Generation of synthetic CT data using patient specific daily MR image data and image registration

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Abstract
To fully exploit the advantages of magnetic resonance imaging (MRI) for radiotherapy (RT) treatment planning, a method is required to overcome the problem of lacking electron density information. We aim to establish and evaluate a new method for computed tomography (CT) data generation based on MRI and image registration. The thereby generated CT data is used for dose accumulation. We developed a process flow based on an initial pair of rigidly co-registered CT and T2-weighted MR image representing the same anatomical situation. Deformable image registration using anatomical landmarks is performed between the initial MRI data and daily MR images. The resulting transformation is applied to the initial CT, thus fractional CT data is generated. Furthermore, the dose for a photon intensity modulated RT (IMRT) or intensity modulated proton therapy (IMPT) plan is calculated on the generated fractional CT and accumulated on the initial CT via inverse transformation. The method is evaluated by the use of phantom CT and MRI data. Quantitative validation is performed by evaluation of the mean absolute error (MAE) between the measured and the generated CT. The effect on dose...
accumulation is examined by means of dose-volume parameters. One patient case is presented to demonstrate the applicability of the method introduced here. Overall, CT data derivation lead to MAEs with a median of 37.0 HU ranging from 29.9 to 66.6 HU for all investigated tissues. The accuracy of image registration showed to be limited in the case of unexpected air cavities and at tissue boundaries. The comparisons of dose distributions based on measured and generated CT data agree well with the published literature. Differences in dose volume parameters kept within 1.6% and 3.2% for photon and proton RT, respectively.

The method presented here is particularly suited for application in adaptive RT in current clinical routine, since only minor additional technical equipment is required.

Keywords: magnetic resonance image guided radiotherapy (MRIGRT), pseudo-CT generation, magnetic resonance imaging based treatment planning, intensity modulated radiation therapy (IMRT), proton therapy, adaptive radiotherapy

(Some figures may appear in colour only in the online journal)

1. Introduction

Physical dose calculation in radiation therapy requires electron density information usually measured by computed tomography (CT). Nowadays, also the increased soft tissue contrast and functional imaging capabilities offered by magnetic resonance imaging (MRI) are intensively exploited to improve patient imaging. However, MRI lacks the electron density information and may suffer from geometric distortions, and therefore is not directly suited for dose calculation. A combination of both, electron density information and advanced imaging capabilities would be the desired solution. Several approaches are investigated to overcome this problem. They can be categorized into methods using MRI-only and hybrid methods that require CT and MR imaging to some extent. MRI only methods often apply bulk electron density assignment to preassigned anatomical structures and have been reported by many authors. For brain tumors, Stanescu et al (2006) and Prabhakar et al (2007) found equivalent dosimetric results using the pseudo-CTs, compared to CT-based calculation. For prostate, dosimetric deviations were found to be within 2% of the original CT-based dose calculation (Lee 2003, Kristensen et al 2008, Lambert et al 2011, Kapanen et al 2013, Korhonen et al 2014). For more challenging regions, such as lung and head-and-neck, bulk electron density assignment still needs further improvement (Karotki et al 2011, Jonsson et al 2013). The major drawback of these methods lies in the need for laborious and subjective structure contouring. However, these methods might be favorable for integrated MR systems, such as the combination of MRI with a linear accelerator or with a 60Co source (ViewRay Inc.). Prior et al (2016) studied the effects of a 1.5 T transverse magnetic field on plan quality present during treatment of pancreas and prostate cancer and found the dosimetric effects to be within 3% for the target volume.

Another method is the classification of voxels into tissue classes and voxelwise conversion of electron density (Johansson et al 2011, Hsu et al 2013, Jonsson et al 2013, Kapanen et al 2013, Rank et al 2013, Edmund et al 2014, Korhonen et al 2014, Prior et al 2016). The major challenge lies in the very short T2 relaxation time of bone, making it hard to discriminate between air and bone. Ultrashort echo time (UTE) sequences are often employed to acquire
bone signal (Johansson et al 2011, Rank et al 2013, Edmund et al 2014). Korhonen et al (2014) reported dosimetric deviations in the target doses within 1% comparing pseudo-CT and measured CT dose calculations using a dual model Hounsfield units (HU) conversion from MRI intensity values within and outside bone.

Atlas-based techniques aim to overcome the problem of lacking electron density in MR images by registration of a set of co-registered CTs and MR images to the patient’s MR image. By application of the resulting transformation to the CT-atlas, a pseudo-CT is generated. For prostate, Dowling et al (2012) report dosimetric differences within 2% between the pseudo-CT and the measured CT-based calculation. Similar results were found by Uh et al (2014) for pediatric brain tumors. The amount and diversity of patient data available limits the usage of atlas-based methods. Uh et al (2014) demonstrated that a reasonable number of CT-MRI atlases is required to yield an acceptable dosimetric result. Additionally, these methods might lead to unsatisfactory results for patients with an atypical anatomy. Sjölund et al (2015) proposed an atlas-based approach using a new fusion method, where the collection of the deformed atlas CTs is iteratively registered to their joint mean. Thus, the resulting mean CT becomes more similar to the target CT.

Chen et al (2016) presented another atlas-based approach for CT data generation for prostate cancer treatment using CT-MRI pairs with corresponding regions of interest (ROIs) for several tissue types. A selection algorithm for determination of image intensity of the generated CT data was established using a selection factor based on ROI intersection. The authors claim that the CT generated with this method could potentially replace measured CT data for dose calculation and also for cone beam CT image guidance.

In this study, we present an alternative method for CT data generation based on MRI and patient specific image registration. In contrast to other CT data generation methods, the technique described here gets along without additional specialized MRI sequences, atlas formation based on interindividual data composition and intermodal deformable image registration. Furthermore, this CT data generation method that is favorably suited for hybrid systems that already employ CT and MR imaging leading to only minor technical and financial effort.

2. Methods and materials

2.1. Data

For evaluation of the presented method of CT data generation, pairs of phantom MRI and CT data showing the same anatomical situation for several scenarios are used as the gold standard. Geometric accuracy of MRI was evaluated by measurements using the ACR (American College of Radiology) phantom (Ihalainen et al 2011) and the multimodality, anthropomorphic and deformable phantom, developed by Niebuhr et al (2016). MRI was compared to CT data and geometric accuracy inside the phantom was found to be below 1 mm. Gradient-nonlinearities of the magnetic field increase with the distance from the center, that could lead to geometric inaccuracies. This might affect the accuracy and reproducibility of the data generated with the help of the phantom MR images. Currently, measurements are being performed at our institute to further quantify these effects.

For real patient data only one single CT-MRI pair would be acquired. Due to the additional radiation dose delivered by daily CT imaging, no fractional patient CT data was acquired. Thus, real patient data cannot be used for systematic evaluation of this method. Therefore, phantom CT and T2-weighted MRI data is used for evaluation. The CT pixel size in x-, y- and z-direction was 0.97 mm, 0.97 mm and 2 mm and the number of pixels was 512 × 512.
in $x$- and $y$-direction. In $z$-direction the number of slices differed. MR images were acquired with a Siemens Symphony scanner using a T2-weighted SPACE sequence (Echo time (TE) = 125 ms, repetition time (TR) = 2000 ms) with the Siemens 3D distortion correction. Pixel sizes were 1.12 mm in $x$- and $y$-direction and 1.21 mm in $z$-direction for the measured images. The phantom comprises the lower abdominal and pelvic region. The phantom used here allows CT and MR imaging of various anatomical situations (Niebuhr et al 2016). An improved version of the phantom as described by Niebuhr et al (2016) was used, in which material composition was adjusted to yield an excellent MR and CT signal in the entire phantom volume. The phantom comprises a realistic reproduction of relevant structures of the human pelvic anatomy. Anatomical deformation was introduced by variation of the bladder (water) and rectum (air) volume. An overview of the measured data is given in table 1 and an example of MR and CT images of depicted slices for fraction number 1 and 3 is shown in figure 1.

Additionally, one anal carcinoma patient case is presented to show the potential application of the method, that is evaluated with the help of phantom data.

Patient immobilization is achieved through a vacuum mattress. To keep the motion between imaging modalities as low as possible an air-based shuttle system (Zephyr System, Diacor, USA) was used. The transport time between the two imaging modalities typically happens within a time frame of 10 min. In this study only the above mentioned T2-weighted SPACE sequence is used for evaluation, which takes about 7.5 min. Mean MR imaging time can be longer for patient data acquisition, since multiple sequences are performed subsequently. Additionally, time for patient positioning must be considered. Due to the patient positioning and transportation system only minimal positioning variation is expected. The patient is moved with the help of a transfer sled allowing for safe and effortless patient transport without acting directly on the patient. This procedure assures the same patient position for MR imaging and during radiation therapy. Further details on real patient data acquisition can be found in the study by Bostel et al (2014).

The reference time point represents the time of treatment planning, and images acquired at this point in time are referred to as $rCT_m$ and $rMRI_m$. Images measured at different time points with different anatomical situations represent different treatment fractions and are denoted as $fxCT_m$ and $fxMRI_m$. This measured CT data is used as the ground truth, with which the CT data generated with the method described below is compared. The data artificially generated by means of image registration, is referred to as $fxCT_{art}$.

For the measured phantom reference CT, a photon and a proton intensity modulated radiation therapy (IMRT) plan are calculated. The photon plan comprises nine equally spaced coplanar beams targeting the prostate. The proton plan comprises two lateral opposed beams. A dose of 78 Gy is prescribed to the target. According to the measured and simulated scenarios, six fractions have been studied. Thus, the fractional dose amounts to 13 Gy. The dose was recalculated on each fractional measured and artificially generated CT data set.

| Fraction | Rectum (ml)       | Bladder volume (ml) |
|----------|-------------------|---------------------|
| 1        | 118.5             | 140                 |
| 2        | 118.5             | 240                 |
| 3        | 118.5             | 340                 |
| 4        | 118.5 (water) + 30 (air) | 140             |
| 5        | 118.5 (water) + 30 (air) | 240             |
| 6        | 118.5 (water) + 30 (air) | 340             |
The patient case comprises 13 fractional T2-weighted MRIs and one initial CT-MRI pair used for treatment planning. A dose of 45 Gy to the planning target volume (PTV) and 55 Gy to the boost volume are prescribed to be delivered in 25 treatment fractions. Some imaging fractions are missing mainly due to technical service of the MRI scanner or insufficient image quality. Thus they cannot contribute to dose accumulation and are replaced by dose distributions from other fractions. Fractional CT data is generated using the method introduced in this study and visualized in Figure 2. This data is used for dose calculation and accumulation. In contrast to the phantom case, no measured fractional CTs exist for comparison with the generated CT data.

2.2. CT data generation and dose accumulation

A method for generation of CT data based on MRIs and image registration was developed. The generated CT data was subsequently used for dose calculation and dose accumulation over several treatment fractions. As indicated in Figure 2, in a first step, the reference CT acquired on the day of treatment planning was matched with the MR image showing a very similar anatomical situation by rigid image registration. For the phantom data used in this work, no rigid transformation was necessary, because the images were already in the same frame of reference. Second, the MR image co-registered with the reference CT, denoted as rMRI2CT, was registered to the fractional MR image (fxMRI). For real patient data, this step is divided into a rigid registration for bone matching and subsequent deformable image registration. However, both registration procedures use landmarks to improve the registration result. For the rigid registration, a fiducial marker system consisting of a PMMA (Polymethylmethacrylate) frame around the patient with embedded contrast agent-filled hoses was used (Bostel et al. 2014). Also anatomical landmarks that indicate clearly identifiable points in bony and soft tissue are

Figure 1. Transversal ((a), (b), (c) and (f)) and sagittal ((c), (d), (g) and (h)) MR ((a), (c), (e) and (g)) and CT ((b), (d), (f) and (h)) image slices of the multimodal phantom. The top row is showing the anatomical situation of fraction 1 and the bottom row is showing the situation for fraction 3.
used. The deformable registration is based on b-spline deformation offered by plastimatch (Shackleford et al 2010). In order to receive an optimal registration result, anatomical landmarks were used as an additional input for image registration.

The transformation gained in step number two is then applied to the reference CT in order to create artificial fractional CT data (fxCTart). Thus, having electron density information of the current treatment fraction, dose calculation is feasible. For this purpose, the dose from the original treatment plan calculated on the reference CT is recalculated on the fractional CT data using an inhouse treatment planning software (Nill 2002, Nill et al 2004, Preiser et al 1998). Subsequently, the dose is transformed to the rCTm by application of the inverse transformation and accumulated over all treatment fractions.

For the evaluation of this method of CT data generation, first the generated phantom CT data (fxCTart) is compared with the measured CT data fxCTm. As a quantitative measure of comparison, the mean absolute error (MAE) and standard deviation (SD) of the two CT data sets (fxCTart and fxCTm) for bone, bladder, target (prostate) and the whole body volume are calculated. The location of possible mismatch is shown by differences of the fxCTart and fxCTm. In order to account for differences between the images with respect to their location, we derived a γ-index as commonly applied for comparisons of dose distributions (Low et al 1998). For calculation we used an inhouse-developed software integrated in the open source multi-modality radiation treatment planning software MatRad (http://e0404.github.io/matRad/) (Cisternas et al 2015).

\[
\gamma(r_m) = \min\{\Gamma(r_m, r_c)\} \forall r_c, \text{ with }
\]

\[
\Gamma(r_m, r_c) = \sqrt{\frac{(H_c(r_c) - H_m(r_m))^2}{\Delta H^2} + \frac{|r_c - r_m|^2}{\Delta r^2}}
\]
where $H(r)$ is the HU-value at position $r$ and the subscripted ‘m’ and ‘c’ refers to the measured and calculated CT cube, respectively. We accepted a HU-value deviation of $\Delta H = 50$ HU and a distance to agreement of $\Delta r = 2$ mm. If $\gamma(r_m) \leq 1$, the calculation at $r_m$ passes and fails otherwise.

To examine the effect of the artificially generated CT data on the dose distribution, the fractional doses as well as the accumulated doses calculated on the generated fxCT art and on the measured fxCT m are compared. The minimum doses received by 98%, 50% and 2% of the corresponding volumes are compared for the two different CTs underlying the dose calculation.

### 3. Results

#### 3.1. Evaluation of CT data generation

For different structures such as the body volume, prostate, bladder and bone, the MAE and SD are presented in table 2 and visualized in figure 3. The MAE is greatest for bone. The MAE amounts to 60.3 HU and 66.6 HU for fraction number three and fraction six, respectively. Differences in HU values for the bladder are 57.8 HU at maximum for fraction number six. Rather small MAEs are observed when the whole body volume is taken into account and for the prostate. The maximum MAE, found for fraction six, amounts to 37.3 HU and 37.6 HU for the prostate and whole body volume, respectively. The maximum difference of the CT values

| Fraction | Structure | MAE ± SD (HU) |
|----------|-----------|---------------|
| 2        | Body      | 30.6 ± 52.7   |
|          | Prostate  | 31.7 ± 27.4   |
|          | Bladder   | 36.8 ± 80.9   |
|          | Bone      | 54.4 ± 98.0   |
| 3        | Body      | 33.9 ± 67.9   |
|          | Prostate  | 31.3 ± 27.3   |
|          | Bladder   | 55.4 ± 140.0  |
|          | Bone      | 60.3 ± 106.9  |
| 4        | Body      | 29.9 ± 53.8   |
|          | Prostate  | 32.1 ± 29.4   |
|          | Bladder   | 35.4 ± 71.4   |
|          | Bone      | 44.8 ± 68.2   |
| 5        | Body      | 31.6 ± 58.0   |
|          | Prostate  | 31.8 ± 29.8   |
|          | Bladder   | 40.8 ± 96.8   |
|          | Bone      | 49.6 ± 79.6   |
| 6        | Body      | 37.6 ± 82.6   |
|          | Prostate  | 37.3 ± 35.8   |
|          | Bladder   | 57.8 ± 146.8  |
|          | Bone      | 66.6 ± 122.1  |
of 37.6 HU inside the body volume was also found for fraction six. These results correlate with the extent of tissue motion, which was maximum in fractions number three and six.

Even though the MAE is rather low for all structures and fractions, the standard deviation around this value is much greater. The MAE for the bladder volume varied with a standard deviation of 146.8 HU around the mean for fraction number six. For fraction number four, where tissue motion is minor, the MAE spread within a standard deviation of ±71.4 HU around the mean for the bladder. The reason for this variance is a difference in voxel assignment at the edges of a volume. Also, air cavities within the phantom bladder caused inaccurate registration results. An example showing the voxelwise absolute difference between the `fxCT_m` and `fxCT_art` for fraction number three is given in figure 4.

The results of the γ-index evaluation are summarized in figure 5. The γ-pass-rate is presented for the individual structures and fractions. The mean γ-pass-rate ± SD amounts to (95.9 ± 0.78)%, (95.6 ± 0.51)%, (99.3 ± 0.26)% and (99.9 ± 0.03)% for the body volume, bone, bladder and prostate, respectively.
3.2. Dose calculation and accumulation

3.2.1. Photon dose distributions. Full results are reported in table 3. Dose values derived by dose calculation on the fxCT_m and fxCT_art for the target volume (prostate) are reported. Dose values are given for individual treatment fractions and for dose accumulation over the

Figure 4. Absolute difference in HU values between fxCT_m and fxCT_art for fraction number three for a transversal slice of the phantom data. In the bladder, an air cavity caused major HU differences. HU values for the bone deviate at the edges.

Figure 5. γ-pass-rates for ΔH = 50 HU, Δr = 2 mm for different structures (a). For bladder and prostate values are above 99%. For body volume and bone γ-pass-rates are reduced. (b) shows the γ-index for ΔH = 50 HU, Δr = 2 mm for an individual transversal slice and fraction number six. The scale indicates the γ-index. Where γ ≤ 1, values are considered to pass.
Table 3. Photon and proton doses calculated on fxCT_m and fxCT_art for the prostate. Individual fractional doses as well as accumulated doses are reported for the individual fractions (fx).

| Prostate | Photon | | | | | | | | Proton | | | |
|----------|--------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|          |        | Fraction dose (Gy) | Accumulated dose (Gy) | Fraction dose (Gy) | Accumulated dose (Gy) |
|          |        | D98 | D50 | D2 | D98 | D50 | D2 | D98 | D50 | D2 | D98 | D50 | D2 | D98 | D50 | D2 |
| 1 fxCT_m | 12.80 | 13.12 | 14.33 | 12.80 | 13.12 | 14.33 | 12.37 | 13.05 | 13.34 | 12.37 | 13.05 | 13.34 |
| fxCT_art | 12.80 | 13.12 | 14.33 | 12.80 | 13.12 | 14.33 | 12.37 | 13.05 | 13.34 | 12.37 | 13.05 | 13.34 |
| 2 fxCT_m | 12.51 | 13.10 | 14.33 | 25.78 | 26.22 | 28.39 | 12.04 | 13.01 | 13.45 | 24.92 | 26.05 | 26.66 |
| fxCT_art | 12.31 | 13.06 | 14.26 | 24.40 | 26.2 | 28.40 | 11.65 | 13.01 | 13.45 | 24.41 | 13.05 | 13.34 |
| 3 fxCT_m | 12.39 | 13.10 | 14.32 | 38.69 | 39.33 | 42.55 | 11.83 | 13.00 | 13.42 | 37.17 | 39.05 | 39.94 |
| fxCT_art | 12.35 | 13.08 | 14.28 | 37.00 | 39.3 | 42.30 | 11.51 | 13.01 | 13.52 | 36.08 | 39.06 | 40.07 |
| 4 fxCT_m | 12.81 | 13.18 | 14.32 | 50.54 | 52.49 | 56.46 | 12.38 | 13.05 | 13.40 | 49.71 | 52.08 | 53.20 |
| fxCT_art | 12.68 | 13.10 | 14.31 | 49.90 | 52.3 | 56.40 | 12.18 | 13.01 | 13.77 | 48.90 | 52.10 | 53.30 |
| 5 fxCT_m | 12.43 | 13.16 | 14.19 | 57.86 | 65.65 | 69.20 | 11.89 | 13.00 | 13.43 | 60.77 | 65.04 | 66.47 |
| fxCT_art | 12.26 | 13.12 | 14.31 | 61.40 | 65.4 | 70.50 | 11.65 | 13.01 | 13.45 | 60.82 | 65.11 | 66.51 |
| 6 fxCT_m | 12.40 | 13.16 | 14.30 | 66.94 | 78.81 | 83.35 | 11.78 | 13.01 | 13.45 | 71.57 | 78.02 | 79.80 |
| fxCT_art | 12.31 | 13.07 | 14.28 | 72.33 | 76.83 | 84.49 | 11.66 | 13.01 | 13.47 | 72.72 | 78.11 | 79.82 |
Looking at the individual fraction doses, the differences in the target doses between the dose distributions calculated on the two CTs are below 0.2 Gy for all reported dose values. The largest deviation can be found for fraction number two, where D98 deviates by 0.2 Gy, which corresponds to 1.6% dose deviation relative to the fractional dose calculated on fxCTr. This can also be seen in figure 6.

The accumulated doses for the prostate differ most for fraction number five and six. A deviation of 3.5 Gy and 5.4 Gy was noticed for D98 for fraction five and six, respectively. This can also be seen in figure 6(b). The dose calculated on the artificially generated CT is higher than the dose based on the measured CTs. For comparison, also the dose planned on the rCTm is shown in figure 6. Whereas the D50 almost fits exactly the planned dose, D2 and D98 deviate from the planned dose for both, measured and generated CT. For the measured CT, D98 is almost 10 Gy less than the planned dose, for the generated CTs D98 is 4.3 Gy lower than planned. Hence, here the generated CT leads to underestimation of organ motion. Differences in the fractional doses based on the measured and generated CT for the bladder are below 0.4 Gy for D2. Dose values for D5 and D2 are reported in table 4 and visualized in figures 6(c) and (d). When the dose is accumulated over the number of fractions, there is a general trend of slightly higher doses for dose calculation based on the fxCtart. After fraction

Figure 6. Photon dose values for prostate ((a) and (b)) and bladder ((c) and (d)) calculated on fxCTr and fxCtart. (a) Shows the dose for individual fractions for the prostate and (c) for the bladder. (b) Shows the dose accumulated along the treatment fractions for the prostate and (d) for the bladder. ‘Planned’ refers to the dose planned on the static rCTm.
six, the minimum dose received by 2% of the bladder volume amounts to 6.68 Gy for the measured \( fxCT_m \) and 7.69 Gy for \( fxCT_{art} \), respectively.

The doses received by the bone volume only vary slightly, when the dose calculated on \( fxCT_m \) and the dose based on \( fxCT_{art} \) are compared. Dose values are reported in table 4.

### 3.2.2. Proton dose distributions.

Regarding the dose values for the target volume listed in table 3, the largest deviations between dose calculation based on \( fxCT_m \) and \( fxCT_{art} \) are below 0.36 Gy for individual treatment fractions. The target volume dose parameters based on \( fxCT_{art} \) deviate within 3.2% from those derived from \( fxCT_m \). A general trend of reduced
minimum doses to 98% of the volume for dose calculation based on fxCT art can be observed as visualized in figure 6.

The accumulated doses differ up to 1.1 Gy for D98 in fraction three and six. After six treatment fractions, the accumulated doses almost match the planned dose distribution that was calculated on a single CT (see figure 6(b)).

Dose differences for the bladder are more pronounced (see table 5). For D2, the largest dose deviation can be observed for fraction six where it amounts to 2.3 Gy. Figures 6(c) and (d) illustrates the fractional doses and the accumulated doses to the bladder. While the fractional dose is generally higher for dose calculation based on fxCTart, the accumulated doses are lower compared with the dose distributions based on fxCTart. This is mainly due to different locations of hot spots in the individual fractions.

3.2.3. Patient case. The fractional doses are calculated on the generated CTs (fxCTart) and accumulated on the rCT (rCTm). As depicted in figure 8, the accumulated dose for the PTV almost approaches the dose planned on the static CT for D2 and D50. D98 is slightly reduced compared to the static dose. As visualized in figure 8(c), the PTV is mainly underdosed at its boundaries. This effect is most likely caused by tissue displacement in between the fractions.
Of course, also residual mismatch between the fractional MRI and the CT derived from this MRI might cause inaccuracy. The rCT\textsubscript{m} and the rMRI\textsubscript{m} do not perfectly match, since some minutes pass by between the two image acquisitions. In this time patient motion as well as bladder and rectum filling variations are possible. Unfortunately, we lack a ground truth here, in terms of measured fractional CTs. Visual comparison between the fxMRI\textsubscript{m} and fxCT\textsubscript{art} showed acceptable anatomical agreement for all fractions.

**Figure 8.** Accumulated and planned doses for the anal carcinoma patient. (a) shows how the dose volume parameters behave over the dose accumulation in comparison with the static dose. (b) and (c) visualize sagittal dose distributions for the dose planned on the static rCT\textsubscript{m}, and the dose accumulated on the fxCT\textsubscript{art} in (b) and (c), respectively. The dose for the PTV (pink) is slightly compromised by dose accumulation (c).
4. Discussion

4.1. CT data generation

MAEs between the measured CT and the CT generated by image registration were found between 31.3 HU for fraction three and 37.3 HU for fraction six, respectively, for the target volume. Over the six fractions the MAE ranged from 44.8 HU to 66.6 HU and from 29.9 HU to 37.6 HU for bone and for the whole body volume, respectively. Also γ-index analysis confirmed that matching of bone is more challenging than for soft tissue indicated by a mean γ-pass-rate of $(95.6 \pm 0.51)\%$ for bone. For the target almost all calculations passed the γ-index analysis. However, it should be mentioned that the statistical evaluation for specific organs is influenced by structure delineation. The results presented here agree well with previously published literature on CT data generation using MR images. Rank et al (2013) found MAEs in the range of 81 and 95 HU applying a classification-based voxelwise intensity conversion. Using an atlas-based approach for CT generation, Dowling et al (2015) found a MAE of 40.5 HU for the body volume, 134.24 HU for the bones and 16.47 HU for the target. Chen et al (2016) found a HU difference (mean ± SD) of $(2.4 \pm 25.23)$, $(1.18 \pm 81.9)$ and $(3.74 \pm 144.76)$ for the prostate, bladder and bone, respectively, when using an atlas of 10 CT-MRI pairs and a voxel intensity selection method based on regions of interest. The results gained with the method of CT data generation presented here, can compete with the data found in the literature. However, absolute numbers are not directly comparable, since study designs differ. The benefit of directly comparing HU values can be doubted, in case the generated CT data is only meant for dose calculation. Diverse effects may influence the HU number within a certain structure, however, the effect on the dose distribution can be minor since HU values are not directly used for dose calculation. We used phantom data to validate the method presented here over the course of a fractionated radiotherapy treatment. A specialized phantom suitable for CT and MR imaging with variable organ fillings was used. Certainly, phantom data cannot entirely reflect the complexity of real patient anatomy. However, the major challenge for the method using deformable image registration lies in strong and opposing tissue motion. This could accurately be modeled and measured with the help of the phantom. Also, here rather extreme organ motion was modeled. For real patients, drinking/emptying protocols could help to suppress extreme bladder and rectum motion. Large standard deviations of the MAE for an individual $f_{\text{CT}_{\text{an}}}$ and $f_{\text{CT}_{\text{art}}}$ comparison are caused by geometrical mismatches of some voxel rows at structure boundaries, such as bone. Also air cavities within the bladder caused unsatisfying results of the image transformation resulting in high local deviations of over 1400 HU. Even though, these were not corrected for, significant misdosage could not be noticed. Altogether, the results gained with the help of phantom data provide important information on the feasibility and applicability of the method introduced here. For patient data a careful evaluation of the resulting image still is not obsolete.

For accurate assignment of soft tissue, deformable image registration was applied. Anatomical landmarks, set manually, helped to improve the registration results. This laborious step in the generation of CT data could prevent the use of the method in clinical routine. Thus, in a preliminary study, we have started to investigate automatic marker assignment. The results of deformable registration were qualitatively evaluated by visual inspection of the overlaying CT and MR image and vector fields. For patient data, a ground truth in terms of measured CT
data is missing. By skilled inspection the plausibility of the vector field must be approved.

For systematic evaluation of image registration for real patient data, a standardized quality
assurance procedure could be imagined. Image registration quality measures such as dice coef-
cients, jacobian determinants, absolute errors and inverse consistency could be automatically
derived for each image registration. When handling real patient data, the resulting transformed
images, however, have to be inspected, additionally. Comparing the method with atlas-based
techniques for CT data generation, no atlas with data from multiple patients is required. A con-
ventional atlas-approach could lead to unsatisfactory results for patients showing an anatomy
strongly differing from the rest of the included patients. Thus, the method is limited to patients
with similar anatomy and requires a large amount of patient data before a specific patient CT
can be generated. The method introduced here is expected to lead to less registration problems,
since registrations are performed only on a patient-specific basis, provided that interfractional
tissue changes are small. Clearly, anatomical mismatch due to large tissue shrinkage or expan-
sion or due to surgical intervention can also lead to unsatisfactory registration results. However,
for the majority of patients, where no surgical tissue extraction is performed, no large interfrac-
tional tissue shrinkage or expansion is expected apart from the physiological motion.

The method introduced is novel with respect to several aspects. No additional non patient-
specific imaging data is required to establish an atlas. The method is based only on the use
of patient specific imaging data. Other methods often require deformable multimodal image
registration, that involve uncertainties within the image registration caused by different image
intensities especially for soft tissue (Nyholm and Jonsson 2014, Zhong et al 2015). In contrast
to other methods, the method presented here, avoids multimodal deformable image registration
by the use of only one initial CT and daily MRIs. A well known and widely available registra-
tion algorithm is used. Between planning and fractional image data only intramodal image reg-
istration is performed. The vector field calculated by image registration between the fractional
and reference image data can be used for dose accumulation. Thus, this method is particularly
suited for adaptive RT. In contrast to this, MR-only methods would require an additional regis-
tration for dose accumulation. Furthermore, low acquisitions costs and relatively simple appli-
cation of the transport system making it affordable for the majority of clinics.

There is no need for prior imaging, but the patient-specific CT and MR image from the
same day, acquired successively, without re-positioning and without time delay. This step also
helps to gain an excellent matching of the reference CT and MRI with the use of only rigid
image registration as a basis for further image transformations. Certainly, this is a crucial
point of this method. The better the two initial images align, the more reliable the CT data
generation is. Thus, the time for changing between the image modalities as well as the image
acquisition time should be kept minimal. By this, deformable image registration is avoided.
For the following treatment fractions, only MRI is required.

Since CT data is mandatory, the CT data generation presented here is favored for clinical
routine, where both imaging modalities are provided, rather than for integrated MR-systems,
that aim for MR-only methods. Moreover, for dose accumulation, vector fields derived from
deformable image registration are required. Other methods for CT data generation usually do
not provide vector fields for dose accumulation. With the method presented here, the vector
field can be directly used for dose accumulation. This makes this technique exceedingly suit-
able for adaptive RT, where it would be desirable to exploit the advantages of MRI for daily
imaging and treatment plan adaptation.
4.2. Dose calculation and accumulation

The dosimetric deviation for the target volume between the generated and measured CT are below 1.6% for photon IMRT. These results agree well with other methods in the literature, where dose deviations within 2% are reported (Dowling et al 2012, 2015, Korhonen et al 2014, Uh et al 2014, Prior et al 2016). Less data has been reported for particle therapy. For proton irradiation we found target dose deviations to be within 3.2% for D98. Rank et al (2013) reported mean dose deviations up to 3.1% for the target volume. However, the relative stopping powers are based on HU conversion using the x-ray CT data. This conversion can lead to additional dose errors due to range uncertainty errors. A potential improvement could be the use of proton CT data or dual energy CT data for proton dose calculation. The fractional dose deviations correlate with the amount of motion. Fractions two, three, five and six, in which a large bladder (and rectum) expansion was noticed, also showed the largest dose deviations. Clearly, this reveals the sensitivity of the proposed method for CT generation to non real-time CT and MR imaging. The patient transport, which currently takes about 10 min between MRI and CT, must be optimized to assure minimal tissue variation between the imaging modalities. The accumulated doses for the target volume approached the dose planned on a static CT for both measured and generated CT even better for proton therapy most likely due to different field configurations.

Slightly more pronounced dose differences were observed for the organs at risk. The effect becomes clearer when the dose is accumulated over all fractions. The dose deviation accumulated to 1.1 Gy after six fractions for the bladder and to 0.94 Gy for the bone, respectively. Whereas the conformity of CT electron densities showed to be most crucial for the bone, most likely due to the reduced contrast in T2-weighted MRI, bony tissue did not show major dose deviations. This is clearly caused by the lack of anatomical distinction of different bone parts. The major part of the bone tissue is not within the primary radiation field. Therefore, the absolute dose values to certain volumes are rather small. When looking at a real patient anatomy and only considering the clinically relevant parts of the bone that are within the radiation field, the dose deviations can be expected to be more pronounced.

A general trend of higher doses to the bladder for dose calculation on the artificially generated CT could be observed for photon as well as for proton irradiation. This is mainly due to small differences in the bladder contours at the intersection area between bladder and prostate. However, neither the dose accumulated on the generated nor on the measured CTs fully matched the dose distribution planned on a static CT. This shows the effect of motion.

The presented patient case demonstrates the applicability of the method for real patient data as well as the favored application for adaptive RT. Clearly, the evaluation of the method suffers from the lack of measured patient CT data for direct comparison. However, based on the examination using the phantom data in combination with visual inspection of the generated CT data, we think this technique may be a reliable way of CT data generation for defined applications.

The promising results for CT data generation based on MRI motivate us to fully exploit this method. We have started to integrate the method into an inhouse-developed sophisticated and user friendly software system. Furthermore, we investigate automatic anatomical landmark detection. For application of the technique in adaptive RT, improved performance is desirable to allow fast and easy treatment plan adaptation from day to day.
5. Conclusion

We have presented a new and easily applicable method for CT data derivation based on MRI. A single CT with a contemporary MR image and in the course of RT treatment only MR images are required.

Similar to atlas-based CT data generation, we also use image registration, but on a patient specific basis. Therefore, no extra non-patient-specific imaging data sets need to be acquired or selected, which helps to reduce daily acquisition time. Only, the patient-specific fractional MRI is required, which is expected to be used for daily patient positioning and tissue imaging. In the future, it can also serve as a basis for adaptive RT (McPartlin et al 2016).

The results with respect to CT similarity and dose accuracy gained with the proposed method for CT data generation compare well with data found in the literature. It is suited for contemporary use in clinical routine, since only minor technical equipment, such as a shuttle system for patient transport between the imaging modalities and the linear accelerator, is required. The most suitable application perspective foreseen is adaptive RT, where MRI could provide enhanced imaging features and could be used for RT treatment planning.

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Conflict of interest statement

The authors declare no potential conflict of interests.

Ethics approval and consent to participate

Patient data is acquired within a clinical study protocol (Bostel et al 2014), which was approved by the ethics committee of the medical faculty Heidelberg, votum number S-144/2013.

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