Influence of MRI-based bone outline definition errors on external radiotherapy dose calculation accuracy in heterogeneous pseudo-CT images of prostate cancer patients

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ABSTRACT

Background. This work evaluates influences of susceptibility-induced bone outline shift and perturbations, and bone segmentation errors on external radiotherapy dose calculation accuracy in magnetic resonance imaging (MRI)-based pseudo-computed tomography (CT) images of the male pelvis.

Material and methods. T1/T2*-weighted fast gradient echo, T1-weighted spin echo and T2-weighted fast spin echo images were used in bone detection investigation. Bone edge location and bone diameter in MRI were evaluated by comparing those in the images with actual physical measurements of fresh deer bones positioned in a gelatine phantom. Dose calculation accuracy in pseudo-CT images was investigated for 15 prostate cancer patients. Bone outlines in T1/T2*-weighted images were contoured and additional segmentation errors were simulated by expanding and contracting the bone contours with 1 mm spacing. Heterogeneous pseudo-CT images were constructed by adopting a technique transforming the MRI intensity values into Hounsfield units with separate conversion models within and outside of bone segment.

Results. Bone edges and diameter in the phantom were illustrated correctly within a 1 mm-pixel size in MRI. Each 1 mm-sized systematic error in bone segment resulted in roughly 0.4% change to the prostate dose level in the pseudo-CT images. The prostate average (range) dose levels in pseudo-CT images with additional systematic bone segmentation errors of −2 mm, 0 mm and 2 mm were 0.5% (−0.5–1.4%), −0.2% (−1.0–0.7%), and −0.9% (−1.8–0.0%) compared to those in CT images, respectively, in volumetric modulated arc therapy treatment plans calculated by Monte Carlo algorithm.

Conclusions. Susceptibility-induced bone outline shift and perturbations do not result in substantial uncertainty for MRI-based dose calculation. Dose consistency of 2% can be achieved reliably for the prostate if heterogeneous pseudo-CT images are constructed with ±2 mm systematic error in bone segment.

Magnetic resonance imaging (MRI) is increasingly applied for target delineation in external radiotherapy planning (RTP) of prostate cancer [1]. Recent studies have suggested that also dose calculation and image guidance could be carried out by relying solely on MRI, thus omitting computed tomography (CT) imaging [2–13]. Application of only one imaging modality for RTP is preferred to avoid uncertainty stemming from co-registration between the target delineation and planning images, and to spare hospital resources.

The inherent geometrical distortion and the lack of electron density information pose major challenges for MRI-based RTP. Recently, the geometric accuracy has been found sufficient for RTP with several scanners [2,5,14–18]. However, the previous studies have mainly focused on evaluating the system-related distortion caused by magnetic
field inhomogeneities and gradient non-linearities by conducting examinations with synthetic phantom materials. The magnetic susceptibility variations between different body tissues can result in additional geometric errors by shifting and distorting the tissue boundaries in the patient MR images [13,19–22]. Kapanen et al. quantified magnitudes for the both types of distortions with the 1.5T imager GE Optima MR450w (GE Medical Systems Inc., Waukesha, WI, USA), but the study did not evaluate the potential bone outline shift stemming from substantially different susceptibility values of bone cortex and surrounding soft tissues [2,19–23].

The susceptibility-induced bone outline shift and perturbations could potentially reduce quality of so called pseudo-CT images. These images are constructed from MR images to provide electron density information for MRI-based RTP [4–13,24]. For the pelvis, the pseudo-CT image construction techniques necessitate a bone segment in order to separately present the high density bony tissues and the low density soft tissues [4–13]. The bone outline contouring accuracy might be especially important with the recently developed dual model Hounsfield unit (HU) conversion technique, because the method relies on separate conversion models within and outside of bone segment transforming intensity values of a single $T_1^*/T_2^*$-weighted MR image series into HUs [13]. Under- or over-segmentation of bone outline could cause either substantial underestimation of the cortical bone HUs or major misrepresentation of the adjacent soft tissues, respectively [13]. Nevertheless, previous studies have not evaluated the influence of bone segmentation errors on dose distribution [12,13]. Quantification of relation between bone contouring precision and dose calculation accuracy is essential in order to evaluate the feasibility of dual model HU conversion technique for routine clinical RTP workflow and to quantify acceptance limits for bone segmentation.

The current study evaluates influence of systematic bone outline definition errors in MR images on external radiotherapy dose calculation accuracy in the dual model HU conversion pseudo-CT images of prostate cancer patients. This includes evaluation of potential susceptibility-induced bone outline shift and perturbations with a dedicated phantom, and quantification of dose consistency in the patient pseudo-CT images constructed from MR images with variable-sized bone segments. Subsequently, the work aims to determine the sufficient bone outline geometric accuracy for the pseudo-CT image construction to reach the dose calculation accuracy recommendations of 1% and 2% [25,26].

### Material and methods

#### Bone and gelatine phantom

In order to evaluate the potential susceptibility-induced bone outline shift and perturbations in MR images with respect to actual physical bone outline locations and to conduct the research with patient-like materials, a dedicated phantom was constructed by using fresh bones of a wild deer and gelatine made out of pig skin [12]. The phantom construction schematic is presented in the Supplementary Figure 1 (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.929737). The investigated femur and tibia were composed of a medullary cavity and an exterior cortical bone layer of approximately 3 mm. The bone diameters were on average roughly 3 cm for the femur and 2 cm for the tibia. Before examinations, the soft tissues located exteriorly to the bone cortex were removed without damaging the bone surface and the bones were attached into a $30 \times 35 \times 20$ cm$^3$ PMMA box. The bone positioning was parallel to the longitudinal imaging direction. The femur was attached approximately 1.5 cm lateral to the box middle axis, roughly 2 cm above the box bottom wall. The tibia was positioned 12 cm lateral to the middle axis to simulate distance of patient femoral bones from the magnet isocenter. The box was filled with a mix of 8 l of warm water and 400 g of solid pig skin-based gelatine. The box was placed in a refrigerator to solidify the gelatine. Predefined locations for the upcoming measurements were marked onto the box walls with laxative pills. The authors affirm that the reported research was conducted in accordance with the ethical policies of Helsinki University Central Hospital (HUCH, Helsinki, Finland).

#### Patients

Dose calculation accuracy in the pseudo-CT images was investigated for 15 prostate cancer patients. Five of the patients were randomly selected from the patient database of HUCH Cancer Center. Ten of the patients were adopted from a previous study to complement the analysis on dose calculation accuracy in the pseudo-CT images and because this test group included patients with varying anatomies [13]. The study did not have any effect on the imaging and RTP of these patients. The patients were imaged with both MRI (target delineation) and CT (dose planning and image guidance).

#### Imaging

MRI and CT were performed following clinical protocols of HUCH Cancer Center using the same
patient positioning and fixation as in radiotherapy [2]. The patient imaging workflow and parameters were adopted for phantom imaging. Table I presents the applied MRI sequence parameters. MRI was performed with the 1.5 T imager GE Optima MR450w. 

### Table I. The applied MRI sequences with their parameters.

| Sequence description | Name | TE (ms) | TR (ms) | Flip angle (degrees) | Bandwidth (kHz) | Pixel size (mm²) | Slice thickness (mm) |
|---------------------|------|---------|---------|----------------------|----------------|-----------------|---------------------|
| T₁/T₂*-weighted 3D FGE | LAVA Flex | 2.1, 4.2 | 6.8 | 15 | 90.9 | 0.98 × 0.94 | 2.4 (interpolated to 1.2) |
| T₁-weighted 2D SE | T₁ SE | 20 | 500 | 90 | 25 | 1 × 1 | 2.0 (interpolated to 1.0) |
| T₂*-weighted 3D FSE | CUBE | 124 | 2000 | 90 | 62.5 | 0.96 × 1.16 | 2.4 (interpolated to 1.2) |

Five MR image series obtained by three different sequences were included into the study. Three of the image series, i.e. in-phase-, out-of-phase-, and water-only images, were constructed using T₁/T₂*-weighted three-dimensional (3D) fast dual gradient echo (FGE) sequence [2]. T₁-weighted 2D spin echo (SE) and T₂*-weighted 3D fast spin echo (FSE) sequences were applied to achieve the other two investigated image series [2]. The MR images were corrected for signal intensity inhomogeneity and geometrical distortion by using imaging software tools; PURE® and GradWarp3®, respectively [2,13]. The CT imaging was carried out with the four-slice CT scanner GE Lightspeed RT (GE Medical Systems Inc., Waukesha, WI, USA). The unit was operated at 120 kVp. The image slice thickness was 1.25 mm and pixel size was 0.98 mm [2]. Figure 1 illustrates the bone contrast in the obtained images of the phantom.

**Measurements for the bone diameter and bone outline location in the phantom**

The accuracy of the bone edge location and the bone diameter in the MR images were evaluated by comparing the measured pixel-based distances with the actual physical measurements. The bone diameter and the distances from the bone edges to the phantom walls were measured to both phase- (lateral) and frequency encoding directions (vertical). Additionally, the examinations were designed to take into account errors in the sums of the distances, which could have revealed whether the possible errors in the distances were compensated for, or whether they accumulated, thereby causing amplified errors.

The measurements were performed at four predefined locations. Three of the locations included the femur within ± 2 cm from the magnet isocenter and one included the tibia 12 cm lateral from the magnet isocenter. The physical measurements were taken by using a caliper and dipsticks. The corresponding distances in the images were measured with a RTP system (Eclipse® 10.0, Varian Medical Systems Inc., Helsinki, Finland). Although the dual model HU conversion technique relies solely on the T₁/T₂*-weighted in-phase MR image, the additional images were included into the study because these images may prove useful for bone segmentation, if the bone outline is presented accurately. Additionally, CT images were included into the examinations to evaluate whether the bone outline location accuracy in CT images is substantially superior compared to that in MR images. With each image series the criterion for the bone edge was determined by measuring the pixel values representing the cortical bone and those representing the gelatine, and setting a threshold pixel-value in between. By considering the image pixel size and the intended segmentation accuracy

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**Figure 1.** Example transversal images of the deer femoral bone positioned in the gelatine; (a) T₁/T₂*-weighted FGE in-phase, (b) T₁/T₂*-weighted FGE out-of-phase, (c) T₁/T₂*-weighted FGE water-only, (d) T₁-weighted SE, (e) T₂-weighted FSE, and (f) CT.
for RTP, both physical and image-based measurements were rounded to the nearest 0.5 mm.

**Bone segmentation in patient MR images, pseudo-CT construction and dose calculation**

Bone outlines in the patient T1/T2*-weighted in-phase MR images were contoured carefully to achieve bone segments for pseudo-CT construction. Furthermore, the bone contours were intently expanded or contracted with 1 mm spacing to obtain pseudo-CT images constructed from MR images with additional systematic errors in the bone segment. The pseudo-CT images were constructed individually for each patient with each of the bone segments by adopting the dual model HU conversion technique. Korhonen et al. have described the method in details earlier [13]. The Supplementary Video-clip 1 (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.929737) shows the image transformation from the MR image to the pseudo-CT image. Figure 2 illustrates examples of the constructed pseudo-CT images with variable-sized bone segments.

The influence of bone segmentation accuracy on dose level in the pseudo-CT images was evaluated by comparing the planning target volume (PTV, including prostate and seminal vesicles) and organs-at-risk (OAR, the rectum and the bladder) dose-volume histogram (DVH) parameters in the pseudo-CT images with those in the standard CT images. The dose distribution differences in the pelvis were evaluated locally with the Gamma index method [27]. To minimize uncertainty for dose comparisons the same isocenter and PTV positioning in the CT and pseudo-CT images were obtained by MR to CT image co-registration (rigid registration relying on mutual information within roughly 15-cm diameter rectangular-shaped volume-of-interest positioned to the image center; MIM Software Inc., version 5.4, Cleveland, OH, USA) before constructing the pseudo-CT images. Moreover, the volumes in which patient body in pseudo-CT image unfilled the body in CT image were set as water-equivalent, and the body volumes in pseudo-CT image locating exteriorly to the body outline in CT image were assigned as air-equivalent. Treatment planning was performed using 6 MV photons with 360° volumetric modulated arc therapy (VMAT) and with seven-field intensity-modulated radiation therapy (IMRT). The dose optimization process was conducted by minimizing high dose volumes in healthy tissues especially at the organs at risk (such as the rectum and the bladder wall) without compromising the target dose. The treatment plans were calculated in standard CT images with the X-ray Voxel Monte Carlo algorithm (XVMC, version 1.6, with 0.2 cm grid-size and 0.5% MC uncertainty, electron density scaled medium, Monaco® 3.20.01, Elekta AB, Stockholm, Sweden) for the VMAT plans, and with the anisotropic analytical algorithm (AAA, version 11.0.31, with 0.1 cm grid-size, electron density scaled water, Eclipse® 11.0) for the IMRT plans. The treatment plans were copied and recalculated in the pseudo-CT images.

**Results**

Figure 3 illustrates the spatial accuracy of bone outline presentation in the images. The determined bone diameter in the MR images was always within 1.0 mm compared to the physically measured diameter. In the distances from the bone edges to the phantom walls the maximum errors were 1.5 mm, which were obtained at two of the 80 measurements (with T1 SE
Figure 3. Differences between the actual physical measurements and the measured distances from each of the image series for the bone outline. Symbols and error bars illustrate averages and ranges of the differences, respectively (open symbols in phase- and solid symbols in frequency encoding direction). The letters represent the investigated distances shown in Supplementary Figure 1.

Table II presents the prostate PTV DVH parameter (PTV volumes 95%, 50% and 5%) differences between dose distributions in the standard CT images and in the pseudo-CT images. Without additional errors in the bone segment the PTV mean dose level inconsistencies were in average (and in the worst cases) −0.2% (−1.0–0.7%) and 0.0% (−0.7–0.8%) in VMAT and in IMRT treatment plans, respectively. With additional systematic bone segmentation errors of −3 mm, −2 mm, … + 3 mm the PTV mean dose level inconsistencies were up to 1.6%, 1.4%, 0.9%, −1.3%, −1.8%, and −2.2%, respectively, in VMAT plans, and 2.1%, 1.8%, 1.2%, −1.1%, −1.8% and −2.2%, respectively, in IMRT plans. The OAR DVH parameter differences were detectable mainly only in high dose volumes, in which the differences were similar with those quantified for the PTV. The dose distribution comparisons with the Gamma index method are presented in Supplementary Table I and Supplementary Figure 2 (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.929737).

Discussion

The bone outline measurements indicated that the bone edges and the bone diameter in the tested MR images are presented precisely within 1 mm pixel size in both of the encoding directions. The error ranges between MR image sets obtained by different sequence parameters were relatively similar, suggesting that any of the investigated images could be adopted for bone contouring. Moreover, the uncertainties in bone diameter and in bone edge location were roughly within similar ranges in MR images and in CT images indicating that the bone edges can be presented approximately as accurately in the pseudo-CT images as in the conventional planning CT images, if the MRI-based bone contouring is performed precisely. Hence, the susceptibility-induced bone outline shift and perturbations are not restrictive issues for precise bone outline contouring and for accurate pseudo-CT image construction.

In this study it was essential to use real fresh bones instead of adopting tissue-representative phantom materials and that the reference measures were obtained by actual physical measurements in a stable phantom. Image intensity values of the deer bones and the gelatine ascertained the similar presentation of these materials with the human bony and soft tissues, respectively. The susceptibility of gelatine can be expected to be similar to soft tissues by considering the material properties [28]. The obtained bone outline uncertainty was roughly within similar level with the theoretical values of susceptibility-related geometrical distortion for the applied imaging parameters, such as frequency encoding gradient strength (5 mT/m in $T_1/H_2^*$-weighted imaging) [2,13,20–23]. Although local susceptibility-induced distortions are unique to individual anatomies and may be different in complex patient anatomy, it is likely that the distortion magnitudes would not be substantially different to those

| Plan | DVH (%) | Additional systematic error in bone segment |
|------|---------|--------------------------------------------|
| VMAT | 95      | 0.7±0.6 (−0.4–1.5) 0.5±0.6 (−0.5–1.4) 0.2±0.6 (−0.7–0.9) −0.3±0.6 (−1.1–0.6) −0.6±0.5 (−1.3–0.3) −1.0±0.6 (−2.0–0.1) −1.3±0.6 (−2.4–0.3) | +3 mm |
|      | 50      | 0.7±0.6 (−0.4–1.6) 0.5±0.6 (−0.5–1.4) 0.1±0.6 (−0.7–0.9) −0.3±0.6 (−1.0–0.7) −0.6±0.6 (−1.3–0.4) −0.9±0.6 (−1.8–0.0) −1.2±0.6 (−2.1–0.1) | +2 mm |
|      | 5       | 0.7±0.6 (−0.5–1.6) 0.5±0.6 (−0.5–1.5) 0.1±0.6 (−0.8–1.0) −0.2±0.6 (−0.9–0.7) −0.5±0.6 (−1.2–0.4) −0.9±0.6 (−1.6–0.0) −1.1±0.6 (−1.9–0.2) | +1 mm |
| IMRT | 95      | 1.2±0.4 (0.5–1.8) 0.9±0.4 (0.3–1.5) 0.4±0.4 (0.3–1.0) 0.0±0.4 (0.7–0.6) 0.3±0.5 (1.1–0.4) 0.8±0.5 (1.7–0.0) 1.0±0.5 (2.1–0.2) | −3 mm |
|      | 50      | 1.2±0.5 (0.4–2.0) 1.0±0.5 (0.3–1.7) 0.4±0.5 (0.3–1.1) 0.0±0.5 (0.8–0.7) 0.4±0.5 (1.2–0.4) 0.9±0.5 (1.9–0.0) 1.2±0.5 (2.3–0.3) | −2 mm |
|      | 5       | 1.4±0.6 (0.6–2.3) 1.1±0.5 (0.4–2.0) 0.5±0.5 (0.3–1.4) 0.1±0.5 (0.7–1.0) 0.3±0.5 (1.0–0.7) 0.8±0.5 (1.7–0.0) −1.1±0.6 (2.1–0.0) | −1 mm |

*The pseudo-CT images were constructed by the dual model HU conversion technique transforming the intensity values of $T_1/T_2^*$-weighted in-phase MR images into HUs by following separate conversion models within and outside of bone segment.
quantified in the current research. The reported bone outline presentation accuracy include potential sub-mm-sized uncertainties stemming from such as system-related distortion, imaging voxel size and software capability of presenting the pixel values at tissue interfaces. In these circumstances quantification of bone outline position more precisely than with the applied 0.5 mm scaling would have been inappropriate. Moreover, specification of possible sub-mm differences is irrelevant considering the goal of the investigation.

This research focused on determining the bone outline accuracy only with MR images obtained by the specific MR platform and sequence parameters. Thus, before adopting any sequences for MRI-based RTP, a verification procedure should be conducted to ensure that the geometric accuracy in the obtained MR images is sufficient, especially if the scanner and the sequence parameters are different to those applied in the present research. A major limiting factor for using some MR sequences for bone contouring can be the obscure appearance of the cortical bone in the images and the bony tissue definition from these images.

This study complemented previous research by quantifying dose calculation accuracy in the dual model HU conversion pseudo-CT images of prostate cancer patients with variable-sized bone segments [13]. This was essential in order to determine the level of needed segmentation accuracy providing sufficient dose calculation accuracy in the pseudo-CT images for routine clinical MRI-based RTP workflow. This work underlined that the ultimate 1% goal of dose consistency between the actual CT and the pseudo-CT images can be reached reliably if the pseudo-CT images of prostate cancer patients are constructed with precisely contoured bone segments and with the dual model HU conversion technique [13,26]. According to Table II, each 1 mm-sized systematic error in the bone outline contour result in approximately 0.4% change to the average prostate PTV dose level in the pseudo-CT images. The systematic bone outline contour error generally decreased the dose calculation accuracy, but with some patients the dose consistency compared to CT was better in agreement with 1 mm or 2 mm systematic errors in bone contour than with the precise segment. In these cases the bone contour errors compensated the uncertainty of HU conversion method [13]. Nevertheless, the 2% goal of dose calculation accuracy was reached reliably for all studied prostate cancer patients when the additional systematic error of bone segment was within ± 2 mm [25].

It is important to recognize that the reported dose consistency in the pseudo-CT images was quantified by regarding as reference the dose distributions optimized and calculated in standard CT images with the XVMC and the AAA. Dose comparisons include potential uncertainties stemming from such as different body positions in the images, co-registration errors, image artefacts, and rectum gas in CT images. Moreover, the dose calculation accuracy was evaluated only for treatment plans with multiple radiation field directions. Local dose distribution errors of over the reported uncertainty level may occur especially at the vicinity of bone outlines and with treatment plans relying only on few static fields [12].

We are currently aiming to introduce automatic bone outline segmentation methods enabling routine MRI-based RTP workflow in a clinic. According to the current study, we have defined a segmentation accuracy goal of 2 mm. Rapid automatic bone segmentation would be of particular value in order to introduce efficient and accurate on-line adaptive radiotherapy techniques with linear accelerators that are integrated into MR scanners [29]. With these MR-Linacs it would be particularly reasonable to rely solely on MR images throughout the RTP process.

Further studies could also evaluate feasibility of the dual model HU conversion technique for obtaining attenuation correction for positron emission tomography/MRI [30].

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Supplementary material available online

Supplementary Figures 1–2, Supplementary Video-clip 1 and Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.929737.