell times normalized to the radioactive source activity for the inverse plans of 3 representative patients, for the sizes of cylindrical vaginal applicator used: **A)** 2 cm, **B)** 2.6 cm, and **C)** 3 cm.

individualized fraction optimization for single channel vaginal cylinders is yet to be determined. Even by simply individualizing the depth of the reference dose in the vaginal mucosa according to its thickness, shortening the applicator's active length, and avoiding applicators with small diameters, the rate of reactions can be reduced without any significant increase in vaginal recurrences.[11,12,21] Yaparpalvi et al[16] analyzed the inter-fraction variations of cylindrical applicator insertion, as well as the fluctuations in bladder and rectal volumes, which have led to variations of bladder and rectal doses; they concluded that the dose to organs at risk should be assessed on individual fraction basis. Consequently, each fraction of vaginal cuff brachytherapy should be image-based, in order to achieve an accurate and complete dosimetric assessment of the treatment. The dose received by normal organs in the pelvis can vary considerably from fraction to fraction during the course of vaginal cuff HDR brachytherapy. A number of patient-based and technique-based factors, as: changes in bladder and rectum filling, inconsistencies in patient orientation, and differences in cylinder position within the vagina may contribute to this variation.[17,22] Contouring of critical organs on CT images and 3D dosimetric analysis provide a reliable method to elucidate the nature of these daily geometric variations,[17,23,24] despite a large inter-observer variations that has been reported.[25] Siddiqui et al[17] showed that over a series of patients, such variations result in an increased volume of rectum receiving a percentage of the prescribed dose, but over the course of multiple fractions for an individual patient, this effect is dosimetrically averaged out.

The current literature is scarce in studies comparing 3D inverse planning optimization versus conventional treatment planning methods of prescribing dose for a cylindrical vaginal applicator in HDR brachytherapy of endometrial cancer. The 3D inverse planning optimization method proved to be superior to conventional treatment planning regarding the CTV coverage. However, prescribing the dose at 0.5 cm along the applicator's surface method provided the best sparing for the organs at risk. In the case of inverse planning, all dose constraints (CTV coverage and OARs sparing) were set to have the same priority. Ultimately, the ability to balance the target dose coverage against the protection of organs at risk is improved and the focus becomes the physician's prescription to the target and the adjustments required to limit injury to normal structure, adapted to individual clinical circumstances. The inverse planning approach opens the path for image-guided brachytherapy of endometrial cancer following

a similar concept as the one developed by GYN-GEC ESTRO working group for cervical cancer[26,27] and applied by Dimopoulos et al for brachytherapy of locally advanced vaginal cancer.[28] Obviously, in order to systematically apply concepts of high-risk CTV and OARs, biological modeling, and dose-volume histogram analysis, a consensus is needed for the clinical target volume definition and dose prescription in brachytherapy of endometrial cancer. In PORTEC-2 trial, comparing vaginal brachytherapy to pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk, brachytherapy was delivered with a vaginal cylinder, with the reference isodose covering the proximal 1/2 of the vagina and the dose prescribed at 5 mm distance from the surface of the cylinder.[29] Similarly, our study considered as CTV the tissue of 0.5 cm thickness around the cylindrical vaginal applicator, along 5 cm measured from the top of the applicator's dome.

An obvious limitation of our study is the small number of patients data considered for analysis. Such a small sample size could not be valid if generalized at patient population level, and future studies with large sample sizes are recommended. The lack of a universal system of dose specification and reporting, as well as variation in treatment techniques for gynecological brachytherapy, has hampered the interpretation of data from different centers. The International Commission on Radiation Units and Measurements (ICRU) has attempted to address this problem in its Report No. 38.[30] In addition to reporting source strength, treatment time, cumulative total dose, and standard isodose contours, the report recommends reporting the TRAK for each treatment. The TRAK is defined as the product of air-kerma strength and dwell time, summed over all dwell positions in the implant. For HDR brachytherapy, TRAK is a useful parameter, since it remains constant for a fixed geometry implant, as the radioactive source decays.[31]

As dose-volume analysis of brachy therapy applications is becoming an important tool for evaluating the outcomes of treatment, several investigators attempted to find correlations between the volumes enclosed by isodose surfaces from TRAK and evaluate its utility to represent doses to organs of interest in the particular case of tandem and ovoids used for intracavitary brachytherapy of cervix cancer.[32-36] They demonstrated that the volume encompassed by a reference isodose surface was uncorrelated with individual implant linear dimensions, but strongly correlated with TRAK for all dose levels in the therapeutic range of interest, and concluded that TRAK can be used as a prognostic factor

for volume dose coverage.[32-35] However, the TRAK failed to correlate with rectal and bladder doses.[34] Even applied to the case of a cylindrical vaginal applicator, our study presents similar results: the TRAK of the inverse plans showed a strong dependence with the diameter of the applicator used, but for a given applicator size, varied from patient to patient, as a result of the dose distribution optimization process. Since the clinical target volume was defined as a geometrical structure in relation with the cylindrical applicator, and its volume is directly correlated to the applicator diameter, the results are not surprising, but further research studies are still needed. For any selected patient, the TRAK of the inverse plans was relatively constant from fraction to fraction. We used the TRAK as a predicting factor for a possible pattern of loading of the vaginal applicator and we could identify a patient related loading pattern, as strong as the standard deviation of TRAK was small. These findings demonstrate that the use of a CT scan only for the first fraction of vaginal cuff HDR inverse planning brachytherapy and apply the resulting dwell loading pattern to all the subsequent fractions is feasible, and the dosimetric impact is minimal. This can be beneficial for busy or limited resources departments, as the implications on the work load will be significant.

In conclusion, as the use of anatomy-based treatment planning for HDR brachytherapy for carcinoma of endometrium becomes more widely used, a systematic method of dose optimization is important for quality assurance, reproducibility, and respect of the clinical issues. The 3D inverse planning optimization method provides the ability to balance the target dose coverage against the sparing of organs at risk. The dosimetric gain achieved by inverse planning may reflect in patient treatment outcome. For the post-operative HDR inverse planning brachytherapy of endometrial carcinoma, the use of a CT scan only for the first fraction of vaginal cuff irradiation and apply the resulting dwell loading pattern to all the subsequent fractions is feasible, and the dosimetric impact is minimal.

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Case Reports

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically or printed on high-contrast glossy paper when submitting print copies. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.