Original Article

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Dosimetric Impact of Deformable Image Registration versus Simple Summation in Multi-Fraction HDR Brachytherapy for Cervical Cancer under Standard Protocol

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Abstract:

Objective: In high-dose-rate brachytherapy for cervical cancer, cumulative dose is commonly estimated using simple summation (SS) of dose–volume histogram parameters, assuming high-dose regions remain spatially consistent across fractions. Deformable image registration (DIR) offers an alternative approach that accounts for interfractional anatomical variations. This study compared the dosimetric outcomes of SS and DIR under standardized clinical protocols.

Material and Methods: This retrospective study included 54 patients with cervical cancer treated with four-fraction intracavitary brachytherapy using standardized applicators and a bladder-filling protocol with CT-based planning. Cumulative doses to the high-risk clinical target volume (HR-CTV), bladder, and rectum were calculated using both SS and DIR, aligned using applicator geometry. DIR accuracy was evaluated using the Dice Similarity Coefficient (DSC), mean distance to agreement (MDA), Hausdorff distance (HD), and Jaccard Index.

Results: DIR yielded significantly lower accumulated HR-CTV doses across all the evaluated parameters (percentage differences were 8.2%, 6.0%, and 3.7% for D98, D90, and D50, respectively; all p-value<0.001) compared with SS, with moderate geometric agreement (DSC=0.72). For organs at risk, dose differences for the bladder and rectum were not statistically significant. Rectal geometric agreement was limited (DSC=0.60), whereas bladder agreement was good (DSC=0.89), likely influenced by the controlled bladder-filling protocol.

Conclusion: DIR-based dose accumulation resulted in significantly lower HR-CTV dose estimates compared with SS, while dose differences for the bladder and rectum remained minimal. Geometric reliability varied across anatomical structures. Future research should correlate DIR-based dosimetry with clinical outcomes to support anatomically adaptive brachytherapy.

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Introduction

Brachytherapy is crucial in curative treatment for patients with locally advanced cervical cancer. One of the significant developments is the transition from two-dimensional point-based treatment planning to three-dimensional volume-based brachytherapy, enabling better tumor control and reduced treatment-related toxicity through improved dose conformity and accuracy[1,2]. Computed tomography (CT)-based planning is widely used in clinical settings, permitting the delineation of target volumes and organs at risk (OARs), supporting volumetric dose evaluation and optimization.

Clinical guidelines recommend delivering high-dose-rate (HDR) brachytherapy in 4 to 6 fractions[3]. The total dose from each fraction is evaluated using a simple summation (SS) of dose-volume histogram (DVH) parameters across fractions, assuming that the high-dose regions remain spatially consistent. Nevertheless, this approach does not account for interfractional variations such as bladder and rectal filling, tumor regression, or applicator repositioning. These variations can significantly alter dose distribution, particularly in the steep gradient near the applicator[4]. To address this limitation, deformable image registration (DIR) has emerged as a voxel-wise dose accumulation method that accounts for organ deformation and motion[5]. Several studies have explored the feasibility of DIR for brachytherapy dose accumulation; however, concerns remain regarding its accuracy and the potential for introducing error[6]. Accordingly, quantitative quality assurance (QA) measures, such as the Dice Similarity Coefficient (DSC), are commonly employed to validate the reliability of DIR[7,8].

While previous studies have compared DIR and SS in terms of either target volumes or OARs, only a few have comprehensively evaluated dose accumulation for both structures using standardized protocols and quantitative DIR assessment[9–11]. Consistent applicator positioning and bladder volume control are essential to minimize registration uncertainty and improve cumulative dose accuracy. To address this gap, we compared two methods of dose accumulation, namely DIR and SS, under consistent clinical protocols with standardized applicator positioning and bladder preparation. In addition, this study explored the feasibility of incorporating DIR-based dose accumulation into routine clinical workflows as a complementary tool to conventional dose reporting in HDR brachytherapy.

Material and Methods

Participants

This single-institution, retrospective study utilized our internally maintained prospectively collected database. Patients with histologically confirmed cervical cancer who underwent definitive radiotherapy, with or without concurrent chemotherapy, were included. HDR brachytherapy was delivered as an intracavitary technique using an intrauterine tube and ovoids as the applicator. In our institution, brachytherapy was administered in four weekly fractions using titanium applicators. Patients were excluded if they had incomplete brachytherapy, planning images unsuitable for DIR, non-standardized bladder volumes, or incomplete organ contouring. The study was approved by the Institutional Review Board of Songklanagarind Hospital, Prince of Songkla University (REC.67-436-7-2), with informed consent waived due to its retrospective nature.

Brachytherapy procedure

Before CT acquisition, the bladder was filled with 50 or 100 mL of sterile water mixed with 3% iodinated contrast media. CT-based planning, without the use of intravenous contrast media, was performed for each fraction using a SOMATOM go.Open Pro scanner (Siemens Healthineers, Germany). The acquisition protocol included a slice thickness of 2–3 mm, tube voltage of 120 kVp, and a metallic artifact reduction filter. All scans were performed with the same imaging parameters across sessions. Contouring and treatment planning were conducted using the Oncentra Brachytherapy Planning System version 4.6 (Elekta AB, Stockholm, Sweden). The high-risk clinical target volume (HR-CTV), bladder, and rectum were delineated by multiple attending radiation oncologists according to routine clinical practice, following the GEC-ESTRO guidelines[12]. Applicator reconstruction was manually performed by medical physicists, and dose optimization was based on DVH constraints for HR-CTV and OARs, according to the EMBRACE II protocol[13]. After dose optimization and plan evaluation, treatment was delivered using Elekta Flexitron remote afterloader (Elekta AB, Stockholm, Sweden) using an iridium-192 source. The applicator was removed after completing each fraction.

Dose accumulation

To evaluate dose distributions to the HR-CTV and OARs, we employed DVH metrics commonly used in brachytherapy. For the HR-CTV, the evaluated parameters were D98, D90, and D50, representing the minimum dose received by 98%, 90%, and 50% of the target volume, respectively. D90 is used to assess adequate target coverage of the HR-CTV. D98 provides an estimate of the near-minimum dose and facilitates identification of potential cold spots within the target volume. D50 represents the median dose and was included to characterize the internal dose distribution and the inherent dose heterogeneity of high-gradient brachytherapy dose profiles, in accordance with ICRU 89 reporting recommendations[14]. For the bladder and rectum, the evaluated metrics were D0.1cc and D2cc, indicating the minimum dose received by the most exposed 0.1 cm^3 and 2 cm^3 of tissue, respectively. These parameters were analyzed using SS and DIR without an equivalent dose in 2 Gy conversion.

Simple summation (SS)

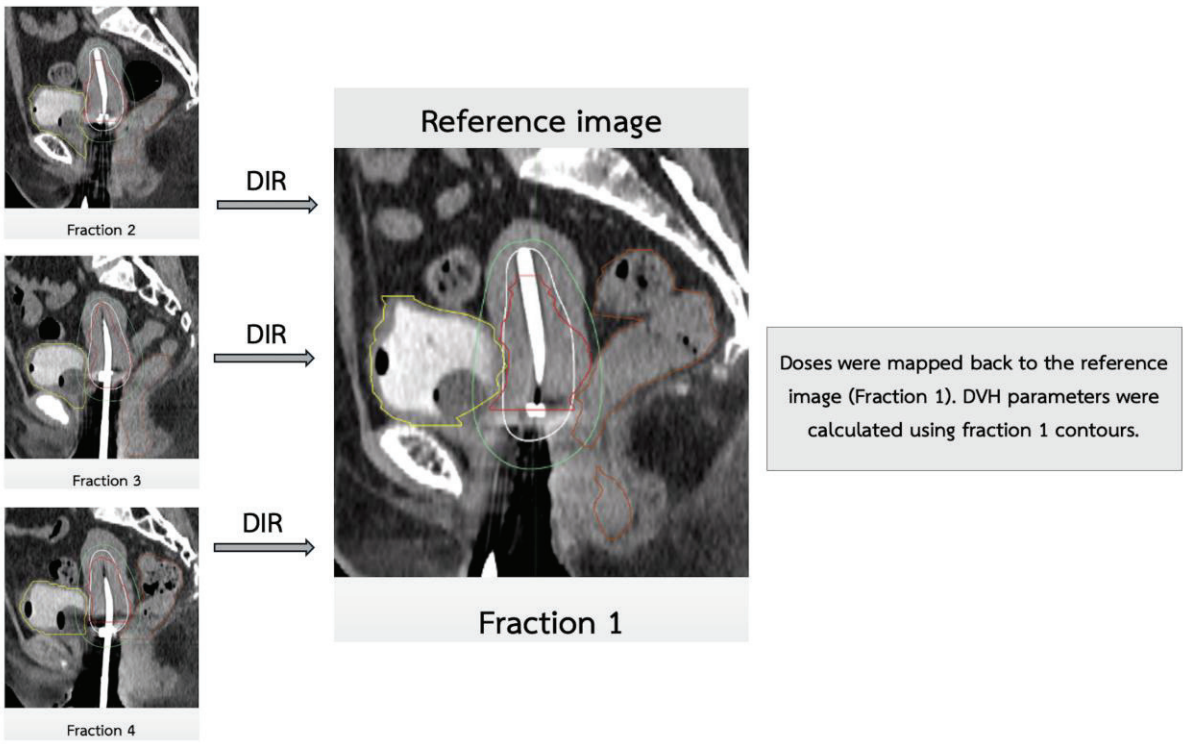
The accumulated doses using SS were based on the recorded DVH values after treatment planning of each fraction and summed across all four fractions, reflecting current practice in most institutions.

Deformable image registration (DIR)

DIR method

For retrospective DIR-based dose accumulation, DICOM RT structure sets (RTStruct), RT dose files (RTDose), and CT images for all fractions were exported from Oncentra and transferred to MIM Maestro version 7.3.3 (MIM Software Inc., Cleveland, OH) via the local network. The CT image from the first fraction (Fx 1) was designated as the reference image.

Each subsequent fraction was initially aligned to the reference image based on the applicator's position, with manual adjustments performed by a medical physicist when necessary to ensure optimal applicator alignment before executing DIR. Deformable registration using the intensity-based free-form deformation algorithm was applied to map both anatomical structures and dose distributions from the second to fourth fractions onto the reference Fx 1 image. DIR-based dose accumulation was performed voxel-by-voxel after registration. DVH parameters for the target and OARs were subsequently calculated from the accumulated dose map on the Fx 1 contours. The overall DIR workflow is illustrated in Figure 1.



DIR=deformable image registration, DVH=dose-volume histogram

Figure 1 Visual summary of the DIR process. Computed tomography images from the 2nd to 4th fractions were deformably registered using the 1st fraction as the reference image. Contours and doses were transferred, and DVH and DIR quality assurance parameters for each contour in each fraction were subsequently extracted. Legend: Red, high-risk clinical target volume. Yellow, bladder. Brown, rectum. White, 100% isodose line. Light green, 50% isodose line.

DIR quality assurance

Each deformation field was visually inspected to verify anatomical correspondence, with a focus on applicator geometry, key anatomical landmarks, and dose distributions. If misregistration was observed, rigid registration was reinitialized to improve global alignment before reapplying DIR with default parameters. No manual editing of the deformation field or DIR parameters was performed.

Geometric accuracy of DIR was evaluated using quantitative similarity metrics between the deformed and reference contours, including the DSC, mean distance to agreement (MDA), Jaccard Index, and Hausdorff Distance (HD). These metrics characterize spatial agreement in complementary ways: the DSC and Jaccard Index assess volumetric overlap (with higher values indicating better alignment), whereas the MDA and HD reflect surface-based deviations[7,8]. Thresholds were based on the AAPM TG-132 recommendations, which define acceptable DIR performance as a DSC ≥0.80 and an MDA <3 mm. However, TG-132 does not specify explicit threshold values

for similarity metrics, such as the Jaccard Index or HD, and recommends that institutions establish site-specific validation criteria based on clinical relevance and imaging modality[15].

Statistical analysis

Descriptive statistics were calculated for DVH parameters from both SS and DIR, as well as for DIR QA metrics. Normality of paired differences was assessed using the Shapiro–Wilk test, and no significant deviation from normality was observed. Paired *t*-tests were conducted to compare DVH parameters between SS and DIR for each anatomical structure. Statistical analysis was performed using Microsoft Excel (version 2505; Microsoft Corporation, Redmond, WA, USA). A p-value less than 0.05 was considered statistically significant. Interfractional consistency of target coverage was evaluated by calculating the intra-patient standard deviation (S.D.) of HR-CTV D90 across the four brachytherapy fractions for each patient. The mean and S.D. of these intra-patient S.D. values were then summarized to characterize overall consistency within the study cohort.

Results

Patient characteristics

A total of 54 patients, comprising 216 treatment fractions administered between October 2022 and October 2024, were included in this study. According to the FIGO 2018 staging system, the most common stage was IIB, comprising 33.3% of the cohort. All treatments were prescribed a dose of 7 Gy to the HR-CTV D90. Patient characteristics are summarized in Table 1.

Interfractional consistency of HR-CTV coverage

Interfractional consistency of HR-CTV coverage was assessed using the intra-patient S.D. of D90 across the four brachytherapy fractions. The intra-patient S.D. of HR-CTV D90 was 0.67±0.29 Gy, indicating limited inter-fractional variation.

Accumulated dose comparison using SS and DIR

Dose to HR-CTV

The accumulated dose to the HR-CTV obtained using SS was higher than that calculated with DIR in 82.7% of D98 cases, 78.4% of D90 cases, and 74.5% of D50 cases. The corresponding mean percentage differences between SS and DIR were 8.2% for D98, 6.0% for D90, and 3.7% for D50, and all parameters were significantly different based on paired t-tests (all p-value<0.001; Table 2).

Dose to bladder and rectum

For the bladder, accumulated dose estimates from SS were higher than those from DIR in 64.7% of D0.1cc cases and 60.8% of D2cc cases. For the rectum, SS produced higher accumulated doses in 46% of D0.1cc cases and 62% of D2cc cases. Mean percentage differences between SS and DIR were 1.0% for bladder D0.1cc, –0.3% for bladder D2cc, 2.7% for rectum D0.1cc, and 3.0% for rectum D2cc, with no statistically significant differences observed for any bladder or rectal parameters on paired *t*-tests (Table 3).

Table 1 Patients' clinical characteristics (n=54)

Characteristics	Value
Age (year), mean (range)	49 (27–83)
FIGO Staging, n (%)	
IB3	2 (3.7%)
IIB	18 (33.3%)
IIIB	12 (22.2%)
IIIC1	16 (29.6%)
IIIC2	3 (5.6%)
IVA	2 (3.7%)
IVB	1 (1.9%)

Table 2 Comparison of accumulated HR-CTV dose parameters between SS and DIR

HR-CTV parameters	SS (Gy) mean±S.D. (range)	DIR (Gy) mean±S.D. (range)	Difference (Gy) mean±S.D. (range)	Difference (%) mean (range)	p-value
D98	22.1±1.8 (15.9–25.3)	20.3±2.8 (14.8–26.9)	1.8±2.2 (−2.5–6.1)	8.2% (−10.3–25.3%)	<0.001
D90	26.5±1.7 (21.2–29.2)	25.0±2.8 (19.5–31.1)	1.6±2.0 (−2.6–5.7)	6.0% (−9.1–22.4%)	<0.001
D50	41.5±2.3 (35.7–46.0)	40.0±3.5 (33.1–48.4)	1.5±2.9 (−5.8–6.8)	3.7% (−16.3–17.0%)	<0.001

DIR=deformable image registration, HR-CTV=high-risk clinical target volume, S.D.=standard deviation, SS=simple summation

Table 3 Comparison of accumulated dose parameters for bladder and rectum between SS and DIR

Organs at risk	SS (Gy) mean±S.D. (range)	DIR (Gy) mean±S.D. (range)	Difference (Gy) mean±S.D. (range)	Difference (%) mean (range)	p-value
Bladder D0.1cc	24.7±2.3 (20.3–31.1)	24.4±2.8 (18.2–30.8)	0.2±1.4 (−2.68–3.8)	1.0% (−11.2–14.7%)	0.239
Bladder D2cc	18.8±1.5 (15.0–23.1)	18.9±1.8 (13.6–22.6)	−0.1±1.0 (−2.3–2.1)	−0.3% (−11.6–10.8%)	0.666
Rectum D0.1cc	22.2±2.3 (15.6–27.6)	21.7±3.6 (11.7–30.2)	0.6±2.6 (−5.7–6.5)	2.7% (−25.0–26.9)	0.122
Rectum D2cc	16.5±1.8 (11.7–19.2)	16.0±2.2 (8.5–21.3)	0.5±2.0 (−4.1–6.1)	3.0% (−23.9–31.7%)	0.060

DIR=deformable image registration, S.D.=standard deviation, SS=simple summation

DIR quality assurance

The quantitative evaluation of DIR accuracy is summarized in Table 4. Based on the DSC and MDA, the bladder showed good geometric agreement, whereas the HR-CTV demonstrated moderate agreement. However, the rectum exhibited poor agreement, indicating substantial anatomical variation and reduced registration reliability.

Discussion

Our study compared the dosimetric outcomes of SS, the currently practiced dose-accumulation method, and those of DIR using generally available software routinely used at our institution, and evaluated the feasibility of incorporating DIR-based dose accumulation into routine clinical workflows. Overall, DIR resulted in lower accumulated doses to the HR-CTV compared with SS, while dose differences for the bladder and rectum were minimal. These findings reflect the fundamental differences between the two dose-accumulation approaches: SS assumes rigid voxel correspondence across fractions and may overestimate cumulative dose when anatomical deformation occurs, whereas DIR performs voxel-wise dose redistribution based on estimated tissue deformation. Consequently, DIR has the potential to provide a more anatomically responsive estimation of cumulative dose, particularly for structures demonstrating acceptable geometric reliability.

Table 4 Quantitative evaluation of DIR accuracy for all structures

Structure	DSC mean±S.D.	MDA (mm) mean±S.D.	HD (mm) mean±S.D.	Jaccard index mean±S.D.
HR-CTV	0.72±0.05	2.78±0.83	13.49±3.21	0.57±0.06
Bladder	0.89±0.04	1.62±0.59	13.79±4.53	0.81±0.05
Rectum	0.60±0.08	5.80±1.87	36.41±10.04	0.44±0.08

DIR=deformable image registration, DSC=Dice Similarity Coefficient, HD=Hausdorff Distance, HR-CTV=high-risk clinical target volume, MDA=mean distance to agreement, S.D.=standard deviation

The quantitative assessment showed good geometric agreement for the bladder and moderate agreement for the HR-CTV, supporting the feasibility of DIR-based voxel-wise dose evaluation for these structures[15]. These findings suggest that DIR reliability is structure-dependent but can be clinically meaningful for key pelvic targets. This structure-dependent behavior can be explained by the fundamental principles of voxel-based DIR, which rely primarily on tissue intensity contrast for deformation estimation. The bladder demonstrated superior geometric agreement due to its high contrast relative to surrounding tissues and controlled filling conditions. In contrast, the HR-CTV showed moderate DIR performance, likely reflecting limited soft-tissue contrast on CT despite stable applicator geometry and low interfractional variability. The rectum exhibited the poorest registration accuracy because of its high deformability, variable content filling due to a lack of standardized rectal preparation, and lower contrast to surrounding tissues. These organ-specific characteristics inherently challenge intensity-based DIR algorithms and directly affect the reliability of voxel-wise dose accumulation, particularly for highly deformable structures.

Although AAPM TG-132 does not define explicit acceptance thresholds for similarity metrics, such as the Jaccard index and HD, the observed values in this study were interpreted in conjunction with DSC and MDA and explicitly evaluated for structure.

For the HR-CTV, DIR produced consistently lower accumulated doses than SS for all the evaluated DVH parameters (D98, D90, D50), with reductions of 8.2%, 6.0%, and 3.7%, respectively. The 6.0% reduction in D90 in our study is comparable to the 2.0% reported previously[16], further supporting the potential of DIR to improve target dose estimation in HDR brachytherapy. These findings are consistent with the moderate geometric accuracy of DIR for the HR-CTV, suggesting that DIR was sufficiently reliable to capture interfractional anatomical variations that rigid summation could not. The use of a fixed intracavitary applicator likely contributed to stable target geometry and enhanced deformation performance.

The relatively low intra-patient variability of HR-CTV D90 across fractions indicates that target coverage was generally consistent throughout treatment. This interfractional consistency supports the interpretation that the observed differences in accumulated dose between SS and DIR were primarily driven by differences in dose accumulation methodology rather than by large inter-fractional variations in target coverage. Stable applicator geometry and standardized treatment protocols likely contributed to this reproducibility.

For the bladder, the dose differences between SS and DIR were minimal and not statistically significant for both D0.1cc and D2cc. This finding is consistent with the excellent geometric agreement observed for bladder DIR,

likely reflecting the standardized bladder-filling protocol. While some studies have reported decreased bladder doses with DIR[9,16–18], our findings indicate little to no overall difference between the two methods. Localized increases in DIR-based bladder dose metrics (e.g., D0.1cc) were occasionally observed in regions of steep dose gradients, where adjacent voxels may map into the ROI during voxel-wise accumulation.

For the rectum, DIR produced slightly lower accumulated doses than SS, although these reductions were not statistically significant. Rectal cumulative dose results derived from DIR should be interpreted with caution, as the limited geometric accuracy observed for this highly deformable structure may have influenced the reliability of voxel-wise dose accumulation and contributed to the modest and non-significant dosimetric differences between the two methods. Our observed 3% reduction falls within the previously reported range of –10.1% to –2.3%, reinforcing the trend that DIR generally yields lower rectal accumulated doses despite geometric limitations[9,16–18]. These findings underscore the need for structure-specific preparation and validation strategies, including standardized rectal emptying protocols and gas reduction measures, to improve registration consistency and dose accuracy in deformable tissues.

A notable strength of this study is the use of standardized clinical protocols that enhance registration accuracy, including controlled bladder filling and fixed intracavitary applicator geometry, which together reduced sources of DIR uncertainty and improved geometric reproducibility across fractions.

Nevertheless, this study has certain limitations. Despite protocol standardization, DIR accuracy remained suboptimal in the rectum, where high deformability and internal variability presented major challenges. Potential inter-observer variability in contour delineation across fractions may have further influenced DIR performance, particularly for deformable structures. Variation in contouring across fractions and the exclusive use of CT may also have affected the HR-CTV delineation. In addition, the intensity-based DIR algorithm used is efficient and clinically accessible, relying solely on voxel intensity similarity, making it sensitive to noise, low contrast, and irregular deformation[19]. Although a metallic artifact reduction filter was applied, artifacts from the titanium applicators persisted, potentially further affecting DIR accuracy. The absence of a ground–truth deformation field is a common limitation in clinical DIR validation[20]. Another limitation is that this study focused exclusively on standardized intracavitary insertions. This choice was intentional to control applicator geometry and anatomical variation across fractions, thereby reducing confounding factors that could influence DIR performance. Disease stage and associated anatomical complexity may further affect registration accuracy and dose accumulation; however, the relatively homogeneous treatment approach in this cohort helped mitigate such confounding effects. However, hybrid implants involving interstitial needles, commonly applied in advanced cases, can significantly alter dose gradients and hotspot distributions, especially around the HR-CTV and adjacent OARs. These more complex geometries may affect both the accuracy of DIR and the magnitude of the dosimetric difference between DIR and SS. Evaluating DIR-based dose accumulation under such scenarios is an important direction for future studies, particularly for expanding the clinical applicability of this approach.

Future research should explore DIR integration into prospective clinical workflows and its correlation with treatment outcomes. The proposed workflow may include DIR after each fraction in addition to the current SS practice. This would allow for intermediate dose summation, enabling adaptation in subsequent fractions. Expanding validation to hybrid implants incorporating interstitial needles, MRI-based planning, and structure-specific preparation protocols may

help establish its robustness across varying applicator geometries and imaging modalities. Studies employing standardized bladder and rectal preparation protocols, combined with structure-specific QA metrics, may help confirm the broader applicability of DIR-based dose accumulation. In the current clinical practice, SS may remain suitable for routine dose reporting due to its simplicity and robustness, whereas DIR-based dose accumulation may serve as a complementary tool for evaluating interfractional dose variation and supporting adaptive decision-making when adequate geometric reliability is achieved. When supported by rigorous QA, DIR has greater potential than SS to capture interfractional anatomical variations and could serve as a more reliable decision support tool for adaptive brachytherapy.

Conclusion

DIR consistently produced lower accumulated doses to the HR-CTV compared with simple summation, with all DVH parameters showing statistically significant reductions. This finding aligns with the moderate geometric agreement achieved for the HR-CTV. For the bladder, DIR and SS yielded nearly identical accumulated doses, reflecting the high reproducibility of bladder geometry under a standardized filling protocol. Rectal doses also trended lower with DIR; however, interpretation is limited by the poor geometric agreement observed for this highly deformable structure. Overall, DIR provides a more anatomically responsive estimation of cumulative dose, but its reliability remains structure-dependent, underscoring the need for protocol optimization and structure-specific QA when integrating DIR into brachytherapy workflows.

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Conflict of interest

The authors declare no conflict of interest.

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