

ORIGINAL ARTICLE

Correction of diffusion-weighted magnetic resonance imaging for brachytherapy of locally advanced cervical cancerSØREN HAACK^{1,2}, JESPER F. KALLEHAUGE^{2,3}, SUNE N. JESPERSEN^{4,5}, JACOB C. LINDEGAARD², KARI TANDERUP² & ERIK M. PEDERSEN⁶

¹Department of Clinical Engineering, Aarhus University Hospital, Aarhus, Denmark, ²Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, ³Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark, ⁴CFIN/MindLab, Aarhus University Hospital, Aarhus, Denmark, ⁵Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark and ⁶Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

ABSTRACT

Background. Geometrical distortion is a major obstacle for the use of echo planar diffusion-weighted magnetic resonance imaging (DW-MRI) in planning of radiotherapy. This study compares geometrical distortion correction methods of DW-MRI at time of brachytherapy (BT) in locally advanced cervical cancer patients.

Material and methods. In total 21 examinations comprising DW-MRI, dual gradient echo (GRE) for B₀ field map calculation and T2-weighted (T2W) fat-saturated MRI of eight patients with locally advanced cervical cancer were acquired during BT with a plastic tandem and ring applicator in situ. The ability of B₀ field map correction (B₀M) and deformable image registration (DIR) to correct DW-MRI geometric image distortion was compared to the non-corrected DW-MRI including evaluation of apparent diffusion coefficient (ADC) for the gross tumor volume (GTV).

Results. Geometrical distortion correction decreased tandem displacement from 3.3 ± 0.9 mm (non-corrected) to 2.9 ± 1.0 mm (B₀M) and 1.9 ± 0.6 mm (DIR), increased mean normalized cross-correlation from 0.69 ± 0.1 (non-corrected) to 0.70 ± 0.10 (B₀M) and 0.77 ± 0.1 (DIR), and increased the Jaccard similarity coefficient from 0.72 ± 0.1 (non-corrected) to 0.73 ± 0.06 (B₀M) and 0.77 ± 0.1 (DIR). For all parameters only DIR corrections were significant (p < 0.05). ADC of the GTV did not change significantly with either correction method.

Conclusion. DIR significantly improved geometrical accuracy of DW-MRI, with remaining residual uncertainties of less than 2 mm, while no significant improvement was seen using B₀ field map correction

Background

Diffusion-weighted magnetic resonance imaging (DW-MRI) measures water motion in tissue [1] over distances comparable to cell dimensions and can thereby provide information about the average tissue microstructure despite image resolution in the order of millimeters. The calculated apparent diffusion coefficient (ADC) can provide a quantitative measure of diffusion for comparing across different time points and patients [2]. With these features, DW-MRI has potential in oncological imaging for detecting tumor tissue and for monitoring tumor response to treatment [2–4]. DW-MRI requires fast imaging techniques, and therefore single shot echo planar imaging (SS-EPI) is currently used in the

body [5]. A major disadvantage of SS-EPI is its sensitivity to local variations in magnetic susceptibility, resulting in geometrical distortions of the image, especially in the pelvis where the cervix and vagina is in near proximity to the bowel and the rectum, which can be filled with air to varying degrees. Furthermore, when performing MRI for treatment planning of brachytherapy (BT) in cervical cancer, the applicator used for delivering the treatment is placed in situ [6]. The presence of the applicator exacerbates susceptibility variations in the region of the tumor. The geometrical uncertainties due to these changes in susceptibility is a major challenge when using DW-MRI and derived ADC maps for treatment planning of locally advanced cervical cancer at time of BT.

Changes in magnetic susceptibility perturb the local magnetic field leading to geometric inaccuracy. The degree of voxel displacement depends on the pixel bandwidth and since this is very high in the read-out (frequency) direction for SS-EPI (Supplementary Table I, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>) the displacement due to B_0 inhomogeneity in this direction is negligible [7]. A well-known method for correction of the EPI-based distortion is based on the B_0 field mapping method (B_0M) [7], where a B_0 field map is acquired separately from the DW-MRI and subsequently used for correcting the position of the individual voxels along the phase encoding direction. Currently, the method is used for correction of functional MR images in the brain prior to matching to the high-resolution anatomic MR images [8]. In the body B_0M is, however, more challenging due to problems with larger field of view (FOV) introducing larger B_0 variations and due to air/tissue transitions, which introduce additional susceptibility artifacts. To our knowledge no studies have examined to which degree correction using B_0M can reduce geometrical distortion during brachytherapy with the applicator in situ.

However, a different way of correcting for geometrical distortions of DW-MR images is to use deformable image registration (DIR) with a non-EPI based image as a reference image. Compared to B_0M the DIR method allows for correction in all directions and not only in the phase-encoding direction. Under the overall aim of improving image-guided brachytherapy of the cervix by adding DW-MRI, it was the specific aim of this paper to evaluate and compare the ability of B_0M and DIR for geometrical correction of DW-MR images and ADC values during brachytherapy with the applicator in situ.

Material and methods

Patients and MRI

The study included 21 MRI examinations from eight patients with locally advanced cervical cancer treated with radio-chemotherapy including MRI-guided BT. External beam radiotherapy (EBRT) of 45–50Gy/25–30fx and a pulsed dose rate (PDR) BT boost of two fractions were employed. Three BT implants and MRI with a plastic tandem and ring applicator (GammaMed, Varian Medical Systems, Charlottesville, VA, USA) in situ were performed in all patients, i.e. week 5 (BT0), week 6 (BT1) and week 7 (BT2) of the treatment. BT0 was used for preplanning of subsequent implantations [9] whereas BT1 and BT2 comprised two equal-sized fractions of PDR BT.

MRI examinations acquired at time of BT0, BT1 and BT2 were analyzed in this study. MR images were collected using an Achieva 3T-X MRI (Philips, Best, The Netherlands). Details on the use of T1- and T2-weighted MRI for contouring, reconstruction of applicator, and treatment planning have been described previously [10,11]. The MRI included DW-MRI, a dual echo GRE including phase-images for B_0 field map calculation and a fat-saturated, single shot T2W sequence with similar contrast as the DW-MRI at $b = 0$ s/mm². The sequences were acquired in the order as listed. All three series were acquired at the same slice position and with same FOV. Automatic shimming including the entire FOV was used. Since FOV and slice position was the same for the three sequences the same shimming was used for all three and no re-shimming was performed between the series. Details regarding acquisition parameters can be found in Supplementary Table I available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>.

B0 field map correction

Based on phase-images acquired at different echo-times the B_0 field map (ΔB_0) can be calculated as described by Jezzard et al. [7], (Equation 1):

$$\Delta B_0 = \frac{\Delta\theta}{2 \cdot \pi \cdot \gamma \cdot \Delta TE} [Hz], \quad (1)$$

where $\Delta\theta$ is the difference in phase between the two echo times, γ is the gyromagnetic ratio and ΔTE is the echo-time difference. The B_0 field map in Hz can be converted to a voxel-displacement map (VDM) by dividing it with the effective bandwidth per pixel. Before subtracting phase-images unwrapping is needed to remove phase jumps occurring when the phase exceeds π and is thereby wrapped to $-\pi$ instead of increasing linearly. This must be done for both phase maps prior to calculating the phase map difference. The phase unwrapping and calculation of the VDM was done using the Fieldmap-tool in the Statistical Parametric Mapping software (SPM12b), which is based on the work by Jezzard [7] and Jenkinson [12]. The resulting VDM contains pixel shifts values for each pixel in the image. Each pixel in the DW-MRI was shifted back to its estimated true position according to the pixel shift value given in the same pixel in the VDM as described by Jezzard et al. [7]. The corrected image was interpolated to its fixed grid using Matlab (Mathworks, Natick, MA, USA). The DW-MR images were only corrected in the phase-encoding direction. In this study the phase-encoding direction was anterior-posterior (AP).

Image registration

The image registration process was separated into a rigid and a non-rigid transformation. A rigid transformation allows translation and rotation, whereas for a non-rigid registration, the transformation can be different for each voxel in the image. Image registration requires a ‘reference image’ and a ‘source image’. The goal was to maximize intensity similarity between the reference and the source images. In this study the fat-saturated T2-weighted image was used as the ‘reference image’, and the DW-MRI at $b = 0$ s/mm² was the ‘source image’ (Supplementary Figure 1, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>). For image registration, the Elastix software package was used [13,14]. The parameter file used was validated for registration of cervix MRI by Staring et al. [15]. The image registration method evaluated was a rigid transformation followed a B-spline transformation. The DW-MRI, $b = 0$ s/mm², was registered to the T2W image resulting in a transformation matrix. The transformation matrix was then applied to the remaining DW-MRI ($b = 150, 600$ and 1000 s/mm²). The advantage of the B-spline registration method is that a transformation of a voxel can be calculated using only few of the surrounding voxels allowing modeling of local deformations, which would be expected to be present in the DW-MRI around, e.g. the tandem and air-filled cavities.

Evaluation

The performance of B₀M and DIR was evaluated and compared to the non-corrected DW-MRI using three different metrics. All image evaluation was carried out using Matlab (Mathworks). Firstly, the normalized cross-correlation between the corrected DW-MRI, $b = 0$ s/mm², and the T2W image was calculated. Secondly, the tandem center was identified on both image sets and the position difference was calculated (Δ tandem center). Also the difference in the x- and y direction was evaluated [x: left-right (LR), y: AP]. Finally, the cervix and lower uterus was manually delineated on both image sets and the Jaccard similarity coefficient (Supplementary Equation 1, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>) was calculated. The Jaccard similarity coefficient compares the common area to the union area [16], and results in a value of 1 in the case of a perfect match.

All parameters were evaluated as a mean from all the slices where the tandem of the BT applicator was visible. The GTV was contoured on T2W images according to the GEC-ESTRO guidelines [17], and the ADC of the GTV was evaluated. The ADC for

the three image sets was estimated using non-linear least-square fitting using the b-values 150, 600 and 1000 s/mm² [18].

Statistics

Initially plots of each parameter as a function of patients were made to evaluate if systematic dependency on patients were present as up to three measurements at different time points were made in each patient (Supplementary Figure 3, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>). No systematic patient effect was seen. This could be expected, as the presence of BT applicator is the same for all patients and as the amount of air present in the rectum and bowel is assumed to be random. The 21 data sets were subsequently considered as independent during statistical analysis. The geometrical performance for each parameter was compared to the non-corrected DW-MRI using paired Student’s t-test with $p < 0.05$ considered a significant difference. The ADC maps were compared using one-way ANOVA. All statistics were calculated using STATA 13 (StataCorp, College Station, TX, USA).

Results

The mean normalized cross-correlation increased from 0.69 ± 0.1 (non-corrected) to 0.70 ± 0.10 (B₀M) (non-significant), and to 0.77 ± 0.1 for DIR ($p < 0.01$). Tandem displacement decreased from 3.3 ± 0.9 mm (non-corrected) to 2.9 ± 1.0 for B₀M (non-significant) and to 1.9 ± 0.6 mm for DIR ($p < 0.01$). The Jaccard similarity coefficient increased from 0.72 ± 0.1 (non-corrected) to 0.73 ± 0.06 for B₀M (non-significant) and to 0.77 ± 0.1 for DIR ($p < 0.01$). Only the improvements for DIR were significant. B₀M reduced the Δ tandem center although not significantly. This reduction was due to a significantly reduced Δy ($p < 0.01$) (Table I). DIR reduced both mean Δx and mean Δy significantly ($p < 0.01$) (Table I). Figure 1 shows the mean Δ tandem center for all MRI examinations as a function of position according to the top of the applicator ring. It is seen that the Δ tandem center is largest

Table I. Displacement of the applicator tandem center.

	Non-corrected Mean \pm SD	B ₀ M Mean \pm SD	DIR Mean \pm SD
Δx (LR) (mm)	1.3 ± 1.2	1.3 ± 1.1	$0.5 \pm 0.6^*$
Δy (AP) (mm)	2.3 ± 1.2	$0.7 \pm 2.0^*$	$0.7 \pm 1.0^*$
Δ tandem center (mm)	3.3 ± 0.9	2.9 ± 1.0	$1.9 \pm 0.6^*$

*Significant difference ($p < 0.05$) when compared to corresponding value for non-corrected DW-EPI (paired Student’s t-test).

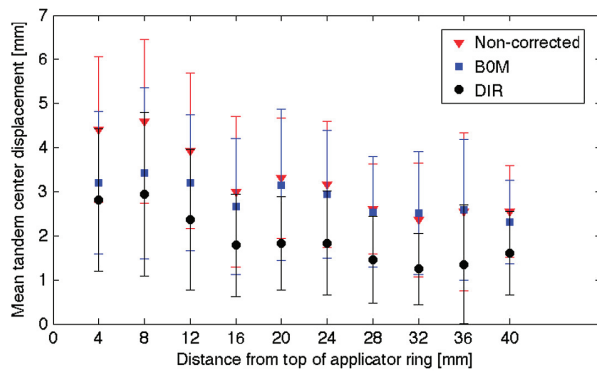


Figure 1. Mean Δ tandem center for all MRI examinations as a function of position in millimeters from the top of the applicator ring for the non-corrected DW-MRI (red), B₀M (blue) and DIR (black). The error bars represent the standard deviation.

close to the ring but also that both B₀M and DIR is able to reduce the displacement at this position. However, the reduction for the B₀M was only significant at 4 mm. The DIR reduced the displacement significantly in almost all positions except for the two most, to the ring, distant positions. In Figure 2 an example of the resulting corrected DW-MR images, $b = 0$ s/mm², is shown together with the non-corrected image. Using one-way ANOVA analysis no significant difference of the ADC in the GTV between the three groups was found ($p = 0.18$) (Supplementary Table II, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>), although the difference between the mean ADC for

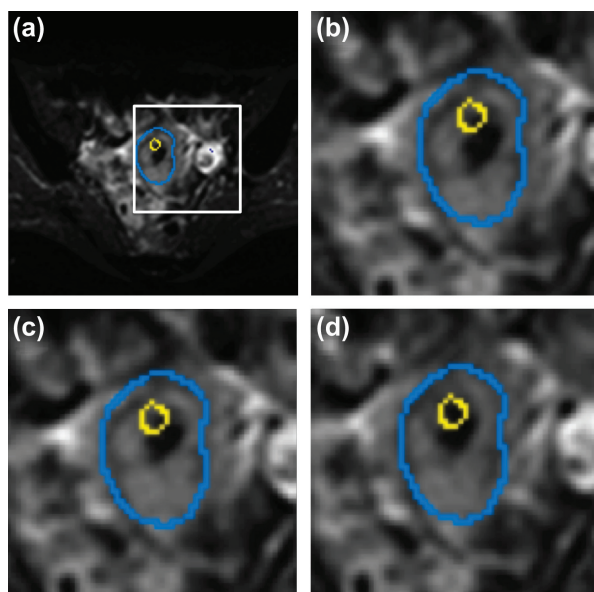


Figure 2. DW-MRI, $b = 0$ s/mm², for the three different image sets with GTV (blue contour) and delineated tandem center (yellow contour): (a) non-corrected with full FOV where the white square indicate the zoomed in area shown in the three other images: (b) non-corrected, (c) B₀M, (d) DIR.

the non-corrected DWI ($0.87 \cdot 10^{-3} \pm 0.4$ s/mm²) and the mean ADC for the DIR ($1.00 \cdot 10^{-3} \pm 0.3$ s/mm²) was close to significant (paired Student's t-test $p = 0.051$).

Discussion

The geometrical distortion of the single shot EPI-based DW-MRI is significant for imaging performed at the time of BT with applicator in place. For diagnostic imaging an offset in the order of millimeters is not a significant issue. However, if DW-MRI is to be used for treatment planning of BT, geometrical fidelity is essential. In this study two approaches for correcting the geometrical distortion were investigated. The study showed that a mean uncertainty of less than 2 mm remains after DIR has been applied to the DW-MRI. This can still be a major issue in RT treatment planning and especially for treatment planning of BT where steep dose gradients are present. Tanderup et al. investigated the impact of geometrical uncertainties on DVH parameters in BT for cervical cancer [19] and found that the D₉₀ of the GTV shifts about 2% per mm of applicator displacement in both LR and AP direction. More severe is the dose delivered to the rectum and bladder where the D_{2cc} shifts more than 5% per mm displacement in the AP direction. This illustrates the importance of reducing the geometrical uncertainties of the position of the applicator.

Variations of the B₀ field in the order of ± 150 Hz was found with large local variations in the vicinity of the ring of the applicator and air/tissue transitions (Supplementary Figure 2, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>). The study showed that calculating the B₀ field map based on phase images from a dual GRE sequence is feasible in the pelvic region, but can be challenging in some patients where phase unwrapping is not successful. The unwrapping of the phase images is sensitive to changes in tissue structures such as air/tissue transitions resulting in errors in the VDM used for pixel-shift correction of the DW-MRI. The B₀M cannot correct for signal pileup due to large susceptibility changes, i.e. in the region of air-filled intestines. Signal pileup can be a severe problem for DW-MRI used for BT with applicator since the tumor typically is located very close to the ring. This will result in both inaccurate location of the tumor on DW-MRI and in an erroneous ADC of the tumor making quantitative comparison impossible. Also, the method used in this study only corrects for pixels in the phase-encoding direction. A possible source of error, when evaluating the performance of the B₀M, is that three image sets are used: the DW-MRI, the dual GRE containing phase

images and the T2W images for reference. The extended time period required for these acquisitions increases the vulnerability of the method to patient motion, motion of the bowel, and filling of the bladder. Also B_0 field and gradient errors could be added to the applied readout gradient resulting in shearing of the DW-MRI and hence displacement in the x-direction. This cannot be corrected using B_0M [20].

DIR using the Elastix software toolkit improved the geometry of the DW-MRI significantly when compared to the T2W image, in contrast to B_0M . The image registration has the advantage of correcting the image in three directions (Table I), and can thereby correct for both motion and susceptibility effects. However, one has to be careful when using DIR since implausible deformations can occur [21]. The method and the associated Elastix image registration parameters used in this study have previously been successfully used for image registration of MR images of the cervix [15]. An uncertainty is of course introduced when the validated method is used for images with different contrast than those used for validation. In this study the same transformation matrix is used for the entire b-matrix assuming the same distortion independent of b-value used. However, in practice the distortions can be different depending on applied diffusion gradients due to eddy currents if the MRI scanner is unable to compensate completely for these [22]. The quantitative effect of artifacts due to eddy currents was not investigated in this study. The resulting ADC of the GTV for the non-corrected DW-MRI and the correcting methods did not show any significant difference, although a difference between the mean ADC of the non-corrected DWI and the DIR corrected DWI was found close to significant.

Both investigated methods depend on additional images acquired during the MR examination: the B_0M requires acquisition of phase images and the image registration requires a reference image. The acquisition time for the phase images is approximately 4 minutes while the T2-weighted reference image typically can be acquired in less than 1 minute. Both methods require an off-line process after the MR acquisition but none of the two are time consuming and an automatic workflow can be set up for performing the off-line processing.

The use of MR image-guided adaptive brachytherapy (IGABT) have improved treatment of patients with advanced cervical cancer [6]. If information from DW-MRI should be added in treatment planning the geometrical accuracy needs improved. It would be preferable if the geometrical distortions of the images of the DW-MRI could be reduced in the acquisition. This could be possible using modified EPI acquisition methods such as segmented EPI [23]

or by using a reduced field-of-view method [24]. These methods still need to be validated for use in abdominal and pelvic applications also ensuring that the ADC does not vary depending on acquisition method used.

In conclusion geometrical correction of SS-EPI-based DW-MRI using DIR improved the geometrical fidelity significantly although residual errors of less than 2 mm persisted after correction. B_0M did not perform as well as DIR with residual errors of less than 3 mm. There was no significant difference in the resulting ADC of the GTV when comparing all methods.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Equation 1, Figures 1–3 and Table I and II available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.938831>.