Original paper

Mapping of dose distribution from IMRT onto MRI-guided high dose rate brachytherapy using deformable image registration for cervical cancer treatments: preliminary study with commercially available software

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Abstract

Purpose: For patients undergoing external beam radiation therapy (EBRT) and brachytherapy, recommendations for target doses and constraints are based on calculation of the equivalent dose in 2 Gy fractions (EQD2) from each phase. At present, the EBRT dose distribution is assumed to be uniform throughout the pelvis. We performed a preliminary study to determine whether deformable dose distribution mapping from the EBRT onto magnetic resonance (MR) images for the brachytherapy would yield differences in doses for organs at risk (OARs) and high-risk clinical target volume (HR-CTV).

Material and methods: Nine cervical cancer patients were treated to a total dose of 45 Gy in 25 fractions using intensity-modulated radiation therapy (IMRT), followed by MRI-based 3D high dose rate (HDR) brachytherapy. Retrospectively, the IMRT planning CT images were fused with the MR image for each fraction of brachytherapy using deformable image registration. The deformed IMRT dose onto MR images were converted to EQD2 and compared to the uniform dose assumption.

Results: For all patients, the EQD2 from the EBRT phase was significantly higher with deformable registration than with the conventional uniform dose distribution assumption. The mean EQD2 ± SD for HR-CTV D_{90} was 45.7 ± 0.7 Gy vs. 44.3 Gy for deformable vs. uniform dose distribution, respectively ($p < 0.001$). The dose to 2 cc of the bladder, rectum, and sigmoid was 46.4 ± 1.2 Gy, 46.2 ± 1.0 Gy, and 48.0 ± 2.5 Gy, respectively with deformable dose distribution, and was significantly higher than with uniform dose distribution (43.2 Gy for all OAR, $p < 0.001$).

Conclusions: This study reveals that deformed EBRT dose distribution to HR-CTV and OARs in MR images for brachytherapy is technically feasible, and achieves differences compared to a uniform dose distribution. Therefore, the assumption that EBRT contributes the same dose value may need to be carefully investigated further based on deformable image registration.

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Key words: cervical cancer, deformable image registration, IMRT, MRI.

Purpose

The standard treatment for locally advanced cervical cancer is to deliver a combination of external beam radiotherapy (EBRT) and brachytherapy as a boost to primary tumor and cervix [1]. High dose rate (HDR) brachytherapy combined with image guided brachytherapy (IGBT) has recently been introduced to treat locally advanced cervical cancer and is now gaining popularity [2,3]. This emerging technique has been shown to provide improvements in dose volume parameters and in clinical outcome [4-8]. In 2005, GEC-ESTRO working group published recommendations for IGBT for cervical cancer. These recommendations are based primarily on the use of repetitive magnetic resonance imaging (MRI) performed at the time of the delivery of each fraction of brachytherapy [9-11]. Magnetic resonance imaging-based IGBT facilitates better delineation of target volume. Dose optimization can then be performed such that the classical pear shaped isodose lines better conform to the shape of the well-delineated target volume. This improvement in target dose coverage and reduc-

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tion in dose to critical organs have shown to improve local control and decreased toxicities [12,13]. To provide consistency in dose reporting, the GEC-ESTRO working group recommended that for MRI-based IGBT of cervical cancer, the total biological dose should be calculated by linearly adding the equivalent dose in 2 Gy fractions (EQD2) resulting from EBRT and HDR brachytherapy [9]. The ongoing international study on MRI-guided brachytherapy for locally advanced cervical cancer, EMBRACE, has adopted these recommendations for dose reporting [14,15].

The current practice for the calculation of total biological dose is to assume that the dose distribution from EBRT is homogenous. For example, all patients who received 45 Gy EBRT would be considered to have a uniform EQD2 (43.2 Gy for organs at risk and 44.3 Gy for tumor) for calculation of the total equivalent dose, regardless of the heterogeneity of dose that is presumed to exist in the EBRT plan. To calculate the total equivalent dose from combined modality treatments, linear addition of EQD2 from each modality is often used [9]. However, this simple linear addition of the dose matrices is based on the rigid image registration. It does not align deforming anatomy adequately [16]. A more accurate methodology would be to perform a deformable registration between the two imaging modalities, CT, and MRI, which will enable a mapping of each dose voxel from one modality to another by taking deformed anatomy into account [16,17].

In this study, we utilized commercially available deformable image registration software to calculate the deformed IMRT dose voxel by voxel, mapped on the MRI image for every brachytherapy fraction to estimate the EBRT dose distribution. Additionally, the deformed IMRT dose mapped on MR images is compared to the current clinical practice (uniform dose distribution from EBRT). To the best of our knowledge, such a study focusing on cervical cancer treatment has not been reported in the literature.

Material and methods

Patient data and treatment planning

Nine cervical cancer patients, FIGO stage IB1 to IIIB, were retrospectively analyzed. All patients were treated to a total dose of 45 Gy in 25 fractions using IMRT, followed by MRI-guided 3D HDR brachytherapy (BT) using a ring and tandem applicator. For three patients, the pelvic and/or para-aortic nodes were treated to a total dose of 55 Gy in 25 fractions using IMRT with simultaneous integral boost (SIB) technique.

Patients underwent a CT simulation for treatment planning in supine position with full bladder and empty rectum without a vaginal marker. For all patients, two clinical target volumes (CTV) were created. The CTV1 included common iliac, external iliac, and internal iliac lymph nodes regions in all patients. The inguinofemoral and para-aortic nodes were included only as clinically indicated. The CTV2 included the uterus, cervix, upper vagina, and parametria. The CTV1 was expanded by 0.7 cm and CTV2 was expanded by 1-2 cm, and combined together to create the final PTV. Brachytherapy was initiated during the fourth or fifth week of external beam treatment, following the placement of a Smit sleeve. Brachytherapy was carried out once a week until the completion of EBRT, at which point it was delivered twice a week. The CT/MRI compatible ring and tandem applicator (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) with a tandem length of 40 or 60 mm, curvature of 45° or 60°, and a ring diameter of 26, 30, or 34 mm was used for brachytherapy. A rectal retractor was used, and a Foley catheter was inserted in all patients. This ensures consistent and reproducible setup for all patients for each fraction. Orthogonal X-ray films were taken for the verification of applicator position reproducibility for each fraction prior to MRI. All nine patients underwent a repetitive MRI (GE SIGNA HD platform 1.5 T) for planning prior to each fraction of brachytherapy. With the applicator in place, T2-weighted sequences in the axial, coronal, and sagittal planes were acquired using 2.0 mm slices. Magnetic resonance imaging-based 3D treatment plans were generated for each of the five fractions for all patients in the study (total of 45 fractions). For each fraction, the high risk clinical target volume (HR-CTV) and organs at risk (OARs) were delineated following the GEC-ESTRO recommendations, and then transferred to Nucletron Plato Brachytherapy Planning System™ Version 14.3 (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). Each patient was evaluated for the gross tumor volume (GTV), which is a part of HR-CTV, with MR images before treatment course and after treatment of external beam. At the time of brachytherapy, physicians evaluated the GTV and HR-CTV based on GEC-ESTRO contouring recommendations. Point A (traditional dose prescription point defined as 2.0 cm above and lateral to the cervical os) was marked on corresponding slices on MR images as a reference starting point for dose optimization. After standard loading of source dwell positions and weighting in tandem and ring, manual optimization was performed based on isodose lines in axial slices of MR images, and evaluation of dose-volume histogram (DVH) constraints for HR-CTV and OARs including rectum, bladder, and sigmoid. The total dose of 27.5-30.0 Gy delivered in 5 fractions (5.5-6.0 Gy/fraction) was prescribed to the HR-CTV. Plans were designed to achieve an EQD2 of 80-85 Gy for HR-CTV and limit dose to 2 cc (D_{2cc}) of bladder, rectum, and sigmoid to be ≤ 85 Gy, ≤ 70 Gy and ≤ 70 Gy, respectively.

Conventional EBRT EQD2 dose calculation – uniform dose distribution method

All prescribed and calculated physics doses to the target and OARs were converted to EQD2 using the linear quadratic model with the assumption of $\alpha/\beta = 3$ for OAR and $\alpha/\beta = 10$ for HR-CTV. As per GEC-ESTRO recommendations, the dose distribution of EBRT to the HR-CTV and OARs was assumed to be uniform. Thus, EQD2 to HR-CTV and OARs was always reported as 44.3 Gy and 43.2 Gy, respectively.

Deformable registration and non-uniform EBRT dose distribution method

To map the actual dose distribution on EBRT CT images onto the OARs and HR-CTV contoured on the MRI for brachytherapy, image registration was required. The EBRT planning CT images were fused retrospectively to the MR images acquired for each fraction of brachytherapy using commercially available software (Velocity AI 2.7., Velocity Medical Solutions, Atlanta, GA, USA). First, a rigid image registration was performed using the bony anatomy and intact uterus as landmarks. Then, EBRT planning CT images were deformed to match to each MR image (five MR image set per patient) using multi-pass iterative optimization using B-Spline deformable image registration algorithm. This algorithm aligns images by maximizing the mutual information. The deformation vector field (DVF) created for the image registration allows Velocity to deform dose distribution voxel by voxel from IMRT on MR images. For each fraction, the deformed dose distribution from IMRT on MR image was then calculated by warping doses based on the quality of the DVF obtained during image registration [18]. We used a qualitative evaluation process to ensure that the deformed images were reasonable. That is, these fused images were visually inspected to identify physically unrealistic deformations such as folds and tears. Also, the displacement (mapping) vectors were reviewed to check the direction and magnitude of the displacement from the deformed images to the reference images [19]. In addition, warping volume histogram was evaluated to estimate the amount of warping voxels across the deformed OARs. The deformed EBRT dose voxel by voxel was calculated for HR-CTV, rectum, bladder, and sigmoid for each fraction of MRI brachytherapy. Dose-volume histogram for each organ was generated for each fraction from the deformed EBRT dose and converted to EQD2.

Statistical analysis

Paired sample *t*-tests were conducted for the comparison between uniform dose assumption and deformed dose. Additionally, correlated data analysis for repeated measures over 5 fractions within a subject was used to identify random effects. Statistical analyses were performed with STATA software version 12.1 (STATA Corp, College Station, TX, USA), and two-tailed *p*-values of < 0.05 were considered to be significant.

Results

The mean HR-CTV ± SD was 35.7 ± 13.2 cc (range: 18-53 cc). The mean EQD2 ± SD of the deformed EBRT dose for HR-CTV D_{90} (dose covering 90% of the volume) was 45.7 ± 0.7 Gy (range: 45.2-47.0) and was significantly greater than that obtained using a uniform EBRT dose distribution (44.3 Gy, $p < 0.001$). The D_{2cc} for bladder, rectum, and sigmoid was 46.4 ± 1.2 Gy (range: 45.0-49.0), 46.2 ± 1.0 Gy (range: 44.5-48.0), and 48.0 ± 2.5 Gy (range: 46.0-52.8), respectively based on deformed EBRT doses. These doses were significantly higher than the D_{2cc} calculated based on a uniform dose distribution (43.2 Gy for all OARs, $p < 0.001$). For all patients, the doses obtained using deformable image registration method was found to be consistently higher than those obtained using uniform dose distribution assumption. We then sought to explore whether the doses to OAR and HR-CTV differed with and without the use of SIB technique with IMRT. The comparison of doses for bladder, rectum, and sigmoid treated with and without SIB were 46.9 Gy vs. 45.4 Gy, 46.4 Gy vs. 45.4 Gy, and 49.3 Gy vs. 46.0 Gy, respectively. The HR-CTV dose difference was not found to be as pronounced (46.0 Gy for SIB vs. 45.2 Gy without SIB).

Additionally, the total EQD2 from the entire course of therapy were recalculated and compared with the current practice. The mean total EQD2 of the HR-CTV between deformed vs. uniform dose was 84.7 Gy vs. 83.5 Gy ($p = 0.43$). The mean total EQD2 to 2cc of the bladder for deformed and uniform dose was 77.2 Gy vs. 74.4 Gy ($p = 0.31$). Similarly, the mean total EQD2 to 2cc of the rectum and sigmoid for deformed and uniform dose was 58.7 Gy vs. 56 Gy ($p = 0.12$) and 68.7 Gy vs. 64.7 Gy ($p = 0.18$), respectively. Table 1 and Table 2 summarize the mean deformed EBRT EQD2 and total EQD2 for all patients, and doses for each individual, respectively.

Interestingly, one patient (11%) had > 85 Gy for total EQD2 to D_{2cc} of the bladder, and three patients (33%) had > 70 Gy for sigmoid when the deformed dose applied. However, based on conventional dose calculation with uniform EBRT dose distribution, none were found to receive higher than 85 Gy and 70 Gy for the total EQD2 to D_{2cc} of the bladder and sigmoid.

For each patient, repeated measures of dose for all OARs over 5 fractions were found to be highly correlated within a subject (bladder, rectum, and sigmoid; $p < 0.001$). Therefore, random effects between fractions were not found within a patient.

Table 1. Mean deformed EBRT EQD2 and total EQD2 for all patients (unit = Gy)

	Bladder D_{2cc}	Rectum D_{2cc}	Sigmoid D_{2cc}	HR-CTV D_{90}
Deformed EBRT	46.4	46.2	48	45.7
Uniform dose EBRT	43.2	43.2	43.2	44.3
p-value	< 0.001	< 0.001	< 0.001	< 0.001
Total EQD2-deformed	77.2	58.7	68.7	84.7
Total EQD2-uniform	74.4	56	64.7	83.5
p-value	0.31	0.12	0.18	0.43

EBRT – external beam radiation therapy; EQD2 – equivalent dose in 2 Gy fractions

Table 2. Mean deformed EBRT EQD2 and total EQD2 for each individual

Bladder 2 cc				
Patient	Deformed EBRT	Total EQD2 (d)	Total EQD2 (u)	Difference
1*	47.6	79.2	76.8	2.4
2*	49.5	85.8	81	4.8
3*	49.5	82.4	78	4.4
4	47	83.3	81.3	2
5	47.9	77.4	74.5	2.9
6	47.4	70	67.8	2.2
7	47.6	74.4	72	2.4
8	46.3	68.4	67	1.4
9	47.6	73.9	71.5	2.4
Mean	47.8	77.2	74.4	2.8
SD	1.1	6.0	5.3	1.1

Sigmoid 2 cc				
Patient	Deformed EBRT	Total EQD2 (d)	Total EQD2 (u)	Difference
1*	52.1	72.2	65.5	6.7
2*	48.8	71	66.4	4.6
3*	53.1	84.3	76.6	7.7
4	48	67.5	64.5	3
5	48.1	67	64	3
6	47.3	61	58.4	2.6
7	47.8	64.5	62.4	2.1
8	47.5	62.7	60	2.7
9	48.6	67.7	64.3	3.4
Mean	49.0	68.7	64.7	4.0
SD	2.1	6.9	5.2	2.0

Rectum 2 cc				
Patient	Deformed EBRT	Total EQD2 (d)	Total EQD2 (u)	Difference
1*	47.6	64.8	62.4	2.4
2*	49.5	61	56	5
3*	47.9	57.4	54.5	2.9
4	48	61	58	3
5	47.4	55	52	3
6	47.5	57	54.6	2.4
7	46.8	54.4	52.4	2
8	46.3	56.3	55	1.3
9	47.4	61.3	59.2	2.1
Mean	47.6	58.7	56.0	2.7
SD	0.9	3.5	3.3	1.0

HR-CTV D_{90}				
Patient	Deformed EBRT	Total EQD2 (d)	Total EQD2 (u)	Difference
1*	46	85.8	84.8	1
2*	47	83.4	81.4	2
3*	47.6	83.2	80.5	2.7
4	46	86	85	1
5	46	83.8	82.8	1
6	46.5	82.3	80.8	1.5
7	46.3	89.3	88	1.3
8	45	88.8	88.8	0
9	45.5	80	79.6	0.4
Mean	46.2	84.7	83.5	1.2
SD	0.8	3.0	3.3	0.8

Unit = Gy, d – deformed, u – uniform
**Patient 1, 2, 3 received SIB dose of 55 Gy*

Discussion

The present study demonstrates that in cervical cancer patients treated with a combination of external beam radiation therapy (IMRT in the present study) and MRI-based image guided HDR brachytherapy, the contribution of HR-CTV and OAR doses from IMRT to total dose vary between patients with a deformable image registration method. Our findings suggest that unlike the current GEC-ESTRO recommendations, where the EBRT dose is assumed be uniform (with an EQD2 of 44.3 Gy for HR-CTV and 43.2 Gy for the OARs for a 45 Gy EBRT prescription) for all patients, we found that deformable registration revealed significant differences. As shown in Table 3, the heterogeneous IMRT dose distributions across PTV area exist. Importantly, we discovered that for 33% of patients in the study (n = 3), the deformable dose calculation method identified that OAR doses exceeded GEC-ESTRO recommendations, but conventional calculation assuming EBRT dose uniformity did not identify this. Much larger further studies are needed to confirm these differences and determine the clinical significance of this.

However, Van de Kamer *et al.* [17] has shown that a homogeneous EBRT dose is a still good approximation for combining the dose from EBRT and brachytherapy. It should be noted that in this study, two brachytherapy fractions that combined intra-cavitary and interstitial pulsed dose rate (PDR) brachytherapy after the EBRT were delivered, and only one fraction of MR image from brachytherapy was fused with the CT images from EBRT by using 3D biological modeling based on the registration with bony anatomy matching. This is different from our clinical practice that consists of delivering five fractions of brachytherapy using only an intra-cavitary applicator after EBRT with

subsequent deformable image registration applied to all 5 fractions of MR images from brachytherapy.

Although the mean differences between a homogeneous dose assumption and deformed EBRT dose contribution is statistically significant in the present study, the mean total EQD2 between homogeneous EBRT dose and deformed dose was not significant, and was less than 10% for all OARs and target. This results in concordance with those from the above study. Thus, while there were no significant differences between the two dose calculation methods when considering the entire treatment course, for a proportion of patients, deformable dose mapping may have altered the brachytherapy plan.

Andersen *et al*. [20] and Jamema *et al*. [21] reported that D_{2cc} of bladder and rectum in MRI-based image guided brachytherapy of cervical cancer is a stable spatial location for direct dose summation for each fraction. Our total D_{2cc} for OARs from the contribution of each brachytherapy fraction is based on the same observation as their study.

The present study also shows that for those patients who were treated using SIB technique, the OAR doses from IMRT were higher than the corresponding doses treated without using the SIB technique. Sigmoid dose had higher difference than ones from bladder and rectum because of proximity of these organs to the pelvic lymph nodes. None of patients in the present study received the total EQD2 to 2cc of the bladder dose > 85 Gy with homogeneous dose assumption, but one patient had 86 Gy after deformed IMRT dose was applied. Similarly for sigmoid dose, three patients had > 70 Gy after the deformed IMRT dose was applied, while none of patients received > 70 Gy with a homogeneous dose distribution. These patients were treated using SIB technique. Since the D_{2cc} of bladder, rectum, and sigmoid is a good predictive value for the normal tissue toxicity [22], it is important to quantify these DVH parameters accurately.

Our preliminary results have several limitations. First, the evaluation of deformable image registration accuracy was based on the qualitative methods, not quantitative assessment. There is a lack of straightforward metrics to evaluate deformable image registration errors [23], although deformable image registration algorithms are widely accepted and implemented in clinical practice [23-28]. Thus, visual inspection (qualitative evaluation) is still the most widely used evaluation method [19]. In those studies, the evaluation of deformable image registration did not deal with the combined modality of external beam and the complex brachytherapy. Secondly, we excluded patients who had unrealistic warping maps which were associated with unreasonable deformation. We initially started retrospective review with 15 patients for deformable image registration, but 9 out of them were reasonable based on our assessment. Due to large organ deformations between external beam treatment and brachytherapy fraction with applicator in situ, image registration causes extreme deformed organs and lead to incorrect dose mapping. Although there are commercially available software packages which have been widely accepted in clinical use, the degree of deformation associated with cervical cancer makes this site particularly challenging [25]. Thirdly, sigmoid D_{2cc} assessment is highly uncertain due to mobility of this organ. In IMRT planning CT, most part of sigmoid is close to PTV area. Thus we assumed that sigmoid D_{2cc} (representing hot spot/high dose area) from IMRT plan is close to PTV area, and the D_{2cc} for sigmoid at the time of brachytherapy would be coincided with the PTV area based on the maximized mutual information using deformed image registration. Additionally, we did not investigate the impact of using deformable image registration between brachytherapy fractions. Brachytherapy linear dose addition between

Table 3. Heterogeneous IMRT dose distributions across PTV area exist. Unit = %; V_{100}: % of PTV, which receives 100% of prescription dose; V_{105}: % of PTV, which receives 105% of prescription dose; V_{110}: % of PTV, which receives 110% of prescription dose; V_{120}: % of PTV, which receives 120% of prescription dose

Patient	V_{100}	V_{105}	V_{110}	V_{120}
1	96	46	12	5
2	95	70	12	6
3	95	57	11	4.5
Mean	95.33	57.67	11.67	5.17
SD	0.58	12.01	0.58	0.76

Patients who received SIB 55 Gy

Patient	V_{100}	V_{105}	V_{110}
4	95	33	1
5	97	48	0.2
6	98	25	0.5
7	95	52	0
8	95	41	0.5
9	96	31	0.2
Mean	96.00	38.33	0.40
SD	1.26	10.46	0.35

Patients who received whole pelvis 45 Gy

Patient	V_{100}	V_{105}	V_{110}	V_{120}
1*	96	46	12	5
2*	95	70	12	6
3*	95	57	11	4.5
4	95	33	1	N/A
5	97	48	0.2	N/A
6	98	25	0.5	N/A
7	95	52	0	N/A
8	95	41	0.5	N/A
9	96	31	0.2	N/A
Mean	95.78	44.78	4.16	
SD	1.09	14.07	5.65	

** Patients who received SIB 55 Gy*

fractions without deformable image registration is based on the assumption that the hot spots are located in the same region of each organ for each fraction that results in an overestimation of dose [29]. Thus, the maximum dose to OARs determined using deformable image registration cannot be higher than the linear dose addition method, because the hot spots do not necessarily overlap for each fraction. Finally, we did not include the effects of inter fraction organ motion during the course of EBRT and used static CT scans at the time of planning for deformation registration and dose calculations. Since daily setup uncertainty causes the variation of the dose distribution from the planning, these factors also need to be accounted for in the deformed dose from EBRT [30].

Conclusions

The present study assessed the composite dose distribution of EBRT and brachytherapy in cervical cancer treatments with a commercially available deformable image registration method. This study demonstrated that cervical cancer patients treated with a combination of external beam radiation therapy (IMRT in the present study) and MRI-based image guided HDR brachytherapy the contribution of HR-CTV and OAR doses from IMRT to total dose vary from one patient to another, and it is prominent in cases where SIB boost is delivered to pelvic nodes. Therefore, the assumption that EBRT contributes the same dose value of HR-CTV and OARs for all patients (an EQD2 of 44.3 Gy for HR-CTV and 43.2 Gy for the OARs) may need to be carefully investigated further based on deformable image registration.

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Disclosure

Authors report no conflict of interest.

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