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Evaluation of the critical organ doses in high dose rate brachytherapy plans using single-and multi-channel applicators

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► ***Original article***

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ABSTRACT

Background: The purpose of our study was to investigate the doses received by critical organs, namely the bladder, rectum, and sigmoid colon, in the treatment plans using single-channel (SC) or multi-channel (MC) applicators in high dose rate (HDR) brachytherapy treatments for vaginal cancer patients. ***Materials and Methods:*** We established treatment plans for 10 patients received 45Gy (1.8Gy×25fractions) external radiotherapy and then subsequently treated with HDR brachytherapy using MC applicators in the Oncentra Brachytherapy Treatment Planning System (OBTPS). These plans, originally created with MC applicator in the OBTPS, were redefined to simulate an SC applicator, where only the central channel active was kept active. To compare the doses to critical organs, new plans were generated with a prescribed dose of 5Gy to the clinical target volume (CTV). During optimization, it was ensured that 90% of the CTV received the prescribed dose (5Gy), in accordance with Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy and Oncology (GEC-ESTRO) criteria. The doses received by critical organs were analyzed for volumes of 0.1, 1, and 2cc in both SC and MC applicator plans. ***Results:*** A significant difference was found in rectal doses at 1cc and 2cc (p=0.022 and p=0.022, respectively); bladder doses at 0.1cc 1cc and 2cc (p=0.013 for all); and sigmoid colon dose at 1cc (p=0.012). ***Conclusion:*** HDR brachytherapy plans using MC applicators delivered lower doses to critical organs compared to SC applicators. Thus, MC applicators are preferable for better organ sparing in vaginal cancer treatment.

INTRODUCTION

Intracavitary HDR brachytherapy is a treatment modality that can be applied either on its own or in addition to external beam radiotherapy for gynecological patients [1-3]. Intracavitary HDR brachytherapy facilitates the treatment of gynecological malignancies, including primary tumors of vaginal, cervical, and endometrial cancers, as well as their metastases. Sparing of healthy critical organs surrounding the tumor must be considered during HDR brachytherapy planning. The transition of brachytherapy applications from two-dimensional to three-dimensional treatment systems has allowed the optimal irradiation of the tumors and better protection of critical organs in the vicinity, such as the rectum, bladder, and sigmoid colon. In the HDR brachytherapy treatments for patients with vaginal cancer, SC as well as MC cylindrical applicators are used [3]. SC applicators provide a symmetrical dose distribution owing to their design. Their use, however, can create a disadvantage in terms of critical organs (rectum, bladder, and sigmoid colon) and dose coverage of the tumor, especially for patients with different anatomies and variable tumor locations. Thus, MC applicators have been developed for gynecological cancers to ensure that the prescribed dose adequately covers the tumor [3, 4]. When used, MC applicators allow the prescribed dose to cover the tumor while reducing the exposure to the surrounding critical organs to radiation [5-8]. In cases of gynecological cancers such as primary vaginal cancer or metastases from cervical and endometrial cancers it can sometimes be difficult to deliver high doses to the CTV with external radiotherapy due to dose limitations for critical organs. HDR brachytherapy is an alternative radiotherapy method to overcome these limitations. This approach allows the delivery of a high dose of radiation directly to the tumor site through applicators placed inside the body while better sparing the surrounding healthy tissues. This approach enables precise targeting of the tumor and the delivery of higher doses, helping to destroy cancer cells while minimizing radiation exposure to critical organs [1-3]. Applicator selection is very

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important in brachytherapy practice SC or MC applicators are used for the treatment of vaginal tumors [3], while Fletcher applicators are used for brachytherapy of cervical tumors [9]. The purpose of this study was to investigate the doses received by critical organs, namely the bladder, rectum, and sigmoid colon, in the treatment plans using the SC or MC applicators for brachytherapy of patients with vaginal cancer. Thus, we aim to provide insights for the selection of MC or SC applicators in terms of critical organ doses for patients undergoing brachytherapy treatment.

MATERIALS AND METHODS

Patient selection

We selected 10 patients with vaginal cancer or vaginal metastasis who were previously treated using the HDR Iridium-192 brachytherapy treatment device (Micro Selectron, Elekta-Nucletron, The Netherlands) with MC applicator (Nucletron, The Netherlands) in our clinic (Istanbul University Oncology Institute). These patients had previously received 45 Gy of radiation therapy (1.8 Gy × 25 fractions) through external radiotherapy.

MC applicators for patients with vaginal cancer are designed considering their anatomy. These applicators consist of either seven channels, including a central channel with a radius of 2.5 cm and six surrounding channels (figure 1); nine channels, including a central channel with a radius of 3 cm and eight surrounding channels (figure 2); or nine channels, including a central channel with a radius of 3.5 cm and eight surrounding channels (figure 3). Patient characteristics are described in table 1.



Figure 1. The applicator has seven channels, including one central channel and six surrounding channels, with a radius of 2.5 cm.



Figure 2. The applicator has nine channels, including one central channel and eight surrounding channels, with a radius of 3 cm.

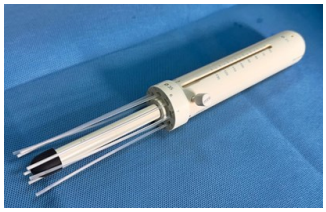


Figure 3. The applicator has nine channels, including one central channel and eight surrounding channels, with a radius of 3.5 cm.

Table 1. Patient s' demographic information.

Case no	Age	Diagnosis	Stage	Pathological Types	Applicator Type
1	65	Vaginal cancer	III	Squamous Cell Carcinoma	3 cm Multichannel Applicator
2	62	Endometrial cancer	Vaginal recurrence	Adenocarci-noma	3 cm Multichannel Applicator
3	74	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	2.5 cm Multichannel Applicator
4	79	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	2.5 cm Multichannel Applicator
5	56	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	3 cm Multichannel Applicator
6	65	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	3 cm Multichannel Applicator
7	55	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	3 cm Multichannel Applicator
8	41	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	3 cm Multichannel Applicator
9	52	Vaginal cancer	Recurrence	Squamous Cell Carcino-ma in Situ	3 cm Multichannel Applicator
10	36	Cervical cancer	Vaginal recurrence	Squamous Cell Carcinoma	2,5 cm Multichannel Applicator

Simulation and contouring

In order to better visualize the bladder in the patients' Computed Tomography (CT) images, 7 cc of diluted radio-opaque solution is injected into the bladder. During the placement of applicators in patients, the regions selected for treatment are marked by a radiation oncologist with markers based on Magnetic Resonance Imaging and clinical examination. After the appropriate applicator is placed, the accuracy of the application position is verified by using a Siemens C-arm X-ray machine (Siemens C-arm, Germany). Subsequently, pelvic CT images with a 3mm slice thicknesses are obtained with the Brilliance Big Bore CT scanner (Philips Healthcare, Cleveland, OH). The images are transferred to the Oncentra Brachytherapy TPS (Oncentra master plan Version 4.5.5, Elekta Brachytherapy, Veenendaal, The Netherlands). For each patient, radiation oncologist delineates the CTV and the volumes of critical organs including rectum, bladder, and sigmoid colon in axial CT sections, according to the GEC-ESTRO criteria [10].

Brachytherapy planning

Using the manual/graphical optimization of the Oncentra TPS software, treatment plans are created to ensure that 90% of the CTV volume receives the prescribed dose according to the GEC-ESTRO criteria, while ensuring the protection of critical organs. We redefined these treatment plans, created for MC

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applicator, in the Oncentra Brachytherapy Treatment Planning System to simulate SC applicator by keeping only the central channel of the MC applicator active and deactivating the surrounding channels. Using the same optimization criteria, we created new plans for the SC applicator. To compare the doses delivered to critical organs in the plans using the MC applicator with the plans using the SC applicator, we prescribed 5 Gy of radiation to the CTV in all plans, and generated new plans. During optimization, the goal was to ensure that 90% of the CTV received the prescribed dose (5 Gy), in accordance with the GEC-ESTRO criteria [10].

Plan evaluation

We analyzed the doses received by critical organs (rectum, bladder, and sigmoid colon) in the plans for both applicators defined in the Treatment Planning System, for volumes of 0.1cc, 1cc, and 2 cc.

Statistical analysis

We compared the results using SPSS Statistics version 22. We used the non-parametric Wilcoxon signed-rank test. We considered $p < 0.05$ as a statistically significant [11].

RESULTS

Tables 2, 3 and 4, show the average doses received by the bladder, rectum, and sigmoid colon, respectively, for the plans using the SC and MC applicators to ensure that 90% of the CTV receives 5 Gy of radiation.

The doses to 0.1cc, 1cc and 2 cc bladder volumes for the MC applicator plan were 4.261±2.322, 3.565±1.833, and 3.257±1.643 Gy, respectively, and for the SC applicator 5.119±3.310, 4.007±1.991, and 3.596±1.694, respectively, and showed statistically significant difference (p=0.013 for all comparisons) (table 2).

Table 2. Comparison of the mean bladder dose per fraction between the plan with the multi-channel applicator and the Single-channel applicator.

	MC (mean±SD)	SC (mean±SD)	p
$D_{0.1cc}$ (Gy)	4.261 ± 2.322	5.119 ± 3.310	0.013
D_{1cc} (Gy)	3.565 ± 1.833	4.007 ± 1.991	0.013
D_{2cc} (Gy)	3.257 ± 1.643	3.596 ± 1.694	0.013

Gy: Gray, SD: Standard deviation, D2cc/D1cc/D0.1cc- cc/1cc/0.1cc of bladder received dose. MC: Multi-channel applicator, SC: Single-channel applicator.

No significant difference was found between the doses received by 0.1cc rectal volume for MC (4.001±1.523), and SC (4.450±1.978) applicators (p=0.059). However, the differences among MC and SC groups for the doses to 1 cc (3.291±1.409 versus 3.683±1.315, respectively) and 2 cc (2.955±1.65 versus 3.303±1.302, respectively) volumes were statistically significant (p=0.022 for both) (table 3).

Between MC and SC groups, the dose differences received by 0.1 cc (2.454±1.140 versus 2.545±1.312) and 2 cc volumes (1.524±1.102 versus 2.098±1.035, respectively) of sigmoid colon showed no significant differences (p=0.069, and p=0.161, respectively). However, there was a significant difference among the 2 cc sigmoid colon volume doses between MC (1.992±1.981) and SC (2.373±1.078) groups (p=0.012) (table 4). The distribution of the isodose lines in the plans created with the MC and SC applicators are presented in figures 4 and 5.

Table 3. Comparisons of the mean rectum dose per fraction between the plan with the multi-channel applicator and the Single-channel applicator.

	MC (mean±SD)	SC (mean±SD)	p
$D_{0.1cc}$ (Gy)	4.001 ± 1.523	4.450 ± 1.978	0.059
D_{1cc} (Gy)	3.291 ± 1.409	3.683 ± 1.315	0.022
D_{2cc} (Gy)	2.955 ± 1.65	3.303 ± 1.302	0.022

Gy: Gray, SD: Standard deviation, D2cc/D1cc/D0.1cc– 2cc/1cc/0.1ccof rectum received dose. MC: Multi-channel applicator, SC: Single-channel applicator.

Table 4. Comparisons of the mean sigmoid colon dose per fraction between the plan with the multi-channel applicator and the Single-channel applicator.

	MC (mean±SD)	SC (mean±SD)	p
$D_{0.1cc}$ (Gy)	2.454 ± 1.140	2.545 ± 1.312	0.069
D_{1cc} (Gy)	1.992 ± 1.981	2.373 ± 1.078	**0.012**
D_{2cc} (Gy)	1.524 ± 1.102	2.098 ± 1.035	0.161

Gy: Gray, SD: Standard deviation, D2cc/D1cc/D0.1cc– 2cc/1cc/0.1ccof sigmoid colonreceived dose. MC: Multi-channel applicator, SC: Single-channel applicator.

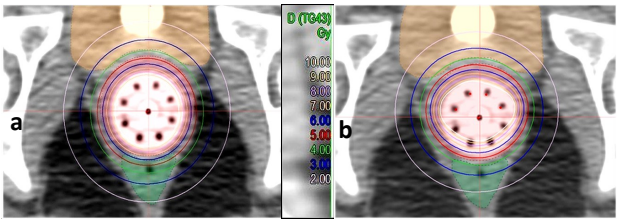


Figure 4. Axial view of computed tomographic images: single-channel applicator plan **(a)** and multi-channel applicator plan **(b)**. While both plans cover the prescribed dose (5Gy) for the clinical target volume, the rectum dose is lower for the multi-channel applicator plan.

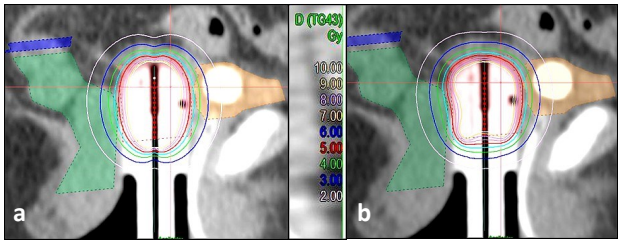


Figure 5. Sagittal view of computed tomographic images: single-channel applicator plan **(a)** and multi-channel applicator plan **(b)**.

DISCUSSION

According to our results, critical organ doses were lower in MC applicator plans compared to the SC applicator. Statistical analysis with the Wilcoxon signed-rank test showed a significant difference

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between the plans with SC and MC applicators for the 1cc (p=0.022) and 2cc (p=0.022) rectum doses, but not for the 0.1 cc rectum dose (p=0.059).

Kim *et al*. [7] treated 20 patients with vaginal cancer with a dose of 20-25 Gy in more than 5 fractions using a MC applicator after external therapy. All patients' treatment plans were re-prepared for the SC applicator. Target volume and critical organ doses were compared between the plans prepared with MC and SC. They reported that plans using an MC applicator for lesions concentrated on one side of the vaginal wall were advantageous compared to plans using an SC applicator. There was increased coverage of the CTV and preservation of healthy tissues. Homogeneity indices were 0.49±0.19 and 0.52±0.23 (p=0.09) for MC and SC, respectively. The dose distribution obtained with the MC applicator is more homogeneous compared to the SC applicator. While no statistically significant difference was found in the comparison of 0.1, 1, and 2 cc bladder doses, significantly lower in rectum doses was found. The 0.1, 1 and 2 cc doses of the rectum were 6.72 and 75.4Gy (p=0.005), 60 and 65.6Gy (p=0.008) and 57.3 and 62 (p=0.15) for MC and SC, respectively. No statistically significant difference in received dose for the sigmoid colon was found between the plans prepared with MC and SC applicators.

Bahadur *et al*. [5] retrospectively compared the potential dosimetric advantages of the MC vaginal applicator over the SC applicator in intracavitary vaginal HDR brachytherapy after hysterectomy in 12 patients. Analysis of dose-volume-histograms showed a limited but statistically significant difference in the dose distribution of single and MC applicators with in terms of CTV. Although bladder and rectum doses were lower in the MC applicatorplans, the differences were statistically insignificant for the bladder, but significant for the rectum. The doses received by the 2 cc of the rectum in MC and SC plans, were 51±0.6 Gy and 6.1±0.7 Gy, respectively (p=0.0001), and the doses received by the 2 cc of the bladder were 4.90±.8 and 50±.9 Gy, respectively (p=0.053).

Gebhardta *et al*. [12] reported the results of treatment of 60 patients with vaginal cancer who received brachytherapy with a MC applicator after external treatment. Brachytherapy applications were performed with an image-based HDR brachytherapy device. The total median applied equivalent dose delivered in 2 Gy fractions in a conventional fractionation schedule (EQD2) was D90 CTVHR (CTV High Risk) 77.2 Gy. The doses of bladder, rectum and 2 cc of sigmod colon were 59.0, 58.4 and 51.6 Gy, respectively. There were no acute complications grades 3 or higher on clinical evaluation. The rate of grade 3 or higher toxicity at 4-year follow-up was 2.9%.

The results of Kim *et al.* [7], Bahadur *et al*. [5] and our study showed that treatment plans prepared with a MC applicator provided better target coverage and lower critical organ doses compared to the treatment plans prepared with a SC applicator. In plans prepared with the MC applicator, dose reductions of 1cc to 2cc for the bladder are small, while dose reductions of 1cc to 2cc for the rectum are significant. In the study conducted by Gebhardta *et al*. [11], the brachytherapy dose was given with a MC applicator, and the rate of reported toxicity grade 3 and above was very low, at 2.9% in the 4-year median follow-up. The clinical results of using the MC applicator support the evidence on dose reduction advantage in critical organs,reported in Kim *et al*. [7], Bahadur *et al*. [5] and in our study.

In recent years, 3D- printed MC vaginal applicators brachytherapy applications have been emerged. Feng *et al*. [13] performed brachytherapy on total 140 cervical cancer patients, and in 41 patient's 3D printed MC applicators and in 63 patients SC applicators were used. They retrospectively analyzed the dosimetric parameters, 5-year local control, progression free survival, and overall survival of the two groups. Homogeneity index and conformal index were equally better in 3D- printed group. In the 3D-printed MC applicator group, the doses of 2 cc, 1 cc, and 0.1 cc of the bladder and rectum were significantly lower ($p<0.05$). The incidence of radiation enteritis and cystitis was lower in the 3D-printed group compared to the SC group, but no statistical difference was noted.

Clinical results support that applications with MC applicators provide better target coverage and lower doses for critical organs compared to applications with a SC applicator. Application of 3D-printed MC applicators contributes to the reduction of bladder and rectum toxicity. Thus, we plan to continuing our work with 3D-printed applicators.

CONCLUSION

We found that plans conducted with an MC applicator provided a more controllable dose distribution to the CTV and showed a significant dose reduction for the bladder, rectum, and sigmoid colon, compared to the SC applicator plans. We concluded that for the treatment of vaginal cancer patients with HDR brachytherapy, MC applicators should be preferred.

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***Author Contributions*:** All authors have contributed equally to the manuscript preparation process.

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