DOSIMETRIC INFLUENCE OF UTERUS POSITION IN CERVIX CANCER HIGH-DOSE-RATE BRACHYTHERAPY

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Brachytherapy is an integrating component for the treatment of locally advanced cervical cancer. While most women present antverted or intermediary position uterus, only 20–25% have retroverted uterus. We evaluated 418 high-dose-rate brachytherapy plans of patients diagnosed with biopsy proven cervical cancer. Urinary bladder and rectal points were identified on the orthogonal digital X-ray images according to ICRU Report no.38. The brachytherapy plans were divided according to uterus position into three groups, antverted, intermediary and retroverted, respectively. The statistical analysis of the dosimetric data confirmed that uterus axis influences radiation doses received by the urinary bladder and rectum.

Key words: brachytherapy, cervix cancer, uterus position, rectum, urinary bladder, high-dose-rate, orthogonal simulator, image-guided, ultrasound, individualized applicator.

1. INTRODUCTION

Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. In Romania, considered the country with the highest World Age-Standardized incidence rates for cervical cancer from Europe, this malignancy represents, after breast cancer, the second most common cause of cancer death in women [1]. Starting the early 1900’s, radiotherapy is currently being used with curative intent in the management of cervical cancer. Because brachytherapy boost to external beam radiotherapy showed increased 5 year PFS, compared to external beam radiotherapy (EBRT) alone [2, 3], it became an integrating component for the treatment of locally advanced cervical cancer (stages IB2 to IVA) [4].

Regarding its axis and position, the uterus assumes anteverted position in 50% women, retroverted position in 25% women whilst the rest have midposed uterus [5]. For patients with gynecologic malignancies undergoing uterine brachytherapy, uterus position and axis are essential to the depth-dose parameters and of the procedure risks. The purpose of this study was to evaluate how the position and axis of the uterus, in cervix cancer biopsy proven patients, influence radiation exposure for the organs at risk during HDR intrauterine brachytherapy procedure.

2. MATERIALS AND METHODS

We evaluated the medical records of 723 patients with uterine cancer treated in our department between January 2013 and December 2014. From those, 218 patients were enrolled in this study based on the following inclusion criteria: biopsy-proven cervical cancer, stage IB1-IVB (according to International Federation of Gynecology and Obstetrics (FIGO) 2009 staging guidelines) and preoperative radiotherapy. Pre-therapeutic examination consisted of: initial clinical examination, complete blood count, liver and renal function assessment, chest X-ray and abdominopelvic CT/MRI. Uterine axis and position were also assessed clinically and radiological.

2.1. TREATMENT SCHEME

All patients underwent pelvic EBRT using a four-field box technique with CT-based treatment planning to a median total dose of 50.4 Gy (37.8 Gy–60.4 Gy). Thirty two patients needed para-aortic nodal radiotherapy. For 78 patients concurrent weekly Cisplatin chemotherapy was used. After EBRT completion all patients received HDR \(^{192}\)Ir brachytherapy using GammaMedplus iX HDR afterloader unit.

2.2. BRACHYTHERAPY PROCEDURE

Each procedure started by the insertion of a Foley catheter into the urinary bladder and the inflation of the catheter balloon with contrast and normal saline (7.0 ml). Before applicator positioning, cervical hysterometry was done, using a straight hysterometer with graduated cursor. The applicators used for the brachytherapy procedure were Fletcher-Suit Delcos-Style Applicator Set (Fig. 1) and Ring Applicator (Fig. 2). After applicator positioning, appropriate vaginal packing was done, in order to fix the applicator and also to push the bladder and rectum away from the vaginal applicators, and an endorectal catheter was inserted.
Fig. 1 – Iridium source Fletcher-Suit-Delcos applicators with half-ovoid pair colpostats.

Fig. 2 – Iridium source Ring applicator (left) and Ring & Tandem Combination Applicator Set (right).
Following that, orthogonal radiographs were taken in supine position (anteroposterior and lateral views) for conventional planning using a Simulix X-ray machine. On the X-ray images geometrical reconstruction of the applicator and point A, bladder and rectal reference points were identified (Fig. 3).

![Fig. 3 – Orthogonal digital anteroposterior (left) and lateral (right) X-ray images.](image)

Treatment planning was done using BrachyVision treatment planning system and the reference points were identified according to International Commission on Radiation Units and Measurements (ICRU) 38 protocol. Dwell positions optimization was used in order to minimize the dose to rectal and bladder points (Fig. 4).

![Fig. 4 – Isodose distribution obtained with Fletcher applicator (left) and Ring applicator (right).](image)

### 2.3. STATISTICAL ANALYSIS

Statistical analysis was done using IBM-SPSS v 20.0 software package. The three groups were compared two by two, calculating the means of two variables
using two-sample $t$-test. To assess the equality of variances for all variables calculated for the three groups, Levene’s test for the homogeneity of variance was used [6, 7]. Statistical analysis was completed by non-parametric Mood Independent Median Sample Test [8] as cited in [9], for mean and maximum values for the variables implied in the analysis.

3. RESULTS

There were analyzed 419 brachytherapy plans. The median number of applications per patient was 2 (range, 1–4 applications), while the median prescribed dose per fraction was 7.5 Gy (range, 5–30 Gy). According to uterine axis, plans were categorized into group 1 ($n = 51.78\%$), where uterus position was antverted, group 2 ($n = 39.63\%$), of patients with midposed uterus, and group 3 ($n = 8.59\%$), of patients with retroverted uterus (Fig. 5).

![Group 1 (anteverse), Group 2 (intermediary), Group 3 (retroverse)](image)

Fig. 5 – Brachytherapy plans.

The mean ICRU bladder point doses were the following: 239.7 cGy (median 238.9 cGy), 219.2 cGy (median 223 cGy) and 191.8 cGy (median 178.85 cGy), respectively, for group 1 (anteverted uterus), group 2 (intermediary uterus) and group 3 (retroverted uterus), respectively. We also calculated the maximum ICRU bladder point doses for the three groups and we identified the following results: 333.4 cGy (median 339 cGy) for group 1, 307.8 cGy (median 313.25 cGy) and 259.6 cGy (median 260.2 cGy) for groups 2 and 3, respectively.

The same variables were calculated for the ICRU rectal point’s doses. The following results were obtained when calculating mean ICRU rectal point doses: 137.8 cGy (median 136.3 cGy), 146.5 cGy (median 145.85 cGy) and 190.1 cGy (median 190.7 cGy), respectively, for groups 1, 2 and 3, respectively. We also calculated maximum ICRU rectal point doses for the three groups and the results were as follows: 298.3 cGy (median 306 cGy) for group 1, 315 cGy (median 321.8 cGy) for group 2, and 399.7 cGy (median 407.7 cGy) for group 3.
By statistical analysis of the resulted data we identified that for the mean ICRU bladder points there is a major decrease of dose starting from the highest values for brachytherapy plans of group 1, through the ones in group 2 and to the brachytherapy plans of the retroverted uterus ones (Fig. 6). Also, we have observed that the maximum ICRU bladder dose follows the same descending trend as the mean ICRU bladder dose.

Fig. 6 – Dosimetric comparison for ICRU bladder point radiation doses.

Regarding mean and maximum ICRU rectal points Fig. 7 shows an increase of radiation doses received starting brachytherapy plans from group 1, through the ones from group 2, the highest values corresponding to the brachytherapy plans from group 3.

Fig. 7 – Dosimetric comparison for ICRU rectal point radiation doses.
The differences, visible in the figures presented above, were tested using the methods presented in the Statistical analysis paragraph. By testing the mean and maximum doses of irradiation for the urinary bladder and rectum between the three groups, the differences proved to be statistically significant, independent of Levene’s Test for Equality of Variances. Also, by using t-test for equality of means between the three groups, grouped into pairs of two, statistically significant differences at a threshold value of 1% were obtained between the anteverted uterus (group 1) and retroverted uterus brachytherapy plans (group 3) for both ICRU rectal and bladder point doses.

The statistically significance between groups given by the position of uterus was sustained by the results when Mood Median Test was applied.

4. DISCUSSIONS

The purpose of our study was to identify if uterine position is an important factor in the distribution of the mean and maximum rectal and bladder ICRU 38 point doses.

Our data confirm that uterine position is responsible for differences of the mean and maximum ICRU rectal and bladder point doses between all the three brachytherapy plans groups.

Brachytherapy is an integral part of the treatment of cervical cancer. The imaging modality and the methods used for the reconstruction of the applicators are the main factors influencing the treatment planning for the delivery of radiation. Currently, orthogonal radiographs are used for treatment planning in our institution. Although published in 1985, the ICRU Report no. 38 recommendations [8] remain as the main reference and guideline for the brachytherapy of cervical cancer [9]. After the publication ICRU tumor and organ at risk (bladder and rectum) reference points were used for the definition of the doses in conventional brachytherapy plans. Over the past two decades multiple studies [10, 11, 12] critically reviewed and challenged the ICRU 38 recommendations for intracavitary brachytherapy in cervical cancer.

While most literature studies referring to cervix cancer brachytherapy are focusing on the significance image acquisition has for the treatment planning, there are limited literature data referring to the influence that the patients anatomy has for it.

Current literature studies [12, 13, 14, 15] that suggest the introduction of the image-guided brachytherapy procedure for the treatment of cervix cancer are comparisons between CT/MRI-based volumetric calculations and ICRU reference-point estimates of the radiation doses delivered to the bladder and rectum during this procedure. All these showed that compared to the image-guided technique, 2D brachytherapy underestimates the radiation dose to the organs at risk and
overestimates the radiation dose to the target volume. Considering this we expect that for the three groups from the current study the differences regarding the maximum bladder and rectal point doses are higher.

To our knowledge, there has been limited published data or literature available regarding the dosimetric comparison of uterine position and its influence on brachytherapy treatment planning in cervical cancers. Referring to uterine axis during radiotherapy, Huh et al. [16] published in 2004 a study in which at patients with cervical cancer, during radiation treatment positional changes of the uterus were detected. Other authors such as Taylor P. [17] have also found that large movements of the uterus can occur in both superoinferior and anteroposterior directions during radiotherapy. Mayr et al. [18] conducted a study on brachytherapy management by ultrasound-guided applicator placement for patients with retroverted uterus, the technique resulting in acceptable outcome and complication rates. Referring to the ultrasound guidance for the applicator placement Sahinler L et al. [19], as well as Small W Jr. et al.’s literature review [20] found that due to the high rate of uterine perforation, undetected by orthogonal radiographs, the use of real-time ultrasound should be considered for all uterine tandem insertions.

The present study brings forward the need for the evolution from the ICRU Report 38 point-based brachytherapy to an image based brachytherapy in the treatment of cervical cancer. Currently there exists a full range of brachytherapy products for the treatment of cervix cancer patients; therefore we would recommend ultrasound assessment of uterine position before applicator placement in order to improve the therapeutic outcome.

5. CONCLUSIONS

Our study suggests that uterine axis is an important factor in brachytherapy treatment planning. ICRU no. 38 rectal and bladder mean and maximal point doses varied according to uterus position, the rectum receiving significantly higher doses in case of retroverted uterus. Due to the limitations of the orthogonal X-rays in evaluating brachytherapy treatment planning rectal and bladder point doses we consider that continuing to use point A dose prescriptions is neither acceptable nor desirable. By considering patient anatomy, individualized applicator geometry and treatment planning, image-guided brachytherapy can be improved to personalized brachytherapy, which lowers even further the dose to the organs of risk with significantly dose distribution in the target volume.

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