MRI-based treatment planning with pseudo CT generated through atlas registration

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Purpose: To evaluate the feasibility and accuracy of magnetic resonance imaging (MRI)-based treatment planning using pseudo CTs generated through atlas registration.

Methods: A pseudo CT, providing electron density information for dose calculation, was generated by deforming atlas CT images previously acquired on other patients. The authors tested 4 schemes of synthesizing a pseudo CT from single or multiple deformed atlas images: use of a single arbitrarily selected atlas, arithmetic mean process using 6 atlases, and pattern recognition with Gaussian process (PRGP) using 6 or 12 atlases. The required deformation for atlas CT images was derived from a non-linear registration of conjugated atlas MR images to that of the patient of interest. The contrasts of atlas MR images were adjusted by histogram matching to reduce the effect of different sets of acquisition parameters. For comparison, the authors also tested a simple scheme assigning the Hounsfield unit of water to the entire patient volume. All pseudo CT generating schemes were applied to 14 patients with common pediatric brain tumors. The image similarity of real patient-specific CT and pseudo CTs constructed by different schemes was compared. Differences in computation times were also calculated. The real CT in the treatment planning system was replaced with the pseudo CT, and the dose distribution was recalculated to determine the difference.

Results: The atlas approach generally performed better than assigning a bulk CT number to the entire patient volume. Comparing atlas-based schemes, those using multiple atlases outperformed the single atlas scheme. For multiple atlas schemes, the pseudo CTs were similar to the real CTs (correlation coefficient, 0.787–0.819). The calculated dose distribution was in close agreement with the original dose. Nearly the entire patient volume (98.3%–98.7%) satisfied the criteria of chi-evaluation ($<2\%$ maximum dose and 2 mm range). The dose to 95% of the volume and the percentage of volume receiving at least 95% of the prescription dose in the planning target volume differed from the original values by less than 2% of the prescription dose (root-mean-square, $\text{RMS} < 1\%$). The PRGP scheme did not perform better than the arithmetic mean process with the same number of atlases. Increasing the number of atlases from 6 to 12 often resulted in improvements, but statistical significance was not always found.

Conclusions: MRI-based treatment planning with pseudo CTs generated through atlas registration is feasible for pediatric brain tumor patients. The doses calculated from pseudo CTs agreed well with those from real CTs, showing dosimetric accuracy within 2% for the PTV when multiple atlases were used. The arithmetic mean process may be a reasonable choice over PRGP for the synthesis scheme considering performance and computational costs. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4873315>]

Key words: MRI-based treatment planning, pseudo CT, atlas approach, pattern recognition with Gaussian process

1. INTRODUCTION

Magnetic resonance imaging (MRI) is widely used in radiotherapy treatment planning for its superior soft tissue delineation. Recently, significant interest has been paid to developing MRI-based treatment planning that does not require a computed tomography (CT) scan on patients. The potential advantages of this technique include elimination of registration errors between MR and CT scans, less exposure to

ionizing radiation, and reduction of imaging cost. The recent invention of integrated MRI-teletherapy systems^{1,2} also supports the pursuit of MRI-based treatment planning.

Several challenges must be overcome to fully establish MRI-based treatment planning.³ Patient aperture, couch, and receiver radio-frequency coils need to be designed to allow exactly the same patient posture as in treatment. The distortion in MR images induced by system hardware or patient-specific magnetic susceptibility needs to be avoided

or corrected.⁴ If the treatment system cannot acquire MR images for patient setup verification, radiograph-like reference images need to be generated. Another more critical challenge is to provide electron density for dose calculation which is not readily available in MRI. A similar problem is shared by positron-emission tomography (PET)-MR, where attenuation correction is challenging without an additional CT scan.

Several approaches have been proposed to generate CT-like images (also known as pseudo CT or synthetic CT) from MRI to derive electron density or perform attenuation correction. A straightforward one is to first segment MR images into distinctive structures (typically bony structure, soft tissue, and air), each having similar CT numbers within, and then assign corresponding bulk CT numbers to each structure.^{5–7} A problem with this approach is that bony structures and air are not easily distinguished in conventional MR images because their signal is weak due to fast MR relaxation in solid tissues and the low hydrogen content of air, which makes it difficult to automatically segment structures based on image intensity. The partial volume effect between segments and inhomogeneous density within bone are additional confounding factors. The segmentation approach can be improved by introducing advanced MR scans such as ultrashort echo time (UTE) sequences^{8,9} or using an *a priori* correlation between MR and CT.¹⁰ A recent study reported a voxel-based approach in which MR intensity in each voxel is converted to CT number using Gaussian mixture regression model on multiple UTE images acquired with different echo times and flip angles.¹¹ While providing a promising result, a practical concern is the need for extra MR scans. In addition, the estimated model parameters may vary depending on specifications of scanner hardware and imaging pulse sequence.

Another approach for generating a pseudo CT is to elastically deform an atlas CT onto a patient space. The atlas can be previously acquired images from other patients in original forms or a combination of them warped into the same coordinates.¹² The required deformation for atlas CT is often found by nonlinearly registering a conjugated atlas MR image to a patient MR image. The atlas approach has not been extensively studied, although it has potential for clinical application in that an automatic process is feasible without extra MR scans. The most critical difficulty in this approach is uncertainty in atlas registration, particularly for anatomy with an atypical shape such as missing tissues or surgical implants. However, it is possible to reduce this uncertainty either by improving the accuracy of deformation¹³ or combining the atlas approach with local pattern recognition as described in Hofmann *et al.*¹⁴

The purpose of this study is to assess the feasibility of atlas registration approach for MRI-based treatment planning on pediatric brain tumor patients, for whom MRI scans are normally performed and minimizing radiation exposure is highly relevant. More specifically, we aim to determine the tradeoff between accuracy and computational intensity of various schemes of synthesizing a pseudo CT from multiple atlas images, including the pattern recognition scheme that has been developed in the context of attenuation correction in

PET-MR.^{14,15} The image similarity between actual patient-specific CT (or simply real CT) and pseudo CTs constructed by different schemes was compared. In addition, we determined dosimetric differences between them to evaluate the suitability of using the pseudo CT for treatment planning. To our knowledge, this is the first study of the use of the atlas approach for pediatric patients. Due to the differences in brain size and shape from adults, we believe the evaluation of the atlas approach on pediatric brain renders a unique value.

2. MATERIALS AND METHODS

2.A. Data selection

This study was approved by the institutional review board. The images were retrospectively selected from patients with common pediatric brain tumors treated in our hospital. The radiotherapy course of the selected patients started between June 2009 and September 2012. The patients' ages at the start of the course were between 4 and 12 years, which is a typical age range constituting the majority of treated patients. We selected a "test group" of 14 patients (9 males, mean $\pm$ standard deviation of age, 8.5 ± 2.8 years) and a separate "atlas group" of 12 patients (4 males, 7.7 ± 2.9 years). To test the effect of the number of atlases on constructed pseudo CTs, another atlas group of 6 patients (2 males, 7.6 ± 3.3 years) was selected out of the 12 atlas patients. The selections were made such that age and gender distributions were not statistically different between the test group and either of the atlas groups (Student's *t*-test on age, $P > 0.5$; Fisher's exact test on gender, $P > 0.1$; see Fig. S1 in the supplementary material²⁶). Pseudo CT images were generated for each patient in the test group using the images provided by the atlas group as described in Sec. 2.B. The selection criteria common to all groups were: availability of MRI at the time of CT acquisition for treatment planning, coverage of entire brain and skull, and no severe motion or metallic artifacts in MRI. Additional criteria were applied to the atlas groups: no significant loss of brain tissue and no surgical implant.

We used MR images acquired with T2-weighted turbo spin-echo (T2 TSE) prior to the injection of contrast agent. An advantage of T2 over T1-weighted image is higher intensity in gray matter rendering clear interfaces with bony structures. In addition, the signals from tumor and blood vessels were enhanced by contrast agent in most T1-weighted images, which often makes accurate nonlinear registration difficult. The MR images included in this study were from various clinical protocols for which image acquisition parameters were optimized differently. The MR images were acquired on a 1.5 T Avanto or 3.0 T Tim Trio scanner (Siemens, Erlangen, Germany) with repetition time = 4000–9720 ms, echo time = 82–123 ms, reconstructed pixel size = 0.4–0.8 mm, slice thickness = 4.0–5.0 mm, and bandwidth = 98–217 Hz/pixel. The CT images were acquired on a Siemens Somatom Sensation Open scanner (Siemens, Erlangen, Germany) with slice thickness = 2 mm and reconstructed pixel size = 0.63–0.98 mm. Tube voltage was 120 kVp.

FIG. 1. The process for constructing a pseudo CT from atlas images. The deformations for atlas MR images were applied to the corresponding atlas CT images to generate multiple deformed atlas images. Then, they were combined to produce a pseudo CT via arithmetic mean or the application of PRGP.

2.B. Construction of pseudo CT

Figure 1 illustrates the process for constructing a pseudo CT from a patient MR image using atlas images. The CT and MR images from each of the atlas group patients were aligned via linear rigid-body registration to produce multiple conjugated CT/MR atlas image pairs. Mutual information between the two image modalities was used as the cost function. The deformation of each atlas CT to the patient MR image was determined by nonlinear spatial registration between the conjugated atlas MR images and the patient MR image. We used FSL (FMRIB, Oxford, UK) for the linear and nonlinear spatial registrations. The parameters associated with nonlinear spatial registration were determined by refining the default configuration provided by FSL. The multiple deformed atlas CT images were combined to produce a pseudo CT, for which we used an arithmetic mean process or pattern recognition with Gaussian process (PRGP).¹⁴

In the arithmetic mean process, the pseudo CT image intensity, μ of a voxel at $\mathbf{x}_0$ is simply the mean of those at the same location in all deformed CT images:

$$\mu(\mathbf{x}_0) = \frac{1}{N_a} \sum_{i=1}^{N_a} y_i(\mathbf{x}_0), \quad (1)$$

where N_a is the number of atlases and y_i is the intensity in deformed CT images. The mathematical formulae for PRGP are elaborated in the Appendix. The intensity of each voxel predicted by PRGP is a weighted average of voxels from deformed atlas CTs. In our implementation, the voxel at the same location and the neighboring voxels defined by a square matrix contribute to the prediction, without searching nearest neighbors as in Hofmann *et al.*¹⁵ Thus, the pseudo CT image intensity, $\mu(\mathbf{x}_0)$, is a linear function of

$$\mathbf{y} = [y_1(\mathbf{x}_0) \ y_1(\mathbf{x}_1) \ \dots \ y_1(\mathbf{x}_{N_n}) \ \dots \ y_{N_a}(\mathbf{x}_0) \ y_{N_a}(\mathbf{x}_1) \ \dots \ y_{N_a}(\mathbf{x}_{N_n})], \quad (2)$$

where N_n is the number of neighbors. The weighting assigned to each element of $\mathbf{y}$ is determined by comparison of

“patches” between the conjugated atlas MR images and the patient MR image. A patch includes surroundings of a voxel of interest so that the typical pattern of a tissue structure can be clearly recognized. All atlas CT/MR and test patient MR images were resampled to a typical MRI resolution of $0.8 \times 0.8 \text{ mm}^2$ in-plane and 4 mm slice thickness for PRGP. To reduce the effect of varying acquisition parameters across atlas and patient MR images, we adopted histogram matching algorithm described by Beyer *et al.*¹⁶ and adjusted image contrasts as well as overall intensities. The parameters associated with PRGP were empirically determined. The neighbor and patch sizes and the variance parameter in a covariance matrix [σ_c^2 in Eq. (A4)] were determined by a leave-one-out procedure on the 12 atlas images. Here, the pseudo CT was generated for each of the 12 atlas group patients using the other 11 as atlases. Out of various parameter sets, the one that minimized differences between pseudo and real CTs was selected. The determined parameters were: $N_n = 0$, patch size = 9×9 in-plane voxels, and $\sigma_c^2 = 1$. The two variance parameters within the Gaussian kernel matrix [σ_p^2 and σ_x^2 in Eq. (A5)] were determined for each test patient by examining the variances of patch intensity and position difference terms [$\|w(\mathbf{p}_u) - w(\mathbf{p}_v)\|$ and $\|\mathbf{x}_u - \mathbf{x}_v\|$ in Eq. (A5), respectively]. We used in-house Matlab (Mathworks, Natick, MA) codes to perform PRGP.

We tested different schemes to combine deformed CTs. We constructed pseudo CTs by the arithmetic mean process with the 6 atlas group, PRGP with the same 6 atlas group, and PRGP with the 12 atlas group (denoted by MEAN6, PRGP6, and PRGP12, respectively). The same groups of atlases were used for all 14 test patients. For comparison, we additionally constructed a pseudo CT based on a single atlas, $\mu(\mathbf{x}_0) = y_1(\mathbf{x}_0)$ (SINGLE) and another pseudo CT assigning Hounsfield unit (HU) of water to the entire volume within the external patient outline, $\mu(\mathbf{x}_0) = 0$ (WATER). The single atlas was selected out of the 12 atlases. To avoid bias posed by this selection, we selected the one showing the median performance of elastic deformation as evaluated by leave-one-out procedure within atlases. The same single atlas was used for all 14 test patients.

2.C. Evaluation

The performance of nonlinear registration of an atlas CT to a test patient CT was evaluated by the root-mean-square difference (RMSD) of the pixel intensities within the patient volume between the two CT images. The accuracy of constructed pseudo CT for each patient was similarly evaluated against the real CT in terms of RMSD and correlation coefficient. The histograms of CT number distributions were compared to detect potential bias in different intensity ranges.

We evaluated the suitability of using pseudo CTs for dose calculation in treatment planning. In the original treatment plan with Pinnacle (Philips, Fitchburg, WI), the real CT was replaced by a pseudo CT, and the dose was recalculated using the same monitor unit for each beam. The treatment plans were either conformal radiotherapy or intensity-modulated radiotherapy with 6 MV photons. The number of beams ranged

from 6 to 12. The dose was calculated with an Adaptive Convolution Superposition algorithm with a dose matrix resolution of $0.3 \times 0.3 \times 0.3 \text{ cm}^3$ or $0.4 \times 0.4 \times 0.4 \text{ cm}^3$. The prescription dose to the planning target volume (PTV) in the original treatment plan ranged from 36 to 59.4 Gy, and primary sites were distributed in various parts of the brain including thalamus, pineal region, cerebellum, optic pathway, and brainstem.

It is well known that immobilization devices attenuate radiation beams.¹⁷ However, implementing immobilization devices into a pseudo CT is not straightforward, because they are not seen in atlas MR images due to fast relaxation. Moreover, deforming such devices is hardly feasible since their position relative to the patient is often inconsistent across atlas and patient images. In this work, we excluded immobilization devices by segmentation in the real CT to avoid this confounding effect. Our plan is to continue investigating how to incorporate immobilization devices into the generation of a pseudo CT.

The dose distribution over the entire volume was evaluated using chi-evaluation¹⁸ with constraints of 2% maximum dose and 2 mm range. The percentage volume of the tissues satisfying chi-value between -1 and 1 was calculated.

We further analyzed dose volume histogram (DVH) and dosimetric parameters in PTV and organs at risk (OARs). We calculated the dose to 95% of the volume (D95) and the percentage of volume receiving at least 95% of the prescription dose (V95) in the PTV, maximum dose to the optic chiasm, and mean dose to the cochleae. The optic chiasm was not analyzed as an OAR for four patients whose target volume was adjacent to or involve the structure.

The performances of different schemes were compared using rank-based repeated measures ANOVA and pairwise tests on the accuracy indices of pseudo CT (RMSD or correlation coefficient), percentage volume satisfying chi-evaluation, or dosimetric parameters. Depending on normality of the data distribution, either pairwise *t*-test or Wilcoxon signed rank sum test was used. An adjustment for multiple hypotheses testing has been made to the *P* values as needed by Bonferroni correction. *P* value smaller than 0.05 was considered statistically significant.

3. RESULTS

3.A. Computing time

All processes were conducted on a typical desktop computer equipped with Intel Xeon CPU (2.8 GHz) and Red Hat Enterprise Linux 5. It took 16.3 min on average to deform one volume of atlas images. The total time for deformation

was proportional to the number of atlases used. Compared to arithmetic mean process, PRGP added 22.6 and 75.4 min for the uses of 6 and 12 atlases, respectively. The total computation times for constructing pseudo CTs by different schemes are summarized in Table I.

3.B. Evaluation of deformed atlas CTs and pseudo CTs against the real CTs

The deformation error of atlas CTs assessed by RMSD between and real and deformed CTs ranged from 218 to 539 HU for all 12 atlas $\times$ 14 patient cases. The deformation error was correlated with gross tumor volume (GTV) ranging $0.7\text{--}201 \text{ cm}^3$ ($R = 0.55$, $P = 0.04$, $N = 14$, see Fig. S2 in the supplementary material²⁶). In addition, the RMSD also tended to increase with larger age difference between patient and atlas ($R = 0.18$, $P = 0.02$, $N = 168$, see Fig. S3 in the supplementary material²⁶). However, there was only 1.5% increase in RMSD per 1 year, which was weak compared with the variation ($\pm 30\%$) within the cases at the same age difference.

The pseudo CTs based on deformed atlas images showed a visual similarity to the real CT [Fig. 2(a)]. The difference from the real CT [Fig. 2(b)] was more pronounced around bony structures than the other tissues possibly because bone-soft tissue interfaces were not precisely registered by the elastic deformation. Consequently, pseudo CTs combining multiple deformed images tend to have a “smoothing” effect, i.e., CT numbers were overestimated at around 0–700 HU and

FIG. 2. Comparison of pseudo and real CTs for a representative patient. (a) Pseudo and real CT images overlaid by PTV contours and isodose lines; (b) difference map of each pseudo CT from real CT; (c) histograms of CT numbers in real CT and pseudo CTs constructed by combining multiple deformed atlases. The upper and lower arrows in (c), respectively, indicate over- and underestimations by pseudo CTs, which reflect the smoothing effect. The figure inset shows that the histograms of PRGP6 and PRGP12 are closer to that of real CT than MEAN6 indicating a smaller degree of smoothing with PRGP. The MR image corresponding to the CT images is also presented for comparison (d).

TABLE I. Computing time for constructing pseudo CT (min).

	WATER ^a	SINGLE	MEAN6	PRGP6	PRGP12
Average	...	16.3	98.0	120.6	271.4
Standard deviation	...	3.2	18.9	19.2	39.4

^aComputing time for WATER is negligible compared to the others.

TABLE II. Root-mean-square-difference and correlation coefficient (Corr. Coeff.) between pseudo CT and real CT ($N = 14$).

		WATER ^a	SINGLE	MEAN6	PRGP6	PRGP12
RMSD (HU)	Average	391	346	224	219	207
	Standard deviation	30	81	36	35	33
Corr. Coeff.	Average	...	0.545	0.787	0.798	0.819
	Standard deviation	...	0.133	0.060	0.059	0.058

^aCorrelation coefficient of WATER was not available due to its uniform intensity.

underestimated at a higher range [Fig. 2(c)]. The figure inset in Fig. 2(c) shows that the smoothing effect was less pronounced by PRGP compared to the arithmetic mean process.

The average RMSD between pseudo and real CTs ranged from 207 to 391 HU (Table II) in the order of WATER > SINGLE > MEAN6 > PRGP6 > PRGP12 [all pair comparisons were significant ($P < 0.01$) except for the pair of WATER and SINGLE ($P = 0.25$)], indicating that the pseudo CT constructed by PRGP12 was closest to the real CT. Correlation coefficients also agreed with this trend ($P < 0.013$ for all comparisons). PRGP12 showed the highest correlation with the real CT (correlation coefficient, 0.819).

3.C. Evaluation of dose calculated on pseudo CTs

Overall, the dose distributions calculated on pseudo CTs were in close agreement with the original doses, as presented by the isodose lines for a representative patient in Fig. 2(a) and chi-evaluation for all 14 patients (Table III). Chi-values for nearly the entire tissue volume (98.3%–98.7% on average) fell between -1 and 1 with the three schemes using multiple atlases (MEAN6, PRGP6, and PRGP12). The WATER scheme was not statistically different from these three schemes (97.8%, $P > 0.2$), but the SINGLE scheme showed a lower performance (95.3%, $P < 0.001$).

DVHs of PTV and OARs from pseudo CTs also closely agreed with those from real CTs in most cases (see Fig. 3 for an example). DVHs from WATER, however, often markedly deviated toward higher doses than the other DVHs (black lines in Fig. 3). This was expected since WATER has a lower CT number than tissues in real CTs, particularly at bony structures [see the left most image in Fig. 2(b)], which would result in less attenuated beams and, in turn, a higher dose distribution.

V95 values in PTV calculated on pseudo CTs were very close to those on real CT ($<0.3\%$ of volume) except for two patients [patients #7 and #14 in Fig. 4(a)]. Overestimations were more pronounced in patient #7 because V95 in the original plan was lower (96.0%) for this patient than the

others (99.3%–100%). V95 of patient #14 showed a high deviation with the SINGLE scheme. It was revealed that the specific nonlinear registration of the single atlas to this patient was problematic possibly due to large missing tissues in the patient brain (see Fig. S4 in the supplementary material²⁶). However, the other schemes did not show such deviation. For D95 and mean dose to PTV, the parameters based on the multiple-atlas schemes (MEAN6, PRGP6, and PRGP12) differed from the original values by less than 1.8% and 1.3% of the prescription dose, respectively [Figs. 4(b) and 4(c)]. Root-mean-square (RMS) values of those differences were within 1% for all three schemes. Statistical comparisons indicated that MEAN6 performed better than PRGP6 ($P < 0.04$) and PRGP12 was not significantly superior to PRGP6. The RMS values of the other two schemes, WATER and SINGLE, were greater than 1%. The RMS value of WATER was significantly greater than all the other schemes ($P < 0.05$).

The maximum dose to the chiasm was within 5% of the original value (RMS ranged from 1.7% to 2.2%, absolute dose difference from the original values < 1.8 Gy) for all five schemes without statistical differences among them ($P = 0.13$). For mean dose to the left and right cochleae, the four schemes other than WATER showed accuracies within 6% (RMS ranged from 3.0% to 3.6%, absolute dose difference < 2.8 Gy). WATER showed deviations from the original values by up to 10%, which was significantly greater than the other four schemes ($P < 0.001$).

4. DISCUSSION

The presented dosimetric accuracy in PTV ($<2\%$ of the prescription dose) was comparable to those in the literature. MRI-based plans differed from the corresponding CT-based plans by less than 2% in studies on prostate treatment.^{5,19,20} The difference was greater than 2% when homogeneous

TABLE III. Percentage volume satisfying chi-evaluation with constraints of 2% maximum dose and 2 mm range ($N = 14$).

	WATER	SINGLE	MEAN6	PRGP6	PRGP12
Average	97.8	95.3	98.7	98.3	98.5
Standard deviation	2.2	7.4	1.3	1.5	1.3

FIG. 3. Dose volume histogram of PTV and OARs for the patient illustrated in Fig. 2.

FIG. 4. Differences of V95 (a), D95 (b), and mean dose (c) in PTV calculated on pseudo CTs from those on real CT. The differences of D95 and mean dose are in percentage of the prescription dose. Root-mean-square value for each scheme is provided in parentheses.

water density was assigned for a pseudo CT.⁵ Another study on prostate treatment reported that 95.2% (average of 37 patients) of the volume satisfied chi-evaluation with the same constraints used in the present study (2% and 2 mm).¹² For MRI simulation on the brain, an early study using a head phantom reported 2%–4% dosimetric errors.²¹ In a recent study based on a segmentation approach,⁶ the difference between CT- and MRI-based doses to PTV (mean and maximum) was less than 1%. The number of patients in that study, however, was too small ($N = 4$) to be fairly compared with the present study. The dosimetric parameters in OARs were not as accurate as in PTV. This is presumably contributed by that the effect of deformation error is more severe for smaller structures particularly if there is a high dose gradient across the structure. It was also noted that the percentage difference is more pronounced as the original dose to OAR is lower.

The error of atlas deformation tends to be higher with the presence of a more severe structural abnormality, often occurring in patients with a larger GTV size or a larger surgical void. The deformation errors may be reduced by using an advanced method such as the one presented in a recent PET-MR study.¹³ They developed a multistep procedure for elastic deformation in which a conventional B-spline transformation was refined by an optical flow algorithm.²² Another potential way to improve deformation is to minimize the age difference between atlas cases and patients. However, the improvement may not be significant because individual variations appeared to be bigger than the age-related trend.

Besides deformation error, the variation of bone density in individual patients may affect the accuracy of constructed pseudo CTs. The use of atlases having bone densities similar to that of a patient would be helpful to produce an accurate

pseudo CT. However, our data implied that the bone density may not be accurately predicted by age (see Fig. S5 in the supplementary material²⁶). Since conventional MRI does not measure bone density, an alternative way of estimating bone density would be needed for this procedure.

Combining multiple atlases either by arithmetic mean process or PRGP reduced the effect of deformation errors on constructed pseudo CTs. One drawback of these schemes was a smoothing effect where high intensities in bone smear into the surrounding soft tissues. Our simulation test (see the supplementary material²⁶ for details) implied that the radiation beams are less attenuated when a CT image has such smoothing effect, which would subsequently result in overestimation of the calculated dose. The schemes using multiple atlases indeed tended to overestimate dosimetric parameters (see Figs. 4 and 5).

PRGP is expected to perform better than the arithmetic mean process particularly at the regions where accurate registration is challenging due to unusual anatomical structures (e.g., see Fig. S4 in the supplementary material²⁶). PRGP with six atlases (PRGP6) produced a pseudo CT closer to the real CT than the arithmetic mean process with the same number of atlases (MEAN6). The smoothing effect was also less pronounced with PRGP6 than MEAN6 (Fig. 2). However, the resultant dosimetric accuracy did not improve. This is possibly because the parameters for PRGP were selected such that they maximized the overall accuracy of pseudo CT in pixel intensity, while the calculated dose was more sensitive to bony structures than soft tissues. A test of other PRGP parameters selected to focus on bony structures will be helpful to test this possibility. The comparison between PRGP6 and PRGP12 implied that increasing the number of atlases does not necessarily result in significant improvements once it is

FIG. 5. Percentage differences of maximum dose to chiasm (a), mean doses to left (b) and right (c) cochleae calculated on pseudo CTs from the original values on real CT. Root-mean-square value for each scheme is provided in parentheses.

sufficiently large. Our results suggested that MEAN may be a reasonable choice for clinical practice since it performs as well as the PRGP with relatively low computational costs.

The use of MR images acquired by different sets of parameters was a limitation in this study since it did not provide consistent contrasts in MR images that are desirable for PRGP. Atlas MR images with contrasts deviating from those of a patient are potentially subject to extra deformation errors and overestimated differences in patch comparison, which would result in diminished weightings to the atlases in PRGP. A subsequent implication is that the corresponding atlas CTs do not fully contribute to constructing the pseudo CT as much as they are entitled to. We applied the histogram matching algorithm to mitigate this effect. For a test patient that an atlas shares the same acquisition parameters with, we did not observe an apparent bias towards this atlas against those processed by histogram matching (see Fig. S6 in the supplementary material²⁶). An additional concern associated with acquisition parameters is patient-induced geometric distortion^{4,23,24} which may vary depending on magnetic field strength and bandwidth. However, the distortion is expected to be minimal in most regions other than tissue–air interfaces in sagittal sinus and ear canals. It has been shown that patient-induced susceptibility is less than 1.1 ppm for 97.4% of the volume of a head on a 3T scanner,²⁵ which corresponds to 0.3–1.1 mm distortions in our MR images.

The use of the same corresponding pixel location (i.e., the neighbor size $N_n = 0$) was another limitation in the PRGP scheme of this work. A preliminary test indicated that the improvement in accuracy of pseudo CTs from an increased neighbor size (e.g., $N_n = 8$ or 24) did not outweigh the considerable computational costs. An advanced computational power will allow a better determination of the uncompromised performance of the PRGP scheme.

5. CONCLUSIONS

This study suggested that pseudo CTs synthesized from multiple deformed atlases are more suitable for treatment planning than those from a single atlas or assigning a bulk CT number to the entire patient volume. The pseudo CTs based on multiple atlases showed a high similarity to the real CTs and the corresponding calculated doses agreed well with those based on real CTs. PRGP better accounted for deformation errors than arithmetic mean process, resulting in more accurate pseudo CTs. However, the dosimetric accuracy was not significantly improved by PRGP despite longer computation time. It suggested that arithmetic means process may be a reasonable choice for clinical practice considering performance and computational costs while a few limitations in our implementation of the PRGP, including the use of MR atlases acquired by different sets of parameters, should be noted.

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APPENDIX: EQUATIONS DESCRIBING PATTERN RECOGNITION WITH GAUSSIAN PROCESS

Pattern recognition with Gaussian process¹⁴ gives a rule to combine $N_a \times (1 + N_n)$ CT numbers from $(1 + N_n)$ voxels (including a voxel of interest and its N_n neighbors) in each of N_a atlas CT images:

$$\mathbf{y} = [y_1(\mathbf{x}_0) \ y_1(\mathbf{x}_1) \dots y_1(\mathbf{x}_{N_n}) \dots y_{N_a}(\mathbf{x}_0) \ y_{N_a}(\mathbf{x}_1) \dots y_{N_a}(\mathbf{x}_{N_n})]. \quad (\text{A1})$$

In the conjugated atlas MR images, a set of voxels surrounding each of these $N_a \times (1 + N_n)$ voxels is called a “patch” and is denoted by a vector $\mathbf{p}$ as a function of position vector $\mathbf{x}$:

$$\mathbf{P} = [\mathbf{p}_1(\mathbf{x}_0) \ \mathbf{p}_1(\mathbf{x}_1) \dots \mathbf{p}_1(\mathbf{x}_{N_n}) \dots \mathbf{p}_{N_a}(\mathbf{x}_0) \ \mathbf{p}_{N_a}(\mathbf{x}_1) \dots \mathbf{p}_{N_a}(\mathbf{x}_{N_n})]. \quad (\text{A2})$$

The patch at $\mathbf{x}_0$ in the patient MR image is denoted by $\mathbf{p}_0(\mathbf{x}_0)$. The pseudo CT number of the voxel at $\mathbf{x}_0$ is then calculated by

$$\mu(\mathbf{x}_0) = m(\mathbf{x}_0) + \mathbf{k}\mathbf{C}^{-1}(\mathbf{y}^T - \mathbf{m}^T). \quad (\text{A3})$$

The vector $\mathbf{m} = [m_1(\mathbf{x}_0) \ m_1(\mathbf{x}_1) \dots m_1(\mathbf{x}_{N_n}) \dots m_{N_a}(\mathbf{x}_0) \ m_{N_a}(\mathbf{x}_1) \dots m_{N_a}(\mathbf{x}_{N_n})]$ is composed of mean function values for which we used $m(\mathbf{x}_j) = m_1(\mathbf{x}_j) = m_2(\mathbf{x}_j) = \dots = m_{N_a}(\mathbf{x}_j) = \frac{1}{N_a} \sum_{i=1}^{N_a} y_i(\mathbf{x}_j)$, $j = 0, 1, \dots, N_n$. The covariance matrix, $\mathbf{C}$, is given by

$$C_{u,v} = K_{u,v} + \sigma_c^2 \delta_{u,v}, \quad u, v = 1, \dots, N_a(1 + N_n), \quad (\text{A4})$$

where $\delta_{u,v}$ is the Kronecker delta, σ_c^2 is a variance parameter, and $K_{u,v}$ is Gaussian kernel matrix defined by

$$K_{u,v} = \exp\left(-\frac{\|\mathbf{w}(\mathbf{p}_u) - \mathbf{w}(\mathbf{p}_v)\|}{2\sigma_p^2}\right) \exp\left(-\frac{\|\mathbf{x}_u - \mathbf{x}_v\|}{2\sigma_x^2}\right). \quad (\text{A5})$$

Here, the patch intensities are differently weighted by a vector function $\mathbf{w}$ for which we used a Gaussian function with a standard deviation of half patch width. The parameters σ_p^2 and σ_x^2 determine how much differences in MR intensity and position between patches affect the kernel value. The column matrix $\mathbf{k}$ is the kernel with respect to the patch in the patient MR image:

$$k_u = \exp\left(-\frac{\|\mathbf{w}(\mathbf{p}_u) - \mathbf{w}(\mathbf{p}_0(\mathbf{x}_0))\|}{2\sigma_p^2}\right) \exp\left(-\frac{\|\mathbf{x}_u - \mathbf{x}_0\|}{2\sigma_x^2}\right). \quad (\text{A6})$$

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