

# Are active dwell positions always necessary in the ring/ovoids channel of the cervical applicator in the intracavitary-interstitial brachytherapy of cervical cancer?

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## Abstract

**Purpose:** To compare dosimetric parameters of brachytherapy (BT) treatment plans made with or without active source positions of the ring/ovoid (R/O) applicator in locally advanced cervical cancer patients.

**Material and methods:** Sixty patients with cervical cancer without vaginal involvement were selected for the study, who received intra-cavitary/interstitial BT. For each patient, two plans with and without active source dwell positions in R/O were created, using the same dose-volume constraints. EQD<sub>2</sub> total doses from external beam and BT of target volumes and organs at risk (OARs) between the competing plans were compared.

**Results:** There was no significant difference in the dose of high-risk clinical target volume (HR-CTV) and gross tumor volume (GTV) between the plans with inactive vs. active R/O. The mean D<sub>98</sub> of intermediate-risk clinical target volume (IR-CTV) was significantly lower with inactive R/O; however, the GEC-ESTRO (EMBRACE II study) and ABS criteria were fulfilled in 96% in both plans. There was no difference in dose homogeneity, but conformity of the plans with inactive R/O was higher. Doses to all OARs were significantly lower in plans without R/O activation. While all the plans without R/O activation fulfilled the recommended dose criteria for OARs, it was less achievable with R/O activation.

**Conclusions:** Inactivation of R/O applicator results in similar dose coverage of the target volumes with lower doses to all OARs, as activation of R/O in cervix cancer patients when HR-CTV does not extend to R/O applicator. The use of active source positions in R/O shows worse performance regarding the fulfilment of the recommended criteria for OARs.

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**Key words:** cervical cancer, ring activation, ring applicator, Venezia applicator, interstitial brachytherapy.

## Purpose

The standard of care in the curative treatment of locally advanced cervical cancer (LACC; stages, 1B2-4A) is external beam radiotherapy (EBRT), and intra-cavitary (IC) and/or interstitial (IS) brachytherapy (BT) boost with concomitant chemotherapy. Both radiotherapy modalities have been developing rapidly, with increasingly sophisticated techniques appearing that escalate the dose to the tumor and spare organs at risk (OARs) [1-7].

To reach this planning aims, BT evolved in terms of image techniques. Using computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), or fusion of these images, helps to determine the residual

disease after EBRT, and irradiation of healthy tissues in the uterus is therefore not required [8-13].

On the other hand, the design and versatility of the applicators are also adapted to a new concept, where spatial anatomy of target volumes and OARs is well-known. Traditional tandem/ring or tandem/ovoid combined with IS-IC applicators are available, including Vienna, Utrecht, Venezia, Geneva, and 3D-printed [14-19]. While IC applicators historically were used with a pre-defined source loading and dose prescription method to specify the dose to points A (Manchester system), in the possession of 3D anatomical information, tailoring the dose to the target volumes became possible

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with individualized dose optimization [20, 21]. Otherwise, this transition cannot be smooth as dose to points A is not suitable for dose prescription when IS needles go through or directly next to the needles, increasing the dose to false value [22].

Advanced inverse optimization methods complicate the situation even more [23-25]. The question is: do we need to implement the historical point of view into the inverse algorithms, or change to a totally new concept? We can restrict the relative loading of intra-uterine, vaginal (ring/ovoid, R/O) part of the applicator and IS needles to reach the well-known pear-shape spatial dose distribution. Or else, we can use these advanced tools (imaging, applicator and optimization) to create a tumor-shape dose. The main difference in loading is the vaginal channel (R/O) of the applicator. In residual tumors without vaginal involvement, the applicator touches the surface of the cervix, so the source can irradiate the target volume from outside only. Mohamed *et al.* tried to reduce the vaginal dose by decreasing dwell times in R/O and increasing dwell times in tandem/needles [26]. However, not loading of channel of the applicator is still an unsolved question.

The aim of the present study was to examine the effect of inactivate R/O channel of IC and combined IS-IC applicators in term of dose coverage and conformity of the target volumes and doses to all OARs, when high-risk clinical target volume (HR-CTV) does not extend to the R/O applicator. Fulfilment of the criteria of international recommendations for targets and OARs was investigated.

## Material and methods

At our institute, sixty patients with cervical cancer without vaginal involvement (stage, IB2-IVA) were selected, who received 7 Gy high-dose-rate BT in each of 4 implantations, following 50.4 Gy EBRT with intensity-modulated arc therapy for HR-CTV. Patients were examined with pelvic MRI and staged with CT or PET-CT at the beginning, and the therapeutic effect was assessed with an MRI at the end of EBRT. Initial and post-EBRT MRI were used to determine the number and position of the needles in the ring or Venezia applicator, if needed [18-20]. Interstitial BT was considered for patients, whose disease could not be adequately encompassed by IC application. Thirty patients had combined IC-IS application, and in other 30 cases, only IC insertion was applied. Delineation of gross tumor volume (GTV), HR-CTV, intermediate-risk clinical target volume (IR-CTV), bladder, rectum, sigmoid, bowel, and vaginal wall was performed following the GEC-ESTRO recommendations for CT-based contouring [21]. Post-EBRT MRI and post-implant CT series were placed side-by-side in the same monitor, and with the help of an expert radiologist, the contours were created on post-implant CT using information of post-EBRT MRI. To avoid inter-observer variability and reduce contouring bias, the same expert radiation oncologist created the contours in all the cases. The distance between the cervix and the surface of R/O was 10.8 mm in average (range, 4.2-24.5 mm), according to the given cervical anatomy (scab, deformity, etc.) and vaginal stenosis after EBRT. As the vagina was not involved in these

patients, none of the target volumes contained the vagina and this air gap. Therefore, necessity of active source dwell positions in R/O part of the applicators – outside of HR-CTV was questionable. Two different treatment plans were created for each 60 patients, with and without activation of the R/O part of IC or IS applicator, using the same planning aims. In all of these cases, the plan with inactive R/O was applied for the treatment of patient. During treatment planning, manual optimization was used to achieve the optimal dose distribution (Oncentra Brachy version v. 4.5.3, Elekta Brachytherapy, Veenendaal, The Netherlands). At first, geometrical optimization was applied in distance mode. Then, where the reference doses did not cover target volumes (GTV and HR-CTV), the reference isodose lines were expanded graphically or an appropriate dwell times were improved manually based on their distance from OARs. In the opposite cases, where the target volumes were covered with an appropriate dose but OARs were over-exposed, isodose lines or dwell times of the source were also modified. The planning aim was to fulfil the criteria of the recommendations of GEC-ESTRO Gynecological Working Group [28, 29], the EMBRACE II study [30] and ABS [31, 32].

EQD<sub>2</sub> total doses of EBRT plus BT plans were calculated using linear-quadratic radiobiological model [33, 34].  $\alpha/\beta$  of HR-CTV was 10 Gy, while for OARs, 3 Gy was applied. The following dose-volume parameters were used for quantitative evaluation of plans [35]:

- V<sub>150</sub>: relative volume of IR-CTV, HR-CTV, and GTV receiving at least 150% of the prescribed dose (%),
- D<sub>90</sub>, D<sub>98</sub>: minimum dose delivered to 90% and 98% of IR-CTV, HR-CTV, and GTV (Gy),
- D<sub>A</sub>: dose to point A (Gy),
- DNR: dose non-uniformity ratio [36],
- COIN: conformal index [37],
- D<sub>2</sub>: minimal dose of the most exposed 2 cm<sup>3</sup> of a critical organ, including the bladder, rectum, sigmoid, bowel, and vaginal wall (Gy),
- D<sub>ICRU</sub>: dose to ICRU reference point of the bladder and rectum (recto-vaginal point) (Gy) [38],
- D<sub>PIBS</sub>: dose to the point of posterior-inferior border of the symphysis (Gy),
- D<sub>PIBS+2</sub>: dose to the point 2 cm above posterior-inferior border of the symphysis parallel to applicator axis (Gy),
- D<sub>PIBS-2</sub>: dose to the point 2 cm below posterior-inferior border of the symphysis parallel to applicator axis (Gy).

EQD<sub>2</sub> dose-volume parameters between the competing plans were compared using Wilcoxon-matched pairs test (Statistica v. 12.5, StatSoft, Tulsa, OK, USA).

Although, this was a dosimetric study, clinical data of the limited patients' cohort were also assessed.

## Results

The mean volume of HR-CTV after EBRT (residual tumor volume) was 35.3 cm<sup>3</sup> (range, 8.7-100.2 cm<sup>3</sup>), while IR-CTV was 102.4 cm<sup>3</sup> (range, 44.2-227.9 cm<sup>3</sup>) and GTV was 15.7 cm<sup>3</sup> (range, 0.0-54.0 cm<sup>3</sup>). These volumes were 39.6 cm<sup>3</sup> (range, 19.4-100.2 cm<sup>3</sup>), 136.1 cm<sup>3</sup> (range,

44.2-227.9 cm<sup>3</sup>), and 16.8 cm<sup>3</sup> (range, 0.0-54.0 cm<sup>3</sup>) in IS, and 18.8 cm<sup>3</sup> (range, 8.7-31.8 cm<sup>3</sup>), 88.9 cm<sup>3</sup> (range, 79.8-95.9 cm<sup>3</sup>), and 11.3 cm<sup>3</sup> (range, 0.0-33.7 cm<sup>3</sup>) in IC applications. In IS implantations, median 4 needles (range, 3-12) were used additionally to the IC applicator.

There was no significant difference in the dose of HR-CTV between the plans with inactive vs. active R/O (mean D<sub>90</sub>: 91.2 vs. 91.5 Gy; mean D<sub>98</sub>: 80.6 vs. 81.0 Gy). Similar results were obtained for GTV (D<sub>90</sub>: 115.3 vs. 109.1 Gy; D<sub>98</sub>: 97.2 vs. 95.5 Gy). The mean D<sub>98</sub> of IR-CTV was significantly lower with inactive R/O (60.8 vs. 63.9 Gy,  $p = 0.0464$ ); however, the GEC-ESTRO (EMBRACE II study) and ABS criteria were fulfilled in 96% in each of the plans. There was no difference in dose homogeneity (DNR: 0.55 vs. 0.54), but the conformity of the plans with inactive R/O was considerably higher (COIN: 0.62 vs. 0.38,  $p < 0.001$ ).

Doses to all OARs were significantly lower in plans without R/O activation: D<sub>2</sub> (bladder): 72.4 vs. 86.5 Gy ( $p < 0.001$ ); D<sub>2</sub> (rectum): 57.9 vs. 75.2 Gy ( $p < 0.001$ ); D<sub>ICRU</sub>(recto-vaginal): 58.8 vs. 77.5 Gy ( $p < 0.001$ ); D<sub>2</sub> (sigmoid): 61.7 vs. 67.3 Gy ( $p < 0.001$ ); D<sub>2</sub> (bowel): 69.2 vs. 72.1 Gy ( $p = 0.0038$ ); and D<sub>2</sub> (vaginal wall): 78.2 vs. 117.3 Gy ( $p = 0.0022$ ) in plans with inactive vs. active R/O, respectively. The same trend was observed in the dose of points on the vaginal wall: D<sub>PIBS</sub> was 50.6 vs. 53.0 Gy ( $p < 0.001$ ),

D<sub>PIBS+2</sub> was 53.1 vs. 57.7 Gy ( $p < 0.001$ ), and D<sub>PIBS-2</sub> was 49.5 vs. 50.7 Gy ( $p < 0.001$ ), respectively (Table 1).

Evaluating separately the IS and IC only applications, the same trends appeared between plans using inactive versus active R/O (Tables 2 and 3). Only the difference in D<sub>90</sub> of GTV between inactive versus active R/O plans was almost statistically significant in IS applications: 113.5 Gy vs. 106.5 Gy ( $p = 0.0531$ ). However, this difference was 7 Gy EQD<sub>2</sub> only, which was clinically insignificant. It has to be noted, that activating the R/O part of the applicator increased D<sub>2</sub> and D<sub>ICRU</sub> of the bladder and D<sub>2</sub> of the rectum in higher degree in IC applications (+19.0 Gy, +21.6 Gy, and +19.4 Gy, respectively) compared with those in IS (+12.7 Gy, +10.1 Gy, and +14.7 Gy, respectively) ( $p < 0.001$ ). There was no significant difference in the changing of other examined dose-volume parameters by R/O activation between the IS and IC only applications.

It was found that HR-CTV was exposed at least with the recommended EQD<sub>2</sub> total dose (D<sub>90</sub>) in 100% of the patients with inactive and active R/O techniques. The criteria for the D<sub>98</sub> parameter were fulfilled in 96% of the plans without activate R/O, and in 92% using active R/O. GTV was covered with D<sub>98</sub> dose in 100% of the cases in plans with inactive R/O, and in 80% with active R/O. However, the D<sub>98</sub> dose coverage of IR-CTV was the same in each of the plans – 96%. Only the EQD<sub>2</sub> dose

**Table 1.** EQD<sub>2</sub> total doses of dose plans with inactive vs. active ring/ovoid (R/O) channel of the applicator in high-dose-rate brachytherapy of cervical cancer

	EQD <sub>2</sub>	Inactive R/O	Active R/O	P-value*
HR-CTV	V <sub>150</sub> (%)	62.0 (51.0-72.1)	55.6 (41.9-71.1)	< 0.001
	D <sub>90</sub> (Gy)	91.2 (88.4-94.8)	91.5 (88.5-98.2)	0.2905
	D <sub>98</sub> (Gy)	80.6 (74.9-86.1)	81.0 (71.9-86.4)	0.3914
GTV	D <sub>90</sub> (Gy)	115.3 (92.5-135.3)	109.1 (97.9-148.2)	0.0787
	D <sub>98</sub> (Gy)	97.2 (79.4-115.2)	95.5 (83.8-114.0)	0.5695
IR-CTV	D <sub>90</sub> (Gy)	64.7 (62.0-67.6)	68.8 (64.1-73.5)	0.0277
	D <sub>98</sub> (Gy)	60.8 (59.0-62.0)	63.9 (59.9-69.0)	0.0464
	D <sub>A</sub> (Gy)	2,201.9 (60.5-48,352.1)	1,085.9 (66.5-21,750.3)	0.0975
	DNR	0.55 (0.48-0.58)	0.54 (0.46-0.58)	0.2301
	COIN	0.62 (0.38-0.86)	0.38 (0.15-0.66)	< 0.001
Bladder	D <sub>2</sub> (Gy)	72.4 (55.3-81.4)	86.5 (69.9-111.4)	< 0.001
	D <sub>ICRU</sub> (Gy)	71.6 (50.1-105.8)	84.1 (60.7-112.9)	< 0.001
Rectum	D <sub>2</sub> (Gy)	57.9 (50.7-65.8)	75.2 (53.3-103.1)	< 0.001
	D <sub>ICRU</sub> (Gy)	58.8 (50.1-68.2)	77.5 (61.4-107.2)	< 0.001
Sigmoid	D <sub>2</sub> (Gy)	61.7 (52.4-73.5)	67.3 (58.2-86.9)	< 0.001
Bowel	D <sub>2</sub> (Gy)	69.2 (50.5-89.2)	72.1 (52.9-100.4)	0.0038
Vaginal wall	D <sub>2</sub> (Gy)	78.2 (60.7-169.6)	117.3 (80.4-229.0)	0.0022
	D <sub>PIBS</sub> (Gy)	50.6 (48.6-54.3)	53.0 (49.8-59.4)	<0.001
	D <sub>PIBS+2</sub> (Gy)	53.1 (49.2-60.7)	57.7 (51.2-65.8)	<0.001
	D <sub>PIBS-2</sub> (Gy)	49.5 (48.6-50.8)	50.7 (49.2-53.3)	<0.001

V<sub>150</sub> – the relative volume of intermediate-risk CTV (IR-CTV), high-risk CTV (HR-CTV), and GTV receiving at least 150% of the prescribed dose (%); D<sub>90</sub>, D<sub>98</sub> – the minimum dose delivered to 90% and 98% of IR-CTV, HR-CTV, and GTV (Gy); D<sub>A</sub> – dose to point A (Gy); DNR – dose non-uniformity ratio; COIN – conformal index; D<sub>2</sub> – minimal dose of the most exposed 2 cm<sup>3</sup> of organs at risk (bladder, rectum, sigmoid, bowel, and vaginal wall) (Gy); D<sub>ICRU</sub> – dose to ICRU reference point of bladder and rectum (recto-vaginal point) (Gy); D<sub>PIBS</sub> – dose to the point of posterior-inferior border of the symphysis (Gy); D<sub>PIBS+2</sub> – dose to the point 2 cm above from posterior-inferior border of the symphysis (Gy); D<sub>PIBS-2</sub> – dose to the point 2 cm below from posterior-inferior border of the symphysis (Gy); \* Wilcoxon-matched pairs test

**Table 2.** EQD<sub>2</sub> total doses of dose plans with inactive vs. active ring/ovoid (R/O) channel of interstitial-intra-cavitary applicator in high-dose-rate brachytherapy of cervical cancer

	EQD <sub>2</sub>	Inactive R/O	Active R/O	P-value*
HR-CTV	V <sub>150</sub> (%)	61.30 (51.0-71.4)	55.8 (42.0-71.1)	<b>0.0014</b>
	D <sub>90</sub> (Gy)	90.9 (88.4-94.8)	91.2 (88.5-98.2)	0.1712
	D <sub>98</sub> (Gy)	80.2 (74.9-86.1)	80.3 (71.9-86.5)	0.7172
GTV	D <sub>90</sub> (Gy)	113.5 (92.5-130.9)	106.5 (97.9-117.5)	0.0531
	D <sub>98</sub> (Gy)	96.6 (79.4-115.2)	93.7 (83.8-107.4)	0.5455
IR-CTV	D <sub>90</sub> (Gy)	64.6 (63.1-65.9)	67.2 (64.1-69.1)	<b>0.0468</b>
	D <sub>98</sub> (Gy)	61.0 (60.0-62.0)	62.3 (59.9-63.5)	0.0841
	D <sub>A</sub> (Gy)	2,762.6 (60.5-48,352.1)	1,352.5 (68.9-21,750.3)	0.0766
	DNR	0.54 (0.48-0.58)	0.54 (0.46-0.58)	0.4939
	COIN	0.64 (0.43-0.86)	0.41 (0.23-0.66)	< <b>0.001</b>
Bladder	D <sub>2</sub> (Gy)	72.8 (55.3-81.4)	85.5 (69.9-110.0)	< <b>0.001</b>
	D <sub>ICRU</sub> (Gy)	71.3 (50.1-105.8)	81.4 (60.7-107.2)	< <b>0.001</b>
Rectum	D <sub>2</sub> (Gy)	58.8 (50.7-65.8)	73.5 (53.3-103.1)	< <b>0.001</b>
	D <sub>ICRU</sub> (Gy)	59.3 (50.1-68.2)	78.8 (63.5-107.2)	< <b>0.001</b>
Sigmoid	D <sub>2</sub> (Gy)	63.0 (55.8-73.5)	68.0 (58.2-86.9)	< <b>0.001</b>
Bowel	D <sub>2</sub> (Gy)	71.4 (53.8-89.2)	73.2 (55.3-100.4)	<b>0.0164</b>
Vaginal wall	D <sub>2</sub> (Gy)	78.2 (60.7-169.6)	117.3 (80.4-229.0)	<b>0.0022</b>
	D <sub>PIBS</sub> (Gy)	50.7 (48.6-54.3)	53.1 (49.8-59.4)	< <b>0.001</b>
	D <sub>PIBS+2</sub> (Gy)	53.3 (49.2-60.7)	57.8 (51.2-65.8)	< <b>0.001</b>
	D <sub>PIBS-2</sub> (Gy)	49.5 (48.6-50.8)	50.7 (49.2-53.3)	< <b>0.001</b>

**Table 3.** EQD<sub>2</sub> total doses of dose plans with inactive vs. active ring/ovoid (R/O) channel of intra-cavitary applicator in high-dose-rate brachytherapy of cervical cancer

	EQD <sub>2</sub>	Inactive R/O	Active R/O	P-value*
HR-CTV	V <sub>150</sub> (%)	65.0 (60.8-72.1)	54.6 (41.9-65.2)	<b>0.0013</b>
	D <sub>90</sub> (Gy)	92.4 (89.2-94.0)	92.3 (89.5-96.5)	0.1893
	D <sub>98</sub> (Gy)	81.8 (79.4-86.1)	83.6 (77.5-85.4)	0.7225
GTV	D <sub>90</sub> (Gy)	117.5 (93.3-135.3)	112.3 (99.9-148.2)	0.0796
	D <sub>98</sub> (Gy)	98.2 (84.8-114.1)	96.4 (84.2-114.0)	0.5930
IR-CTV	D <sub>90</sub> (Gy)	64.8 (62.0-67.6)	71.0 (68.5-73.5)	<b>0.0197</b>
	D <sub>98</sub> (Gy)	60.3 (59.0-61.5)	65.9 (62.3-69.0)	<b>0.0285</b>
	D <sub>A</sub> (Gy)	71.3 (61.5-83.0)	73.0 (66.5-80.9)	0.3452
	DNR	0.55 (0.54-0.57)	0.54 (0.52-0.55)	0.2249
	COIN	0.57 (0.38-0.74)	0.26 (0.15-0.36)	< <b>0.001</b>
Bladder	D <sub>2</sub> (Gy)	71.1 (60.7-77.3)	90.1 (80.4-111.4)	< <b>0.001</b>
	D <sub>ICRU</sub> (Gy)	72.8 (54.8-92.8)	94.4 (67.4-112.8)	< <b>0.001</b>
Rectum	D <sub>2</sub> (Gy)	53.9 (52.0-55.8)	83.3 (74.4-92.8)	< <b>0.001</b>
	D <sub>ICRU</sub> (Gy)	56.8 (52.4-64.3)	78.7 (61.4-100.4)	< <b>0.001</b>
Sigmoid	D <sub>2</sub> (Gy)	57.1 (52.4-60.0)	64.8 (62.1-72.6)	< <b>0.001</b>
Bowel	D <sub>2</sub> (Gy)	62.7 (50.5-75.4)	68.7 (52.9-84.7)	<b>0.0068</b>
Vaginal wall	D <sub>2</sub> (Gy)	81.3 (61.5-170.0)	118.5 (81.2-234.3)	<b>0.0018</b>
	D <sub>PIBS</sub> (Gy)	49.9 (49.5-50.5)	52.2 (50.5-53.8)	< <b>0.001</b>
	D <sub>PIBS+2</sub> (Gy)	51.4 (50.5-52.0)	57.1 (52.0-63.5)	< <b>0.001</b>
	D <sub>PIBS-2</sub> (Gy)	49.2 (48.9-49.5)	50.1 (49.4-50.5)	< <b>0.001</b>

criteria of the points A was fulfilled less without active R/O, showing 88%. While using active dwells in R/O, 100% of the plans fulfilled this criterion.

Even though all the plans without R/O activation fulfilled the GEC-ESTRO (EMBRACE II study) and ABS dose criteria ( $D_2$ ) in 100% for the bladder, rectum and sigmoid, the plans with activated R/O complied with the same criteria in 72%, 56%, and 88%, respectively (Table 4).

These proportions were similar in the IS and IC applications when analyzed separately; however, the effect of R/O activation was slightly higher in IC only cases. The ratio of the plans that fulfilled the criteria were lower in almost all of the examined parameters in IC applications than IS cases using active R/O (Tables 5 and 6).

In the cohort of the present study, the median follow-up time was 64 months. The local control rate was

**Table 4.** Percentage of dose plans using inactive vs. active ring/ovoid (R/O) channel of the applicator, which fulfilled the criteria of the GEC-ESTRO (EMBRACE II study) and ABS recommendations (hard/soft constraints)

	EQD <sub>2</sub>	Inactive R/O	Active R/O
HR-CTV	D <sub>90</sub> (Gy)	83%/100%	63%/100%
	D <sub>98</sub> (Gy)	96%	92%
GTV	D <sub>98</sub> (Gy)	96%/100%	68%/80%
IR-CTV	D <sub>98</sub> (Gy)	96%	96%
	D <sub>A</sub> (Gy)	88%	100%
Bladder	D <sub>2</sub> (Gy)	96%/100%	32%/72%
Rectum	D <sub>2</sub> (Gy)	92%/100%	16%/56%
	D <sub>ICRU</sub> (Gy)	92%/100%	21%/52%
Sigmoid	D <sub>2</sub> (Gy)	88%/100%	76%/88%
Bowel	D <sub>2</sub> (Gy)	76%/82%	42%/52%

**Table 5.** Percentage of dose plans using inactive vs. active ring/ovoid (R/O) channel of interstitial-intra-cavitary applicator, which fulfilled the criteria of the GEC-ESTRO (EMBRACE II study) and ABS recommendations (hard/soft constraints)

	EQD <sub>2</sub>	Inactive R/O	Active R/O
HR-CTV	D <sub>90</sub> (Gy)	85%/100%	66%/100%
	D <sub>98</sub> (Gy)	97%	92%
GTV	D <sub>98</sub> (Gy)	96%/100%	70%/81%
IR-CTV	D <sub>98</sub> (Gy)	100%	96%
	D <sub>A</sub> (Gy)	90%	100%
Bladder	D <sub>2</sub> (Gy)	97%/100%	40%/73%
Rectum	D <sub>2</sub> (Gy)	93%/100%	18%/60%
	D <sub>ICRU</sub> (Gy)	93%/100%	22%/53%
Sigmoid	D <sub>2</sub> (Gy)	90%/100%	76%/90%
Bowel	D <sub>2</sub> (Gy)	80%/83%	45%/58%

**Table 6.** Percentage of dose plans using inactive vs. active ring/ovoid (R/O) channel of intra-cavitary applicator, which fulfilled the criteria of the GEC-ESTRO (EMBRACE II study) and ABS recommendations (hard/soft constraints)

	EQD <sub>2</sub>	Inactive R/O	Active R/O
HR-CTV	D <sub>90</sub> (Gy)	80%/100%	60%/100%
	D <sub>98</sub> (Gy)	95%	91%
GTV	D <sub>98</sub> (Gy)	96%/100%	67%/78%
IR-CTV	D <sub>98</sub> (Gy)	93%	96%
	D <sub>A</sub> (Gy)	87%	100%
Bladder	D <sub>2</sub> (Gy)	95%/100%	26%/70%
Rectum	D <sub>2</sub> (Gy)	92%/100%	12%/52%
	D <sub>ICRU</sub> (Gy)	92%/100%	19%/48%
Sigmoid	D <sub>2</sub> (Gy)	87%/100%	75%/85%
Bowel	D <sub>2</sub> (Gy)	73%/80%	38%/46%



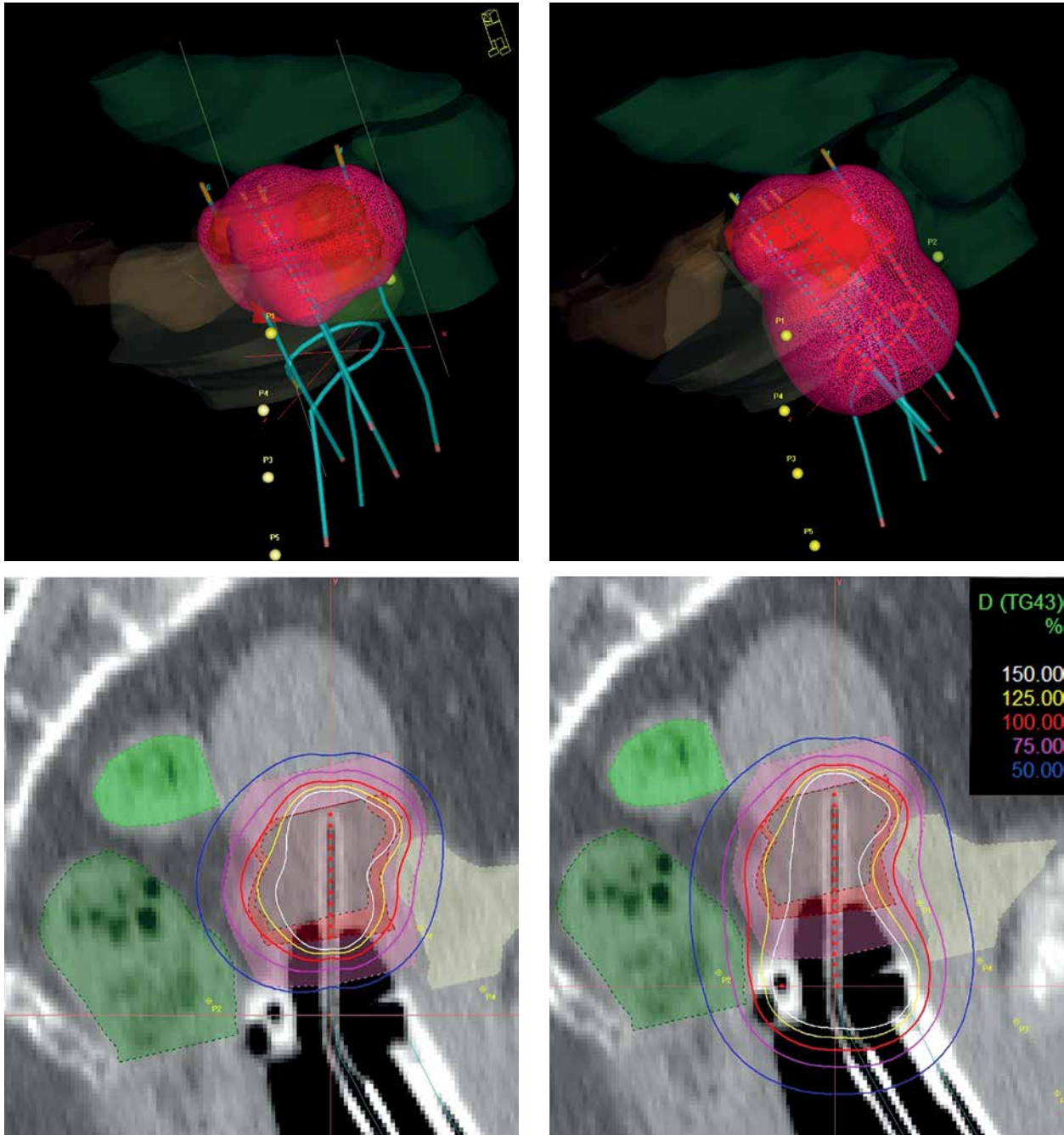
97.6% (2 patients had local recurrence), 4 patients had distant metastases, and 2 patients died during this time. No necrosis was reported.

**Discussion**

Brachytherapy boost has a fundamental role in the radiotherapy of LACC. It is used to guarantee local control with irradiation of residual tumor with appropriate dose, apart from avoiding treatment-related morbidity with sparing dose to OARs [6]. Evidence confirm its effective-

ness in local control; the EMBRACE study has reported rates of over 90% for all FIGO stages at 3 years [30, 39, 40]. However, various severe toxicities were also reported, with most serious including rectal fistula and vaginal stenosis. As certain dose-volume parameters of the target volumes correlate to local control [41, 42], the dose parameters of these organs predict the prevalence of side effects [43, 44]. Recently, the main question is: how we can reach the optimal value of these dose-volume parameters?

In the era of advanced imaging modalities, special IS-IC applicators with the opportunity of oblique nee-



**Fig. 1.** Isodose surface (light red) of the prescribed dose (top) and dose distribution (bottom) without (left) and with using active dwells in the ring/ovoid of the applicator (right). Pink - IR-CTV; Red - HR-CTV; Grey - GTV; Yellow - bladder; Dark green - rectum; Light green - sigmoid

dles and inverse dose optimization methods, there is no strong evidence available for implementing one approach over another. Tanderup *et al.* recommended dose planning aims and dose prescription in image-guided cervical BT [45]. However, these conclusions were based on the clinical evidence of treatment plans using the traditional pear-shape spatial dose only. Earlier, the same team tried to de-escalate the vaginal dose by decreasing dwell times in R/O and increasing it in tandem/needles [27]. The aim was to maintain the target dose while reducing the dose to the surface of the vagina to be < 140% of the physical fractional BT dose corresponding to a total EQD<sub>2</sub> of 85 Gy. The R/O loading was reduced from 51% to 33% of total loading, which resulted in a reduced dose to ICRU recto-vaginal point by a mean of 4 ± 4 Gy EQD<sub>2</sub>, and D<sub>2</sub> doses to the bladder and rectum were reduced by 2 ± 2 Gy and 3 ± 2 Gy, respectively. In the current study, we achieved the total dose de-escalation of the critical tissues, as source loading in the R/O channel of the applicators was reduced to zero in cases where residual tumors did not involve the vagina. This approach simply follows the basic rule of BT that active dwell positions have to be inside or on the surface of the target volume. This technique results in a highly conformal tumor-shape dose distribution around the target volumes, breaking the rules of the conventional pear-shape dose (Figure 1).

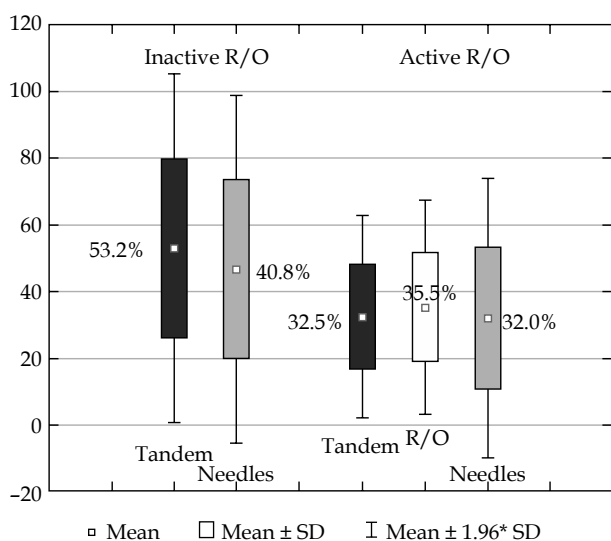
While dose coverage of the target volumes is similar to using active R/O, the EQD<sub>2</sub> total D<sub>2</sub> dose to the bladder, rectum, sigmoid, small bowel, and vaginal wall were reduced by 14.1 Gy, 17.3 Gy, 5.6 Gy, 2.9 Gy, and 39.1 Gy, respectively. However, the dose to the IR-CTV was smaller without loading the R/O (D<sub>98</sub> were 60.8 Gy using inactive, and 63.9 Gy with active R/O); these dose plans fulfilled the GEC-ESTRO (EMBRACE II study) and ABS recommendations in the same degree, i.e., 96%. In terms of residual GTV, the D<sub>90</sub> non-significantly increased with inactive R/O (97.2 Gy vs. 95.5 Gy). Loading R/O shifts

higher doses to the direction of R/O, where there is no GTV, and accordingly, unnecessarily increases the dose to OARs. The loading patterns also illustrate this effect. The tandem dominates the contribution to TRAK between the tandem and needles without R/O loading (53.2% vs. 40.8%), and these shifts to a harmonized distribution with R/O activation (Figure 2). Dose to points A is not interpretable, because of the proximity of IS needles. With the same level of homogeneity, inactive R/O results in almost 2 times higher dose conformity of the target volumes (COIN: 0.62 vs. 0.38).

The planning aim in both dose plans with inactive or active R/O was to fulfil the GEC-ESTRO (EMBRACE II study) and ABS dose recommendations. The HR-CTV was exposed at least with the recommended EQD<sub>2</sub> total dose (D<sub>90</sub>) in 100% of the patients with inactive and active R/O techniques. Criteria for the D<sub>98</sub> parameter were fulfilled in 96% of the plans without active R/O, and in 92% using active R/O. The GTV was covered with D<sub>98</sub> dose in 100% of the cases in plans with inactive, and in 80% with active R/O. However, the D<sub>98</sub> dose coverage of IR-CTV was the same in both the plans, i.e., 96%. Only the dose criterion of points A was fulfilled to a lesser extent without active R/O, i.e., 88%. While using active dwells in R/O, 100% of the plans fulfilled this criterion. While all the plans without R/O activation fulfilled the dose criteria (D<sub>2</sub>) in 100% for the bladder, rectum, and sigmoid, the plans with active R/O satisfied the same criteria in 72%, 56%, and 88%, respectively. Reducing R/O loading to zero showed better optimal dose plan as recommended by the GEC-ESTRO (EMBRACE II study) and ABS.

In IS applications, dwell positions in the needles can replace the dwells of R/O if needed, and can shape the dose distribution to conformal. Using R/O without active dwells is a recognized routine in IS applications; several centers use special (i.e., 3D-printed) template instead of the original R/Os [14-18]. This question is more interesting in the case of IC only applications, where without R/O, only a one-channel applicator has a rule in shaping the appropriate dose distribution. Since IC applications is applied for irradiation of smaller and symmetrical HR-CTVs, the cylindrical dose distribution from this one channel can cover the tumor conformally. Moreover, the reason can be the same that activating the R/O part of the applicator increases the dose to the bladder and rectum in higher degree in IC only applications compared with IS only applications. That is why the ratio of the plans fulfilled dose-volume criteria and were lower in IC applications than IS cases using active R/O.

Basically, the distance of the R/O source path from HR-CTV and from OARs is a good starting point to decide the activation of R/O. If the surface of the R/O part of the applicator touches the inferior border of HR-CTV, the former distance is 5-10 mm, depending on the applicator used. Especially in the case of a narrow vagina, an air gap can exist between R/O and the surface of HR-CTV (Figure 1), which may affect the use of vaginal component. It strongly influences dosimetric parameters, mainly dose conformity of the plans. If after dose optimization the dose exposition is higher to an OAR than to HR-CTV,



**Fig. 2.** Contribution of TRAK between tandem, ring/ovoid (R/O) and needles of cervical brachytherapy applicators using inactive and active R/O channel in interstitial-intra-cavitary applicator

an alternative dose plan is recommended without activation of R/O as well as evaluation of the fulfilment of dose recommendations in both the plans. The necessity of loading R/O strongly depends on an individual anatomy of a patient. Of note, in case of tumors with vaginal involvement, when HR-CTV includes a portion of the vagina, source dwell positions in R/O (in HR-CTV) has to be activated accordingly the basic rules of BT. However, majority of residual tumors of the cervix does not involve the vagina. In this case, the R/O part of the applicator can be only a template for IS needles, or a fixation tool for the intra-uterine tandem.

Nevertheless, the reported clinical data of the current dosimetric study, which focused on the improvement of the dose-volume parameters that were in correlation with tumor control and side effects, are promising, despite rather limited cohort of 60 patients. Reducing dose to OARs, especially to the vaginal wall, without compromising the dose coverage of the target volumes carries itself the promise of reducing the development of rectal fistula and vaginal stenosis, and therefore contribute to preservation of sexual function. Therefore, this study can be a starting point for a prospective clinical study to explore the clinical relevance of this dose planning method.

## Conclusions

Inactivation of the R/O applicator results in similar dose coverage of the target volumes with lower doses to all OARs as activating R/O in cervix cancer patients when HR-CTV does not extend to the R/O applicator. The use of active source positions in the R/O performs worse regarding the fulfilment of the criteria of the international recommendations for OARs.

## Disclosure

The authors report no conflict of interest.

## References

- Hsieh CH, Tien HJ, Hsiao SM et al. Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients – A preliminary result. *Onco Targets Ther* 2013; 6: 59-66.
- Guckenberger M, Bachmann J, Wulf J et al. Stereotactic body radiotherapy for local boost irradiation in unfavourable locally recurrent gynaecological cancer. *Radiother Oncol* 2010; 94: 53-59.
- Gill BS, Lin JF, Krivak TC et al. National cancer data base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. *Int J Radiat Oncol Biol Phys* 2014; 90: 1083-1090.
- Molla M, Escude L, Nouet P et al. Fractionated stereotactic radiotherapy boost for gynecologic tumors: an alternative to brachytherapy? *Int J Radiat Oncol Biol Phys* 2005; 62: 118-124.
- Haas JA, Witten MR, Clancey O et al. CyberKnife boost for patients with cervical cancer unable to undergo brachytherapy. *Front Oncol* 2012; 2: 25.
- Tanderup K, Eifel PJ, Yashar CM et al. Curative radiation therapy for locally advanced cervical cancer: brachytherapy is NOT optional. *Int J Radiat Oncol Biol Phys* 2014; 88: 537-539.
- Georg D, Kirsits C, Hillbrand M et al. Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy. *Int J Radiat Oncol Biol Phys* 2008; 71: 1272-1278.
- Pötter R, Dimopoulos J, Georg P et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007; 83: 148-155.
- Mazeron R, Gilmore J, Dumas I et al. Adaptive 3D image-guided brachytherapy: a strong argument in the debate on systematic radical hysterectomy for locally advanced cervical cancer. *Oncologist* 2013; 18: 415-422.
- Koh V, Choo BA, Lee KM et al. Feasibility study of toxicity outcomes using GEC-ESTRO contouring guidelines on CT based instead of MRI-based planning in locally advanced cervical cancer patients. *Brachytherapy* 2017; 16: 126-132.
- Zolciak-Siwinska A, Kowalczyk A, Sikorska K et al. Comparison of computed tomography with magnetic resonance imaging for imaging-based clinical target volume contours in cervical cancer brachytherapy. *Brachytherapy* 2018; 17: 667-672.
- Pötter R, Federico M, Sturdza A et al. Value of magnetic resonance imaging without or with applicator in place for target definition in cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2016; 94: 588-597.
- Schmid MP, Nesvacil N, Pötter R et al. Transrectal ultrasound for image-guided adaptive brachytherapy in cervix cancer – An alternative to MRI for target definition? *Radiother Oncol* 2016; 120: 467-472.
- Kirsits C, Lang S, Dimopoulos J et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer. Design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys* 2006; 5: 624-630.
- Fokdal L, Tanderup K, Hokland SB et al. Clinical feasibility of combined intracavitary/interstitial brachytherapy in locally advanced cervical cancer employing MRI with a tandem/ring applicator in situ and virtual preplanning of the interstitial component. *Radiother Oncol* 2013; 107: 63-68.
- Jürgenliemk-Schulz IM, Tersteeg RHA, Roesink JM et al. MRI-guided treatment optimisation in intracavitary or combined intracavitary/interstitial PDR brachytherapy using tandem ovoid applicators in locally advanced cervical cancer. *Radiother Oncol* 2009; 93: 322-330.
- Walter F, Maihofer C, Schuttrumpf L et al. Combined intracavitary and interstitial brachytherapy of cervical cancer using the novel hybrid applicator Venezia: Clinical feasibility and initial results. *Brachytherapy* 2018; 17: 775-781.
- Fröhlich G, Vízkeleti J, Anhhong NN et al. Dosimetric evaluation of combined intracavitary-interstitial image-guided adaptive brachytherapy of cervical cancer and comparison with conventional treatment techniques. *Magy Onkol* 2018; 62: 242-248.
- Vízkeleti J, Fröhlich G, Anhhong NN et al. Clinical results of combined intracavitary-interstitial image-guided adaptive brachytherapy in locally advanced cervical cancer. *Magy Onkol* 2018; 62: 249-257.
- Tod MC, Meredith WJ. A Dosage system for use in the treatment of cancer of the uterine cervix. *Br J Radiol* 1938; 11: 809-824.
- Mahantshetty U, Pötter R, Beriwal S et al. IBS-GEC ESTRO-ABS recommendations for CT based contouring in image guided adaptive brachytherapy for cervical cancer. *Radiother Oncol* 2021; 160: 273-284.
- Paul AG, Nalichowski A, Abrams J et al. Dosimetric evaluation of Point A and volume-based high-dose-rate plans: a single institution study on adaptive brachytherapy planning for cervical cancer. *J Contemp Brachytherapy* 2018; 10: 202-210.
- Mazeron R, Gouy S, Escande A et al. Locally advanced cervical cancer: Is it relevant to report image-guided adaptive brachytherapy using point A dose? *Brachytherapy* 2017; 16: 862-869.



24. Thibault I, Lavalley MC, Aubin S et al. Inverse-planned gynecologic high-dose-rate interstitial brachytherapy: Clinical outcomes and dose-volume histogram analysis. *Brachytherapy* 2012; 11: 181-191.
25. Trnková P, Pötter R, Baltas D et al. New inverse planning technology for image-guided cervical cancer brachytherapy: Description and evaluation within a clinical frame. *Radiother Oncol* 2009; 93: 331-340.
26. Fröhlich G, Geszti Gy, Vizkeleti J et al. Dosimetric comparison of inverse optimisation methods versus forward optimisation in HDR brachytherapy of breast, cervix and prostate cancer. *Strahlenther Onkol* 2019; 195: 991-1000.
27. Mohamed S, Lindegaard JC, de Leeuw AAC et al. Vaginal dose de-escalation in image guided adaptive brachytherapy for locally advanced cervical cancer. *Radiother Oncol* 2016; 120: 480-485.
28. Haie-Meder C, Pötter R, Van Limbergen E et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment on GTV and CTV. *Radiother Oncol* 2005; 74: 235-245.
29. Pötter R, Haie-Meder C, Van Limbergen E et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (II): Concepts and terms in 3D image-based 3D treatment planning in cervix cancer brachytherapy – 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78: 67-77.
30. EMBRACE study, <https://www.embracestudy.dk/>
31. Viswanathan AN, Thomadsen B, American Brachytherapy Society Cervical Cancer Recommendations Committee. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles. *Brachytherapy* 2012; 11: 33-46.
32. Viswanathan AN, Beriwal S, De Los Santos J et al. The American Brachytherapy Society treatment recommendations for locally advanced carcinoma of the cervix. Part II: high dose-rate brachytherapy. *Brachytherapy* 2012; 11: 47-52.
33. Fowler JF. The linear-quadratic formula on progress in fractionated radiotherapy. *Br J Radiol* 1989; 62: 679-694.
34. Nag S, Gupta N. A simple method of obtaining equivalent doses for use in HDR brachytherapy. *Int J Radiat Oncol Biol Phys* 2000; 46: 507-513.
35. ICRU Report 89. Prescribing, Recording and Reporting Brachytherapy for Cancer of the Cervix. Oxford University Press, 2013.
36. Saw CB, Suntharalingam N, Wu A. Concept of dose nonuniformity in interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 1993; 26: 519-527.
37. Baltas D, Kolotas C, Geramani K et al. A conformal index (COIN) to evaluate implant quality and dose specification in brachytherapy. *Int J Radiat Oncol Biol Phys* 1998; 40: 515-524.
38. Limkin EJ, Dumas I, del Campo ER et al. Vaginal dose assessment in image-guided brachytherapy for cervical cancer: Can we really rely on dose-point evaluation? *Brachytherapy* 2016; 15: 169-176.
39. Pötter R, Georg P, Dimopoulos JC et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011; 100: 116-123.
40. Fallon J, Park SJ, Yang L et al. Long term results from a prospective database on high dose rate (HDR) interstitial brachytherapy for primary cervical carcinoma. *Gynecol Oncol* 2017; 144: 21-27.
41. Dimopoulos JCA, Lang S, Kirisits C et al. Dose-volume histogram parameters and local control in magnetic resonance image-guided cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2009; 75: 56-63.
42. Dimopoulos JCA, Pötter R, Lang S et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. *Radiother Oncol* 2009; 93: 311-315.
43. Georg P, Kirisits C, Goldner G et al. Correlation of dose-volume parameters, endoscopic and clinical rectal side effects in cervix cancer patients treated with definitive radiotherapy including MRI-based brachytherapy. *Radiother Oncol* 2009; 91: 173-180.
44. Susko M, Craciunescu O, Meltsner S et al. Vaginal dose is associated with toxicity in image guided tandem ring or ovoid-based brachytherapy. *Int J Radiat Oncol Biol Phys* 2016; 94: 1099-1105.
45. Tanderup K, Nesvacil N, Kirchheiner K et al. Evidence-based dose planning aims and dose prescription in image-guided brachytherapy combined with radiochemotherapy in locally advanced cervical cancer. *Semin Radiat Oncol* 2020; 30: 311-327.