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Deformable image registration

Structure-based deformable image registration: Added value for dose accumulation of external beam radiotherapy and brachytherapy in cervical cancer



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ABSTRACT

Background and purpose: Structure-based deformable image registration (DIR) can be used to calculate accumulated brachytherapy (BT) and external-beam radiation therapy (EBRT) dose–volume histogram (DVH) parameters in cervical cancer. Since direct parameter addition does not take dose non-uniformity into account, the added value of DIR over addition methods was investigated for bladder and rectum.

Materials and methods: For twelve patients (EBRT: 46 Gy, EBRT + BT: D_{90} 85–90 Gy_{EQD2} in equivalent dose in 2 Gy fractions) the EBRT planning CT and BT planning MRI were registered using DIR. Affected lymph nodes, located far from the BT boost region, received an EBRT boost (9.2 Gy) not contributing to the BT boost dose. Cumulative bladder/rectum $D_{2\text{cm}3}/D_{1\text{cm}3}$ were calculated and compared to direct addition methods, assuming uniform EBRT doses (UD), or overlapping high dose volumes (OHD).

Results: Between the three methods, the maximum differences in the cumulative DVH parameters were 3.2 Gy_{EQD2} (bladder) and 3.3 Gy_{EQD2} (rectum). The difference between DIR and UD was <1.8 Gy_{EQD2} for both organs.

Conclusions: The UD method provides a better estimate of $D_{2\text{cm}3}/D_{1\text{cm}3}$ than the OHD method. There is no added value of DIR since differences with direct addition methods are clinically insignificant. EBRT dose distributions can be considered uniform in bladder and rectum for the evaluated dose parameters.

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For locally-advanced cervical cancer, concurrent radiotherapy and chemotherapy is the standard of care. The radiation treatment typically combines external beam radiotherapy (EBRT) with a brachytherapy (BT) boost to the tumor area using an intracavitary/interstitial applicator. The recommended EBRT dose to the target is 45–50 Gy in 1.8–2.0 Gy/fraction [1], with a BT boost up to a total dose of at least 90 Gy_{EQD2}, expressed as equivalent dose in 2 Gy fractions (EQD2), to 70% of the clinical target volume (CTV) at high risk. To spare the bladder and rectum, the minimum cumulative dose from EBRT and BT, to the most irradiated 2 cm³ ($D_{2\text{cm}3}$) should not exceed 90 Gy_{EQD2} and 75 Gy_{EQD2} for these organs respectively.

According to GEC-ESTRO recommendations, a straightforward summation of the EBRT prescription dose and the BT DVH parameters is adequate to predict toxicity in the organs-at-risk (OARs). The underlying assumption of this so-called uniform dose (UD) method,

is that the EBRT dose to the OARs can be considered as uniform and equal to the prescription dose [2]. However, intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) are used increasingly to create highly conformal dose distributions, resulting in non-uniform EBRT dose distributions in the OARs (Fig. 1, left panel). Alternatively, a number of previous investigations evaluated cumulative doses by assuming overlapping high dose volumes for both treatments [3,4], denoted as the OHD method, the worst-case scenario. Since the UD/OHD methods do not take non-uniformity in OAR doses into account, this may cause the cumulative $D_{2\text{cm}3}$ and $D_{1\text{cm}3}$ to be underestimated/overestimated at the time of BT planning. It may therefore be preferable to sum the 3D dose distributions instead.

Three-dimensional doses can be accumulated by matching the planning images of EBRT and BT (CT and/or MR). Accumulated doses for cervical cancer patients were previously evaluated by registering the planning images using rigid registration [3,5]. However, the accuracy of the cumulative DVH parameters using rigid registration is limited since organ deformations due to the applicator and/or rectum/bladder filling are not considered. As a possible

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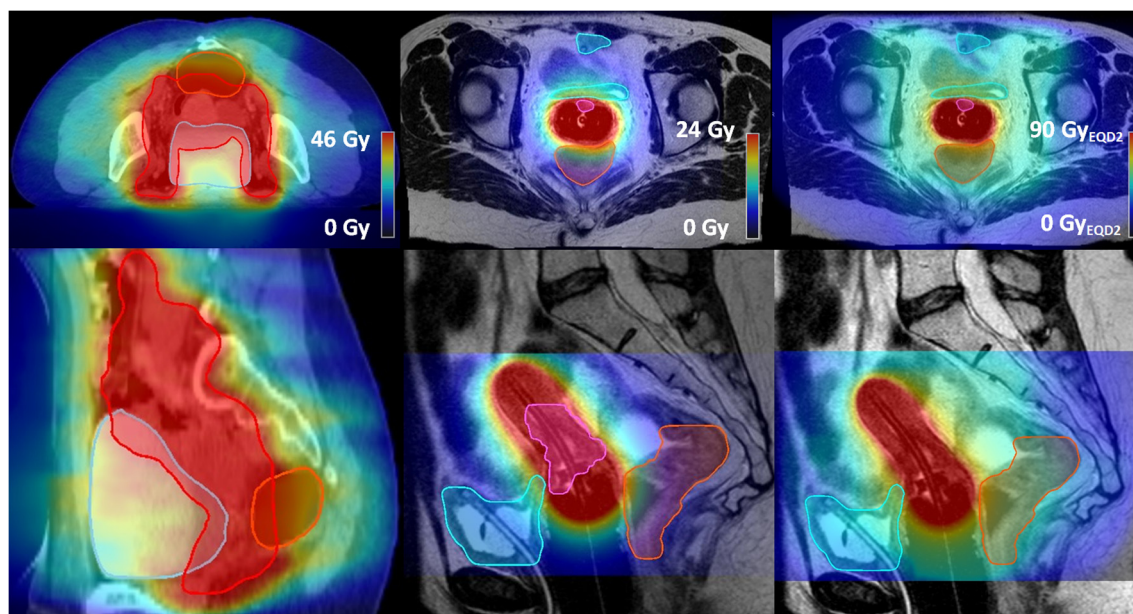


Fig. 1. Axial and sagittal view of a patient CT/MRI with a color wash of the planned VMAT/BT dose and the accumulated dose from EBRT and BT. The EBRT dose is not uniform in proximity of the bladder/rectum walls (blue/orange) closest to the target.

solution, several deformable image registration (DIR) algorithms have been investigated [3,4,6,7]. Planning images of EBRT and brachytherapy in gynecological cancer were registered for dose warping with deformable image matching. These studies compare cumulative DVH parameters calculated using DIR with either the UD or the OHD method.

Deformable matching is often based on image intensity values [3,4,6,7], but this remains challenging and may lead to physically impossible solutions [4,7,8]. Structure-based DIR requires organ delineation but reduces the influence of different imaging modalities. Since the objective of structure-based DIR is to decrease the distance between points on the moving and reference contours, it is most reliable near the structure edges, making DIR most suitable for hollow organs like bladder and rectum. Several studies show that structure-based matching performs better than intensity-based matching in the bladder [8–11] and rectum [11].

Jamema et al. [8] performed 3D dose addition of multiple BT fractions in cervical cancer using intensity-based DIR and compared this to structure-based DIR. They reported that intensity-based DIR may underestimate doses due to implausible DIR. Andersen et al. [12] used a structure-based, biomechanical DIR algorithm to compare cumulative DVH parameters in the bladder to the UD method for fractionated BT. However, there is currently no study exploring the added value of structure-based DIR to the UD/OHD methods for dose accumulation of EBRT/BT doses in both bladder and rectum.

The aim of the present study is therefore to investigate accumulated BT and EBRT 3D doses by calculating cumulative DVH parameters in the bladder and rectum using structure-based DIR and compare this to the uniform dose method and the overlapping high dose method.

Materials and methods

Patients and treatment

Twelve consecutive patients treated for locally-advanced cervical carcinoma (FIGO stages IIA–IIIB) were investigated in this

study. Patients were irradiated using VMAT, receiving 46 Gy in daily fractions of 2 Gy. Two patients received an additional simultaneous-integrated boost (SIB) of 0.4 Gy per fraction to affected lymph nodes in the common iliac region. These nodes were located in the region between the aortic bifurcation and above the internal/external iliac, and the dose to these nodes will not contribute to the BT boost region. For the VMAT and VMAT + SIB plan the same bladder and rectum dose constraints were considered during plan evaluation. The CTV consists of gross tumor volume (GTV), cervix, parametrium, corpus-uterus and the upper part of the vagina, expanded with a 10 mm isotropic margin. The planning target volume (PTV) consisted of the CTV with an 8 mm margin including the lymph nodes. The planning aims for EBRT started that $\geq 99\%$ of the PTV should receive $\geq 95\%$ of the prescription dose, with a conformity index ($V_{95}/\text{PTV volume}$) < 1.35 . A hotspot criterion was used for bladder and rectum ($D_{1\text{cm}^3} < 103\%$ of the prescription dose). The dose fall-off region from 45 to 22.5 Gy was aimed at to be < 1.2 cm.

All patients received a pulsed-dose rate BT boost. A dose of 24 Gy in pulse doses of 1 Gy every hour was delivered to the high-risk CTV (CTV_{HR}). The radiotherapy techniques are described in Table 1, while typical EBRT and BT dose distributions are shown in Fig. 1. The BT dose was planned with the applicator in situ, using a library for applicator reconstruction, after which the plan was manually optimized. On the CT and MRI scans, the total bladder volume was delineated and the rectum was delineated from the rectosigmoid junction to the level of the anal sphincter. For EBRT, patients were instructed to have a full bladder daily, while a catheter was inserted for BT. Bladder and rectum volumes at the time of EBRT and BT are described in Supplementary Table 1.

Study-specific image preparation

The EBRT and BT doses were converted to EQD₂ on a voxel-by-voxel level (Matlab R2014b, Mathworks Inc., MA), using LQ-model based equations with an α/β value of 3 Gy for late OAR toxicity and a 1.5 h repair half-time [2,13].

Table 1

Radiotherapy techniques for EBRT and PDR BT (PTV: planning target volume, CTV_{HR}: clinical target volume at high risk; D₉₀: dose received by 90% of the volume, V₉₅: the percentage of the volume receiving $\geq 95\%$ of the prescription dose, V_{45Gy}/V_{45Gy}: the percentage of the volume receiving $\geq 45/40$ Gy, D_{2cm3}/D_{1cm3}: dose to the most irradiated 2 cm³/1 cm³).

	External Beam Radiation Therapy	Brachytherapy
Treatment type	VMAT	PDR
Treatment planning system	Oncentra 4.3 (Elekta AB, Stockholm, Sweden)	Oncentra Brachy 4.5 (Elekta AB, Stockholm, Sweden)
Dose calculation algorithm	Collapsed Cone using CT HU values	Based on the TG-43 formalism
Imaging	CT images	T ₂ -weighted Turbo Spin Echo MRI
Scanner specification	LightSpeed RT16 (GE, WI, USA)	Ingenia 3T (Philips Healthcare, Best, The Netherlands)
Imaging resolution (mm ³)	1.2 × 1.2 × 3	0.7 × 0.7 × 3.3
Dose calculation grid size (mm ³)	3 × 3 × 3	1 × 1 × 1
Planning aims	PTV V ₉₅ $\geq 99\%$ Bladder V _{45Gy} < 40%; Rectum V _{40Gy} < 70%; Bladder + Rectum D _{1cm3} < 103%	CTV _{HR} D ₉₀ 85–90 Gy _{EQD2} Bladder/rectum D _{2cm3} < 80/65 Gy _{EQD2}

Deformable image registration

The Feature-Based Deformable Registration (FBDR) tool, available in a research version of Oncentra Brachy (Elekta Brachytherapy, Veenendaal, The Netherlands) was used for structure-based DIR with the EBRT CT as the reference frame. The DIR algorithm in the FBDR tool is directly derived from the symmetric unidirectional thin plate spline robust point matching algorithm [14–16]. A symmetric DIR method has the advantage that the change of anatomy is independent of the order in which images are registered [17]. Delineated structures were converted to 3D surface meshes, and a mapping was established to propagate elements on the primary (EBRT) reference surface to the secondary (BT) surface. For each patient, we performed two registrations for bladder and rectum separately to improve the quality of each registration in the proximity of the evaluated organ.

Dose accumulation

For both organ-specific matches, the deformation field obtained with DIR was used to inversely map the EBRT dose distribution and organ contour to the frame of reference of the BT dose distribution. Finally, the propagated EBRT/BT doses were summed to create the accumulated dose (Fig. 1, right panel).

DIR accuracy

The Dice Similarity Coefficient (DSC) [18] was used to compare the propagated and reference contours. DSC quantifies the spatial overlap of the matched bladder and rectum. Additionally, the surface distance error (SDE) was determined for every voxel of each bladder/rectum, which is the Euclidean distance between the reference and propagated contours [10,19]. Mean DSC and range over all patients were calculated. The 25th, 50th, 75th and 95th percentiles of the SDEs were computed for all bladders/rectums. Finally the percentage of points with an SDE < 3 mm (the EBRT dose grid resolution) was calculated.

Data analysis

Bladder and rectum D_{2cm3}/D_{1cm3} were acquired for the three dose accumulation methods (Fig. 2) using VelocityAI (version 3.1.0, Velocity Medical, GA). For the DIR method, D_{2cm3}/D_{1cm3} were calculated from the accumulated dose distributions for both rectum and bladder. For the UD method, the cumulative D_{2cm3}/D_{1cm3} were calculated by adding the prescription dose of 46 Gy to D_{2cm3}/D_{1cm3} from the BT boost. For the OHD method, a summation of D_{2cm3}/D_{1cm3} from EBRT and the BT boost was performed. For the three methods, the mean and range of D_{2cm3}/D_{1cm3} of bladder and rectum were calculated over all patients.

Results

Cumulative DVH parameters

The mean and range of D_{2cm3}/D_{1cm3} was calculated for bladder and rectum (Table 2). For the bladder, maximum absolute differences in D_{2cm3}/D_{1cm3} were 1.8/1.1 Gy_{EQD2} (UD vs. DIR), and 3.2/3.3 Gy_{EQD2} (OHD vs. DIR). In the rectum, maximum absolute differences were 1.7/1.6 Gy_{EQD2} (UD vs. DIR) and 2.2/2.3 Gy_{EQD2} (OHD vs. DIR). Individual patient results can be found in Supplementary Fig. 1.

DIR accuracy

The bladder DSC, averaged over all patients, was 0.98 (0.97–0.99). The average rectum DSC was 0.94 (0.89–0.98).

For the bladder, the average 95th percentile of the SDE was 1.3 mm (0.7–1.5 mm), ranging between 0.7 and 1.5 mm. For the rectum, the average 95th percentile of the SDE over all patients was 3.5 mm (1.0–6.4 mm). Individual patient results are shown in Supplementary Fig. 2.

Averaged over all patients, bladder/rectum structures had SDE values < 3 mm for 98%/87% of the points. In Fig. 3, visualization is presented of the rectum match for patient 3 (DSC = 0.89, 95th percentile = 6.4 mm) and patient 10 (DSC = 0.95, 95th percentile = 3.7 mm).

Discussion

The present study is the first to use structure-based DIR to evaluate cumulative DVH parameters in combined EBRT and BT treatment for cervical cancer for bladder and rectum. The results were compared to UD and OHD methods. The difference in cumulative D_{2cm3}/D_{1cm3} in the bladder and rectum was always <1.8 Gy_{EQD2} (UD vs. DIR) and <3.3 Gy_{EQD2} (OHD vs. DIR). The results of our study suggest that, even for highly conformal dose distributions (VMAT), EBRT dose distributions can be considered uniform in the rectum and bladder for evaluation of cumulative D_{2cm3}/D_{1cm3}.

The DIR method was used to benchmark assumptions made with other methods. By comparing DIR to UD, differences in D_{2cm3}/D_{1cm3} were always <1.8 Gy_{EQD2}. This shows that planned EBRT dose distributions were indeed uniform at the location of the high dose volumes. The OHD method overestimated D_{2cm3}/D_{1cm3} with differences up to 3.3 Gy_{EQD2} in all cases as compared to DIR, showing that the high dose volumes did not overlap for the evaluated dose distributions of EBRT and BT, and that the worst case scenario did not occur.

The differences in cumulative D_{2cm3}/D_{1cm3} between DIR and the other two methods were relatively small. In a study by Georg et al., [20] the dose response for OARs in cervical cancer was modeled.

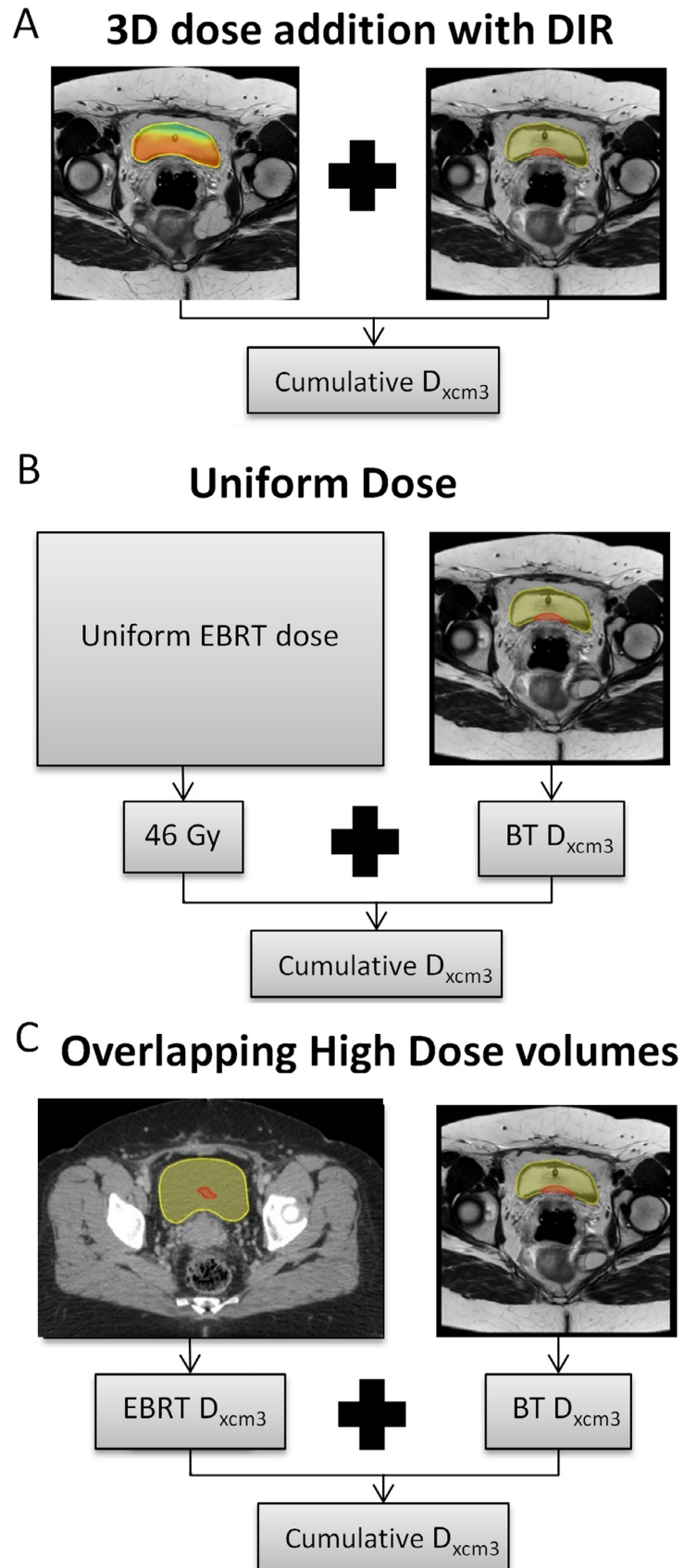


Fig. 2. The cumulative D_{xcm3} in the bladder (yellow) is calculated using three methods. A) For 3D addition with DIR, D_{xcm3} is calculated from the cumulative 3D dose. B) For the uniform dose (UD) method, the D_{xcm3} is calculated in the BT structure (red) and added to the EBRT prescription dose. C) For the overlapping high dose (OHD) method D_{xcm3} is calculated separately for EBRT (red) and BT (red) and then added to obtain the cumulative D_{xcm3} .

Table 2

The mean and the range over all patients of the planned cumulative $D_{2\text{cm}3}$ and $D_{1\text{cm}3}$ calculated with the DIR method, UD and OHD method, and the difference $\Delta D_{2\text{cm}3}$ and $\Delta D_{1\text{cm}3}$ with the DIR method, in bladder and rectum.

Method	DIR Mean (Range)	Uniform dose Mean (Range)	Overlapping high dose Mean (Range)
Bladder			
$D_{2\text{cm}3}(\text{Gy}_{\text{EQD}2})$	69.8(58.1;81.1)	69.7(56.6;80.9)	71.6(59.9;84.0)
$\Delta D_{2\text{cm}3}(\text{Gy}_{\text{EQD}2})$	–	0.1(–1.8;–1.5)	–1.8(–3.2;–1.0)
$D_{1\text{cm}3}(\text{Gy}_{\text{EQD}2})$	73.6(60.5;84.2)	73.4(59.4;84.0)	75.6(63.0;87.6)
$\Delta D_{1\text{cm}3}(\text{Gy}_{\text{EQD}2})$	–	0.2(–0.8;1.1)	–2.0(–3.3;–0.9)
Rectum			
$D_{2\text{cm}3}(\text{Gy}_{\text{EQD}2})$	59.6(51.6;67.4)	60.0(50.6;68.6)	60.7(53.0;69.2)
$\Delta D_{2\text{cm}3}(\text{Gy}_{\text{EQD}2})$	–	–0.4(–1.7;1.1)	–1.1(–2.2;–0.6)
$D_{1\text{cm}3}(\text{Gy}_{\text{EQD}2})$	62.1(52.0;71.8)	62.4(51.0;72.0)	63.4(53.8;73.8)
$\Delta D_{1\text{cm}3}(\text{Gy}_{\text{EQD}2})$	–	–0.3(–1.6;0.9)	–1.3(–2.3;–0.6)

The cumulative $D_{2\text{cm}3}/D_{1\text{cm}3}$ were calculated using the UD method in the bladder and rectum for patients receiving EBRT and BT, and related to the incidence of late effects. For the cumulative dose values found in this study, the risk of late effects remained within 5–10%, regardless of dose differences between the methods of up to 3.2 $\text{Gy}_{\text{EQD}2}$. Since dose differences between the methods are not clinically relevant, DIR provides no added value and at the time of BT planning the UD method is sufficient for evaluation of cumulative $D_{2\text{cm}3}/D_{1\text{cm}3}$ to predict organ toxicity.

DIR accuracy was evaluated by calculating the DSC and SDE distributions. Although a high DSC was reached in both organs, it was, on average, higher in the bladder (0.97) compared to the rectum

(0.94). The SDE distribution showed that the distance between points on the matched contours was small after DIR (75th percentile < 0.6/0.7 mm for bladder/rectum) compared to the imaging resolution of the planning scans ($\text{CT} = 1.2 \times 1.2 \times 3 \text{ mm}^3$, $\text{MRI} = 0.7 \times 0.7 \times 3.3 \text{ mm}^3$). Since EBRT doses were calculated with a $3 \times 3 \times 3 \text{ mm}^3$ resolution, dose points warped at this precision or lower were considered reliable. For the worst bladder/rectum match, only 3%/5% of the points had an SDE > 3 mm, showing that the DIR algorithm is able to match the bladder and rectum contours with high accuracy.

For the evaluation of $D_{2\text{cm}3}/D_{1\text{cm}3}$, it is relevant to know whether mismatches are located near the BT boost region. Detailed analysis showed that for the patient with the worst rectum match, this mismatch was not near the target, but more caudally (Fig. 3).

However, implications for accumulated $D_{2\text{cm}3}/D_{1\text{cm}3}$ are limited even if the mismatch is near the high dose region. As a result of both the large PTV margin and the planning aims, the variation of the EBRT dose near the BT high dose volumes in bladder and rectum is small, limiting the dose warping error to 3%.

Previous research already investigated 3D accumulated doses with rigid registration [5] and different DIR methods [3,4,6,7]. In these studies, the intensity values of the images were used to register planning images of EBRT and BT in gynecological cancer for dose warping. However, with structure-based DIR, it is possible to reach a higher DSC and better accuracy than with other DIR methods [8,9]. Additionally, registering the organs separately and assessing the dose only in the matched region further improves the accuracy of the match. In the aforementioned studies, the dose

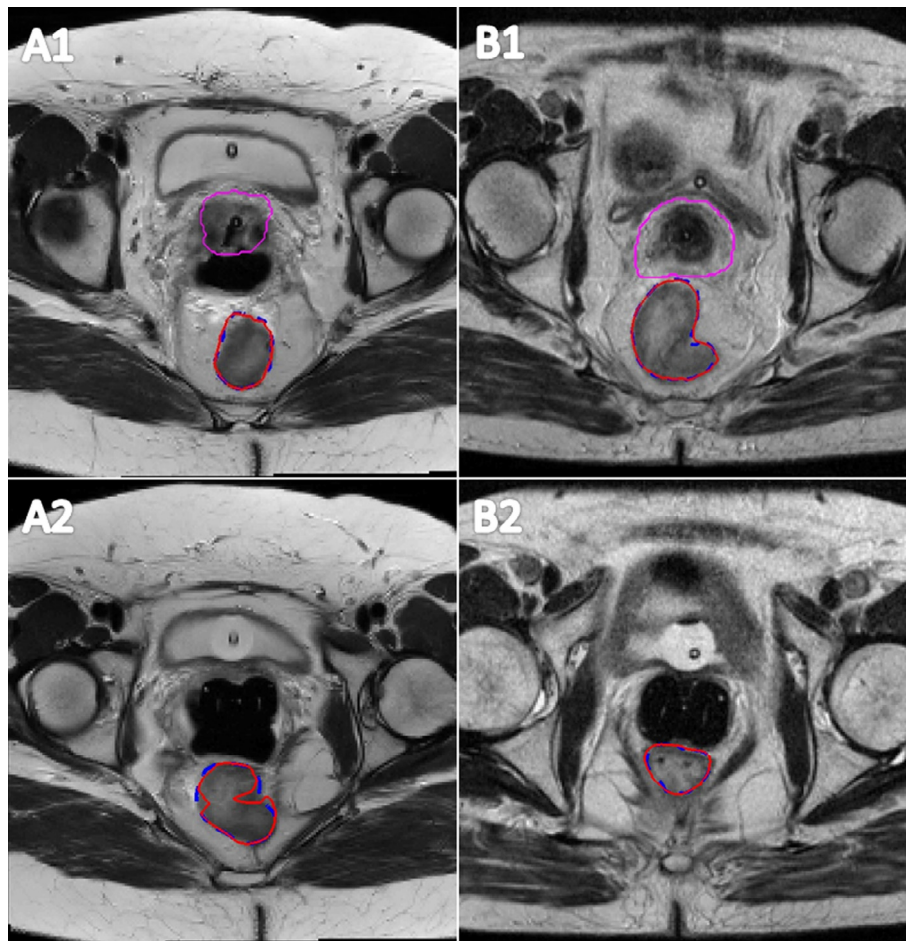


Fig. 3. Axial view of the BT MRI where the propagated rectum contour (solid) is shown together with the reference contour (dashed). The contours are shown either close to the target (magenta) (patient 3: A1, patient 10: B1), or on different MR images located caudally (patient 3: A2, patient 10: B2).

was propagated only once and evaluated for all organs, decreasing the dose summation accuracy. In addition, not all studies have extensively evaluated the accuracy of deformable registration. A potential limitation of our study is that the quality of the delineations is limited by the different imaging modalities, as well as the (axial) resolution of the images. Regardless of the differences in methods, our results are consistent with earlier studies using DIR that found variations $<5\%$ for $D_{2\text{cm}^3}/D_{1\text{cm}^3}$ between the methods. This shows that there is no clinically relevant difference between the DIR method, and the UD/OHD method.

For patients 1 and 5, the affected nodes could not be reached by BT and were therefore treated with an additional SIB. Small differences were found with the UD method ($<1.5 \text{ Gy}_{\text{EQD2}}$). For the patients in our study, EBRT dose uniformity near the location of the BT boost was specifically addressed by setting a hotspot criterion during planning. When the boosted nodes are located closer to the target (e.g. obturator lymph nodes) care should be taken that the EBRT dose near the BT high dose region is still uniform. For the select group of patients where dose spillage from the SIB into the region of the BT boost cannot be avoided because the lymph nodes are very close to the BT boost, DIR might have added value over the UD method.

It should be noted that the value of DSC and SDE as accuracy metrics is limited. Using structure-based DIR, a high DSC is typically reached since the optimization strives to increase the overlap of reference structure and propagated structure. Similarly, the SDE does not measure voxel-to-voxel agreements, but solely provides information about the remaining distance between the structure surfaces. No information is provided about the accuracy within the organ. For the present study, however, this does not affect the results. The bladder and rectum are hollow organs for which only the organ wall is clinically relevant, and DIR accuracy within the organ is not relevant. For non-hollow organs like the target, markers within the organ could be used to assess the registration accuracy [14,21].

As of yet no anatomical landmarks were used to evaluate the DIR, since these are difficult to detect in bladder and rectum. A separate verification for this same algorithm using lipiodol markers on the bladder showed that there was a remaining error in marker distance in the bladder of 0.9–4.0 mm in bladder cancer patients, demonstrating that the algorithm performs well in the bladder [10]. However, no such study was done for the rectum. Since the results from our study show that the rectum match was worse, the deformation error is expected to be higher than in the bladder (>0.9 –4.0 mm).

The effects of EBRT inter-fraction motion on the dose uniformity of bladder and rectum were not considered for these patients. As a result of the large PTV margin and the instructions to have a full bladder at the time of treatment, the BT high dose volumes were not expected to move out of the uniform part of the EBRT dose. For future investigations, we plan to investigate the feasibility of dose accumulation with DIR using the daily cone beam CT for patients treated using smaller margins.

The DIR and OHD methods resulted in maximum differences of $<3.3 \text{ Gy}_{\text{EQD2}}$ in $D_{2\text{cm}^3}$ and $D_{1\text{cm}^3}$ for the bladder and rectum, while the DIR and UD method resulted in differences $<1.6 \text{ Gy}_{\text{EQD2}}$. For the parameters under consideration, the DIR method provides no added value and the EBRT dose can be considered uniform both in bladder and rectum.

Conflicts of interest

AB is involved in several projects funded by Elekta. Elekta had no involvement in the study design, analysis and interpretation and the writing of the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2017.03.015>.

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