

Teaching Case

Adaptive Magnetic Resonance-Guided External Beam Radiation Therapy for Consolidation in Recurrent Cervical Cancer



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Abstract

Purpose: Adaptive magnetic resonance (MR)-guided brachytherapy takes an important place as consolidation within the care of cervical malignancies, but may be impracticable in some unusual cases. 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.

Methods and Materials: We report on a case of a parametrial recurrence in a 31-year-old patient who already underwent a trachelectomy as treatment for her primary growth. After concomitant radio-chemotherapy, a brachytherapy boost was performed. Because of its position in relation to the left uterine artery after 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 to allow for achievement of the dosimetric goals.

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

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

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Introduction

With a probability of 1 in 157 women, cervical cancer is the third most common gynecologic malignancy,¹

representing a large part of indications for brachytherapy, either as monotherapy or after external beam radiation therapy. Despite its decreasing use, the role of brachytherapy in cervical cancer remains uncontested.²⁻⁴

The main techniques are pulsed dose-rate and high-dose-rate brachytherapy. Brachytherapy requires a running workflow with well-trained operators and a suitable environment (magnetic resonance imaging [MRI] availability and specific materials, including a source projector). Therefore, brachytherapy is often performed at a referral center. Actual guidelines recommend magnetic

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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 anatomic setup, contraindications to anesthesia, or refusal. Alternative options are scarce, but adaptive MR-guided external beam radiation therapy (aMRgRT) might offer 2 main advantages. First, aMRgRT enables the accurate visualization of both tumor and pelvic structures. Second, aMRgRT allows for adaptive treatment through a dedicated workflow, including tumor gating and real-time contouring and planning.

Herein, 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 gynecologic 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. A pelvic MRI revealed a 13-mm cervical growth.^{6,7} The patient was referred to our center, where she underwent an examination under anesthesia. A 3.5 × 3 cm bleeding growth was found, invading the whole uterine cervix without any parametrial or vaginal invasion, and diagnostic cervical conization was performed at the same time. Histologic analyses revealed a 4-mm stroma-infiltrating 13-mm diameter squamous cell carcinoma (SCC) that was incompletely resected (stage pT1b1 according to 8th TNM classification and IB1 according to International Federation of Obstetrics and Gynecology 2018). Both SCC and carcinoembryonic antigens were negative. As recommended during the multidisciplinary meeting, a bilateral pelvic lymph node dissection was performed and was negative (0 N +/15), with likewise peritoneal cytology.

We informed the patient about the necessity of definitive treatment with brachytherapy, followed by a total hysterectomy, and also referred her to a reproductive endocrinology fertility expert. 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 for a complete resection of a 6-mm well-differentiated keratinizing SCC with lymphovascular invasion associated with high-grade intraepithelial neoplasia (finally staged International Federation of Obstetrics and Gynecology IB1). There was no parametrial infiltration. Close surveillance was established, including quarterly colposcopies and biannual pelvic MRIs.

Sixteen months later, the patient complained about persistent pelvic pain, dyspareunia, and intermittent

metrorrhagia. Biologic analyses found a concomitant SCC antigen elevation (4.6 μg/L vs 2.2 μg/L 4 months prior). In the end, morphometabolic explorations in November 2020 highlighted a highly vascularized, hypermetabolic (SUV_{max} = 5.7) 15 × 19 × 17 mm left proximal parametrial nodule (Fig. 1). A biopsy performed in January 2021 confirmed a recurrence of SCC, and the multidisciplinary team proposed concomitant radio-chemotherapy (45 Gy in 25 fractions delivered using volumetric modulated arc therapy, associated with weekly cisplatin perfusions) as a treatment, followed by a high-dose-rate brachytherapy boost using a combined intracavitary/interstitial device given the parametrial involvement. Concomitant radio-chemotherapy 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.

Afterward, 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 2 daily 6 Gy fractions, according to the Groupe Européen de Curiothérapie and European Society for Radiation therapy and Oncology (GEC-ESTRO) recommendations (Table 1).^{5,10} However, the upper part of the left parameter was insufficiently covered (Fig. 2). Therefore, given the history of trachelectomy that may have altered the local vascular anatomy, we performed a computed tomography angiography aiming to precisely localize the course of the left uterine artery, allowing for deeper interstitial catheter positioning to maximize HR-CTV coverage during the second part of 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 We undertook to substitute the second part of the brachytherapy treatment with stereotactic hypofractionated aMRgRT, using the MRIdian linear accelerator (ViewRay Inc). The initial aMRgRT planning is presented in Figure 4. By analogy with adaptive brachytherapy, the delineation of the tumor and organs at risk (OARs) followed the aforementioned brachytherapy guidelines, taking into account tumor shrinkage after 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 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-CTV.¹² According to the GEC-ESTRO guidelines and given the use of real time

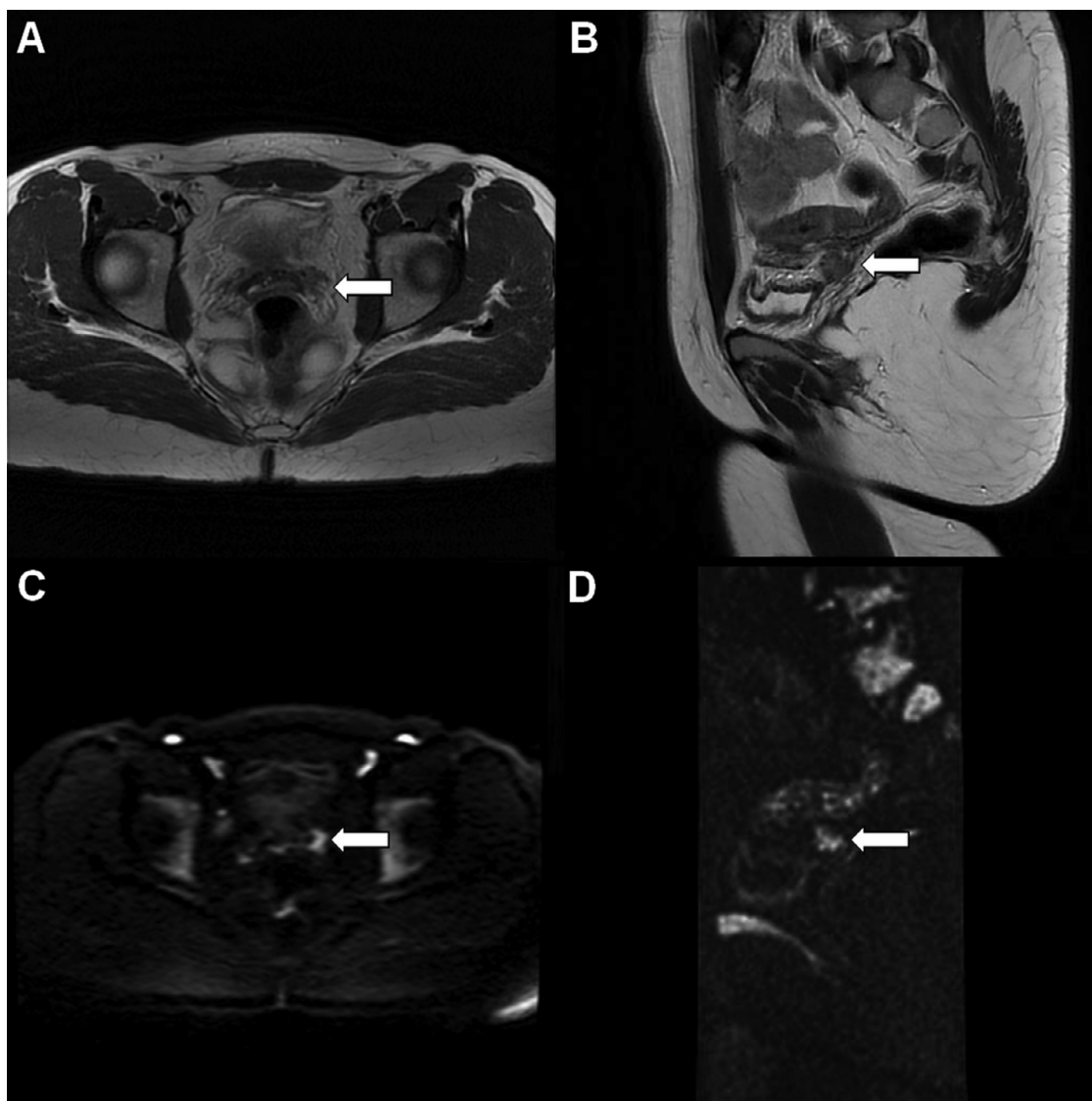


Fig. 1 A, B, Axial and sagittal T2, and C, D, diffusion magnetic resonance imaging slices showing left parametrial recurrence (white arrow).

MRI adaptive planning, we chose not to apply planning target volume margins in this case. Treatment was well tolerated.

Follow-up MRIs at 2 and 4 months showed a waning scar instead of 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 with guidelines. In this case, we faced a

high risk of severe bleeding given the proximity between recurrence and left uterine artery, all the more because 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 contours. Some

Table 1 Dosimetric data about both BT and aMRgRT

		BT	aMRgRT					Total (EQD2) EBRT + BT + aMRgRT	
		Total	Initial	First fraction		Second fraction			Total
				Planned	Adapted	Planned	Adapted		
Gross target volume	D ₉₈	14.2	18	8.52	9	9.35	10	19	95.4
High-risk CTV	D ₉₀	12	15.72	7.73	7.93	7.68	7.77	15.7	83.6
	D ₉₈	8.8	14.01	6.95	7.255	6.84	7	14.255	75.2
Intermediate-risk CTV	D ₉₀	7.6	8.99	4.535	4.585	4.475	4.455	9.04	63.9
	D ₉₈	7	8.01	4.09	4.21	3.87	3.845	8.055	61.5
Bladder	2 cc	7.1	6.33	2.365	2.27	2.935	3.135	5.405	58.8
Rectum	2 cc	8	6.93	3.32	3.405	3.32	3.36	6.765	63.1
Sigmoid	2 cc	4.2	5.08	4.645	4.45	3.105	2.985	7.435	57.7
Bowel	2 cc	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: aMRgRT = adaptive magnetic resonance-guided radiation therapy; BT = brachytherapy; CTV = clinical target volume; D_x = dose received by x% of volume; EBRT = external beam radiation therapy; EQD2 = equivalent dose in 2 Gy per fraction.
Doses are in Gy. The most favorable dose received is highlighted in green for each clinical goal. Initial doses were obtained by applying pretreatment planning on initial dosimetric imaging, planned doses by applying initial planning on daily imaging, and adapted doses after delineation considering daily imaging.

Table 2 Dose constraints according to EMBRACE II study¹²

Target	D ₉₀ CTV _{HR} EQD2 ₁₀	D ₉₈ CTV _{HR} EQD2 ₁₀	D ₉₈ GTV _{res} EQD2 ₁₀	D ₉₈ CTV _{IR} EQD2 ₁₀	Point A EQD2 ₁₀
Planning aims	> 90 < 95	> 75	> 95	> 60	> 65
Limits for prescribed dose	> 85	–	> 90	–	–
Organ at risk	Bladder D _{2cm3} EQD2 ₃	Rectum D _{2cm3} EQD2 ₃	Rectovaginal point EQD2 ₃	Sigmoid D _{2cm3} EQD2 ₃	Bowel D _{2cm3} EQD2 ₃
Planning aims	< 80	< 65	< 65	< 70	< 70
Limits for prescribed dose	< 90	< 75	< 75	< 75	< 75

Abbreviations: CTV = clinical target volume; D_x = dose received by x% of volume; EQD2 = equivalent dose in 2 Gy per fraction; HR = high risk; IR = intermediate risk.
Doses are in Gy. EQD2 is calculated using a/b = 10 for targets, a/b = 3 for organ at risk and a repair half-time of 1.5 hours. Total EQD2 includes 45 Gy per 25 fractions delivered by external beam radiation therapy.

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 (eg, internal and planning target volumes) and optimization volumes are applied per the rules defined in the structure derivation system. Thus, new planning is 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, such as the CyberKnife).¹⁶⁻²¹ According to reports, even if tolerance appears to be acceptable for most, these treatments never showed superiority compared with 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 (eg, rectal fistula leading to death in 2 of 15 patients). Some authors suggested that the poor tolerance was due to 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 managed successfully 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 these toxicities, as well as lasting clinical efficiency.

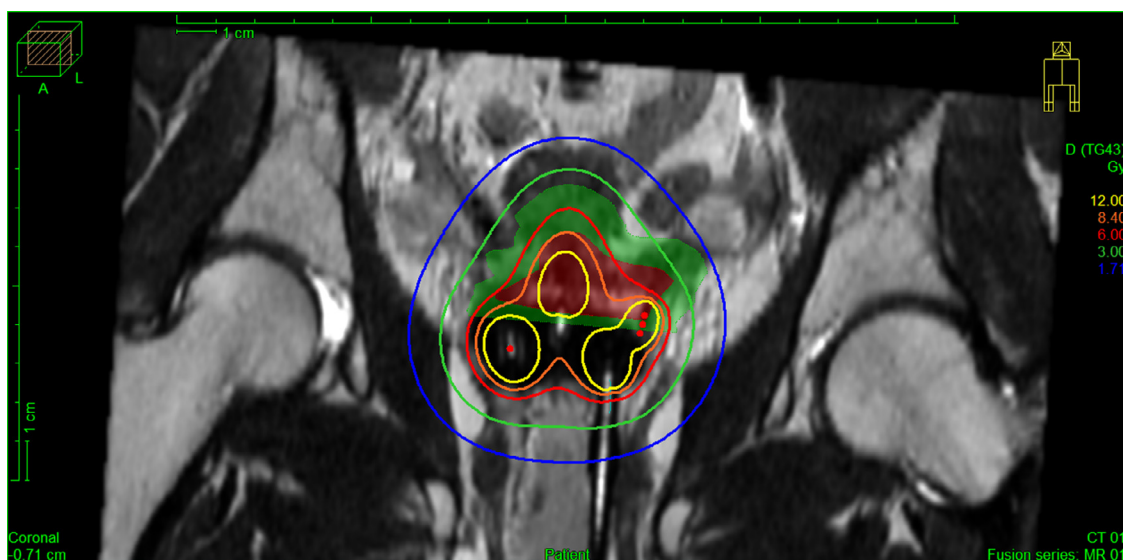


Fig. 2 Brachytherapy planning (coronal view) with insufficient left upper high-risk (red) and intermediate-risk (green) clinical target volume coverage. Isodose lines are 12 Gy (yellow), 8.4 Gy (orange), 6 Gy (red), 3 Gy (green), and 1 Gy (blue).

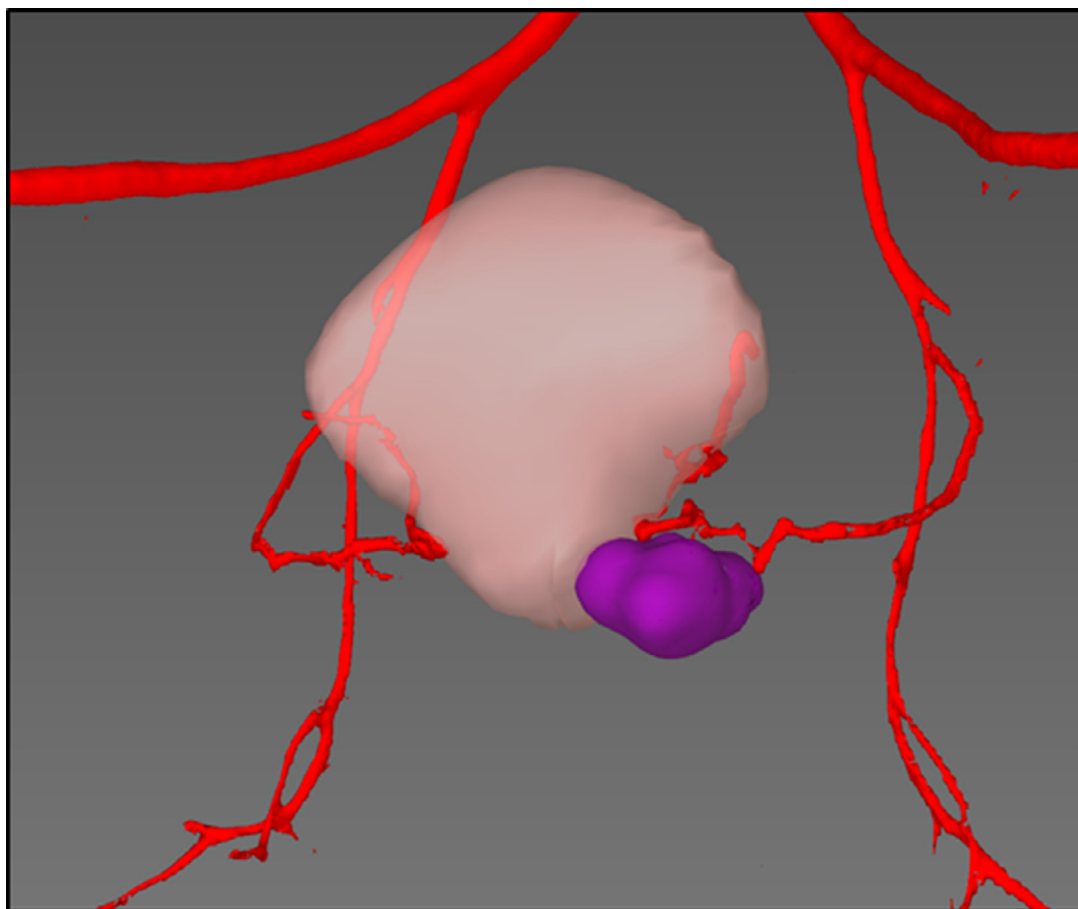


Fig. 3 Three-dimensional reconstruction from computed tomography angiography showing relative position of left uterine artery in relation to remaining uterus and recurrence.

The performance of x-ray imaging is limited to the pelvis (especially as image guided radiation therapy), but 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 one hand, the use of MRI in brachytherapy is one of the most noteworthy advances in the care of cervical malignancies, allowing for adaptive treatment, and, on the other hand, MR-Linac (eg, MRIdian or Elekta Unity) is the only modality providing native MRI (for both planning and image guided radiation therapy), 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 D_{98} isodose of GTV (up to 18 Gy, which allowed for 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 to describe the use of aMRgRT instead of brachytherapy as consolidation after chemosensitized radiation therapy for cervical cancer. Indeed, Sayan et al. reported on a case in 2020 in which they used this technique for a patient who did not want to go to a referral center.²⁶ The researchers also described well-tolerated treatment, with middle-term favorable outcomes, and the patient was clinically free of disease after 9 months. At the dawn of an aMRgRT blooming period, this and our cases 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 regard to limited follow up, concerning as much efficacy as long-term toxicities.

Conclusion

In very specific circumstances of cervical cancer, combining favorable tumoral features and appropriate

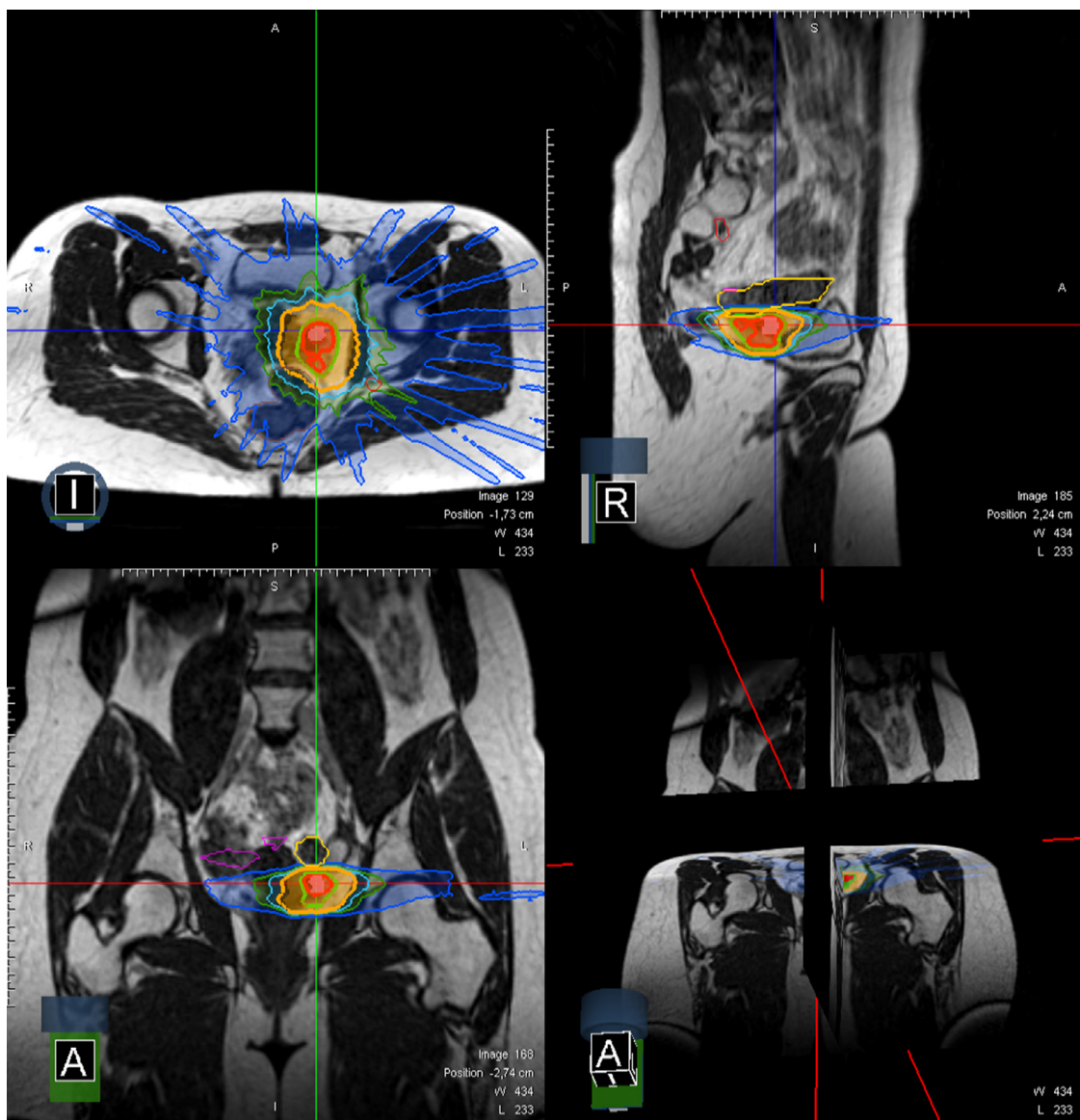


Fig. 4 Dose distribution as stated in initial MRIdian planning. Isodose lines are 22.5 Gy (red), 18 Gy (orange), 15 Gy (light green), 7.6 Gy (yellow), 6 Gy (light blue), 5 Gy (green), and 3 Gy (blue).

anatomic setup, aMRgRT as a boost seems to be practicable, allowing for good coverage of target volumes and acceptable sparing of surrounding organs. However, while waiting for a longer follow up and further studies, aMRgRT still must be strictly restricted to situations in which brachytherapy is not feasible.

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