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Original article

Assessment of dosimetric errors induced by deformable image registration methods in 4D pencil beam scanned proton treatment planning for liver tumours

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ABSTRACT

Purpose: Respiratory impacts in pencil beam scanned proton therapy (PBS-PT) are accounted by extensive 4D dose calculations, where deformable image registration (DIR) is necessary for estimating deformation vector fields (DVFs). We aim here to evaluate the dosimetric errors induced by different DIR algorithms in their resulting 4D dose calculations by using ground truth(GT)-DVFs from 4DMRI.

Materials and methods: Six DIR methods: ANACONDA, Morfeus, B-splines, Demons, CT Deformable, and Total Variation, were respectively applied to nine 4DCT-MRI liver data sets. The derived DVFs were then used as input for 4D dose calculation. The DIR induced dosimetric error was assessed by individually comparing the resultant 4D dose distributions to those obtained with GT-DVFs. Both single-/three-field plans and single/rescanned strategies were investigated.

Results: Differences in 4D dose distributions among different DIR algorithms, and compared to the results using GT-DVFs, were pronounced. Up to 40 % of clinically relevant dose calculation points showed dose differences of 10 % or more between the GT. Differences in V_{95}(CTV) reached up to 11.34 ± 12.57 %. The dosimetric errors became in general less substantial when applying multiple-field plans or using rescanning.

Conclusion: Intrinsic geometric errors by DIR can influence the clinical evaluation of liver 4D PBS-PT plans. We recommend the use of an error bar for correctly interpreting individual 4D dose distributions.

When treating moving targets in the thorax or abdomen with pencil beam scanned proton therapy (PBS-PT), due to the presence of breathing motion, a time-resolved 3D (4D) image is necessary for quantifying the motion characteristics and performing a 4D dose calculation. For treating this type of tumour with a highly precise technique such as PBS-PT, a 4D dose calculation is crucial in order to take into account the deterioration of the dose distribution due to the relative motion between the target and the delivered pencil beams (interplay effects) [1–3].

To calculate motion induced geometric differences between two image phases, deformable image registration (DIR) is the standard approach for building up a point-to-point correlation between corresponding features. To perform DIR, a fixed and a moving image are pre-defined to estimate the patient's deformable motion between these two images [4]. The result of DIR is a deformation vector field (DVF), which contains vectors for each voxel pointing from the fixed image towards the moving image.

For any form of radiotherapy, DIR is one of the irreplaceable components for both inter- and intra- fractional dosimetric evaluation. It is especially important for PBS-PT, due to its high sensitivity to geometric accuracy. However, it is well known that DIR is an ill-posed problem intrinsically [5]. When applying different DIR methods to the same image pair, the resulting motion estimations can be inaccurate and differ significantly from each other [6]. Some of these errors are quantifiable, and can be calculated by comparing the DIR estimated motion of well-defined landmarks to their actual positions in both images (the so-called ground truth (GT) data). This is the classic approach of evaluating any DIR algorithm performance, as used by many previous publications [7,8]. Despite compromising the efficiency for the error quantification, the more landmarks that are defined, the more reliable the results will be. In contrast, there are also unquantifiable errors in featureless regions of the images, where the deformable problem is intrinsically ill-defined. Motion vectors in these regions will directly depend on

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the transformation model and regularization of the selected algorithm, and it is therefore unavoidable that ambiguity between different algorithms will exist.

Any form of registration uncertainty can directly lead to distinguishable differences in dose distributions, which consequently influence any further dosimetric analysis and clinical decision-making [9]. In the literature, a number of studies have investigated the dosimetric uncertainties induced by a particular DIR method [10,11]. However, their conclusions were restricted to their selected DIR method, and a consensus on the clinical impact of DIR uncertainty is still difficult to achieve. Yeo et al. [12] compared calculated doses based on results from several available DIR algorithms with a measured dose using a deformable 3D dosimeter. However, DIR errors for real patient geometries may perform differently in contrast to the rather simple experimental setup used in that work.

Zhang et al. [6] showed that the ambiguity of two DIR approaches can lead to significant differences in the estimated motion maps, and subsequent 4D dose distributions, among liver cancer patients for PBS-PT, even if landmark registration errors were similar. Due to the lack of a comprehensive GT-DVF however, it is often impossible to validate the accuracy of DIR in the whole region of interest.

In this work, we would like to improve the above studies in two aspects. First, to investigate the systematic errors induced by DIRs in 4D dose calculations, using the unique advantage of comprehensive GT-DVFs extracted from synthetic 4DCT-MRI [13]. Second, we include multiple DIR methods to reveal the extent of potential variation induced by different algorithms. As such, six DIR methods (five commercially available and one research version) have been applied to nine 4DCT-MRI data sets to estimate deformable motion within the abdomen region. Compared to previous works, we also consider comprehensive GT-DVFs as reference to quantify the absolute accuracy for deformable motion estimation. Consequently, the resulting 4D dose distributions generated using different DIR algorithms can be directly compared under conditions of varying plan configurations, rescanning scenarios, patient geometries, and motion scenarios.

Materials and methods

Synthetic 4DCT-MRI and ground truth deformation vector fields (GT-DVFs)

4DCT-MRI data sets consist of end-of-exhalation 3DCTs (reference phases) modulated by consecutive and extended breathing motion extracted from 4DMRI data through a validated image processing method [13–15] (Fig. 1, upper left). Through this process, synthetic 4DCT-MRI data sets within the liver are obtained by warping the reference phase with DVFs extracted from 4DMRI using a combination of multiresolution affine registration and B-spline non-rigid registration [15].

Nine such 4DCT-MRI data sets, generated from motion artefact-free 3DCTs of three liver cancer patients (denoted as PI, PII, and PIII respectively), were included in this study. The reference phases of the three patients were modulated by three different 4DMRI motion scenarios indicated as motions A, B, and C [16]. Clinical target volumes (CTVs) at the reference phase were 122, 264, and 403 cm^3 for patients I, II, and III respectively. Only 4DCT-MRI data sets corresponding to the first breathing cycle were analysed, and no consideration of motion irregularity has been included in the study. For the nine data sets, the amplitude for the first breathing cycle (given by the mean of the amplitude of all different points within the whole liver region) of motion scenarios A, B, and C were 7.82 (SD = 2.01), 20.61 (SD = 3.39), and 16.88 (SD = 2.78) mm respectively. Additionally, motion periods (extracted using Fourier analysis) for this first cycle equalled 3.66, 4.62, and 7.22 s for A, B, and C respectively. The corresponding DVFs extracted from 4DMRI to generate these nine 4DCT-MRI data sets were then defined as the GT-DVFs. Subsequently, new DVFs were extracted from these nine 4DCT-MRI data sets using the different DIR methods being investigated (see Fig. 1). These GT-DVFs and DIR estimated DVFs were used for the 4D dose calculation analysis.

Deformable image registration (DIR) methods and derived deformation vector fields (DVFs)

Six DIR methods have been included in this study. DIR1 and DIR2 are available in the RayStation (RaySearch Laboratories, Stockholm, Sweden) treatment planning system used in the UMCG, whereas DIR3 and DIR4 [6] are algorithms provided in open source software (Plastimatch; www.plastimatch.com) and used at PSI. DIR5 and DIR6 were developed in turn by the commercial medical imaging software company Mirada Medical (Oxford, UK) and by the Computer Vision Laboratory in ETH Zurich (Zurich, Switzerland) respectively. The different DIR methods are based on the ANACONDA [17], Morfeus [18,19], B-splines, Demons, CT Deformable [20,21], and Total Variation [22] algorithm respectively (Suppl. 1). For each data set, all six approaches were applied to the reference phase as the fixed image. The remaining phases were defined as successive moving images (see Table S.1).

4D dose calculation

The DVFs resulting from the application of the six DIR methods were used as input to the in-house 4D dose calculation engine at PSI, which is an extension of the 3D dose calculation algorithm. The gantry (beam) coordinate system is defined as (s, t, u), in which s is the pencil beam central axis direction and (t_0, u_0) its position orthogonal to the field direction (Fig. 2(a)). The clinically used dose grid size in this coordinate system is $4 \times 4 \times 2.5$ mm^3.

To extend the 3D dose calculation to a 4D dose calculation, time-dependent displacements of dose grid points for motions in the t and u directions are taken into account using displacement and density-variation maps derived from each phase of the relevant 4DCT-MRI data. The 4D dose calculation algorithm first estimates the time stamp of each delivered pencil beam [13]. The DIR extracted DVFs are then geometrically translated and rotated into the gantry (s, t, u) coordinate system, and sampled by the dose grid size to provide displacement maps for each dose grid point [6]. Density-variation maps are derived from the different 4DCT-MRI phases using Siddon's algorithm [23]. With these displacement and density-variation maps, the offsets of the dose grid points from their nominal positions are calculated and a 4D dose distribution obtained.

4D planning configurations

Static, single-field uniform dose (SFUD) plans [24] were calculated on each of the reference phases of the three patients. Both single- and three-field plans were investigated. Field arrangements were anterior-posterior (F1), right lateral (F2), and anterior-inferior oblique (F3), with the three-field plan being a combination of all fields. 4D dose distributions for these were then subsequently obtained by using either the GT-DVFs or the DVFs resulting from the six DIR methods in the 4D dose calculation algorithm (Fig. 1). Single scan or five times layered rescanning [16] were simulated with the scanning parameters of Gantry 2 at PSI [25–27]. Plan delivery started at the reference phase of the corresponding 4DCT-MRI. All analysed plan configurations and respective notations are given in Suppl. 2.

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