Prolonged treatment planning can increase real rectal dose in 3D brachytherapy for cervical cancer

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Purpose
The purpose of this study was to evaluate the influence of 3D brachytherapy planning time on the real dose distribution.

Material and methods: 10 patients with cervical cancer were evaluated using 2 computed tomography (CT) scans brachytherapy. The first scan was performed after the insertion of UVAG applicators, and the second was done after creating the treatment plan, just before the irradiation of first and third fraction. Both plans were compared in terms of changes of volumes and differences in the dose for high-risk organs using GEC-ESTRO Working Group parameters.

Results: The median planning time was 54 minutes (36-64 minutes). The absolute median change of volume for bladder, rectum, and sigmoid was 32.1 cm³ (1.6-108.6 cm³), 5.6 cm³ (0.4-61.8 cm³), and 8.4 cm³ (0.2-74.1 cm³), respectively. This difference led to an increased dose for bladder and sigmoid for D0.1cc by 46.7 cGy and 25.7 cGy, for D1cc by 59.2 cGy and 11.8 cGy, and for D2cc by 44.7 cGy and 10 cGy, respectively, per each fraction. Measured volume change in case of rectum led to a decreased dose per each fraction for D0.1cc with 7.1 cGy, for D1cc by 59.2 cGy and 11.8 cGy, and for D2cc with 4.8 cGy. We observed that statistically significant dependency between the planning time and the dose was proved for rectum. The longer time for planning, the higher dose for rectum. The correlation coefficient for D0.1cc was 0.6715 (p = 0.0061), for D1cc was 0.6404 (p = 0.011), and for D2cc was 0.5891 (p = 0.0197).

Conclusions: Extended treatment planning time for brachytherapy due to the changes in topography of small pelvis can lead to different dose in high-risk organs than previously planned. It seems that the most significant changes are related to rectum.

Key words: cervical cancer, 3D brachytherapy, treatment planning.

Purpose
Cervical cancer is the most common gynecological malignancy, representing the fourth most common malignancy among women. Radiotherapy has been used for more than a century, with the first documented application of radium (Ra) performed in 1903, and the first cured patient reported in 1913. Radiation therapy is currently a method of choice in patients with early stage disease (I-IIA) and represents, in combination with chemotherapy, a standard treatment option for patients with locally advanced tumors.

Brachytherapy is an integral component of cervical cancer radiotherapy, significantly improving overall survival [1]. With technological progress and development of computed tomography/magnetic resonance (CT/MR) compatible applicators, 3D imaging was gradually implemented to brachytherapy treatment planning. The use of CT and MR images allow to determine the exact target volume and contours of organs at risk (bladder, rectum, and sigmoid), followed with targeted plan optimization using 3D images [2,3,4,5,6,7,8,9,10]. Shin reported the effect of imaging methods on final plan quality, aiming at conformity of targeted volume and contouring of organs at risk [7]. The positive effect of 3D brachytherapy using magnetic resonance on locoregional recurrence and overall survival was recently published by Pötter [3,11].

Gynecological GEC-ESTRO working group published the 3D brachytherapy recommendations related to determination of targeted volumes, planning concept based on the dose volume histogram parameters (DVH), reconstruction of applicators, and basic principles and parameters for MR imaging [12,13,14,15]. With these guidelines, the Gynecological GEC-ESTRO working group presented a common concept and terminology for different clini-
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In a confirmatory CT scan, the clinical target volumes and high-risk organs were contoured. Applicators were reconstructed and this plan consisted of stepping source positions based on the original plan. Twenty plans based on planning CT scans and 20 confirmation plans based on confirmatory CT scans were compared in terms of changes of volumes and differences in doses to high-risk organs. At the same time, the relation between planning time and dose to organs at risk were evaluated. Plans created in less than 54 minutes versus plans generated in 54 minutes or more were compared. To evaluate the doses for bladder, sigmoid, and rectum, the Gynecological (GYN) GEC-ESTRO working group doses parameters for 0.1 cm$^3$, 1 cm$^3$, and 2 cm$^3$ ($D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$) were used. The difference of dose between confirmation CT and planning CT for each dose parameter was assessed ($\Delta D$), and the correlation coefficient was used to evaluate this association. Additionally, the correlation coefficient was used to express a linear relationship between two random variables $X, Y$. The sample correlation coefficient $R_{X,Y}$ of random variables $X, Y$ is a number defined by the relation:

$$R_{X,Y} = \frac{S_{X,Y}}{S_X S_Y}$$

where

$$\bar{X} = \frac{1}{n} \sum_{i=1}^{n} X_i$$

is the average,

$$S_X = \frac{1}{n-1} \sum_{i=1}^{n} (X_i - \bar{X})^2$$

is the sample variance, and

$$S_{X,Y} = \frac{1}{n-1} \sum_{i=1}^{n} (X_i - \bar{X})(Y_i - \bar{Y})$$

is the sample covariance.

A $P$-value less than 0.05 was considered significant.

Results

The median planning time for performing planning CT scan and confirmatory CT scan before the irradiation was 54 minutes (range, 36-64 minutes). In 10 patients, planning time was less than 54 minutes and in 10 patients was 54 minutes or more.

The median volume of the bladder in the planning CT scan was 119.6 cm$^3$ and 141.0 cm$^3$ in the confirmatory CT. The absolute median change of volume was 32.1 cm$^3$ (range, 1.6-108.6 cm$^3$). This change represents a difference of 27.9% from the original volume (range, 0.96-155.5%). This difference led to an increased median dose for $D_{0.1cc}$ by 46.7 cGy, for $D_{1cc}$ by 59.2 cGy, and for $D_{2cc}$ by 4.8 cGy per each single fraction (Table 1, Figure 1A-C).

The median volume of rectum in the planning CT scan was 45.5 cm$^2$ and 41.6 cm$^2$ in the confirmatory CT. The absolute median change was 5.6 cm$^3$ (range, 0.4-61.8 cm$^3$), with a difference of 14.4% from the original volume. This volume change led to decreased dose per each fraction for $D_{0.1cc}$ of 7.1 cGy, for $D_{1cc}$ of 3.5 cGy, and for $D_{2cc}$ of 4.8 cGy (Table 1, Figure 2A-C).
The median volume of sigmoid in the planning CT scan was 33.7 cm$^3$ and 32.1 cm$^3$ in the confirmatory CT. The median absolute volume change was 8.4 cm$^3$ (range, 0.2-74.1 cm$^3$), corresponding to 26% (range, 0.8-428.7%).

The dose for sigmoid for D$_{0.1cc}$ was increased per each separate fraction by 25.7 cGy for D$_{0.1cc}$, 11.8 cGy for D$_{1cc}$, and 10.0 cGy for D$_{2cc}$ (Table 1, Figure 3A-C).

The relation between the planning time and the delta dose was evaluated. No significant changes were noted for sigmoid (R for D$_{0.1cc}$ was –0.2267, for D$_{1cc}$ –0.3482, and for D$_{2cc}$ –0.3184) and bladder (R for D$_{0.1cc}$ was 0.2067, for D$_{1cc}$ was 0.2637, and for D$_{2cc}$ was 0.2398). However, a statistically significant association between the planning time and delta dose was detected in all observed volumes for the rectum. The longer the planning, the higher the dose. The correlation coefficient for D$_{0.1cc}$ was 0.6715 ($p = 0.0061$), for D$_{1cc}$ was 0.6404 ($p = 0.011$), and for D$_{2cc}$ was 0.5891 ($p = 0.0197$).

The median absolute volume change for bladder, rectum, and sigmoid in plans created less vs. more than 54 minutes were 24.24 cm$^3$ vs. 32.26 cm$^3$, 6.25 cm$^3$ vs. 4.62 cm$^3$, and 8.44 cm$^3$ vs. 7.9 cm$^3$, respectively. The median delta dose between the original plans and actual plans for patients with a planning time more than 54 minutes and for women with shorter period of planning time than median was increased for rectum and bladder by 99 cGy and 91.9 cGy for D$_{0.1cc}$, 61 cGy and 52.1 cGy for D$_{1cc}$, and 29.8 cGy and 44.9 cGy for D$_{2cc}$ per each fraction. On the contrary, a decrease of dose for sigmoid by 133.96 cGy, 70.3 cGy, and 48.6 cGy, respectively, was observed.

**Discussion**

Image-guided CT/MR brachytherapy significantly improves therapeutic results for patients with locally advanced cervical cancer [11,16]. The Gynecological GEC-ESTRO working group has initiated the multicenter observational EMBRACE studies (“Image-guided intensity modulated external beam chemoradiotherapy” and “MRI-based adaptive brachytherapy in locally advanced cervical cancer”), bringing new data regarding locoregional control, nodal control, overall survival, morbidity, quality of life, and prognostic and predictive parameters [17,18,19,20].

| Patient | ΔD$_{0.1cc}$ sigmoid (cGy) | ΔD$_{1cc}$ sigmoid (cGy) | ΔD$_{2cc}$ sigmoid (cGy) | ΔD$_{0.1cc}$ rectum (cGy) | ΔD$_{1cc}$ rectum (cGy) | ΔD$_{2cc}$ rectum (cGy) | ΔD$_{0.1cc}$ bladder (cGy) | ΔD$_{1cc}$ bladder (cGy) | ΔD$_{2cc}$ bladder (cGy) |
|---------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| 1a      | 165.97                   | 127.11                  | 102.57                 | –73.27                   | –83.58                  | –74.46                 | 19.16                    | 38.59                   | 33.83                  |
| 1b      | –149.19                  | –98.61                  | –89.37                 | 54.28                    | 14.23                   | 12.62                  | –37.79                   | –29.75                  | –25.87                 |
| 2a      | –71.12                   | –61.38                  | –56.5                  | 3.6                      | 31.99                   | 36.27                  | –88.04                   | –29.04                  | –11.41                 |
| 2b      | –74.13                   | –64.75                  | –73.57                 | 84.81                    | 62.25                   | 57.73                  | 275.8                    | 616.38                  | 518.09                 |
| 3a      | –57.05                   | 9.77                    | 31.83                  | 150.05                   | 92.91                   | 70.73                  | 169.13                   | 16.1                    | 41.75                  |
| 3b      | 116.85                   | 132.58                  | 142.8                  | –312.58                  | –280.04                 | –255.26                | 144.76                   | 126.29                  | 111.35                 |
| 4a      | 181.24                   | 81.89                   | 59.7                   | –64.49                   | –62.01                  | –55.65                 | 361.37                   | 198.37                  | 144.82                 |
| 4b      | 89.74                    | 80.04                   | 88.85                  | 5.51                     | 24.14                   | 29.56                  | 197.56                   | 147.56                  | 133.45                 |
| 5a      | 67.39                    | 46.57                   | 10.71                  | –44.2                    | –25.23                  | –17.13                 | –32.05                   | –68.75                  | –74.18                 |
| 5b      | –31.97                   | –37.23                  | –33.55                 | –68.89                   | –43.17                  | –31.32                 | 382.05                   | 144.32                  | 85.38                  |
| 6a      | 15.69                    | –59.55                  | –71.37                 | –15.57                   | –4.67                   | –5.65                  | 19.72                    | 15.53                   | 25.2                   |
| 6b      | 66.22                    | 10.82                   | 7.45                   | 16.8                     | 16.59                   | 21.54                  | 217.21                   | 114.44                  | 80.88                  |
| 7a      | 138.85                   | 101.78                  | 9.89                   | –15.51                   | –9.52                   | 47.55                  | 33.4                     | 34.87                   | 47.55                  |
| 7b      | –81.74                   | –1.45                   | –8.69                  | –338.83                  | –327.05                 | –305.16                | 139.46                   | 119.07                  | 111.38                 |
| 8a      | –33.34                   | –128.95                 | –134.32                | 137.69                   | 76.65                   | 61.61                  | 111.61                   | 90.65                   | 78.69                  |
| 8b      | –287.86                  | 65.35                   | 29.4                   | 38.55                    | 35.71                   | –8.63                  | –12.51                   | –15.83                  | –8.63                  |
| 9a      | 376.44                   | 212.42                  | 158.52                 | –8.86                    | 2.14                    | –1.72                  | 702.03                   | 288.59                  | 193.85                 |
| 9b      | 30.54                    | 10.52                   | –10.87                 | –5.38                    | –4.67                   | –4.01                  | 60                      | 71.75                   | 32.76                  |
| 10a     | 88.76                    | 94.5                    | 70.43                  | –113.8                   | –98.76                  | –66.75                 | 46.67                    | 46.67                   | 21.63                  |
| 10b     | 25.72                    | 12.81                   | 12.63                  | 110.65                   | 105.6                   | 75.7                   | 125.86                   | 155.83                  | 115.87                 |
| Median  | 25.72                    | 11.82                   | 10.0                   | –7.12                    | –3.53                   | –4.83                  | 46.7                    | 59.21                   | 44.65                  |
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**Fig. 1.** A) Time vs. change of dose for $D_{0.1cc}$ bladder; B) Time vs. change of dose for $D_{1cc}$ bladder; C) Time vs. change of dose for $D_{2cc}$ bladder

**Fig. 2.** A) Time vs. change of dose for $D_{0.1cc}$ rectum; B) Time vs. change of dose for $D_{1cc}$ rectum; C) Time vs. change of dose for $D_{2cc}$ rectum
The 3D treatment planning time is more time-consuming than regular 2D planning. Based on the changes of small pelvis topography in time, the focus of the present study was to determine whether a longer treatment planning time can have dosimetric consequences with regards to the dose for organs at risk [21,22]. The most significant changes observed were for the rectum. With the prolongation of planning time, the rectal volume increased, leading to a significant dose increase. The median delta doses between the original plans and actual plans were compared for women with planning time longer than median (54 minutes) and patients with shorter planning time. A dose increase of 99 cGy for $D_{0.1cc}$, 61 cGy for $D_{1cc}$, and 29.8 cGy for $D_{2cc}$ per each fraction was observed in women with planning time longer than 54 minutes. In comparison with the median original planning dose, this means a possible increase by 22.3% for $D_{0.1cc}$, 18.4% for $D_{1cc}$, and 9.6% for $D_{2cc}$. We believe that most important reasons for the difference in planning times was difficulties in some of the plans with respect to the small pelvis topography and due to time-consuming manual optimization used.

Interestingly, correlation between change of volume and change of the dose was confirmed only for rectum. It is possible that changes in volume in sigmoid and bladder are more variable, while increasing the volume of rectum during planning process is more associated with the reduction of distance between rectum wall and applicators.

To the best of our knowledge, this is the first study focusing on the impact of planning time on the actual dose to organ at risk. Based on the present results, it seems that longer period of high-dose-rate (HDR) brachytherapy planning time can lead to incorrect estimation of dose distribution, principally to the rectum. The actual dose distribution does not correspond to the dose distribution at planning CT, because of the temporal changes in pelvic topography. It is therefore imperative to decrease the planning time.

The small number of patients is a significant limitation of the present study. In order to fully confirm current observations, a larger patient cohort is needed. However, despite this limitation, the present data support the conclusion that the planning time affects the real dose distribution. Based on these findings, a strive for a minimal delay between application and radiotherapy seems to be appropriate.

**Conclusions**

Extended brachytherapy planning time for brachytherapy due to changes in topography of small pelvis can lead to different dosage in high-risk organs than previously planned. It seems that the most significant changes are related to the rectum.

**Disclosure**

The authors report no conflict of interest.

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