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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Cervix cancer dosimetry

Vaginal dose point reporting in cervical cancer patients treated with combined 2D/3D external beam radiotherapy and 2D/3D brachytherapy

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ARTICLE INFO

Article history:

Received 16 December 2012
Received in revised form 3 March 2013
Accepted 5 April 2013
Available online 29 April 2013

Keywords:

Brachytherapy
Radiotherapy
Cervical cancer
Vagina
Dose reporting
Dose points

ABSTRACT

Background and purpose: Traditionally, vaginal dose points have been defined at the vaginal source level, thus not providing dose information for the entire vagina. Since reliable vaginal dose volume/surface histograms are unavailable, a strategy for comprehensive vaginal dose reporting for combined EBRT and BT was established and investigated.

Material and methods: An anatomical vaginal reference point was defined at the level of the Posterior-Inferior Border of Symphysis (PIBS), plus two points ± 2 cm (mid/introitus vagina). For BT extra points were selected for the upper vagina at 12/3/6/9 o'clock, at the vaginal surface and 5 mm depth. A vaginal reference length (VRL) was defined from ring centre to PIBS. Fifty-nine patients treated for cervical cancer were included in this retrospective feasibility study.

Results: The method was applicable to all patients. Total EQD2 doses at PIBS and ± 2 cm were 36.7 Gy (3.1–68.2), 49.6 Gy (32.1–89.6) and 4.3 Gy (1.0–46.6). At the vaginal surface at ring level doses were respectively 266.1 Gy (67.6–814.5)/225.9 Gy (61.5–610.5) at 3/9 o'clock, and 85.1 Gy (55.4–140.3)/72.0 Gy (49.1–108.9) at 12/6 o'clock. Mean VRL on MRI was 5.6 cm (2.0–9.4).

Conclusions: With this novel system, a comprehensive reporting of vaginal doses is feasible. The present study has demonstrated large dose variations between patients observed in all parts of the vagina, resulting from different contributions from EBRT and BT.

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The worldwide established standard treatment for patients with locally advanced (\geq FIGO stage IB2) cervical cancer is definitive radiotherapy in combination with chemotherapy. Intracavitary brachytherapy (BT) plays an essential role in the curative treatment. According to the gynaecological (GYN) GEC-ESTRO guidelines [1,2] the D0.1 cm³ and D2 cm³ of the major organs at risk (OAR), i.e. bladder, rectum and sigmoid, were suggested to be reported at time of BT. Dose constraints for these OAR have been reported and established for rectum and bladder [3,4]. However, the clinical situation is different for the vagina as it is at the same time target organ and organ at risk. Especially the upper vagina is frequently treated to high doses, as it is directly adjacent to the macroscopic tumour. In case of no or minimal involvement of the vagina, however, there is no rationale to include large parts of the non-adjacent part of the vagina.

Vaginal morbidity after radiotherapy has not been extensively investigated so far and the upper vagina has been referred to as “radioresistant” [5,6]. Nevertheless, it has been documented that radiotherapy could lead to (sub-) mucosal changes like atrophy, fibrosis, telangiectasia and fragility, and as a consequence to shortening and tightening of the vagina. In addition, even ulceration, necrosis and fistulae may occur [5,7,8]. Fortunately, a low incidence of severe vaginal toxicity \geq grade 3 of 1–7% has been reported [6,9–12]. On the other side, sexual dysfunction, diminished lubrication and pain during sexual intercourse, associated with a significant impact on quality of life, are frequently reported by patients after treatment for cervical cancer [13–15]. It can be assumed that dose–effect relationships exist for both vaginal morbidity and patient reported symptoms/quality of life. Only one study has investigated the correlation between DVH parameters (D2 cm³) and vaginal toxicity. However, no dose–effect relationships could be established for the upper vagina [16].

The assessment of the vaginal dose and dose distribution seems to be challenging due to the large sensitivity for geometrical changes in the high-dose regions of the upper vagina due to steep dose gradients. In addition, uncertainties in the delineation and

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reconstruction of small wall volumes are still unsolved problems in the currently available treatment planning systems [17,18]. For reproducible and comprehensive reporting of doses to different longitudinal and circumferential parts of the vagina, a 3D vaginal dose map, in analogy to that introduced for reporting rectal dose distributions, has been suggested [19,20]. This vaginal dose map takes into account the contribution of EBRT as well as of BT. However, such advanced 3D dose reporting is far from being introduced into clinical practice. Thus, there is an urgent need for an easy-applicable, reliable 2D/3D reporting method for the dose distribution throughout the vagina. However, the currently used vaginal dose points at the surface and at 5 mm depth on the lateral surface of the ring or ovoids [21,22] do not give a good representation of the dose throughout the vagina. In addition, the surface points are located in the steep dose gradient region. Since it remains unclear where the target structures for the individual vaginal morbidity endpoints are located, additional dose points are needed at the level of the vaginal sources as well as throughout the lower parts of the vagina.

The aims of this study are:

- To find a straightforward and reliable representation of the dose throughout the vagina based on anatomic landmarks;
- To define dose points which can be used in both 2D (conventional radiography) and 3D (CT or MRI) brachytherapy planning;
- To establish a method which can be applied both for brachytherapy and external beam radiotherapy.

Material and methods

Sixty-five patients with cervical cancer FIGO stage IB2-IVA treated with definitive radiotherapy in the Department of Radiotherapy of the Medical University of Vienna were included in the present investigation. All patients participated in the EMBRACE study between August 2008 and March 2012. The EMBRACE study is an international prospective study on MRI-guided brachytherapy in locally advanced cervical cancer (www.embracestudy.dk). Complete datasets of 62 patients were available for analysis. Three additional patients were excluded since they were treated with pulse dose rate (PDR) brachytherapy.

All patients were treated with a combination of external beam radiotherapy (EBRT) and intracavitary +/- interstitial needles MRI-guided brachytherapy (BT). All patients were treated with a tandem-ring applicator. The EBRT prescribed dose was 45 Gy in 25 fraction of 1.8 Gy. HDR brachytherapy was performed in four fractions (in two applications) of 7 Gy. Details of this institutional protocol are described in detail elsewhere [23].

For EBRT 3D based CT-assisted treatment planning and fluoroscopic simulation was performed for all patients. A small radiopaque vaginal marker was inserted into the vagina to identify the vaginal top and the anatomical vaginal length on CT (Fig. 1A). For BT, orthogonal radiographs, CT and MRI with the applicator in place were available in all patients. MRI was used for image guided treatment planning, according to the GEC-ESTRO recommendations [24].

The Posterior-Inferior Border of the pubic Symphysis (PIBS) was chosen as an anatomic landmark as it is visible on radiographs, CT (Siemens) and MRI (T2 SE, 0.2 T, Siemens) (Fig. 1A and B). In addition, it represents the transition zone between the lower and middle third of the vagina (E-appendix I) [25]. Gynaecologists classify the vagina into three parts: (1) the upper third between the cervix and the level of the urethrovaginal junction; (2) the middle third between the level of the urethrovaginal junction and the level of the PIBS and (3) the lower third below the PIBS (Fig. 1A and B and E-appendix I) [25]. The PIBS

vaginal dose point served as a reference to define several further anatomical dose points along the vagina and also the vaginal reference length (VRL) (Fig. 1A and B). The PIBS vaginal dose point was defined 2 cm posterior from PIBS in the sagittal direction for EBRT and for BT at the point of this line where it crosses the applicator tandem (Fig. 1A). Additional vaginal dose points for EBRT were selected for every centimetre (PIBS + 3 cm until PIBS - 2 cm) and midVRL in the cranio-caudal body axis. For BT the same vaginal dose points were taken on the tandem axis which is assumed to represent the centre of the vagina. The PIBS - 2 point was regarded as indicator of the vaginal introitus, the PIBS + 2 point as indicator of the anatomical mid of the vagina [25]. The top of the vagina was depicted through the top of the radio-opaque marker in EBRT and for BT at the intersection between tandem and intravaginal source, which is by definition the centre of the ring.

For the high dose area at ring level additional dose points were taken in the (para-transverse) application orientation at 3,6,9 and 12 o'clock (surface and 5 mm depth) (E-appendix II). The clockwise circumferential assessment was also done in case of a measured dose ≥ 4.5 Gy ($\sim 70\%$ of the prescribed dose) in the tandem axis at the midVRL or ≥ 3.5 Gy ($\sim 50\%$ of the prescribed dose) at PIBS level. The length of the 85 and 60 Gy isodose lines was reported as measured on a (para-)coronal MRI from the cervical os along the vaginal axis until the 7 Gy and 3.5 Gy isodose lines, taking into account the total EBRT dose of 45 Gy (E-appendix II).

The vaginal reference length (VRL) was introduced as the distance between PIBS and the vaginal top to overcome the difficulty of defining the vaginal introitus, which is often not clearly identifiable on images (Fig. 1B). In BT VRL was measured between the PIBS and the ring centre. In addition, the distance from the centre of the ring to the cervical os was measured. The VRL in BT is assumed to provide a straightforward tool to assess the topography of the implant and surrogate vaginal length. In EBRT the VRL was measured at the mid-sagittal view of the multi-plane-reconstruction (MPR) of the planning CT.

The total dose was calculated by summing the total EBRT dose and four times the BT fraction dose (in EQD_{2,3 Gy}) for each point at the same level (e.g. PIBS) for each patient by applying the linear quadratic model ($\alpha/\beta = 3$ Gy and $T_{1/2} = 1.5$ h) [26].

The lower parts of the vagina were not always visible in the transverse view on the treatment planning system due to the MR scanning protocol. To be able to interpolate missing dose data, a dose profile was designed which takes into account individual VRL and loading pattern.

Descriptive statistics were used indicating mean, median, standard deviation and range.

Results

Patient characteristics are shown in Table 1. Twenty-eight (48%) of the patients had vaginal involvement to a greater or lesser extent. The median length of the vaginal involvement at diagnosis was 17.5 mm (5–70). At time of the first brachy-application, 12 (20%) patients still had vaginal involvement, however only one of the patients had infiltration of the vagina to the lower third. The median vaginal involvement at BT1 was 10 mm (10–60).

Median vaginal reference length (VRL) was 5.8 cm (3.0–8.7) on the planning CT for EBRT. At time of BT, VRL was 6.1 cm (1.6–11.0) on conventional radiographs and 5.6 cm (2–9.4) on MRI. The median distance from the centre of the ring to the cervical os was 0.5 cm (0.0–2.5).

Dose from EBRT, BT and summed dose in EQD_{2,3 Gy} are shown in Figs. 1A and 3 and E-appendix III. Almost all patients received full EBRT dose from the vaginal top until PIBS + 2 level (Fig. 1A). A wide

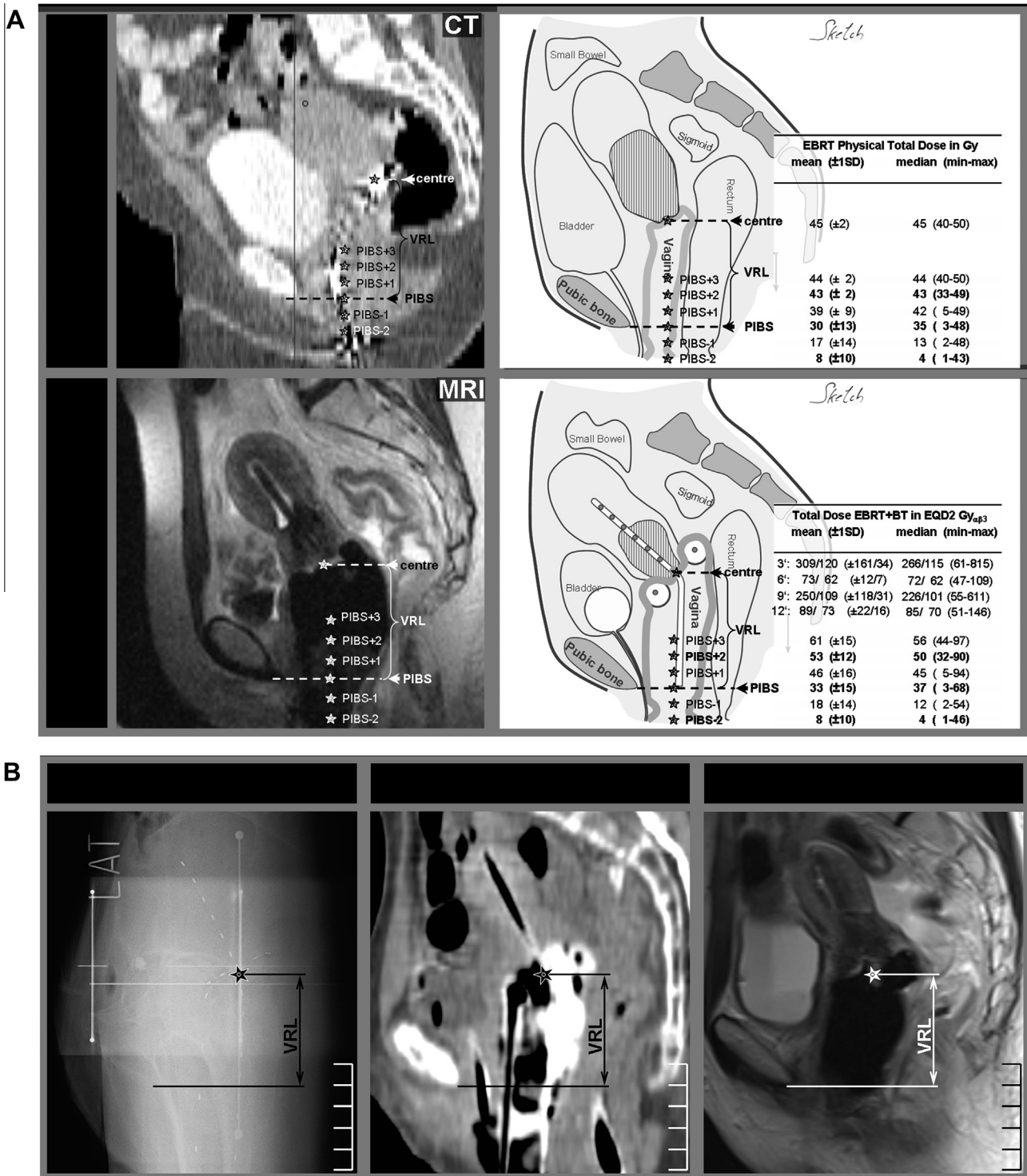


Fig. 1. Definition of vaginal dose points and vaginal reference length (VRL). (A) Vaginal dose points are defined in relation to a point at the level of the posterior–inferior border of the symphysis (PIBS) on sagittal (reconstructed) CT or MR images used for EBRT and BT treatment planning. The star at PIBS level represents the vaginal reference point. In the table on the right side mean (SD) and median (min–max) values are given for each level in EBRT and for total dose in EQD2. Additionally, total doses to the top are given for all four clockwise positions at the vaginal surface and 5 mm depth (e.g. median total dose at 3 o'clock is respectively 266 and 115 Gy for surface and 5 mm depth). (B) VRL at time of BT with a ring applicator in situ on a lateral radiograph, sagittal MPR CT image and sagittal MRI view. VRL is measured from centre of the ring (indicated by a star) to the PIBS level, indicated by the solid line orthogonal to the body axis.

range of dose was seen below the PIBS + 2 level, depending on the location of the field border. The field border was on average located 0.5 cm caudal from the PIBS, ranging from 2 cm cranial to 4 cm caudal.

Regarding the dose to the upper vagina at time of BT, dose to the lateral vaginal surface was ~2–3 times higher than to the anterior and posterior wall (Fig. 1A). Although known steep dose gradients at the vaginal surface at ring level, a good correlation between the

Table 1
Patient characteristics ($n = 59$).

| | |
|--|------------|
| Mean age (range) | 55 (32–82) |
| FIGO stage ($n, \%$) | |
| IB | 4 (7) |
| II | 43 (73) |
| III | 10 (17) |
| IVA | 2 (3) |
| Vaginal involvement at time of diagnosis ($n, \%$) | |
| No | 31 (52) |
| Upper third | 21 (36) |
| Middle third | 6 (10) |
| Lower third | 1 (2) |
| Vaginal involvement at BT1 ($n, \%$) | |
| No | 47 (80) |
| Upper two-third | 11 (18) |
| Middle third | 0 (0) |
| Lower third | 1 (2) |
| Bulky disease (>4 cm) ($n, \%$) | |
| No | 17 (29) |
| Yes | 42 (71) |
| Histology ($n, \%$) | |
| Squamous cell carcinoma | 51 (86) |
| Adenocarcinoma | 7 (12) |
| Other | 1 (2) |
| EBRT techniques ($n, \%$) | |
| 4-Field box | 54 (92) |
| IMRT | 5 (8) |
| BT with interstitial needles ($n, \%$) | |
| No | 24 (41) |
| Yes | 35 (59) |

surface and 5 mm depth vaginal dose at the upper vagina was seen (E-appendix IV). However, standard deviations were much smaller at 6/12 o'clock than at 3/9 o'clock (Fig. 1A).

Fourteen patients (24%) received a physical dose of ≥ 4.5 Gy per fraction to the vaginal surface at midVRL level (E-appendix V). In these patients, median doses up to 96.9 Gy (55.4–212.1) in EQD₂ Gy were seen at midVRL level, approximately corresponding to PIBS + 2 (data not shown). One of these patients had vaginal involvement of the lower third of the vagina (IIIA) with substantial residual disease at time of BT. The other thirteen patients had either no involvement ($n = 7$) or upper third involvement (IIA: $n = 6$) with small residual vaginal disease at time of BT. The VRL of these patients was 3.4 cm (2.0–5.2), which is 2.2 cm shorter than the VRL of the entire group.

Five patients (8.5%) received a dose of 3.5 Gy or higher to the vagina in the transitional zone from the middle to the lower third part (PIBS level). The median dose in these patients was 4.5 Gy (4.0–4.8) per fraction and total median dose in EQD₂ Gy 48.3 Gy (40.5–68.2). The median VRL was 2.4 cm (2.0–3.0). The median distance from cervical os to ring centre was 1.2 cm (0.5–2.6), which is 0.7 cm longer than the median length in the entire group.

The median length of the 85 Gy and 60 Gy isodose lines was 2.0 cm (1.0–3.0) and 3.0 cm (1.7–3.7), respectively.

Discussion

To date, despite frequently reported vaginal morbidity like dryness and sexual dysfunction, there is limited awareness of the vaginal dose in cervical cancer patients treated with definitive radio (chemo)therapy. Information on the dose to the mid or lower parts of the vagina is usually completely lacking, despite suggestions in literature that the lower part may be even more vulnerable to irradiation than the upper third of the vagina [5]. It therefore seems to be logical – in particular in the era of fast developing image guided radiotherapy – to relate vaginal morbidity to detailed and comprehensive dose volume information throughout the whole vagina. However, 3D DVH analysis has been shown to be critical to the vagina due to both major contouring and dosimetric uncertainties

[17]. In addition, dose volume/surface histograms are not available in the current brachytherapy treatment planning systems.

In order to improve this unsatisfactory situation within a clinically meaningful context, a straightforward easily applicable 2D point dose reporting method throughout the whole vagina has been introduced. An anatomical vaginal reference point, located 2 cm posterior from the Posterior–Inferior Border of the Symphysis (PIBS) was introduced. This PIBS reference point indicates the transitional zone from lower to middle third of the vagina according to long standing gynaecologic knowledge [25]. This pelvis diaphragm level also indicates the location of part of the clitoris and the anal sphincter [27]. The dose to the vaginal introitus and to the mid of the vagina can be calculated starting from this reference point. It was selected as respectively 2 cm below and above PIBS level. The level of the mid vagina also represents the region of the vesico-urethral junction (E-appendix I) [25]. Dose points in the upper vagina were selected along the long standing MD Anderson and ABS tradition at the level of the vaginal sources (ring level) [21,22] and extended to the positions at 12 and 6 o'clock in order to assess the dose inhomogeneity in the upper vagina. No extra dose points for the upper vagina were selected for EBRT as dose was assumed to be represented by the target dose. Our experience suggests this method as a straightforward easily applicable clinical method by which a dose profile throughout the entire vagina can be obtained for the individual patient (Fig. 2).

In most patients the EBRT dose was at least 95% of the prescribed dose (45 Gy) for the upper two-third of the vagina. This is due to the fact that the upper half of the vagina is included in the CTV for EBRT. Due to PTV margins of 1–2 cm, the lower border of the EBRT field is on average located 0.5 cm below the PIBS. This can also be assumed for 2D EBRT in general, since the caudal field border along long standing traditions is placed at the lower border of the obturator foramina which is at the level of the PIBS [22,28].

BT doses are very high in the upper vagina with large dose variation. They are most pronounced in the lateral parts when using the ring applicator with median surface doses of 15.3 and 13.7 Gy (left/right). The contribution of BT is smaller in the lower parts of the vagina, but nevertheless may become considerable in some individual patients with maximum doses per fraction up to 6.4 Gy in the anatomical mid vagina (PIBS + 2), 4.8 Gy at PIBS and 2.7 Gy at introitus level.

The sum of the EBRT and BT doses provides a good overview of the dose throughout the vagina. For the anatomical mid vagina (PIBS + 2) median dose in the centre of the vagina was 50 Gy, mainly coming from EBRT (Figs. 1A and 3). However, the variation is significant with maximum doses of 90 Gy (Figs. 1A and 3). For the transition zone from middle to low vagina (PIBS level), the median total dose is 37 Gy with the major contribution from EBRT, which is also true for the vaginal introitus level (median 4 Gy) (Figs. 1A and 3). For both levels a considerable dose variation has been seen with maximum doses of 68 and 47 Gy for PIBS and PIBS–2 level, respectively. This variation may come from both EBRT and BT (Fig. 1A, E-appendix III).

Patients with vaginal involvement of the middle or lower third of the vagina (extensive stage IIA, IIIA) receive an intermediate to high dose to the whole vagina due to external beam radiotherapy and in case of residual disease at the time of BT due to additional treatment by BT. Consequently, these patients have a higher chance of entire vaginal occlusion or other grade 3 or 4 vaginal toxicities compared to those patients without extensive (residual) vaginal involvement. In addition, if the vaginal reference length is relatively short (VRL <4 cm), the middle third of the vagina also receives a high dose which may even spread to the lower third. Interestingly, adjacent structures like bladder neck, urethra, ano-rectal region and clitoris also receive a significant dose under these circumstances. The same is true if the applicator cannot be placed

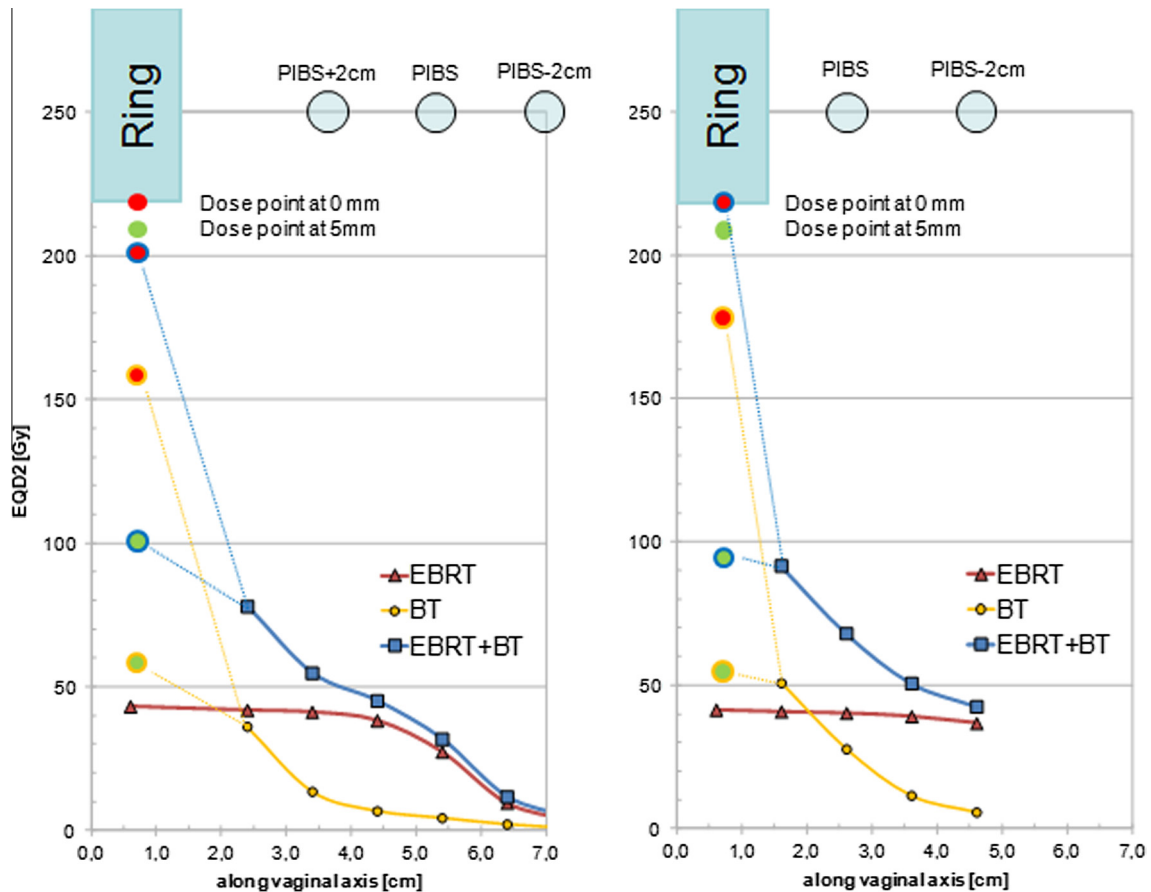


Fig. 2. Vaginal dose profile for two different cases showing the contribution of EBRT and BT dose to the total dose in EQD₂. The x-axis starts at the upper vaginal surface and continues in caudal direction along the central axis of the vagina. PIBS and PIBS±2 cm points are shown. At the level of the ring source path, a point at the applicator surface (red) and in 5 mm depth (green) is indicated. The left case had dose values as well as a VRL closest to the median values of all analysed cases and is therefore illustrate a representative situation. The lower field border of EBRT is located close to PIBS, at a distance of 5.4 cm from the upper vaginal surface. The right case shows a situation with PIBS very close to the ring applicator. Definition of PIBS + 2 cm is not applicable anymore. EBRT dose is substantially higher at PIBS as well as PIBS–2 cm compared to the “median” case at the left. (For interpretation to colours in this figure, the reader is referred to the web version of this paper.)

at the vaginal top. Relatively high doses (up to ~70 Gy EQD₂) to this part of the vagina were seen in almost one quarter of our patients. Only 7/14 patients had vaginal involvement and the majority of them (6/7) limited to the upper third at time of BT.

As long as 3D vagina assessment tools such as vaginal dose maps or vaginal surface histograms are not incorporated into the currently available treatment planning systems and basic difficulties with the thin vaginal wall delineation are not solved, vaginal dose points should be used as surrogate for evaluation of the spatial dose distribution in the upper vagina, and the dose in the middle and lower parts of the vagina. In EBRT and BT the doses at the PIBS and PIBS ± 2 cm levels should be reported to achieve an overall dose profile for the lower half of the vagina, since these levels correspond to important anatomic levels of the vagina, namely the transitional zones to respectively the mid and lower third of the vagina (E-appendix I). In addition, for EBRT especially PIBS and PIBS–2 cm seem to be important to report, because these points give an estimation of the location of the field border and consequently an indication if the entire vagina is irradiated or not (Fig. 1A and 3). Furthermore, for BT especially the dose at PIBS and PIBS + 2 cm seems important to indicate the location of the transitional zone from very high to intermediate dose (Figs. 1A and 2 and E-appendix III). In BT the following additional dose points should be reported at the level of the vaginal sources, namely at 12, 3, 6 and 9 o'clock at the surface and 5 mm depth (Fig. 3). Due to uncertainties of the exact location of the vaginal

source and/or wall and steep dose fall-off nearby the sources, the surface dose points seem to be more prone to uncertainties in dose assessment than the 5 mm depth dose points. Standard deviations of the dose at 5 mm depth are small and thus perhaps better predictors for vaginal toxicity. This should however be investigated in a prospective vaginal morbidity study.

Although the anatomy of the vagina is different during EBRT from BT due to vaginal packing, vaginal reference length did not differ at time of EBRT and BT. This is probably due to different methods for indicating the vaginal top (posterior fornix in EBRT versus cervical os in BT). Vaginal packing mainly stretches the vagina in lateral direction in the mid part of the vagina. Consequently, doses from EBRT and BT to the vaginal top, PIBS and PIBS–2 cm can be safely summed. There are however some uncertainties about the PIBS + 2 cm level. In addition, some uncertainties are present about the dose to the vagina during EBRT. It is known that, at least in postoperative patients, the vagina can move considerably [29].

In conclusion, the suggested vaginal dose points and length measurements can be easily introduced in clinical practice and provide an overview of the spatial dose distribution resulting from EBRT and BT in the upper vagina and the dose in the middle and lower vagina. We also have shown that these dose points are distinctive, since considerable differences are revealed in the study patient population despite using a fixed institutional protocol. Further research is needed to investigate if the proposed dose points

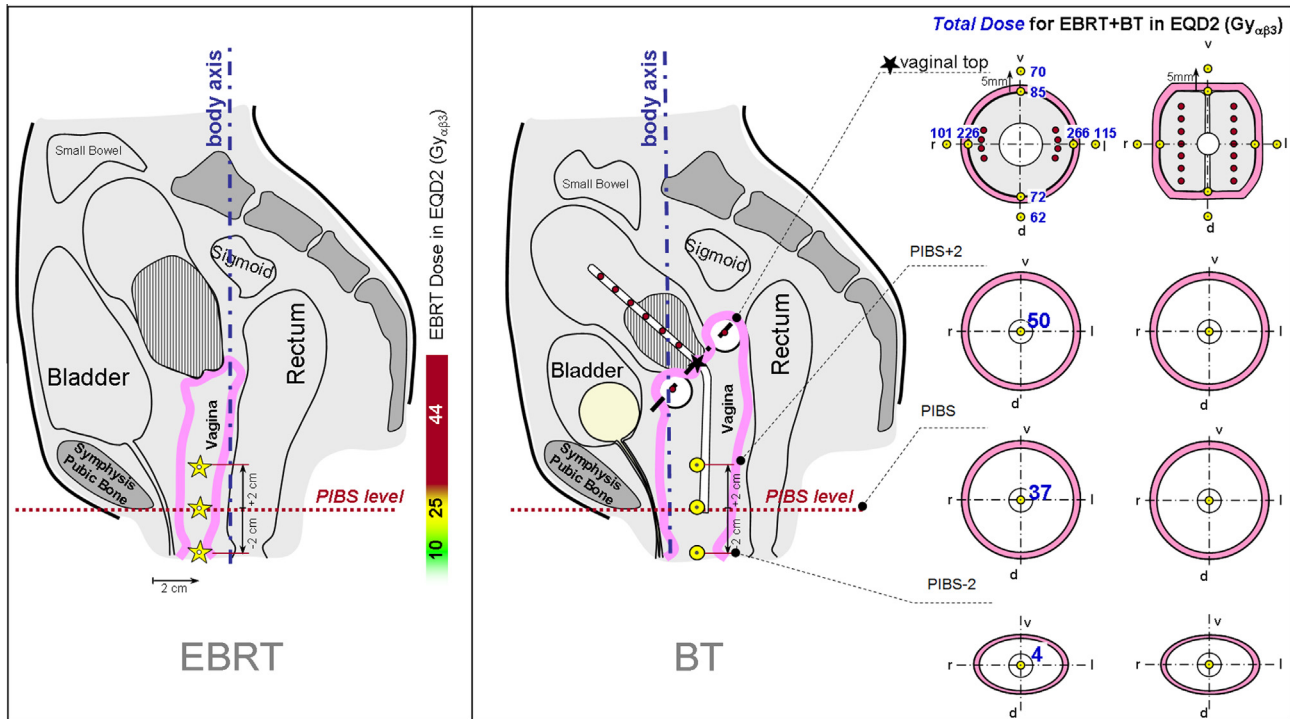


Fig. 3. Para-sagittal and para-transverse schematic representation for ring and ovoid applicator of the recommended vaginal dose points (yellow dots) at time of EBRT and BT. Four levels are indicated (mentioned in cranial-to-caudal direction): (1) vaginal top level which represents the level at the intersection of the intrauterine source and the centre of the ring or ovoid sources along the vaginal source axis; (2) PIBS + 2 which represents the anatomical mid of the vagina (3) PIBS level which represents the transitional zone from mid to lower third of the vagina and (4) PIBS-2 level which represents the introitus level. On the right side of the schematic EBRT figure the dose gradient along the vaginal axis is shown. On the right side of the schematic BT figure the median total doses in each recommended dose point is given. (For interpretation to colours in this figure, the reader is referred to the web version of this paper.)

are applicable and useful for different applicators, different planning systems and different dose rates within various institutional protocols. Ultimately, such points may contribute to find dose-effect relationships when correlated to various vaginal morbidity endpoints.

Conflicts of interests

The Department of Radiotherapy at the Medical University of Vienna receives/received financial and/or equipment support for research and educational purposes from Nucletron B.V. an Elekta Company, and Varian Medical Systems, Inc. C Kirisits is a consultant to Nucletron.

Acknowledgments

The stay of G.H. Westerveld at the Department of Radiotherapy of the Medical University of Vienna (Austria) was supported by a grant of the Dutch Cancer Association (grant number AMC2011-4963). The stay of P. Dankulchai at the Department of Radiotherapy of the Medical University of Vienna (Austria) was supported by a grant of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok (Thailand).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2013.04.009>.

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