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ADAPTIVE MAGNETIC RESONANCE-GUIDED EXTERNAL BEAM
RADIATION THERAPY FOR CONSOLIDATION IN RECURRENT
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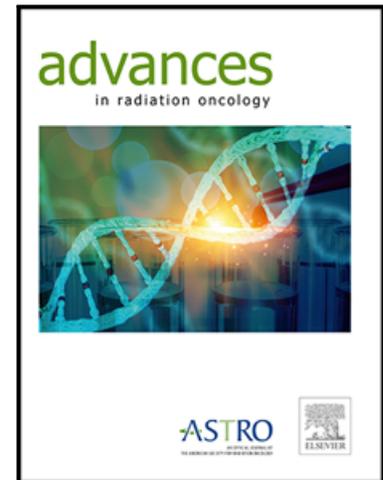
ADAPTIVE MAGNETIC RESONANCE-GUIDED EXTERNAL BEAM RADIATION THERAPY FOR CONSOLIDATION IN RECURRENT CERVICAL CANCER.

Short running title: Adaptive MR-guided EBRT cervical boost.

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ABSTRACT

INTRODUCTION: Adaptive magnetic resonance (MR)-guided brachytherapy takes an important place as consolidation within the care of cervical malignancies. However, in some unusual cases, it may be impracticable. This work aimed to present the case of adaptive MR-guided external beam radiation therapy (aMRgRT) used as a boost in a recurrence of cervical cancer.

CASE: Here, we report a case of a parametrial recurrence in a 31-year-old patient, who already underwent trachelectomy as a treatment for her primary growth. After concomitant radiochemotherapy, a brachytherapy boost was performed. Because of its position in relation

to the left uterine artery following trachelectomy, impeding interstitial catheters set up, the relapse was insufficiently covered. With the aim to refine the coverage of target volumes, aMRgRT treatment was undertaken, allowing the achievement of dosimetric goals.

DISCUSSION: In such clinical circumstances where the brachytherapy step was hindered, aMRgRT presented many advantages. First, daily native MR-imaging outperforms usual X-ray imaging in the pelvis, refining repositioning. Second, its specific workflow allows us to perform adaptive treatment, with consideration of both the inter- and intrafraction motions of organs at risk and target volumes.

CONCLUSION: In non-feasible brachytherapy situations, aMRgRT could be a satisfying substitute. Nevertheless, brachytherapy remains the standard of care as a boost in locally advanced cervical cancer.

INTRODUCTION

With a probability of 1/157 women, cervical cancer is the third most common gynecologic malignancy[1], representing a large part of the indications for brachytherapy, either as monotherapy or following external beam radiation therapy.

Despite its decreasing use, the role of brachytherapy in cervical cancers remains uncontested.[2–4]

The main techniques are pulsed dose-rate and high dose-rate brachytherapy. It requires a running workflow with well-trained operators and a suitable environment (magnetic resonance imaging [MRI] availability and specific materials, including a source projector). This makes brachytherapy often performed in a referral center. Actual guidelines recommend magnetic resonance (MR)-guided adaptive brachytherapy as a standard of care.[5]

Nevertheless, many reasons may impede the brachytherapy consolidation step, such as patient medical history, pelvic anatomical setup, contraindications to anesthesia, or refusal. Alternative options are scarce, but adaptive MR-guided external beam radiation therapy (aMRgRT) might offer two main advantages. First, it enables accurate visualization of both tumor and pelvic structures. Second, it allows adaptive treatment through a dedicated workflow, including tumor gating and real-time contouring and planning.

Here, we present the case of an aMRgRT boost in a patient with a parametrial recurrence of cervical cancer, in which brachytherapy failed to offer satisfying target volume coverage.

CASE

Initially, a cervical lesion was found in March 2019 during a routine gynecological examination in a 29-year-old patient without any medical history, except for an elective abortion. Biopsies showed a chorion-infiltrating neoplasia and high-grade intraepithelial vaginal neoplasia. Pelvic MRI revealed a 13 mm cervical growth.[6,7] The patient was then referred to our center. She underwent examination under anesthesia, finding a 3.5 x 3 cm bleeding growth invading the whole uterine cervix without any parametrial or vaginal invasion, and diagnostic cervical conization was performed at the same time. Histological analyses revealed a 4 mm stroma-infiltrating 13 mm diameter squamous cell carcinoma that was incompletely resected, staged pT1b1 according to the 8th TNM classification and IB1 according to FIGO 2018. Both squamous cell carcinoma (SCC) antigen and carcinoembryonic antigen were negative. As recommended during the multidisciplinary meeting, a bilateral pelvic lymph node dissection was performed and happened to be negative (0 N+/15), with likewise peritoneal cytology. We informed the patient about the necessity of definitive treatment with brachytherapy, followed by total hysterectomy, and also referred her to a

reproductive endocrinology fertility expert. But to preserve her fertility[8,9] and according to her preferences, despite a higher risk of recurrence, a trachelectomy was performed in May 2019, allowing complete resection of a 6 mm well-differentiated keratinizing SCC with lymphovascular invasion associated with high-grade intraepithelial neoplasia, finally staged FIGO IB1. There was no parametrial infiltration. Close surveillance was established, including quarterly colposcopies and bi-annual pelvic MRIs.

Sixteen months later, the patient complained about persistent pelvic pain, dyspareunia, and intermittent metrorrhagia. Biological analyses found a concomitant SCC antigen elevation (4.6 µg/L versus 2.2 µg/L 4 months ago). In the end, morphometabolic explorations realized in November 2020 highlighted a highly vascularized, hypermetabolic (SUV max = 5.7) 15 x 19 x 17 mm left proximal parametrial nodule (Fig. 1). Biopsy performed in January 2021 confirmed a recurrence of SCC. Therefore, the multidisciplinary meeting proposed concomitant radiochemotherapy (45 Gy in 25 fractions delivered using volumetric modulated arc therapy, associated with weekly cisplatin perfusions) as a treatment, followed by an HDR-brachytherapy boost using a combined intracavitary/interstitial device given the parametrial involvement. Concomitant radiochemotherapy was completed in March 2021 and well tolerated, resulting in a partial response (MR-assessed 15 mm residual mass) and normalization of the SCC antigen marker.

Afterwards, the first part of the brachytherapy was performed using a 192-Ir source and Utrecht device (Elekta, Sweden) made up of a 15° intrauterine tube, two 25 mm ovoids, and two left interstitial catheters. Because of the lateral recurrence location, only 12 Gy (instead of 15 Gy) could be administered on the high-risk clinical target volume (HR-CTV) in two daily 6 Gy fractions, according to the Groupe Européen de Curiethérapie and European SocieTy for Radiotherapy and Oncology (GEC-ESTRO) recommendations (Table 1).[5,10] However, the upper part of the left parameter was insufficiently covered (as shown in Fig. 2).

Therefore, given the history of trachelectomy that may have altered the local vascular anatomy, we performed a computed tomography (CT) angiography aiming to precisely localize the course of the left uterine artery, allowing deeper interstitial catheter positioning to maximize HR-CTV coverage during the second part of the treatment.

Unfortunately, this was not feasible because, due to the previous radical trachelectomy, the artery in question appeared to be in a very proximal position (Fig. 3), exposing the patient to a bleeding risk.[11] This is why we undertook to substitute the second part of brachytherapy treatment with stereotactic hypofractionated aMRgRT using the MRIdian linear accelerator (ViewRay Inc). The initial aMRgRT planning is presented in Fig. 4. By analogy with adaptive brachytherapy, the delineation of tumor and organs at risk (OARs) followed the aforementioned brachytherapy guidelines, taking into account tumor shrinkage following the first part of treatment (chemosensitized radiation therapy). For each fraction, we delineated both target volumes and surrounding organs (bladder, bowel, sigmoid, and rectum), and we optimized the treatment plan in real-time to prevent planning imprecisions due to interfraction organ movement or repletion. Except for D90 of HR-CTV (due to suboptimal brachytherapy), dose constraints as exposed in Table 1 met the EMBRACE II study recommendations, including gross tumor volume (GTV) and intermediate-risk (IR)-CTV.[12] According to GEC-ESTRO guidelines and given the use of real time MRI adaptive planning, we chose not to apply planning target volume (PTV) margins in this case. Treatment was well tolerated.

Follow-up MRIs at 2 months and 4 months showed a waning scar instead of the recurrence, and metabolic imaging at 4 months revealed a complete metabolic response. Seven months later, the patient did not report any symptoms, and the SCC antigen marker remained normal.

The patient agreed to share her medical data as part of clinical research.

DISCUSSION

Our case illustrates the complexity of some clinical circumstances, compelling clinicians to adapt their practice in comparison to guidelines.

In this case, we faced a high risk of severe bleeding, given the proximity between the recurrence and the left uterine artery, all the more as active sources should be longer than the target volume as described in the Paris System.[13] In cervical cancer brachytherapy, the risk of vascular injury resulting from interstitial needle positioning has already been described in the literature, reaching up to 5.2% of catheter removal cases. Although sometimes efficiently controlled by vaginal tamponade or stitches, these bleeds may also require blood transfusions, endoscopic interventions, or even embolization.[11,14,15] This risk of hemorrhage needs to be known and assessed, especially in unusual clinical contexts, such as in our patient's case.

The MRIdian equipment offers the possibility of administering an adaptive treatment called "on ART." During the session, MRI is performed with the patient on the treatment table to determine all the contours. Some volumes, such as OARs, are automatically deformed. Once checked and corrected, the radiation therapist will outline target volumes, such as HR-IR CTV. The construction of target volumes (internal target volume,PTV, etc.) and optimization volumes are then applied following the rules defined in the structure derivation system. New planning is thus carried out on this new imagery.

Many brachytherapy alternatives have already been tested, involving as much proton beam therapy as intensity-modulated X-ray radiation therapy (using helical tomotherapy, a classic linear accelerator, or a stereotactic dedicated one like the CyberKnife).[16–21] According to the reports, even if tolerance appears to be acceptable for most of them, these treatments never showed superiority when compared to brachytherapy, which remains the standard of care for locally advanced cervical malignancies.[22] Moreover, a 2019 phase II trial precisely

investigated the outcomes of stereotactic ablative radiation therapy as a boost for locally advanced cervical cancer, replacing brachytherapy.[23] Tolerance appeared poor, with high rates of late and sometimes severe toxicity (such as rectal fistula leading to death in two patients among 15). Some authors suggested that it may arise from the large tumor size, which, coupled with intrafraction motion, required an increase in the amount of healthy tissue in the radiation field for adequate target coverage. Target motion may be successfully managed by using gating, such as that allowed by aMRgRT in our patient. With a modestly sized recurrence (apart from OARs), she should possibly remain free from late toxicities, yet a longer follow-up is necessary to gauge them, as well as lasting clinical efficiency.

The performance of X-ray imaging is limited in the pelvis (especially as image-guided radiation therapy [IGRT]), while MRI provides better soft tissue contrast. Thus, using aMRgRT, the tumor and surrounding OARs can be accurately visualized, characterized, and gated. For these reasons, aMRgRT seems to represent a good opportunity when a brachytherapy boost appears to be unsuitable.[21,24,25] Considering that, on the one hand, the use of MRI in brachytherapy is one of the most noteworthy advances in the care of cervical malignancies, allowing adaptive treatment, and, on the other hand, MR-Linac (like MRIdian® or Elekta Unity) is the only modality providing native MR images (for both planning and IGRT), it could constitute an interesting treatment option.

Our patient's treatment was delivered using a stereotactic hypofractionated protocol, with a simultaneous integrated boost method to mimic brachytherapy dose gradients. Doses were consequently prescribed on the basis of the D98 isodose of GTV (up to 18 Gy, which allowed 14 Gy on HR-CTV and 7.6 Gy on IR-CTV). The lateralized position of the recurrence, away from OARs, enabled us to achieve a 30 Gy dose within GTV. Such a dose would have been likely unachievable in a classic central pelvic situation.

To our knowledge, our article is the second one describing the use of aMRgRT instead of brachytherapy as consolidation after chemosensitized radiation therapy for cervical cancer. Indeed, Sayan et al. reported, in 2020, a case in which they used this technique for a patient who didn't want to go to a referral center.[26] They also described a well-tolerated treatment, with middle-term favorable outcomes, and the patient being clinically free of disease after 9 months. At the dawn of an aMRgRT blooming period, this case and ours open the door to further studies to evaluate with more acuteness its utility in such clinical instances. Nonetheless, these data should be carefully interpreted with regards to limited follow-up, regarding as much efficacy as long-term toxicities.

CONCLUSION

In very specific circumstances of cervical cancer, combining favorable tumoral features and appropriate anatomic setup, aMRgRT as a boost seems to be practicable, allowing a good coverage of target volumes and acceptable sparing of surrounding organs. However, waiting for a longer follow-up and further studies, it still must be strictly restricted to situations in which brachytherapy is not feasible.

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TABLES AND FIGURES

Table 1: Dosimetric data about both brachytherapy (BT) and adaptive magnetic resonance-guided radiation therapy (aMRgRT).

The most favorable dose received is highlighted in green for each clinical goal. Initial doses were obtained applying pre-treatment planning on initial dosimetric imaging, planned doses were obtained applying initial planning on daily imaging, and adapted doses were obtained after delineation considering daily imaging.

Table 2: Dose constraints according to the EMBRACE II study.[12] The EQD2 is calculated using a/b = 10 for targets, a/b = 3 for organs at risk, and a repair halftime of 1.5 h. The total EQD2 includes 45 Gy/25 fractions delivered by external beam radiation therapy.
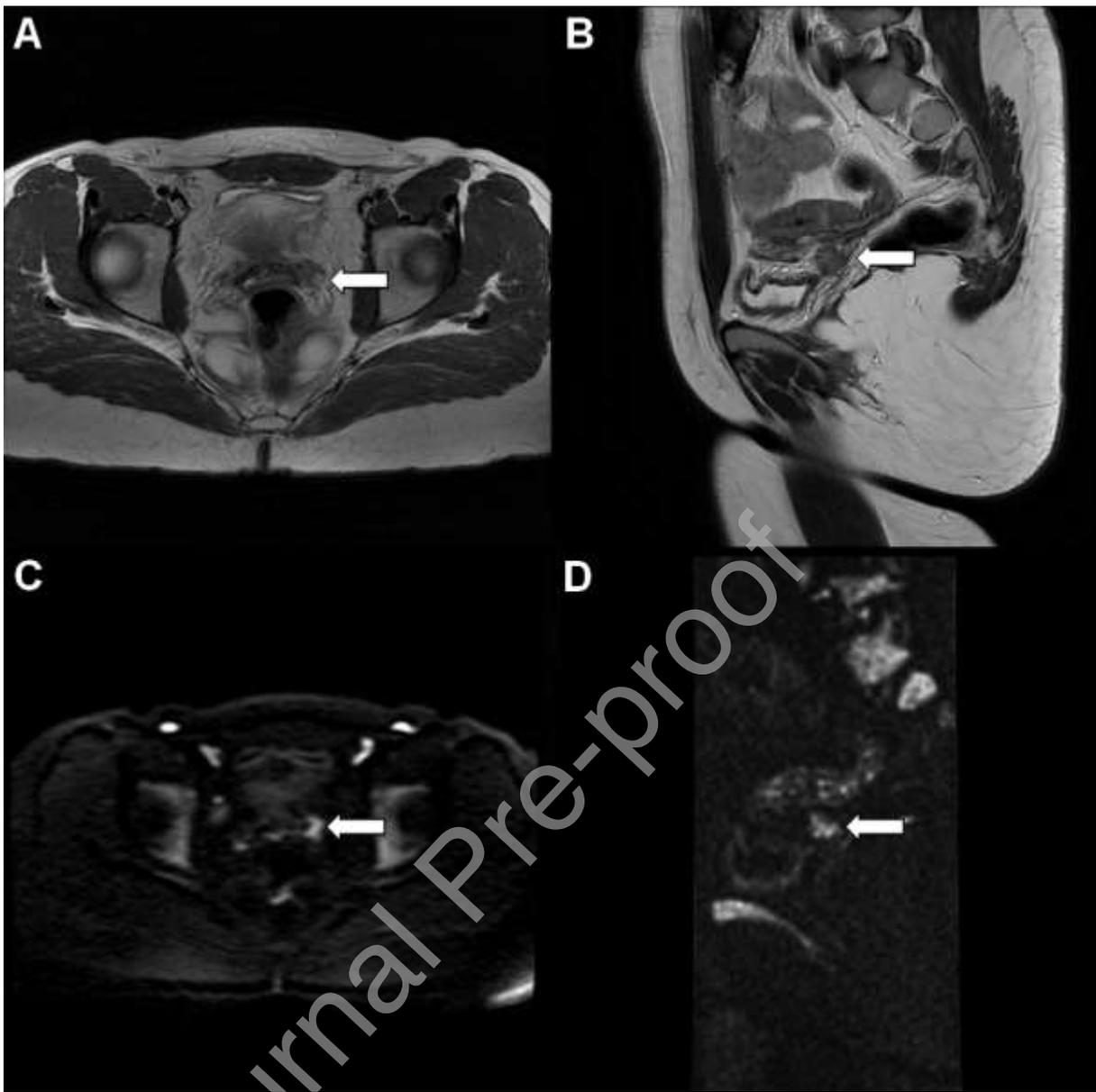
Figure 1: Axial and sagittal T2 (A, B) and diffusion (C, D) magnetic resonance imaging

slices showing the left parametrial recurrence (white arrow).
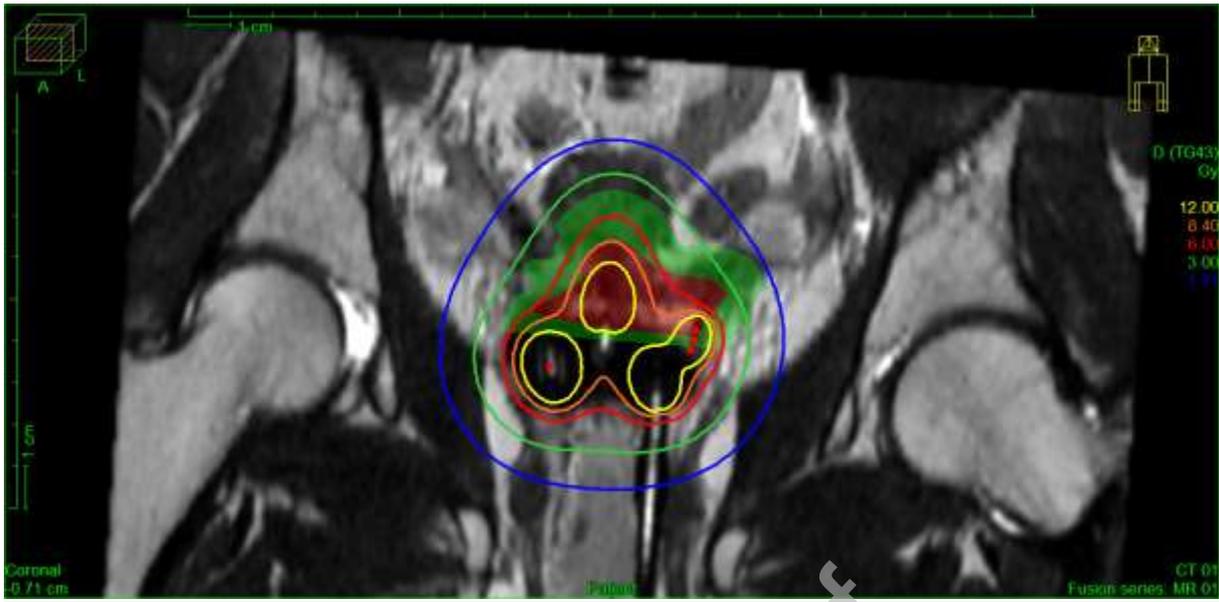
Figure 2: Brachytherapy planning (coronal view), with insufficient left upper HR-CTV (red) and IR-CTV (green) coverage. Isodose lines are as follows: 12 Gy (yellow), 8.4 Gy (orange), 6 Gy (red), 3 Gy (green), and 1 Gy (blue).

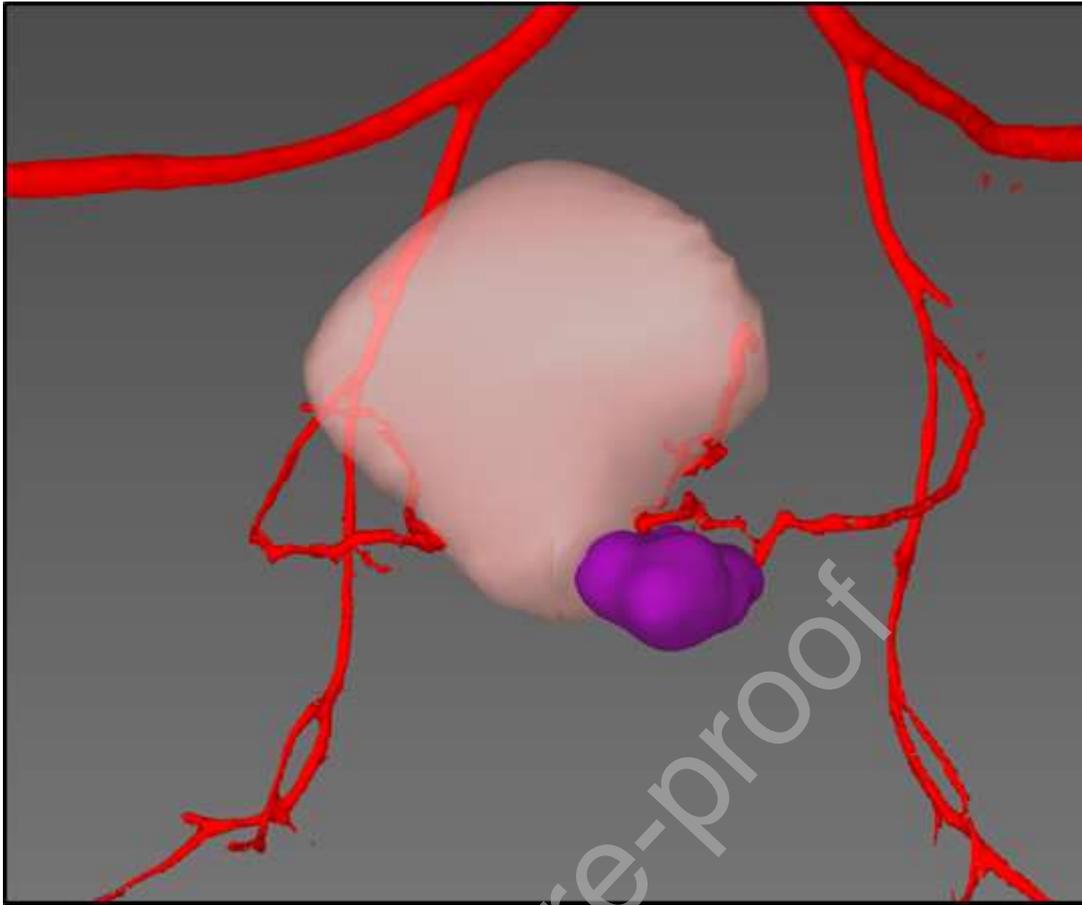**Figure 3:** 3D reconstruction from computed tomography angiography showing the relative

position of the left uterine artery in relation to the remaining uterus and to the recurrence.

Figure 4: Dose distribution as stated in initial MRIdian planning. Isodose lines are as follows:
22.5 Gy (red), 18 Gy (orange), 15 Gy (light green), 7.6 Gy (yellow), 6 Gy (light blue), 5 Gy
(green), and 3 Gy (blue).

Table 1: Dosimetric data about both brachytherapy (BT) and adaptive magnetic resonance-guided radiation therapy (aMRgRT).

The most favorable dose received is highlighted in green for each clinical goal. Initial doses were obtained applying pre-treatment planning on initial dosimetric imaging, planned doses were obtained applying initial planning on daily imaging, and adapted doses were obtained after delineation considering daily imaging.

		BT	aMRgRT						Total (EQD2) EBRT + BT + aMRgRT
					First fraction		Second fraction		
		Total	Initial	Planned	Adaptated	Planned	Adaptated	Total	
GTV	D98	14.2	18	8.52	9	9.35	10	19	95.4
HR-CTV	D90	12	15.72	7.73	7.93	7.68	7.77	15.7	83.6
	D98	8.8	14.01	6.95	7.255	6.84	7	14.255	75.2
IR-CTV	D90	7.6	8.99	4.535	4.585	4.475	4.455	9.04	63.9
	D98	7	8.01	4.09	4.21	3.87	3.845	8.055	61.5
Bladder	2cc	7.1	6.33	2.365	2.27	2.935	3.135	5.405	58.8
Rectum	2cc	8	6.93	3.32	3.405	3.32	3.36	6.765	63.1
Sigmoid	2cc	4.2	5.08	4.645	4.45	3.105	2.985	7.435	57.7
Bowel	2cc	2.9	3.58	1.68	1.95	2.21	2.205	4.155	50.8
Left sciatic nerve	0.5 cc	0.7	5.25	2.555	2.46	2.59	2.545	5.005	49.7

Abbreviations: Dx, the dose received by x% of the volume; GTV, gross tumor volume; HR-CTV, high risk-clinical target volume; IR-CTV, intermediate risk-clinical target volume; cc, cubic centimeters; EBRT, external beam radiation therapy; EQD2, equivalent dose in 2 Gy per fraction.

Doses are in Grays.

Table 2: Dose-constraints according to the EMBRACE II study.[12] The EQD2 is calculated using $a/b = 10$ for targets, $a/b = 3$ for OAR and a repair halftime of 1.5 h. The total EQD2 include 45 Gy/25 fractions delivered by external beam radiation therapy.

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	> 95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	> 90 Gy	-	-

OAR	Bladder D_{2cm3} $EQD2_3$	Rectum D_{2cm3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm3} $EQD2_3$	Bowel D_{2cm3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy	< 70 Gy
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy	< 75 Gy