Dual-energy CT

Dual-energy CT based proton range prediction in head and pelvic tumor patients

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Abstract

Background and purpose: To reduce range uncertainty in particle therapy, an accurate computation of stopping-power ratios (SPRs) based on computed tomography (CT) is crucial. Here, we assess range differences between the state-of-the-art CT-number-to-SPR conversion using a generic Hounsfield look-up table (HLUT) and a direct patient-specific SPR prediction (RhoSigma) based on dual-energy CT (DECT) in 100 proton treatment fields.

Material and methods: For 25 head-tumor and 25 prostate-cancer patients, the clinically applied treatment plan, optimized using a HLUT, was recalculated with RhoSigma as CT-number-to-SPR conversion.

Material and methods: Depth–dose curves in beam direction were extracted for both dose distributions in a regular grid and range deviations were determined and correlated to SPR differences within the irradiated volume.

Results: Absolute (relative) mean water-equivalent range shifts of 1.1 mm (1.2%) and 4.1 mm (1.7%) were observed in the head-tumor and prostate-cancer cohort, respectively. Due to the case dependency of a generic HLUT, range deviations within treatment fields strongly depend on the tissues traversed leading to a larger variation within one patient than between patients.

Conclusions: The magnitude of patient-specific range deviations between HLUT and the more accurate DECT-based SPR prediction is clinically relevant. A clinical application of the latter seems feasible as demonstrated in this study using medically approved systems from CT acquisition to treatment planning.

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Here, we analyze 100 treatment fields of 50 proton-therapy patients to quantify range deviations caused by two CT-number-to-SPR conversions (clinical HLUT [19] and direct patient-specific SPR prediction [16]) and to observe whether these are of clinical relevance as expected by the results of previous theoretical [11] and experimental studies using tissue surrogates [14,15,17,20,21], polymers [22] or biological tissues [23].

Material and methods

DECT-based SPR prediction

For routine proton treatment planning of patients with several cancer types in head and pelvic regions, a sequential DECT scan (80/140 kVp) with 1 × 1 × 2 mm³ voxel spacing is acquired at a single-source CT scanner SOMATOM Definition AS (Siemens Healthineers, Forchheim, Germany) [19]. Both CT datasets are reconstructed using an iterative reconstruction kernel with beam hardening correction concerning bone (Q34/5, SAFIRE) to decrease image noise (controlled by Siemens CARE Dose4D) and increase patient-size dependent CT number stability. The clinical proton treatment is planned on a 79 keV MonoCT using a generic HLUT [19]. In addition to MonoCTs, voxelwise material parameters, namely electron density and photon absorption cross section, were directly derived from DECT for a patient-specific SPR prediction (RhoSigma) [16]. The accurate performance of this approach has been shown previously [20,24]. Implementation and calibration of both SPR prediction approaches were identical to [20] and are summarized in Supplementary materials.

Patient cohort and treatment planning

To evaluate the impact of SPR differences between the HLUT and RhoSigma approach on therapeutic dose distributions, 25 head-tumor (ependymoma, germinoma, Ewing’s sarcoma, astrocytoma and glioblastoma) and 25 prostate-cancer patients treated with protons at Oncoray (Dresden, Germany) were selected according to the approval of the local ethics committee (EK55122015). Both cohorts were assembled to representatively cover the respective range of patient ages (head: 2–73 a, prostate: 53–84 a). The head-tumor cohort includes 5 children, 10 women and 10 men. The passively scattered proton treatment plan of each patient consists of 2–5 treatment fields and was generated with XIO (Elekta AB, Stockholm, Sweden) using a 1 × 1 × 1 mm³ dose calculation grid. All prostate-cancer patients were treated with two beams from 90° and 270°. Within the head-tumor patient cohort, the number of treatment fields, including beam and couch angle, varies depending on tumor position. The clinically applied treatment plan was recalculated on the SPR map derived from the RhoSigma approach and relative dose difference maps (normalized to prescribed dose) between both methods were created.

Assessment of proton range shifts

For the two treatment fields of each patient with the highest beam weights, depth–dose curves in beam direction were extracted in an orthogonal grid of 1 mm isotropic spacing using an in-house implemented ray-tracing algorithm according to [25]. The origin of all depth–dose curves is defined by the external patient contour including immobilization devices. Depth–dose curves inside each treatment field with a dose maximum larger than 95% of reference dose per beam were evaluated. The geometrical proton range in tissue (R80HT) was defined as distal range at 80% of reference dose. The range difference between line–dose profiles obtained with two CT-number-to-SPR conversion methods corresponds to the geometrical range shift in tissue (∆R80HT = R80HT,RhoSigma – R80HT,HLUT). This shift ∆R80HT can be transferred into a water-equivalent range shift (∆R80WET) according to

$$\Delta R_{80WET} = \sum_{n=1}^{N} SPR_{RhoSigma}(n) \cdot \delta z(n).$$

with n as voxel number going from 1 to the total number of voxels N between R80HT,HLUT and R80HT,RhoSigma and δz(n) as path length between two consecutive voxel boundaries. This conversion allows a direct comparison with range uncertainties used for treatment planning, where standardly water-equivalent quantities are used. Relative range shifts are derived by dividing ∆R80WET by R80WET,RhoSigma.

The intra-patient and inter-patient variability of range shifts are defined as mean of the standard deviation and as standard deviation of the mean of patient-specific range shifts, respectively.

To determine whether both methods predict significantly different water-equivalent proton ranges, a one-sided t-test with significance criterion of 5% is applied.

Assessment of SPR deviations

In addition to range shifts derived from dose distributions, the mean SPR deviation between both CT-based SPR prediction approaches (ΔSPR = SPRRhoSigma – SPRHLUT) was calculated including all CT voxels within the 20% isodose of at least one of the two dose distributions. Furthermore, the frequency distribution of voxelwise correlations of CT number and SPR derived from RhoSigma was determined, as exemplarily shown in Figs. 1c and 2c for a head and a prostate case, respectively.

Results

First, an exemplary patient is presented for both cohorts to explicitly describe the different effects causing range deviations determined in the systematic cohort evaluation.

Exemplary head case

As shown in Fig. 1, patient-specific DECT-based SPR predictions lead to dose differences up to 26% at the distal fall-off compared to applying a HLUT. The illustrated depth–dose curve reveals a range shift in tissue of 1.6 mm (1.2%). Since the proton beam traverses a considerable amount of water-filled ventricles and the HLUT is optimized to better fit soft tissues instead of water (H = 0 HU, SPR = 1), the HLUT overestimates the SPR of water (zoomed inset of Fig. 1c). To quantify its influence on range, ventricles were delineated, their SPR assigned to the one of water and the dose distribution was recalculated. As result, SPR deviations in ventricles add up to a range shift of 0.4 mm. The residual range shift of 1.2 mm is mainly induced by the systematic larger SPR for brain using the HLUT instead of RhoSigma (indicated by red ellipse in Fig. 1c). The dose differences were not only present in a single treatment field but remained in the overall treatment. Within both investigated treatment fields, a mean relative range shift and inter-patient variation (±1s.d.) of (1.6 ± 0.7) mm was determined.

Exemplary prostate case

Dose distributions derived from both SPR prediction methods differ considerably as exemplarily shown in Fig. 2. Here, dose differences of more than 50% were determined at the distal fall-off. For an exemplary depth–dose profile, this corresponds to a range shift of 5.1 mm in tissue. Even in the target volume dose reductions of up to 1.5% occur, which cannot be compensated in the overall
treatment. The HLUT predicts systematically larger SPRs for muscle, bone marrow and trabecular bone (indicated by red ellipse in Fig. 2c).

**Systematic cohort evaluation**

The results obtained from the presented individual patient cases are representative for the systematic evaluation of 5001 (min: 2682, max: 9450) depth–dose curves in beam direction on average for each treatment field.

Regarding all evaluated depth–dose curves independent from the individual patient (Fig. 3), an overall median water-equivalent range shift (±1σ) of (1.2 ± 1.0)% or (1.1 ± 0.9) mm for head-tumor and (1.7 ± 0.9)% or (4.1 ± 2.2) mm for prostate-cancer patients were observed.

The mean relative water-equivalent range shift of each patient (Fig. 4) is significantly larger than 1% for both cohorts (p < 0.001) and still significantly larger than 1.5% for prostate-cancer patients (p < 0.001). As summarized in Table 1, about 34% and 66% of all depth–dose curves for the head-tumor and prostate-cancer cohort, respectively, reveal water-equivalent range shifts larger than 1.5%. Mean SPR deviations within the irradiated volume agree well with range differences obtained from dose distributions (Fig. 4). Furthermore, for head-tumor (prostate-cancer) patients, the intra-patient variation of relative water-equivalent range shifts with 0.91% (0.44%) is considerably larger than the inter-patient variability of 0.22% (0.24%). This is caused by differences in type and relative amount of tissues traversed, i.e., soft tissues like fat, muscle or brain, low-density bone like trabecular bone and high-density bone as cortical bone. To illustrate the intra-patient variability, a range deviation map is shown in beam’s eye view (BEV) for one patient of each cohort (Fig. 5).

In head-tumor cases (Fig. 5a), proton beams penetrate mainly soft tissue. Since the HLUT predicts systematically larger SPR for...
brain compared to RhoSigma, a positive overall range shift arises. However, for parts of the beam mainly passing through cortical bone or along a bone edge, the HLUT predicts systematically lower SPR resulting in larger proton ranges as predicted by RhoSigma (negative dose difference and range shifts in BEV). This is important for beams of short penetration depth, because directly after traversing the cranial bone, the WET difference caused by cortical bone cannot be fully compensated by the systematically larger SPR of brain.

Within treatment fields of prostate-cancer patients (Fig. 5b), especially muscle, bone marrow and trabecular bone occur. Since the HLUT predicts larger SPRs for all these tissues compared to RhoSigma, a systematic shorter proton range is calculated. Traversing the femoral head causes the highest range shift (Figs. 5b and 2c), which is mostly induced by the high amount of trabecular bone in beam direction. This effect is only partly compensated by the small amount of cortical bone ($SPR_{HLUT} < SPR_{RhoSigma}$) in the beam path.

**Discussion**

In this study, the feasibility of direct patient-specific SPR prediction based on DECT could be demonstrated under clinical conditions using a commercial CT scanner, image post-processing software and treatment planning system (TPS). Proton range deviations induced by different CT-number-to-SPR conversions were quantified in 100 clinical treatment fields of 50 proton-therapy patients. Using a generic HLUT [19] instead of a patient-specific DECT-based SPR prediction approach [16] leads to mean relative range shifts of 1.2% and 1.7% for representative patients with various head-tumor entities and prostate cancer, respectively. These
results are in good agreement with range shifts obtained in 5 head-trauma patients with hypothetical base of skull tumor [18]. The magnitude of range deviation between both CT-number-to-SPR conversion methods is supposed to be representative for tumor entities in the pelvic, abdominal as well as head-and-neck region and underlines the clinical relevance of accurate range prediction in particle therapy. However, to judge which of the two evaluated approaches is closer to reality, the respective SPR accuracy needs to be known.

Since it is highly challenging to perform range verification in patients using measurements of emitted prompt-gamma rays during treatment [26–29] or two-dimensional proton transmission measurements at baseline [30,31] with an accuracy of (1–2) mm, which has not been reached so far, we did not directly verify the accuracy of DECT-based SPR prediction in patients. Instead, we indirectly demonstrate the SPR accuracy by translating previously shown validation results in a ground-truth anthropomorphic head phantom with known SPR in each CT voxel [20] and homogeneous biological tissue samples [23] to patients. Although a minor uncertainty can remain in this chain of evidence, the major advantage of this indirect verification is that an accuracy of 1 mm or even less [20,23] can be achieved in each single study. Since in both studies, SPR prediction using RhoSigma has proven to be more robust, reliable and accurate than a HLUT, in our opinion it is justifiable to conclude that SPR prediction using RhoSigma is also more reliable and accurate for patients. Consequently, the range differences determined in patients indicate that DECT-based SPR prediction can improve particle range calculation and eventually lead to reduced range uncertainty margins. However, further studies are required to finally assess the remaining uncertainties caused by image smoothing at high-density gradients [20] and to allow for an appropriate estimation of CT-based range uncertainties in clinical practice.

Due to the high SPR accuracy of RhoSigma [20,23], in our opinion the mean SPR deviation within the irradiated volume of patients is certainly dominated by a systematic SPR overestimation of the HLUT for the major tissue types in beam direction (head-tumor cohort: brain; prostate-cancer cohort: muscle, bone marrow and trabecular bone) as illustrated in Figs. 1c and 2c. These tissues mainly occur as large, almost homogeneous volumes (without high-density gradients) and are thus not influenced by smoothing during CT image reconstruction, which could hamper range prediction irrespective of the selected CT-number-to-SPR conversion [20]. This effect of image smoothing, arising in small-volume tissues (cortical bone, air cavities), remains as uncertainty of absolute range prediction. However, since both methods are affected equally, the range shifts obtained within the investigated patients are virtually independent from this influence. Moreover, since the mean SPR deviations are comparable to mean relative range shifts derived from depth–dose curves (Fig. 4), we concluded that the

![Fig. 3. Distribution of relative and absolute water-equivalent range shifts.](image)
previously shown SPR accuracy of RhoSigma translates into mean range shifts. Furthermore, the large intra-patient variation of range shifts illustrates the case dependency of a generic HLUT. Changes in the amount of different tissues traversed in beam direction can lead to large deviations in range prediction (Fig. 5). Therefore, a patient-specific DECT-based SPR prediction with high accuracy in each individual tissue type would be advisable. In contrast, it is not admissible to hope for compensation of SPR over- and underestimation in different tissue types as this highly depends on the respective relative tissue amount along the beam path.

The presented study is subject to some restrictions. To assess range shifts directly related to the planned treatment, we used the clinically applied HLUT, which was defined following the clinical state-of-the-art procedure for CT calibration using tissue surrogates and tabulated human tissues. One could argue this HLUT is not optimized for the investigated patient cohorts and would thus contribute to an overestimation of range shifts. However, using only prior knowledge of currently available tabulated human tissues [10], a sophisticated HLUT refinement is rather challenging if not impossible without including additional patient-specific information, e.g., derived from DECT. This illustrates a disadvantage of a generic HLUT, which cannot cover the overall tissue diversity and patient variability per definition and potentially leads to a systematic bias [11,32]. On the other hand, the potential benefit of adapting a HLUT using DECT information to reduce systematic

### Table 1
Criterion-based classification of absolute range shifts.

| Patient cohort | Relative amount of absolute range shifts | $dR < 1.0\%$ | $dR > 1.0\%$ | $dR > 1.5\%$ | $dR > 2.0\%$ | $dR > 2.5\%$ | $dR > 3.0\%$
<table>
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<tbody>
<tr>
<td>Head</td>
<td>Relative amount of absolute range shifts</td>
<td>35.5%</td>
<td>64.5%</td>
<td>33.9%</td>
<td>14.5%</td>
<td>6.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Prostate</td>
<td>Relative amount of absolute range shifts</td>
<td>8.8%</td>
<td>91.2%</td>
<td>66.0%</td>
<td>28.8%</td>
<td>5.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>$dR &lt; 1\ mm$</td>
<td>$dR &gt; 1\ mm$</td>
<td>41.5%</td>
<td>58.5%</td>
<td>16.8%</td>
<td>2.0%</td>
<td>0.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>$dR &gt; 2\ mm$</td>
<td>$dR &gt; 3\ mm$</td>
<td>0.4%</td>
<td>99.6%</td>
<td>95.0%</td>
<td>80.1%</td>
<td>53.1%</td>
<td>23.9%</td>
</tr>
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Fig. 4. Distribution of intra-patient water-equivalent range shifts and inter-patient mean water-equivalent range shifts and mean SPR deviations.
deviations, as currently investigated at our clinic in consequence of the presented study, should be addressed in a further evaluation.

Furthermore, absolute proton ranges depend on the beam model and the dose calculation algorithm in the TPS. This influence can be neglected here, because only range shifts were evaluated. The results are also transferable to pencil beam scanning, since the overall treatment field dose was analyzed. Further studies should assess CT-related range differences in other treatment regions such as lung.

A further limitation is the resolution of the CT scan and the dose calculation grid. We reduced the overall influence on geometrical range calculation by linear interpolation of adjacent voxels to achieve a sub-voxel precision as standardly done in TPS.

Finally, it should be emphasized that this comprehensive patient study is an important step toward clinical application of a patient-specific DECT-based SPR prediction. However, a routine clinical use of scanner-specific DECT-based SPR prediction still requires an approved medical device provided by CT manufacturers, which is fully integrated in clinical workflow and its calculated SPR datasets are supported by all commercially available TPS.

**Conclusions**

The influence of CT-number-to-SPR conversion on proton range was assessed for 100 representative clinical proton treatment fields. Clinically relevant relative range shifts between the state-of-the-art heuristic look-up table and a patient-specific DECT-based SPR prediction were obtained, which are on average significantly larger than 1%. Depending on tissues traversed, large intra-patient range shift variations were observed confirming the case dependency of a generic HLUT. The importance of accurate CT-number-to-SPR conversion in general and the feasibility of patient-specific DECT-based SPR prediction has been demonstrated under clinical conditions.

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Conflict of interest statement

The authors report no conflict of interest. OncoRay and DKFZ have institutional research agreements with Siemens Healthineers.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.radonc.2017.09.042.

References


