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Clinical Use of Magnetic Resonance Imaging Across the Prostate Brachytherapy Workflow

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Abstract

Magnetic resonance imaging (MRI) produces better soft tissue contrast than does ultrasonography (US) or computed tomography (CT) for visualizing male pelvic anatomy and prostate cancer. Better visualization of the tumor and organs at risk could allow better conformation of the dose to the target volumes while at the same time minimizing the dose to critical structures and the associated toxicity. Although the use of MRI for prostate brachytherapy would theoretically result in an improved therapeutic ratio, its implementation been slow, mostly because of technical challenges. In this review we describe the potential role of MRI at different steps in the treatment workflow for prostate brachytherapy: for patient selection, treatment planning, in the operating room, or for post-implant assessment. We further present the current clinical experience with MRI-guided prostate brachytherapy, both for permanent seed implantation and high-dose-rate brachytherapy.

Keywords

prostate cancer; brachytherapy; low dose rate; high dose rate; magnetic resonance imaging

Introduction

The improved soft tissue contrast with magnetic resonance imaging (MRI) relative to ultrasonography (US) and computed tomography (CT) has prompted the prostate cancer

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brachytherapy community to explore the potential benefits of using MRI in the management of prostate cancer. Post-implant dosimetry seems to be more accurate when evaluated with MRI versus CT/transrectal ultrasonography (TRUS) for low-dose-rate (LDR) brachytherapy (1–3). These findings have prompted the American Brachytherapy Society to include in its 2012 guidelines the use of MRI for disease staging or treatment planning in “clinically relevant circumstances” by “experienced teams” and to encourage the use of MRI-CT image fusion for post-implant dosimetry to improve the reproducibility of contouring and the reliability of dosimetry (4). Using MRI for post-implant assessment allows organs at risk to be identified that cannot be seen on CT (e.g., the external urinary sphincter) that have been linked with increased toxicity when they receive excessive doses (5). If this enhanced accuracy could be implemented earlier during the treatment process, namely at the time of treatment planning and seed implantation for LDR or during the high-dose-rate (HDR) planning procedure in the operating room, that might translate into improved outcomes. The aim of this article is to describe the potential benefits of using MRI before, during, and after LDR or HDR prostate brachytherapy and to describe the clinical workflows currently in place or under evaluation at selected institutions.

Methods

Literature search

From a Pubmed search with the equation “(MRI or “magnetic resonance”) AND brachytherapy AND prostate,” we retrieved 425 references, of which 57 were analyzed and 23 were eventually selected for consideration (see Supplementary Table S1). These 23 reports included 12 clinical reports on LDR brachytherapy (including 7 from a Dana-Farber study) (6–17) and 11 clinical reports on HDR (18–28). The 34 excluded reports consisted of 11 reports on contouring/registration, 12 planning studies, and 11 studies on post-planning dosimetry. We focused on the clinical reports that describe and analyze the clinical workflow used to implement MRI in routine practice, as the aim of our review is to discuss potential clinical benefits of MRI-guided brachytherapy and to provide guidance regarding its implementation.

Clinical data

Clinical data from the MD Anderson cohort come from a prospectively maintained institutional database of all patients treated with prostate brachytherapy and a group from a prospective phase II study of patients with intermediate-risk prostate cancer treated with brachytherapy as monotherapy.

Results

Use of MRI before brachytherapy: its role in disease staging

The usefulness of MRI in terms of its improved capability for tumor staging is of paramount importance and really is the first step to integrate MRI into the routine care of patients undergoing prostate brachytherapy. The European Association of Urology 2015 prostate cancer guidelines state that multiparametric (mp) MRI is indicated for standard initial disease staging for men with high-risk localized or high-risk locally advanced prostate

cancer and for some men with low-risk disease who are candidates for brachytherapy (29). mpMRI is defined as the use of two different MRI sequences during the same examination, namely a T2-weighted sequence with a diffusion-weighted, a dynamic contrast-enhanced, or an H1-spectroscopy sequence. MRI facilitates visualization of intraprostatic primary tumors and rules out macroscopic posterolateral extracapsular extension (ECE) or seminal vesicle invasion. However, a meta-analysis has demonstrated that the sensitivity of mpMRI for detecting ECE remains low at around 0.6, because it cannot detect microscopic ECE (30). The sensitivity increases with the radius of ECE extension within the periprostatic fat (31). In another study, MRI scans showing no evidence of ECE in patients with T1c or T2a disease had a negative predictive value of 91% for ruling out ECE and 97% for ruling out ECE >3 mm (32). Patients with gross ECE visible on MRI are usually not candidates for LDR brachytherapy as monotherapy. The use of the Prostate Imaging Reporting and Data System (PIRADS) scoring system is encouraged to reduce inter-reader variability and standardize MRI interpretation (33). MRI can also be used to evaluate the risk of pubic arch interference, measure prostate volume, rule out a prominent median lobe, or detect anteriorly located tumors that would require a specific implantation technique for appropriate tumor coverage (34). Although the frequency of anterior tumors has not been clearly established, it is probably underestimated; indeed, a large series from the Princess Margaret Hospital of 1112 men with prostate cancer suggested that up to 20% could have anterior tumors (35).

Use of MRI during LDR prostate brachytherapy: the MD Anderson workflow

The initial experience with using MRI during LDR prostate brachytherapy was reported by the Dana-Farber Cancer Institute team, who from 1997 through 2007 has treated 318 men with cT1c, prostate specific antigen (PSA) <15 ng/mL, and Gleason 3 + 4 or less prostate cancer by using an intraoperative real-time MRI-guided brachytherapy technique in which only the peripheral zone is targeted (11). The implantation took place using a peripheral loading technique and involved iodine-125 sources, an MR-compatible perineal template and catheters, and an intraoperative 0.5-Tesla MRI scanner. Long-term biochemical control results were disappointing for patients with favorable intermediate disease (36, 37), with rates of 73.0% at 5 years and 66.4% at 8 years (12). The reasons for these results are unknown but could be related to patient selection, focal treatment of only the peripheral zone, or the reliability of the technical process used. Also, whether the quality of the coverage was evaluated with post-implant MRI-based dosimetry is unclear. However, this clinical trial paved the way for future research using advanced imaging techniques in prostate brachytherapy.

In addition to reports from the Dana-Farber Cancer Institute (11–17), we also evaluated five other reports, two on focal salvage brachytherapy (7, 8), two on MRI spectroscopy (9, 10), and one a preliminary report of the MD Anderson experience (6). The major drawback of these studies is that even though they used MRI at the treatment-planning stage and three of them (7–9) involved adequate fusion with TRUS during the implantation, none seem to have confirmed the quality of the implant on MR images. Therefore these reports cannot confirm that the seeds were actually implanted where they should have been, and the clinical results cannot be fully attributed to the use of MRI guidance.

The treatment paradigm at MD Anderson is described below and in Box 1. At 2-4 weeks before implantation, patients undergo diagnostic MRI, during which an endorectal coil is inserted and a planning MR image obtained for treatment simulation. For patients who have not undergone diagnostic MRI prior to their brachytherapy consultation, only one pretreatment MR image is obtained and used for both planning and diagnostic purposes. The prostate and organs at risk are delineated on the T2 3D sequence, including the anterior fibromuscular stroma or external urinary sphincter, which is poorly visible on ultrasonography or CT (5, 38). The virtual treatment simulation takes place after insertion of a reusable rigid endorectal coil (InVivo®, Gainesville, FL) that improves image quality, does not deform the prostate anatomy, and mimics the ultrasonography probe used in the operating room. During the planning process, a virtual probe is angled by 8° to account for displacement of the prostatic apex from the legs-down position used during simulation to the lithotomy position used in the operating room (see figure 1C). This angle was determined from the first 20 patients treated with this process and was found to be adequate for the patients who followed. Virtual needles are placed according to a standard peripheral loading template, and treatment is planned according to this placement (Fig. 1). During the actual implantation, the TRUS/MRI fusion is usually done manually rather than with the treatment planning system owing to the lack of adequate software for this purpose. The quality of the fusion is checked initially and regularly during the implantation by using the following landmarks: urethra at prostate base; external urinary sphincter at prostate apex; and the posterior and lateral edges of the prostate contour. The implanted strands consist of radioactive seeds and MRI-visible marker-spacers (Sirius™ by C4-Imaging) to facilitate accurate seed identification after the implantation for post-implant dosimetry (39).

MRI for post-implant dosimetry after permanent seed implantation: Dosimetric results from MD Anderson

Currently, two MRI scans are obtained for post-implant dosimetry, one on day 0 and the other on day 30 after the procedure. These scans typically consist of a T2 and a modified T1 sequences (Box 1), the T2 sequence for anatomic contouring and the modified T1 sequence for seed/marker identification (Fig. 2). Use of a single protocol sequence is being investigated that would reduce potential geometric uncertainties with MRI fusion and reduce the scanning time to less than 4 minutes; this would allow immediate assessment of the quality of the implant and an additional assessment after resolution of glandular edema. CT scans can also be obtained at day 0 and day 30 to help localize the seeds, depending on the quality of the MR image. The step-by-step process for simulation and treatment planning, seed identification, and post-implant dosimetry is shown in Box 1. The day 30 MRI can be omitted if the dosimetric results on the day 0 scan are as expected.

Results from dosimetric analysis of the first 71 patients treated are shown in Table 1. Doses are reported as percentages of the prescribed dose to facilitate pooling the patients who were treated with different isotopes and therefore different physical doses. The results show an expected decrease in coverage between baseline (pretreatment planning) and day 0 dosimetry, likely due to swelling of the prostate during the implantation and to imperfect placement of needles during the procedure. Day 30 dosimetry could be analyzed in 48 patients who had both baseline (pretreatment planning) and day 30 MRI. Coverage was

partly improved compared with day 0 but remained significantly lower than the pretreatment dosimetry for D90, V100, and V200. Prostate coverage was within target (D90>90%) for more than 95% of the patients, confirming the reliability of the procedure between the planned and the achieved doses. To further compare MRI-guided findings with those of the earlier TRUS/CT workflows, the MRI patients were each matched according to the isotope used (iodine-125, palladium-103, or cesium-131) to 2 patients treated previously at the same institution by the same physician using the TRUS/CT workflow. The procedure for post-implant contouring on CT was to export the baseline pre-planning prostate contours and use them on post-implant dosimetry, in an effort to be consistent in terms of prostate volume and shape and to avoid overestimating prostate contours because of the low visibility of the prostate on post-implant CT. As shown in Table 2, no relevant differences were seen at day 0. At day 30, the decrease in prostate coverage was more important for the MRI patients than for the TRUS/CT patients. However, the major bias of such an analysis is that MRI-based contouring and therefore dosimetry are more reliable than TRUS/CT-based strategies. Contouring reproducibility is enhanced (40) and contouring bias is reduced because of the poor visibility of the seeds on T2 images. The matched group is presented here to serve as a historical reference group with respect to other published cohorts, not for direct comparison with the MRI-planning cohort.

In summary, the MRI workflow described here and used at MD Anderson Cancer Center provides an easy and reliable way to integrate MRI at each stage of a permanent seed implant brachytherapy procedure. Prostate coverage is adequate and consistent with what had been previously reported for TRUS/CT guided procedures, while offering an additional opportunity to identify and spare organs at risk.

MRI during prostate brachytherapy: MRI-based planning for high-dose-rate brachytherapy

The standard of care for imaging-based treatment planning for HDR prostate implants is currently migrating from CT to TRUS. This evolution has substantially improved workflow efficiencies (41), and was enabled by the technical development of 3D TRUS through new robotic aids and computational tools. Although depiction of prostate boundaries with TRUS is superior to that on CT, uncertainties remain at the anterior gland because of echogenic artifacts created by implanted catheters. Also, visualization of catheters, especially catheter tips, becomes more challenging when using TRUS instead of CT. Finally, visualization of malignant tumors remains elusive.

For these reasons, some centers have adopted MRI-based needle insertion (22, 23, 25, 42) or MRI-based planning of HDR prostate implants (22, 23, 25), sacrificing workflow efficiency in the hopes of improving accuracy. This approach has been shown to be feasible at several specialty centers, with overall procedure times approaching 4-5 hours. Visualization of both prostate anatomy and implanted catheters is improved on MRI over CT or TRUS (Fig. 3), although blurring of anatomic boundaries at the prostate apex caused by bleeding from catheter insertion is evident. Dosimetric objectives were achieved and no unexpected toxicity was encountered, although at this time the follow-up period is too short to draw conclusions about tumor control.

More importantly however, is that with MRI, tumors can be visualized and delineated in most patients with intermediate- or high-risk disease (23). This improves confidence in tumor coverage during planning, especially in the small subset of patients with extraprostatic extension of disease. However, owing to substantial resource and infrastructure requirements, MRI-based planning has not been widely adopted or implemented.

A few general principles must be considered when designing an MRI acquisition protocol for treatment planning for HDR implants. First, the use of an endorectal coil can substantially improve the signal-to-noise ratio and image quality while also stabilizing the prostate. However, care must be taken to reduce pressure and displacement of the anterior rectal wall against the prostate. Second, a 2D T2- weighted spin-echo acquisition with a moderate echo time (TE, 50-80 ms) is most commonly used, balancing the need for anatomic resolution and catheter tip visualization. An alternate approach is a dual-echo acquisition, whereby proton density (low-TE) images are used for catheter reconstruction, and T2 (high-TE) images for anatomic delineation. All 2D acquisitions, however, are plagued with slice-thickness averaging error (2-3 mm). The acquisition of a 3D isotropic volume using newer turbo spin echo–based sequences (variable flip-angle) is increasingly being adopted. Gradient echo techniques must be explored with care given their greater vulnerability to susceptibility artifacts and geometric distortion.

Discussion

Our intent with this report is to demonstrate the feasibility of MRI-guided brachytherapy in clinical settings and to present an overview of the various steps at which MRI can be integrated into the brachytherapy workflow. The improved soft tissue contrast is the clear advantage of MRI over other imaging techniques, allowing better visualization of the prostate and normal tissues as well as potential identification of the dominant intraprostatic lesion to ensure proper coverage or even to plan dose escalation. As such, prostate MRI is highly valuable for the initial staging and definition of treatment strategy.

The dosimetric results of the first group of patients treated at MD Anderson demonstrate that the planned coverage can be achieved when using a pretreatment planning MRI for simulation, which in essence validates the process used. The process described is straightforward and allows elimination of the TRUS or CT that were usually obtained for planning and to evaluate pubic arch interference. The critical step is at the implantation stage, as currently the information derived from MRI is cognitively fused to the operative TRUS owing to the absence of reliable and straightforward commercial solutions for intraoperative MRI/TRUS co-registration. The use of multiple anatomic landmark checks before and during the implantation provides confidence and verification that the cognitively fused TRUS and MRI are correctly aligned. A limitation of this approach is that the inherent error and uncertainty in manually fusing the MR and TRUS are unknown and may be operator-dependent. Image fusion between MRI and TRUS is challenging. Deformation of the prostate during image acquisition from the MRI endorectal nonrigid coil or during implantation by the endorectal TRUS probe (34), image distortion during processing (43), and prostate swelling during needle introduction are key issues that need to be addressed by deformable image fusion procedures, which should be reliable and straightforward enough

to be performed repeatedly during the implantation. MRI-TRUS fusion as a way of integrating diagnostic MRI into the navigation workflow is discussed in a separate paper in this issue of *Brachytherapy* [REFERENCE THE ARTICLE BY MENARD ET AL].

Technical challenges remain the major barriers to the wider implementation of MRI in prostate brachytherapy. The early experience from the Dana Farber Cancer Institute has demonstrated the feasibility of direct intraoperative MRI-guided seed implantation (12). However dedicated MRI in brachytherapy operating rooms are unlikely to be widely available in the near future. Potential solutions include performing the implantation in a diagnostic MRI suite to avoid the need to move the patient for image acquisition (23), or performing the MRI and the treatment on the MRI couch, avoiding the need to transfer the patient to another couch once the imaging process is complete. These alternative necessitate the use of MRI-compatible equipment and specific processes, which may be feasible in tertiary centers, but the overall procedure time in two prospective studies was shown to be 4-5 hours (22, 23). The fine-tuning of MRI sequences is another barrier. Although we present the sequences currently used at MD Anderson (Box 1), they are still being improved and would need to be adapted for clinical use at other institutions. The process of sequence development is discussed in detail elsewhere in this issue [REFERENCE THE ARTICLE BY J. MA ET AL].

The next steps, along with improving and streamlining the processes, include demonstrating the value of the enhanced treatment accuracy enabled by MRI. Two improvements can be envisioned. The first is a reduction of toxicity through the reduction of the dose delivered to normal tissues. Reduction of the dose to erectile structures or to the external urinary sphincter may improve sexual and urinary function while preserving tumor control (5, 44). The demonstration of this clinical benefit is challenging, because it is unlikely that a randomized trial could be done and because reliable dose-toxicity relationships have not been established so far for these side effects. The second improvement would be in tumor control. The superiority of the combination of external beam radiotherapy plus brachytherapy over external beam radiotherapy alone in terms of biochemical control for unfavorable intermediate- and high-risk cancers has been suggested several times (45) and was recently demonstrated in a randomized trial (46). Translation of this trial's findings is currently limited by the lack of a demonstrated clinical benefit and by the higher occurrence of severe urinary complications and lower quality of life observed in the combination-therapy group (47). The use of a more focused brachytherapy technique through MRI guidance could be a way to maintain the high cure rates of the combination therapy while reducing the risk of severe urinary side effects. At present, the cohorts are too small and the follow-up time too short to address the clinical efficacy of MRI guidance. Finally, the additional costs of these strategies need to be assessed. Assuming there is a clinical benefit, adding serial MRI and prolonging operating room time would add costs that would need to be justified by improved clinical outcomes, especially knowing that the main driver of costs in prostate brachytherapy is the time spent in the operating room (48). The procedure duration has been shown to follow a learning curve and to decrease over time, leading to a decrease in operating room costs (22, 23). For LDR brachytherapy, it is possible to reduce the costs by using the diagnostic MRI instead of obtaining an additional scan and to omit the day 30 scan if the day 0 dosimetry is satisfactory.

In conclusion, MRI can readily be used for patient selection, treatment planning, and treatment delivery in prostate brachytherapy. Both LDR and HDR brachytherapy face different challenges for wider development and the application of these techniques. Further research is warranted to streamline the use of MRI in the brachytherapy operating room and to demonstrate the clinical significance and the value of adding MRI guidance to prostate brachytherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MRI	magnetic resonance imaging
US	ultrasonography
CT	computed tomography
HDR	high dose rate
TRUS	transrectal ultrasonography
LDR	low dose rate
ECE	extracapsular extension
mpMRI	multiparametric MRI
PIRADS	Prostate Imaging Reporting and Data System
PSA	prostate-specific antigen

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Box 1**Step-by-step process for MRI-based post-implant dosimetry at MD Anderson Cancer Center****Characteristics of MRI sequences used**

Name	Objective	FOV, cm	Slice thickness, mm	Slice resolution, oversample	Slice number	Nx	Phase resolution, oversample	TR/TE, ms	Flip angle	Bandwidth, Hz/pixel	ETL	NEX	Acceleration factor	Scan time, min
FSPGR	Seed Identification	15	1.2	50%, 9.1%	88	256	85%, 100%	5.5/2.4	25°	560	N/A	2	none	3:50
FSE	Anatomy	15	1.2	71%, 9.1%	88	256	80%, 85%	1500/278	variable	488	120	1.4	2	3:32
trueFISP	Both	15	1.2	50%, 9.1%	88	256	100%, 100%	5.3/2.3	~50°	558	N/A	1	none	4:02

Step-by-step process**Simulation and treatment planning**

1. Diagnostic MRI obtained using the Invivo® inflatable endorectal coil, filled with 30 cc of sterile water to avoid prostate deformation (17)
2. Prostate is contoured, with dominant lesion (if relevant), seminal vesicles, rectum, penile bulb, bladder, and external urinary sphincter
3. Virtual simulation is done with a probe tilted by 8° and a peripheral loading technique
4. Strands are implanted under TRUS guidance using a “cognitive” fusion based on multiple anatomic landmarks

Post - implant dosimetry

1. MR images are obtained on day 0 and day 30 after the implant, using the Invivo® inflatable endorectal coil filled with 30 cc of sterile water (if the day 0 dosimetric results are as expected, no day 30 MRI is ordered)
2. Transfer of the images to the treatment planning system
3. Independently performed:
 - a. Contouring of the prostate and organs at risk on the T2-weighted sequence (FSE)
 - b. Identification of the seeds using the markers and the signal void attributed to the seeds, best visualized on the T1-weighted sequences (FSPGR). The pre-planning needle loading diagram is used to verify that all seeds are accounted for. Further validation can be obtained by fusing the CT and MRI depending on the quality of seed identification on MRI.
4. Dosimetry is assessed, with input the isotope used, the activity of the seeds, and the dose prescribed. Reports are generated.

Abbreviations: FOV, field of view; Nx, number of sampled points in the x direction; TR/TE, relaxation time/echo time; ETL, echo train length; NEX, number of excitations; FSPGR, fast spoiled gradient; FSE, fast spin echo; trueFISP, fast imaging with steady-state free precession; TRUS, transrectal ultrasonography

Sequence characteristics are adapted from [PLEASE REFERENCE ARTICLE BY J. MA FROM THE SAME SPECIAL ISSUE].

Figure 1. Screen shots showing an example of simulation and planning process used at MD Anderson Cancer Center

T2 sequence images (A) are used for delineation of tumor and organs at risk (B), virtual simulation using a probe angled by 8° (C) and treatment planning using a peripheral loading template (D).

Figure 2. Example of a post-implant dosimetry assessment that uses the C4® MR-visible markers on a modified T1 sequence

C4® markers appear hyperintense in this T1 like sequence (see inside the dotted white square) and help localize the radioactive seeds on axial (A), sagittal (B) and coronal views (C). Isodose lines depicted here are yellow (50%), red (100%) and purple (150%). The prostate contour is in blue, bladder in yellow, rectum in green and external urinary sphincter in light green

Figure 3. MRI-based planning of HDR brachytherapy for prostate cancer

T2-weighted spin-echo images demonstrating clear anatomic boundaries (blue, prostate; yellow, bladder; brown, rectum; green, urethra), as well as a hypointense tumor at the right base (arrow) extending into seminal vesicles (coronal image, right). Note also the clear signal void for the implanted catheters (left) reconstructed for treatment planning.

Table 1

Comparison between dosimetric variables on pretreatment, day 0, and day 30 MRI.

Variables	Pretreatment Planning, mean (SD) n=71	Day 0, mean (SD) n=71	Day 30, mean (SD) n=48 [†]
Prostate D90, %	131 (8)	109 (9) *	113 (13) *
Prostate V100, %	100 (4)	94 (4) *	94 (4) *
Prostate V150, %	67 (12)	51 (14) *	60 (11)
Prostate V200, %	28 (15)	22 (11) *	27 (8) *
Rectum V100, cm ³	0.35 (0.3)	0.14 (0.3) *	0.5 (0.8)
Rectum V150, cm ³	0.014 (0.03)	0.004 (0.02) *	0.04 (0.2)

* Indicates significant difference (paired t test) between day 0/30 and pretreatment planning dosimetric measurements

[†] Statistical tests are based on the 48 patients who had both pretreatment planning and day 30 MRI scans

Table 2

Differences between the planned dose and the measured dose at day 0 or day 30

Variable	Pretreatment Planning – Day 0 (expressed as % of planned dose)			Pretreatment Planning – Day 30 (expressed as % of planned dose)		
	Patients with MRI planning (n=71)	Patients with TRUS/CT planning (controls; n=141)	P Value [†]	Patients with MRI planning (n=48)	Patients with TRUS/CT planning (controls; n=93)	P Value [†]
Prostate D90, %	21 (10)	18 (8)	0.04	14 (12)	8 (11)	<0.001
Prostate V100, %	6 (4)	3 (2)	0.14	6 (7)	2 (2)	0.002
Prostate V150, %	16 (12)	17 (9)	0.77	2 (10)	– 4 (12)	0.002
Prostate V200, %	6 (9)	5 (9)	0.91	– 5 (6)	– 9 (8)	0.001
Rectum V100, cm³	0.2 (0.4)	0.2 (0.2)	0.69	– 0.2 (0.8)	– 0.03 (0.6)	0.26
Rectum V150, cm³	0.01 (0.03)	0.01 (0.02)	0.31	– 0.04 (0.2)	– 0.01 (0.1)	0.41

[†] t tests were used to compare the two groups.

Patients were matched according to the isotope used (iodine-125, palladium-103, or cesium-131) and the treating physician, but only those with dosimetry at two time points were actually analyzed