Assessment of dose accuracy for online MR-guided radiotherapy for cervical carcinoma

Shouliang Ding, Hongdong Liu, Yongbao Li, Bin Wang, Rui Li, Biaoshui Liu, Yi Ouyang, Dehua Wu and Xiaoyan Huang

ABSTRACT
This study aims to evaluate the dose accuracy of synthetic CT based bulk relative electron density (rED) assignment for application in 1.5 T MR-Linac for cervical carcinoma patients. Five cervix patients previously treated on 1.5 T MR-Linac were retrospectively investigated. Two sCTs were generated assigning bulk values to the different bone regions: the $sCT_{FH}$ was generated with delineation of femoral head, and the $sCT_{AB}$ was generated with the delineation of all the bone regions. The rest tissue of the patient data was set to mean rED values of the region of interests in CT. The same treatment plan based on original CT was recalculated or reoptimized on the $sCT_{FH}$ and $sCT_{AB}$. The result of gamma analysis showed that gamma passing rate of treatment plans based on $sCT_{AB}$ was higher than plans based on $sCT_{FH}$. And the differences of dose volume parameters between plans on sCTs and original CT showed that the differences for plan based on $sCT_{AB}$ were much smaller than $sCT_{FH}$. The sCT generated with bulk rED assignment approach guarantees an acceptable level of dose accuracy for cervix carcinoma patients with 1.5 T MR-Linac. The accuracy can be improved by using complete delineation of the pelvic bone regions.

1. Introduction
In the clinical radiotherapy workflow, a radiation treatment plan is usually generated using both Magnetic Resonance Imaging (MRI) and Computer Tomography (CT) imaging modalities in order to pool the advantages of both imaging modalities together. The utility of using CT in radiation therapy includes reference image generation for patient position verification based on in-room x-ray imaging and dose calculations used the electron density information, while the advantages of MRI rest with its high soft tissue contrast and biological/functional imaging capabilities (Prior et al., 2016). The integrated MRI with linear accelerator delivery systems (Elekta 1.5 T Unity MR-Linac and ViewRay Inc 0.35 T MRIdian MR-Linac), or with Co$^{60}$ teletherapy system (ViewRay Inc) have been clinical available and the potential advantages of MRI guided radiotherapy have been explored (Fallone, 2014; Lagendijk et al., 2008; Matic & Dempsey, 2014). Online adaptive radiotherapy can today be administered by these hybrid MR-Linac systems. The MR-guided radiotherapy systems can create the online adaptive radiotherapy treatment plan directly on the daily MRI by the on-board scanner, considering the actual patient anatomy and so addressing the inter-fraction organ variability. However, a major limitation in the use of MRI for radiotherapy planning is the lack of a relationship between the electron density (ED) information and MRI signal intensity, making it challenging for dose calculation (Paulson et al., 2015; Prior et al., 2017). This leads to the concept of MRI-based treatment planning, where synthetic CT (sCT, also referred to as substitute CT or pseudo CT) data are generated directly from the MRI for the purpose of dose calculation.

Many studies have explored the techniques to overcome the difficulty of converting the MRI to sCT for accurate dose calculation (Andreasen et al., 2015; Edmund & Nyholm, 2017; Korsholm et al., 2014). They can be roughly categorized into three aspects: atlas-based, hybrid-based methods. The atlas-based sCT generation approaches focus on aligning the MRI voxels locations to the corresponding MRI voxels in a previously built atlas through registration, the CT numbers are typically derived from the co-registered pair of CT and MRI scans in the atlas (Dowling et al., 2012; Uh et al., 2014). Once the patients’ MRI was registered and aligned properly with the atlas, the corresponding CT numbers can be assigned and hence converting the MRI into sCT dataset. The voxel-based methods typically use the MRI voxel intensities to assign electron densities, directly convert the MRI signal intensities to hounsfield unit (HU), ED, or relative

CONTACT Xiaoyan Huang huangxiaoy@sysucc.org.cn No. 651 Dongfengdong Road, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China.

These authors contributed equally to this work.

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ED (rED) (Kapanen & Tenhunen, 2013; Korhonen et al., 2014; Rank et al., 2013). The voxel-based methods are dominated by machine learning and ED assignment. Convolutional neural network (CNN) and cycle generative adversarial networks (GAN) have been investigated to predict the CT numbers and then generate the sCTs from conventional MR images (Dinkla et al., 2018; Fu et al., 2019; Peng et al., 2020; Qi et al., 2020). In contrast, the ED assignment approaches are much easier to achieve by assigning the generic values (e.g. from ICRU report 46), or values from intensity conversion relationship, or manually contoured structure’s mean ED to bulk groups of MRI voxels, while the last is the most common method available and clinically employed by MR-Linac system (Karotki et al., 2011; Prior et al., 2016, 2017).

Recently, the Elekta Unity MR-Linac system (Elekta, AB, Stockholm, Sweden) which combines the Philips 1.5 T MRI device and a 7 MV linear accelerator has been introduced into clinical practice. In the implementation of this system, MRI-based treatment planning is the indispensable process for adaptive treatment planning with ‘adapt to shape (ATS)’, in which the daily MRI will be registered and re-contoured for adapting the treatment plan (Winkel et al., 2019). Voxel-based bulk rED assignment method was routinely implemented by the Unity MR-Linac specific treatment planning system (TPS) Monaco (v5.40.01) to perform MRI-only planning. Several studies have investigated the dosimetric accuracy of bulk rED assigned MRI-only radiotherapy planning for pancreatic, spinal bone, and nasopharynx (Dalah et al., 2014; Hoogcarspel et al., 2014; Young et al., 2018). Prior et al. studied the combined effects of bulk rED assignment and magnetic field on the pancreas and prostate intensity-modulated radiotherapy (IMRT) plan quality, they found that uniform rED assignment resulted in dose-volume parameters (DVPs) differences within 3% and 5% for target and OAR, respectively (Prior et al., 2016). Additionally, in the Cusumano et al. study, they also indicated that the bulk sCT guarantees a high level of dose calculation accuracy also in presence of a 0.35 T magnetic field, making this approach suitable to MRI-guided radiotherapy (Cusumano et al., 2020). These studies mainly focused on the effect of bulk rED assignment on plan quality but did not consider the impact of the undelineated bone regions. Bone is a special issue for MRI based planning in that the sCT representation is important but at the same time challenging. For cervical cases, pelvic bones include sacrum, ilium, ischium, pubis, coccyx, and femoral heads. But for conventional cervical patients planning, only part of the bony regions for example femoral heads will be contoured on the original planning CT because the radiation oncologist only focuses on dose to the femoral heads, which can lead to the misinterpretation of the remaining undelineated bones in the bulk rED assigned MRI-only planning. Utilizing the inaccurate sCT for adaptive planning with ‘adapt to shape’ will result in errors in both dose calculation and inverse optimization process, thus potentially affecting the final plan quality.

Therefore, this study aims to evaluate the dose accuracy of using the bulk sCT in presence of a 1.5 T magnetic field and quantify the dose impact caused by the undelineated bone regions in MRI based planning, to assess the reliability of this approach in the case of online adaptive MR-guided radiotherapy treatments of cervical lesions.

2. Materials and methods

2.1. Patient data

Five patients with cervical cancer treated on the Elekta 1.5 T MR-Linac from 2019.9 to 2020.2 were retrospectively investigated in this study, with the median age of 57 years old (range 56–70). According to the FIGO tumor stage criteria, three of the patients were in stage IIA, the other two were in stage IIIB and stage IIB, respectively. The original planning CT and daily MRI T2 datasets were used in this study. CT simulations of the five patients were performed on a large-bore CT scanner (Philips Brilliance™, Netherlands) in the supine position, with the 140-kVp X-rays, the field of view (FOV) of 80-cm and a uniform slice thickness of 0.3 cm. The planning MRI was acquired with the 1.5 T Unity MR-Linac during treatment, using an identical setup but with the anterior/posterior (28 channel) receive coils. The attenuation effect of these coils was also considered during dose calculation. Online T2-weighted MRI scan was performed using 3D spoiled gradient recalled acquisition in steady state (3D SPGR), with a flip angle of 90°, echo time (TE) of 278 ms, repetition time (TR) of 1535 ms, and slice thickness of 0.1 cm.

Based on the planning images, target and organs at risk (OARs) were delineated on original CT in the Monaco system by a senior radiation oncologist specialized in cervical cancer. All macroscopic as well as potential microscopic diseases were covered by CTV. Then the planning target volume (PTV) was created by expanding the CTV with a 6 mm margin all around except 10 mm on the anterior side. The normal tissues including rectum, bladder, sacrum, ilium, ischium, pubis, coccyx, and femoral heads were contoured according to our institute’s guidelines.

2.2. Synthetic CTs generation

A deformable registration with manual adjustments and careful inspection was performed to align the planning MRI with the original CT. The sCT was then generated in the Monaco system using the bulk rED
assignment method, based on the mean rED values of the delineated region of interests (ROIs) in original CT and adapting to shape on the MRI. For each patient, two sets of sCT data were generated. The first synthetic CT (sCTFH) was created using the patient-specific mean rED values of femoral heads in CT, and the water equivalent value of 1 g/cm (Fallone, 2014) for other pelvic bones (sacrum, ilium, ischium, pubis, coccyx). The rest tissue of the patient data was set to mean rED values of the ROIs in CT.

To investigate the dosimetric impact of the undelineated bone regions on MRI based planning, another set of synthetic CT (sCTAB) was generated with the patient-specific mean rED values of all the bone regions (sacrum, ilium, ischium, pubis, coccyx, and femoral heads) in CT. And the rest tissue of the patient data was also set to mean rED values of the ROIs in CT.

An overview of two sets of s-CT data are presented in Figure 1. Figure 1A is the sCT generated with only femoral heads assigned, Figure 1B shows the s-CT generated with full delineation of the bone regions. For comparison, Figure 1C presents the corresponding original CT. For clarity sake, all the transversal, coronal, and sagittal views of the s-CT were displayed in this figure.

2.3. Treatment planning

First of all, it should be illustrated online adaptative radiotherapy planning workflow for MR-Linac. The daily online procedure started with acquiring an MRI scan. This scan was registered to the pre-treatment CT scan using rigid registration. Subsequently, the pre-treatment CT contours were automatically propagated to the online planning MRI. Then a synthetic CT was generated using the bulk rED assignment method. Finally, a plan recalculation or reoptimization was performed on the planning MRI using the ‘adapt segments’ or ‘optimize weights and shapes from fluence’ option with the same planning parameters that were used to generate the pretreatment plan.

For each case, a nine coplanar fields IMRT plan was firstly generated on the pretreatment CT dataset using Unity MR-Linac specific TPS offline Monaco (v5.40.01), with consideration of the effect of 1.5 T magnetic field by employing a graphic processing unit (GPU)-based Monte Carlo dose calculation platform (GPUMCD) (Chuter et al., 2019; Hissoiny et al., 2011). The plan was defined as a pretreatment plan. The prescription dose of all the five patients was 45 Gy in 25 fractions. The dose objectives and constraints for each plan were defined following our institute’s protocols, as shown in Table 1. The plan also accounted for the MRI cryostat, Unity system-specific couch, and receiver coils. All the plans were designed with step-and-shoot technique distributed into 0°, 40°, 80°, 110°, 160°, 200°, 250°, 280°, 320°. And these IMRT plans were calculated with 7 MV flattening filter free (FFF) photons using 0.3 cm grid spacing and a 3% statistical uncertainty.

Figure 1. Overview of all the s-CTs used in this study. (A) shows the s-CT generated with only femoral heads, (B) shows the s-CT generated with all the bone regions, (C) shows the original CT.
Table 1. Dose-volume criteria used in treatment planning for five cervix patients.

| Structures (target and OAR) | Dose (prescription and constrains) |
|-----------------------------|-----------------------------------|
| PTV                         | $D_{95} \geq 45 \text{ Gy}$       |
| Rectum                      | $V_{60} \leq 60\%$                |
| Bladder                     | $V_{40} \leq 35\%$                |
| Femoral head (right)        | $V_{10} \leq 15\%$                |
| Femoral head (left)         | $V_{10} \leq 15\%$                |

Table 2. Calculation and segmentations for the IMRT plans.

| Plan parameters | MR-Linac IMRT |
|-----------------|---------------|
| Energy          | 7 MW FFF      |
| Algorithm       | GPUMCD        |
| IMRT technique  | Step-and-Shoot|
| Grid spacing (cm) | 0.3          |
| Statistical uncertainty (%) per control point | 3 |
| Minimum segment area (cm$^2$) | 4 |
| Minimum segment width (cm) | 0.7 |
| Minimum MU/segment | 5 |
| Maximum # segments per plan | 100 |

...per control point. Other parameters pertaining to the IMRT plans such as segment area, segment width, number of segments per plan, etc. have been outlined in Table 2.

Firstly, the two types of recalculated plans were generated in our study. The pretreatment plan was recalculated on the sCTFH and sCTAB images using the ‘adapt segments’ option, without applying any optimization, which donated as ‘RC-sCTFH’ and ‘RC-sCTAB’. The two recalculated plans have the same segments number and shape. To quantify the dose impact of different sCT sets, the RC-sCTAB plan was then transferred to the original CT (RC-CT).

Secondly, the pretreatment plan was reoptimized on the sCTFH and sCTAB images using the ‘optimize weights and shapes from fluence’ option, with the same dose objectives and constraints. The reoptimized plans were donated as ‘RO-sCTFH’ and ‘RO-sCTAB’, respectively. The segments number and shape of the two reoptimized plans were different because of undergoing the reoptimized process. To evaluate the dose impact of different sCT sets, the RO-sCTFH and RO-sCTAB plans were transferred to original CT, respectively, with denotations of ‘RO-CTFH’ and ‘RO-CTAB’, respectively.

In total, for each case, there existed four relevant plans for the s-CT dataset and meanwhile, three transferred plans for the original CT, as outlined in Figure 2.

2.4. Plan evaluation and analysis

All these plans were assessed for dose error through dose-volume histogram (DVH) parameters evaluation and dose distribution gamma analysis. DVH parameters such as $D_{\text{mean}}$ (the mean dose), $D_{98\%}$ (the dose covered by 98% of PTV volume), $D_{50\%}$ (the dose covered by 50% of PTV volume), $V_{100\%}$ (% PTV volume covered by 100% of prescription dose), $D_{1cc}$ (the maximum dose covering 1 cm$^3$ volume) were used to evaluate the target dose, while the $D_{\text{mean}}$ was used for OARs evaluation.

Furthermore, gamma analysis with criteria 2 mm/2% or 1 mm/1% coupled with 10% dose threshold were respectively performed to evaluate the plan dose differences (Hoogcaspers et al., 2014; Low et al., 1998).

Figure 2. Different plan’s dataset, optimization, and dose calculation combinations investigated. ATS: Adapt to shape.
3. Results

3.1. Dose accuracy of recalculation plans based on MR images

The comparison of dose accuracy for sCT-based recalculated plans is shown in Figure 3. The transversal view of a representative case was selected and presented. Figure 3A is for the RC-sCT\textsubscript{AB} treatment plan on the sCT with all bone regions contoured, Figure 3B is for the RC-sCT\textsubscript{FH} treatment plan based on the sCT with only femoral heads delineated. To investigate the dosimetric differences between original CT- and sCT-based plans, all the plans on two sCT sets were recalculated on the gold standard original CT, which denote as 'RC-CT', as shown in Figure 3 (A2, B2). Noted that the red line contoured structure here represents the PTV region. Comparing the sCT based recalculation plans (RC-sCT\textsubscript{AB} and RC-sCT\textsubscript{FH}) with the benchmarking CT based plan (RC-CT), the dose distribution of RC-sCT\textsubscript{AB} is more alike to that of CT based plan RC-CT. While the plan RC-sCT\textsubscript{FH} obviously overestimated the dose, especially for the regions behind the undelineated ilium, leading to more inaccurate hot-spots. Dose difference maps for the two sCT-based plans comparing with the gold standard are also presented in Figure 3 (A3, B3) respectively, which were derived by subtracting the dose distribution of the RC-CT voxel-by-voxel from the dose distribution of plan RC-sCT\textsubscript{AB} and RC-sCT\textsubscript{FH}.

Figure 3C presents the DVH comparisons of PTV and OARs about the three plans. Noticeable differences were observed for PTV, bladder, and rectum, but the only slight difference was observed for bilateral femoral heads. Figure 4 reports the box plot analysis regarding the difference of the DVH curves calculated on the two sCT images with respect to the corresponding values calculated on the CT. According to the DVH curves and the key metrics, it is observed that the difference in the DVH parameters calculated on sCT\textsubscript{AB} is closer to 0 if compared to those calculated on sCT\textsubscript{FH}. The mean difference in evaluating the V\textsubscript{100\%} of PTV was found 2.7% using sCT\textsubscript{AB} and 4.5% using sCT\textsubscript{FH}.

![Figure 3](image-url)
with respect to the reference values calculated on the CT. As to OARs, the DVH difference of plan on sCT_{AB} was higher than plan on sCT_{FH}, with respect to the reference values calculated on the CT.

Gamma analysis was also performed to compare the sCT based recalculation with the original CT based plan dose. Table 3 lists the gamma passing rates of the recalculation plans for all five patients, with a 1 mm/1% and 2 mm/2% criteria and 10% dose threshold. For both criteria, GPR results of s-CT plan RC-sCT_{AB} are always higher than plan RC-sCT_{FH} when compared with gold standard CT based plan RC-CT. With stricter criteria, the GPR differences between plan RC-sCT_{AB} and plan RC-sCT_{FH} are also larger. On average, the 1 mm/1% GPR for plan RC-sCT_{AB} and RC-sCT_{FH} were 82.3 ± 4.3 and 74.0 ± 5.1, respectively. While for criteria with 2 mm/2%, GPR for plan RC-sCT_{AB} and RC-sCT_{FH} were 98.8 ± 0.5 and 96.9 ± 0.8, respectively.

3.2. Dose accuracy of reoptimized plans based on MR images

Figure 5 presents the dose distribution comparisons between sCT based plan and the corresponding original CT based plan (RO-sCT_{AB} vs RO-CT_{AB} and RO-sCT_{FH} vs RO-CT_{FH}) for the representative case. Figure 5 (A1, A2) is the transversal dose distribution of plan RO-sCT_{AB} and RO-CT_{AB}. Similarly Figure 5 (B1, B2) is for plan RO-sCT_{FH} and RO-CT_{FH}. Difference maps for sCT based re-optimized plan versus gold standard CT based plan are shown in Figure 5 (A3, B3). As observed, the major difference occurred in regions where bulk bones existed in the beam incident passage. For plan RO-sCT_{FH}, due to only femoral heads of bony regions were assigned with mean rED, a significant difference was observed at the boundary region of PTV and nearby ilium bones when compared with the original CT based plan, with

| Table 3. Global Gamma analysis for between sCTs-based recalculation plan and original CT based plan dose distribution for five cases and average with ± SD. |
|------------------|------------------|------------------|------------------|------------------|
|  |  |  |  |  |
| y (1 mm and 1%)  | y (2 mm and 2%)  |  |  |
| RC-sCT_{AB}/CT  | RC-sCT_{FH}/CT  | RC-sCT_{AB}/CT  | RC-sCT_{FH}/CT  |
| Patient 1  | 79.4  | 68.5  | 99.2  | 97.0  |
| Patient 2  | 88.8  | 81.3  | 99.3  | 97.8  |
| Patient 3  | 79.4  | 72.6  | 98.4  | 97.1  |
| Patient 4  | 84.3  | 76.7  | 99.1  | 96.9  |
| Patient 5  | 79.1  | 70.8  | 98.1  | 95.7  |
| Mean ± SD  | 82.2 ± 4.3  | 74.0 ± 5.1  | 98.8 ± 0.5  | 96.9 ± 0.8  |
a maximum relative difference of 4.4%, as pointed out by the red arrow in Figure 5B2. While for plan RO-sCT_AB, all bone regions were delineated and assigned properly, so the maximum dose difference at the corresponding boundary of PTV and bone regions was 1.7% when compared with plan RO-CT_AB.

DVH curves for those re-optimization results of both sCTs and original CT-based plans are also presented in Figure 5. According to the DVH curves, both PTV and OARs of plan RO-sCT_AB are much closer to the CT based plan RO-CT_AB, comparing with the plan RO-sCT_FH. We also found that the mean difference in evaluating the $V_{100\%}$ of PTV was found at 2.2% using sCT_AB and 4.9% using sCT_FH, with respect to the reference values calculated on the CT. As to OARs, the DVH difference of plan on sCT_AB was also higher than plan on sCT_FH, with respect to the reference values calculated on the CT.

The Gamma analysis results of re-optimization plans of both sCTs and original CT-based plans for all the five
cases are presented in Table 5. Obviously, the overall GPR of plan RO-sCT_{AB} are better than the RO-sCT_{FH} plan. On average, the 1 mm/1% GPR for plan RO-sCT_{AB} and RO-sCT_{FH} were 84.6 ± 3.7 and 74.9 ± 3.6, respectively. Additionally, the 2 mm/2% GPR for plan RO-sCT_{AB} and RO-sCT_{FH} were 98.9 ± 0.6 and 97.0 ± 1.4, respectively.

### 3.3. Discussion

MRI-only planning is an indispensable step to achieve ATS (adapt to shape) adaptive radiotherapy on Unity MR-Linac. Though various techniques including an atlas, voxel, and hybrid-based methods have been developed to generate the sCT dataset from MRI, the bulk rED assignment is straight-forward to use and also currently the only one available adopted by Unity specific Monaco system. However, this approach is challenged by the subjectivity of contouring, leading to the dosimetric accuracy of bulk rED assignment behave tumor-site specific. What makes it more complicated is to account for the effect of the 1.5 T transverse magnetic field. For cervical patients, when treated on conventional Linac with gold standard planning CT, commonly only femoral heads of the bony regions will be contoured because the radiation oncologist only focuses on dose to the femoral heads. While for MRI based planning with bulk rED assignment method, this can result in the misinterpretation for the remaining undelineated bone regions, such as the sacrum, ilium, ischium, et al. To our knowledge, this study is the first to investigate the impact of these undelineated bone regions on the dosimetric accuracy of MRI based planning for cervical cancer treated on the 1.5 T MR-Linac. Complete delineation of all the bone regions has the potential to improve planning accuracy and thereby patient treatment outcomes.

The assigned rED values used in our study were the mean realistic rED for each delineated region of

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**Table 5.** Global Gamma analysis for between sCTs-based reoptimization plan and original CT based plan dose distribution for five cases and average with ± SD.

| Patient | γ (1 mm and 1%) | γ (2 mm and 2%) |
|---------|-----------------|-----------------|
|         | RO-sCT_{AB}/RO-CT_{AB} | RO-sCT_{FH}/RO-CT_{FH} | RO-sCT_{AB}/RO-CT_{AB} | RO-sCT_{FH}/RO-CT_{FH} |
| Patient 1 | 82.8 ± 3.7 | 71.6 ± 3.6 | 99.3 ± 0.6 | 98.3 ± 1.4 |
| Patient 2 | 80.9 ± 3.7 | 79.4 ± 3.6 | 99.5 ± 0.6 | 97.0 ± 1.4 |
| Patient 3 | 84.6 ± 3.7 | 73.8 ± 3.6 | 98.7 ± 0.6 | 96.4 ± 1.4 |
| Patient 4 | 85.6 ± 3.7 | 78.1 ± 3.6 | 99.2 ± 0.6 | 98.3 ± 1.4 |
| Patient 5 | 79.9 ± 3.7 | 71.8 ± 3.6 | 97.9 ± 0.6 | 95.1 ± 1.4 |

**Figure 6.** Box-plot analysis related to the dose differences of reoptimized plans based on sCT_{AB} and sCT_{FH} respect to the original CT for different DVH parameters related to PTV and OAR.
interests (ROIs) derived from the original planning CT. Following ROIs including PTV, rectum, bladder, femoral heads, and bones in the cervical site were considered. Some previous studies investigated to use the rED values derived from ICRU Report 46 or the uniform water density, and a difference of 5–9% in presence of magnetic field was reported when compared with gold standard CT (Prior et al., 2016). But considering the individual difference, caution should be used in applying uniform rED assignment to all sites, and implementing realistic mean rED values should be more accurate. For instance, several literature have demonstrated an improved dosimetric accuracy by using mean rED assignment for bone, air, and water compared with uniform water assignment (Karotki et al., 2011; Rank et al., 2013). Full delineation of all the important ROIs has the potential to improve the sCT generation and hence dosimetric accuracy, though the contouring can be subjective and time consuming.

Both dose calculation and optimization process will be influenced by the undelineated bone regions in bulk rED assigned MRI based planning for cervical cancer. For recalculation plans, the original planning CT based calculation is benchmarked as the gold standard, while the inaccurate ED assigned in the sCT generation process can introduce uncertainties to the final dose calculation. Apart from femoral heads, there are multiple large bone regions including the sacrum, ilium, ischium, pubis, and coccyx in the cervical site. If they are not correctly contoured in planning CT, then the corresponding regions in sCT will be filled with the mean rED of the body, typically close to soft tissues (rED=1.0). According to ICRU report 46, typically the mean rED of bones should be 1.21, and for sacrum bone, the rED value can even be as high as 1.39. Considering the extensive bone regions that existed in the cervical site according to our study, incorrectly assigned mean rED of these regions can yield a relatively large error exceeding 4.4%. However, when full delineation of the bone regions and assigned the mean rED correctly, then the dose calculation error can be as low as within 1.7%. In addition, while the plan based on sCT80 obviously overestimated the dose, especially for the regions behind the undelineated ilium, leading to more inaccurate hot-spots. As observed, the major differences occurred in regions where bulk bones existed in the beam incident passage, which was due to the dose decay of the bone regions. The considered effects of all bone region rED assignment on plan quality results in the difference in DVPs that were reduced to 2% for PTV, comparing to the 4% difference for a plan based on sCT only considered femoral heads. This indicates that full delineation of bone regions can significantly improve the dose calculation accuracy, which was demonstrated again by the gamma analysis results. No matter in criteria 2 mm/2% or 1 mm/1%, the GPR of plan RC-sCTAB versus plan RC-CT for all five patients were always higher than that of plan RC-sCTFH versus plan RC-CT. But when using stricter criteria of 1 mm/1%, the GPR difference between sCT based plan RC-sCTAB and plan RC-sCTFH became larger and more easily to distinguish.

As to the reoptimization process, the uncertainty is more difficult to quantify because the dose calculation error can in turn affect the optimization. The reoptimization error will potentially produce a suboptimal plan and the final dose on s-CT would also be incorrect. For the ‘worst’ sCT based reoptimization plan RO-sCTFH, there existed a relatively large discrepancy both in dose and DVH distributions comparing with the plan RO-CTFH based on the gold standard planning CT. While for plan RO-sCTAB based on s-CT with all bone regions’ mean rED correctly assigned, the corresponding discrepancy was much smaller when compared with plan RO-CTAB based on gold standard CT. When transfer the reoptimized plan to gold standard planning CT, some cold spots were observed, especially around the vicinity of the PTV near the ilium (Figure 5). Complete delineation of the bones can effectively reduce the discrepancy. The reason also was that the dose decay of the bone regions when bulk bones existed in the beam incident passage. This indicates that incorrect bulk rED assignment of these bone regions can have a large effect on the optimization results. It was also confirmed by gamma analysis results. The GPR of plan RO-sCTAB versus plan RO-CTAB with criteria 2 mm/2% or 1 mm/1% were higher than that of plan RO-sCTFH versus plan ROICTFH. The differences of GPR between ROI-sCTAB and RO-sCTFH were statistically significant (1 mm/1% GPR: ROI-sCTAB: 84.6 ± 3.7, ROI-sCTFH: 74.9 ± 3.6; 2 mm/2% GPR: ROI-sCTAB: 98.9 ± 0.6, ROI-sCTFH: 97.0 ± 1.4).

This study investigated the dose accuracy due to differences in rED assignment for converting the MRI datasets to sCT for dose calculation. There existed some limitations presented in this study. First of all, the MRI-only planning and sCT generation are highly dependent on the image registration process. Though the deformable registration was performed between planning CT and MRI, some errors still can be introduced, and also the evaluation of registration quality is somehow subjective. Furthermore, because the planning CT and MRI were not acquired simultaneously, the delineated PTV and OARs may have different anatomic characteristics such as position or volume in the two sets of images. These differences in anatomical changes due to different image acquisition can also lead to errors when comparing the sCT based plans with planning CT based plans. Additionally, compared with other site, geometric distortions are ubiquitous in cervical MRI, especially for regions close to the FOV boundary. The distortion can affect the quality of image registration and may result in the sCT-based optimization and dose calculation errors. This issue is inevitable but the induced errors are insignificant and typically acceptable. Wang et al. assessed the image quality of the Unity MR-Linac system and reported that
the geometric distortion was within 0.5 mm in the both axial and sagittal plane, which was clinically acceptable (Wang et al., 2018). Uniform rED assignment of bones with their realistic mean rED values was adopted to generate the sCT in this study, however, the interpretation accuracy can be further improved by adopting other methods. For example, Korhonen et al. reported that absorbed radiation doses in material bone parts, and to evaluate dose calculation errors in different sCTs images (Korhonen et al., 2013). Their another study reported that assigning different rED for the cortical and spongey parts of femoral heads can model the bone attenuation more accurately and implemented a dual model to convert the MRI intensity values into Hounsfield units (HUs) for male prostate cancer. It is reported that the average HU differences between the s-CT images and gold standard CT images ranged from −2 to 5 HUs and 22 to 78 HUs for soft and bony tissues, respectively (Korhonen et al., 2014). However, some of the methods are scanner dependent and more importantly, the bulk rED assignment is currently the only one available in the Unity Monaco system. With the development of these techniques, more and more advanced atlas-based and voxel-based methods, especially the recently emerged promising deep learning-based s-CT generation will be applied for clinical MRI-only planning.

Overall, utilizing the inaccurate sCT for adaptive planning with ‘adapt to shape’ will result in errors in both dose calculation and inverse optimization process, thus potentially affecting the final plan quality. We found that the rED assignment of all bone regions results in differences in DVPs within 3% for the PTV, compared to the 5% difference for a plan based on sCT only considered femoral heads. The major difference occurred in regions where bulk bones existed in the beam incident passage, which was resulted from the dose decay of the bone regions. The difference within 3% is acceptable in clinical practice. The results of this study pave the way to clinical implementation of the bulk sCT in high-tesla MR-guided radiotherapy. During the radiotherapy for cervix patient, the inter-fraction organ variability is very obvious, such as bladder, rectum, and small intestine. And the interfraction organ variability represents one of the main sources of uncertainty conditioning the treatment outcome. Therefore, it is necessary to modify the radiation treatment according to the patient’s daily anatomy. This study demonstrated the generation of sCT using bulk rED assignment is a reliable method for the radiation oncologist to carry out online adaptive radiotherapy for cervix patients according to the daily MR images, considering the actual patient anatomy and addressing the interfraction organ variability.

4. Conclusion
This study demonstrated that synthetic CT generated with bulk rED assignment approach guarantees an acceptable level of dose accuracy for cervix carcinoma patients, making the approach suitable to MR-guided radiotherapy with 1.5 T MR-Linac. Fully delineation of the pelvic bones and considering the bone electron density correction can be helpful to reduce the error of synthetic CT generation and thus improving the MRI based planning accuracy.

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No potential conflict of interest was reported by the authors.

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