Clinical Implementation of MR-guided Radiotherapy for Prostate Cancer in Halcyon-System

Zimmermann M.[1]; Lange A.[2]; Sabatino M.[1]; Giro C.[1]; Lorenzen J.[3]; Struck J.[3]; Dahle J.[1]; Würschmidt F.[1]; Kretschmer M.[1]

[1]Radiologische Allianz, Strahlentherapie, Hamburg, Germany
[2]Beuth Hochschule für Technik, Berlin, Germany
[3]Radiologische Allianz, Diagnostische Radiologie, Hamburg, Germany

Introduction

In Germany, prostate cancer is the most common cancer among men. Approximately 58,000 men are diagnosed with prostate cancer each year, and more than 14,000 men die from it [1]. Almost half of all patients receive external beam radiotherapy (EBRT). Before treatment, a three-dimensional radiation therapy plan is created. Many clinics use thin-slice CT images to define the clinical target volume (CTV). Because of the limited soft tissue contrast of CT images, and the uncertainties in the treatment planning process, a large margin is needed to create the planning target volume (PTV). Early studies have shown that co-registered CT/MRI images improve target volume definition for radiotherapy planning of prostate cancer [2]. However, the image registration introduces an additional error in delineating targets and organs at risk (OARs) due to the modified geometry by two different examinations at two different time points.

A workflow based only on MR images (MR-only workflow)[1] offers considerably improved soft tissue contrast for CTV definition and improved OAR delineation without

Case	Age [years]	Weight [kg]	Gleason score	iPSA [ng/ml]	TNM
1	76	92	3 + 3 = 6	10.25	cT2a cN0 M0
2	78	85	5 + 4 = 9	6.50	cT2a cN0 cM0
3	78	84	3 + 3 = 6	32.80	pT3b pN0 (0/18) R1 Pn1 cM0
4	82	95	4 + 5 = 9	88.61	cT2b-c cN0 cM0
5	58	–	4 + 4 = 8	5.70	cT2c cN0 cM0
6	79	82	4 + 5 = 9	12.70	cT2c cN0 cM0
7	75	87	4 + 3 = 7	9.53	cT2c cN0 cM0
8	77	86	3 + 3 = 6	7.80	cT2b cN0 cM0
9	80	72	4 + 3 = 7	42.00	cT2c cN0 M1
10	68	83	3 + 4 = 7	9.45	pT1b pN0 cM0
11	72	84	5 + 4 = 9	11.00	cT2c cN0 cM0 Pn1
12	67	80	3 + 4 = 7	–	cT1c
13	71	72	3 + 4 = 7	101.00	pT3a pN0 (0/6) cM0 L0 V0 pM1 R1
14	74	85	4 + 5 = 9	6.58	cT2 cN0 cM0 pn1, G3
15	67	115	4 + 3 = 7	8.00	pT3b pN0 (0/5) L0 V0 Pn1 R1

Table 1: Clinical profile and tumor stages of the patients included in the implementation phase. Patients 6, 11, and 14 received radiation therapy to their lymph nodes.

registration errors. The acquisition and maintenance price is higher than that of CT imaging, but it can be considerably reduced by shared-use models including diagnostic radiology departments, so diagnostic images and MR-only sequences can be acquired in one session.

Optimizing the dose distribution requires electron density (or mass density), which is not provided by MR images. Moreover, modern image-guided radiotherapy (IGRT) linear accelerators need CT images as a reference to compare cone beam CT (CBCT) images with planning CT images for patient position correction before each treatment session. For these reasons synthetic CTs (sCT) have been introduced into clinical routine. Tissue classification methods as well as atlas-based and machine learning algorithms are used to generate sCT datasets from MR sequences. These algorithms have moved in recent years from research to the clinical world (so far for brain and pelvis cases). Commercially available solutions use somewhat different methods to generate the sCT images, and come with different business models. Spectronic offers a cloud-based pay-per-use approach, whereas Siemens Healthineers offers a classic software license model.

The main objective of our analysis was clinical implementation of the MR-only workflow in a novel ring-gantry linear accelerator system (Halcyon; Varian, Palo Alto, CA, USA) with daily CBCT based IGRT. We discuss in particular how daily CBCT guided IGRT based on sCT images compares with the traditional approach using a planning CT (pCT) image as reference. Detailed dose calculations are part of the comparison and complete the discussion.

Materials and methods

The implementation phase of MR-only radiotherapy took place from May to August 2019. It included all prostate patients without contraindications (such as pacemakers, extensive endoprosthesis, claustrophobia). During the consent discussion, patients were required to follow an empty rectum protocol before each imaging and treatment session. For radiotherapy planning, patients received first a planning CT scan with virtual simulation, and immediately afterwards (within a maximum of 30 minutes) an MRI scan in identical position.

1. Patient collective

In total 15 patients with different tumor stages were included in this study: 11 patients with localized tumors (T1–2, N0, M0), three patients with locally advanced tumors (T3a–T3b, N0, M0) and one patient with metastasis to the sacrum. Twelve of the patients included in this study

received radiotherapy as primary therapy, and the other three received postoperative radiotherapy. Because of their PSA values and Gleason scores, three of the patients also had radiation therapy to their lymph nodes (Table 1).

2. CT/MRT virtual simulation

For pCT imaging, the SOMATOM Definition AS (Siemens Healthcare, Forchheim, Germany) with a slice thickness of 2 mm, 120 kV and iterative image reconstruction was used.

As MRI simulator, the 1.5T MAGNETOM Aera (Siemens Healthcare, Erlangen, Germany) installed in our clinic. Images are reconstructed with 2.5 mm slice thickness was used. Table 2 shows the acquired sequences.

For simulation purposes, patients must be scanned in the same position as on the treatment couch of the linear accelerator. So in the MRI scanner patients were positioned on a flat tabletop overlay using a knee immobilization device, reproducing the positioning setup during pCT imaging and during the treatment with the Halcyon system.

Figure 1 shows the body coil (Body 18 long MR coil 1.5T) fixed in place with a coil positioning aid (INSIGHT Body Coil Holder; Qfix, Avondale, PA, USA).

In addition to the diagnostic images (sequences listed in Table 2), the T1- and T2-sequences, together with the generated sCT are imported into the oncology information system (OIS) ARIA (Varian, Palo Alto, CA, USA). Contouring of the target volumes is performed on the images obtained from these sequences, using the diagnostic findings recorded in ARIA as support. The workflow is integrated into the ARIA CarePath.

Step	Sequence	Time in min
Orientation	localizer bh	00:17
	localizer @center	00:17
Overview	t2 tse sag 3.5 mm	04:30
	t2 haste cor mbh	00:49
Diffusion	ep2d diff b50 800 1400 tra 3 mm	04:36
sCT Spectronic	t2 tse tra p2 2.5 mm	13:35
sCT Siemens	t1 sCTp1-Dixon	02:32
Perfusion with KM	t1 vibe tra dyn 4 mm	02:05
	t1 fl2d fs tra mbh	01:20
Total		30:17

Table 2: Description of sequences used.

3. Generation of sCT

3.1 Pay-per-use model (Spectronic)
Spectronic (Helsingborg, Sweden) uses an atlas-based algorithm for sCT image generation, offered as a cloud-based service[2]. Anonymized MRI datasets are transferred from PACS or directly from the MRI scanner to the cloud using a DICOM-receiver installed at the clinic network. After being de-anonymized in the DICOM-receiver the generated sCTs are transferred to PACS. Customers are informed by E-mail that new data are available. The sCT images are generated using a statistical decomposition algorithm (SDA) [3]. The atlas-based method is combined with machine learning. The algorithm calculates the most probable CT representation for an MRI image set, according to previously acquired datasets. So it is important always to follow the same protocol and use the same scan parameters when scanning patients, to obtain the same contrast as in the training datasets.

3.2 License-based model (Siemens Healthineers)
Siemens Healthineers combines a tissue classification and an atlas-based method to generate the sCT image. From the required T1 VIBE Dixon sequence, four MR datasets with different weighting in water, fat, in-phase and opposed-phase were obtained. The four sets or image sets are used by the *syngo*.via RT Image Suite to generate an sCT dataset in a few minutes (Fig. 2). Bones are rendered in the sCT image set using a multi atlas-based algorithm, so the three lowest lumbar vertebrae must be scanned during the sequence acquisition.

4. Treatment planning

A VMAT treatment plan was optimized using a Halcyon system (V2.0) with 6 MV flattening filter-free beam and Eclipse V15.6. Later, the sCT image and pCT image are registered rigidly and the structures and beam configurations are transferred to the sCT image. On the sCT image, the treatment plan is re-calculated, without new optimization.
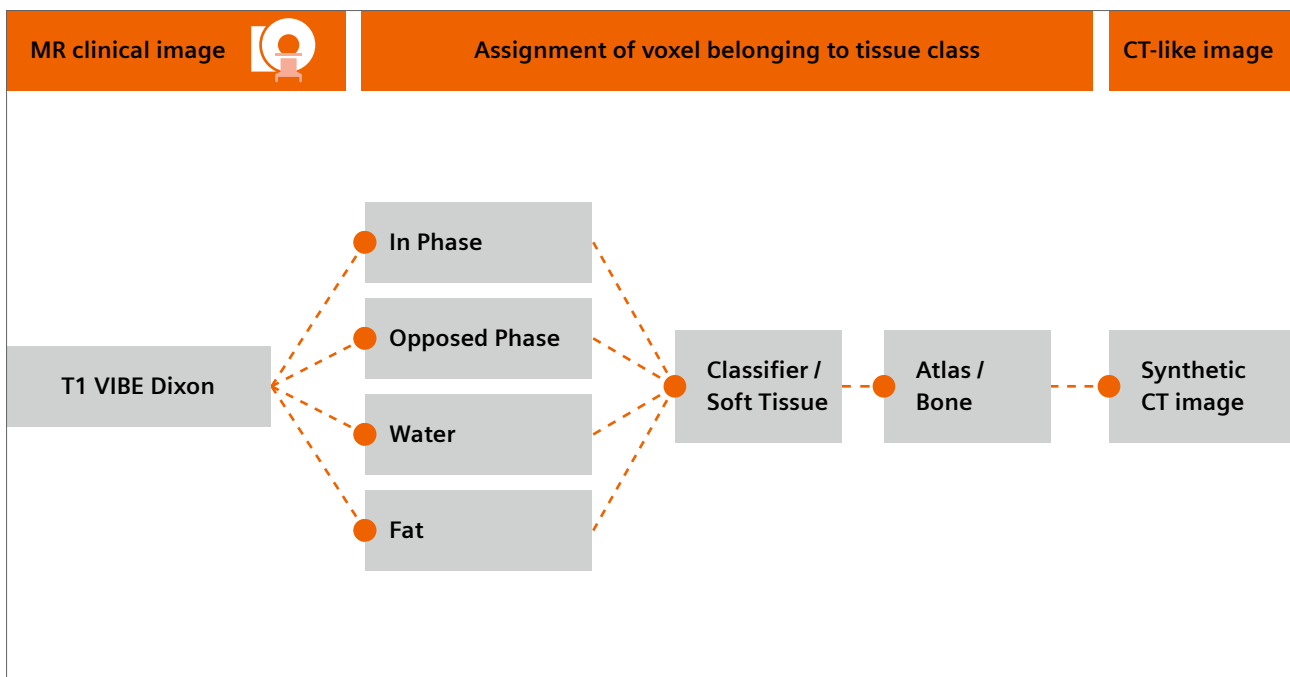
5. Treatment and image guided radiotherapy

5.1 Halcyon with iCBCT (online matching)
For IGRT, the Halcyon linear accelerator uses daily CBCT with iterative image reconstruction (iCBCT) and slice thickness of 2 mm. A treatment session without imaging before dose application is not possible with this system.

1 Patient positioning in an MRI device using MRI compatible positioning aids: flat table top with knee immobilization device to reproduce the patient positioning from the simulation to the treatment, in this case using the Halcyon.

---

[2]*The information shown herein refers to products of a 3rd party, which are their regulatory responsibility. Please contact the 3rd party for further information.*

MR clinical image	Assignment of voxel belonging to tissue class	CT-like image

T1 VIBE Dixon → In Phase, Opposed Phase, Water, Fat → Classifier / Soft Tissue → Atlas / Bone → Synthetic CT image

2 The synthetic CT algorithm for the pelvis, from image acquisition to synthetic CT image generation.

3 Patient positioning on the Halcyon.

5.2 Offline matching

In the implementation phase, each CBCT image is registered offline with the pCT and sCT images (Siemens and Spectronic). Registration is based on intensity differences and a pixel-based similarity optimization. For this auto-registration, a region including the PTV and a margin of 2 cm was selected (Fig. 4). To calculate translations in x-, y- and z-directions, the following equation was used:

$$\Delta \vec{V} = \Delta \vec{V}_{CBCT/pCT} - (\Delta \vec{V}_{CBCT/sCT} + \Delta \vec{V}_{pCT/sCT})$$

where the term $\Delta \vec{V}_{pCT/sCT}$ expresses the intrinsic offset between pCT and sCT images.

In order to perform this analysis analog to the clinical work, image registration was limited to translations, so rotation, pitch, and roll were not considered.

6. Quality assurance

Currently there is no official guideline for quality assurance (QA) for MRI systems used for radiotherapy planning. To measure geometric distortions in MRI, the GRADE Phantom (Spectronic) was used. As result of the analysis, a PDF is generated with a 3D overview of the distortion in a clinically relevant scan volume (Fig. 5).
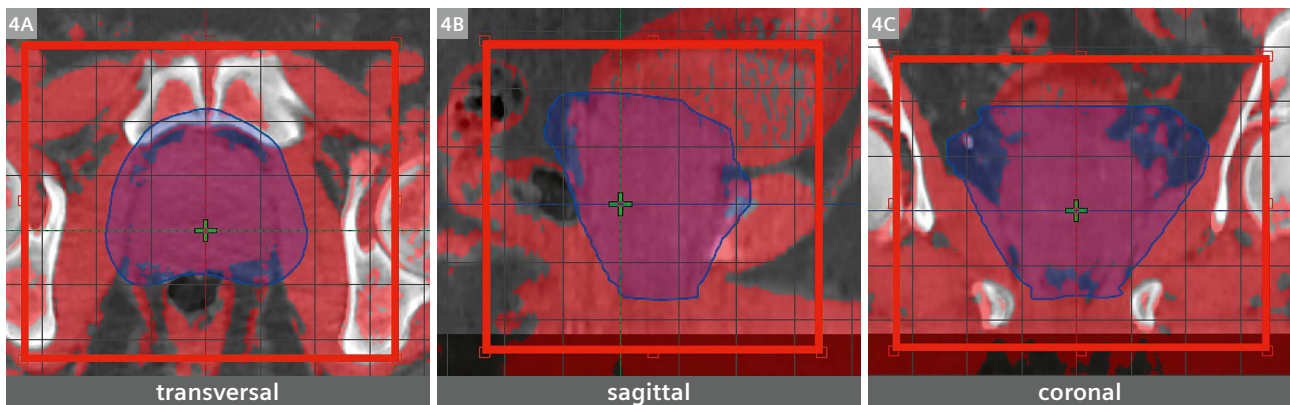
4 Example of image registration between CBCT images and CT images using soft tissue. The contoured PTV is in blue and the soft tissue used for the auto-registration algorithm is in red. The red line defines the volume of interest (VOI) used for the registration.
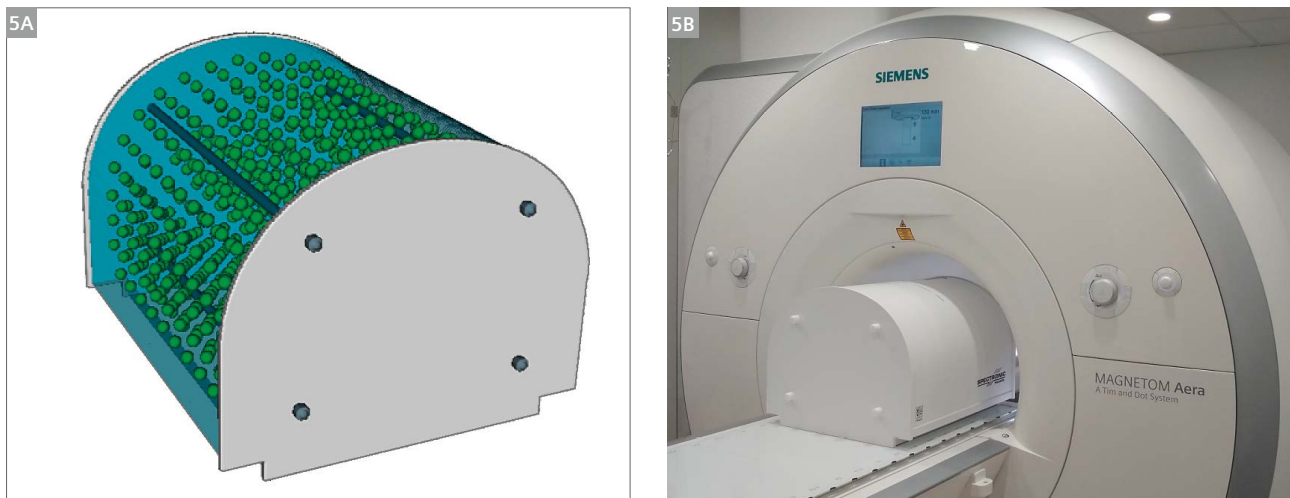
5 GRADE phantom from Spectronic, used to measure geometrical distortion. **(5A)** Image of the phantom. **(5B)** Phantom on the scanner allowing the measurement of geometric distortion in the entire scan field.
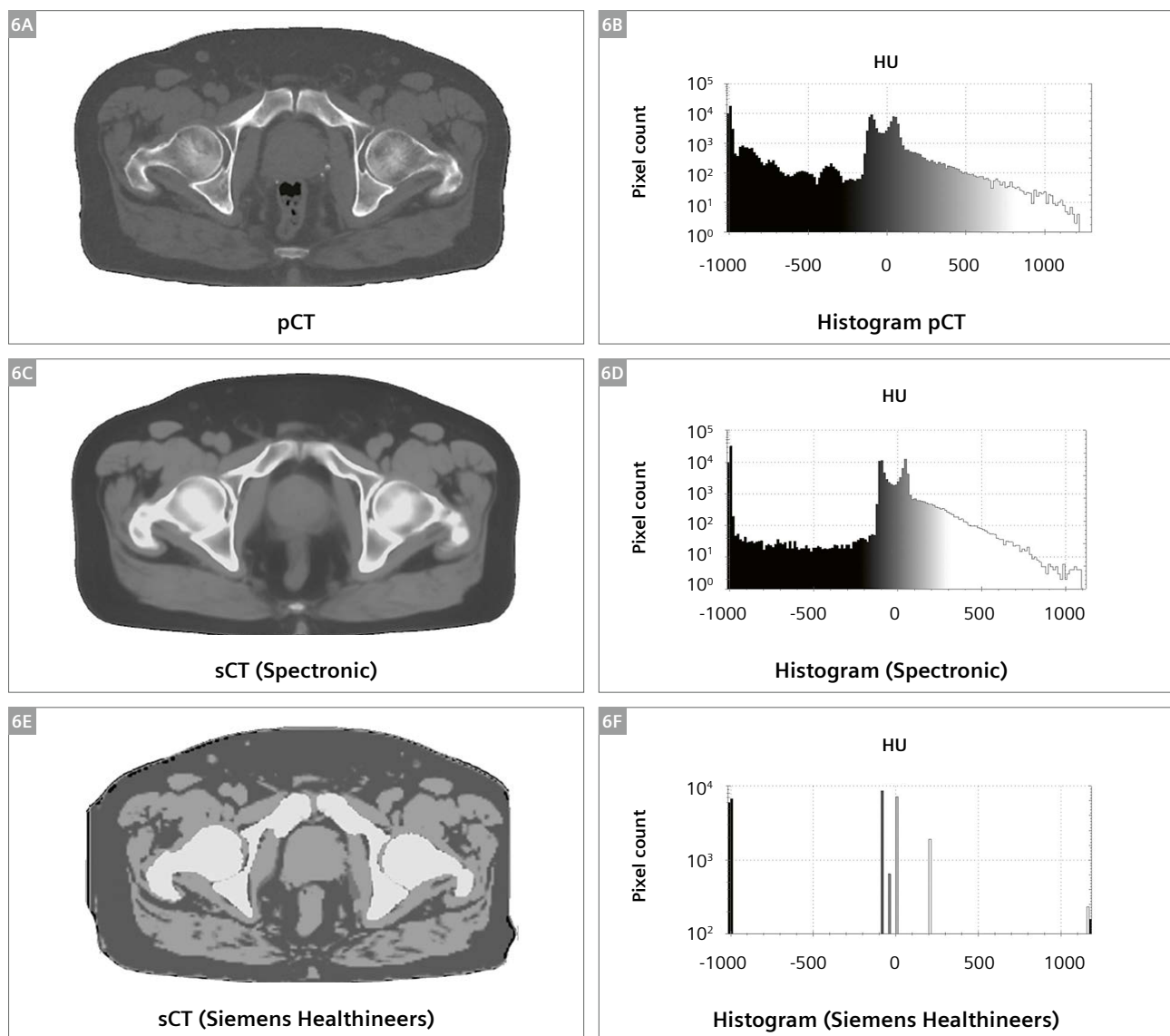
Results

Figure 6 shows an example of the results from the different sCT generation methods. The solution from Spectronic with its continuous Hounsfield units (HU) distribution is similar to a planning CT image whereas the Siemens solution uses a discrete HU distribution: Air (-1000 HU), fat (-75 HU), water (0 HU), spongy bone (204 HU) and cortical bone (1170 HU) (Fig. 6). The soft tissue of bladder, rectum and prostate is assigned 0 HU, like water. The sCT images from Spectronic use different HU values for different soft tissues, in analogy to pCT images.

Dose distributions

Different therapy concepts regarding the total dose were used during this study. For comparison reasons, the calculated plans were all normalized to the mean PTV dose and only relative dose deviations were considered.

In Figure 7, mean dose differences of the 15 patients are represented using a boxplot diagram, showing the results for the following OARs: rectum, bladder, and right- and left femoral head. The plot gives the difference between the calculated dose based on the sCT (Spectronic) and pCT (left box); and between the calculated dose based on the sCT (Siemens) and pCT (right box). The total mean difference is below 2%.

pCT

Histogram pCT

sCT (Spectronic)

Histogram (Spectronic)

sCT (Siemens Healthineers)

Histogram (Siemens Healthineers)

6 Examples of pCT (6A), sCT (Spectronic: 6C) and sCT (Siemens: 6E) representation including HU surface histogram (pCT: 6B; Spectronic: 6D; Siemens: 6F) of the shown cross-sectional images. The HU histograms of the pCT and the sCT (Spectronic) have a continuous spectrum from -1000 to 1210 HU and -1000 to 1071 HU, respectively. The HU histogram of the sCT (Siemens) has discrete values.

Offline matching

For both manufacturers, we evaluated translations after offline IGRT between CBCT/pCT and CBCT/sCT of 15 patients with a total of 513 CBCTs. In Figure 8, each point represents the deviation in one-dimensional direction from the registration (PTV + 2 cm, see Figure 4) between the CBCT and the respective pCT (vertical axis) and between CBCT and the respective sCT (horizontal axis). Considering all one-dimensional directions as independent parameters the correlation between sCT (Spectronic) and pCT images has a coefficient of determination of $R^2 = 0.895$. The correlation between sCT (Siemens) and pCT has a coefficient of determination of $R^2 = 0.851$. In the lateral (x) direction both sCT solutions show best correlations to CBCT compared to the CT (considered the gold standard).

For Spectronic, the worst correlation is in the z-direction whereas with the Siemens solution the lowest correlation is in the y-direction. Analyzing the registrations between CBCT and pCT images, 94% of the one-dimensional translations in the three directions are smaller than 10 mm. For registrations between sCT (Spectronic) and sCT (Siemens) respectively with CBCT images, 95% of the translations are smaller than 10 mm. The maximum difference between CBCT and pCT is 1.9 ± 5.2 mm in longitudinal direction (z), between CBCT and sCT (Spectronic) −2.5 ± 5.6 mm in vertical direction (y) and between CBCT and sCT (Siemens) 1.2 ± 5.5 mm in longitudinal direction.

The calculated translations between pCT and sCT differ significantly ($p < 0.001$) in all spatial directions, but they do not exceed 1 mm on average (Figure 9).
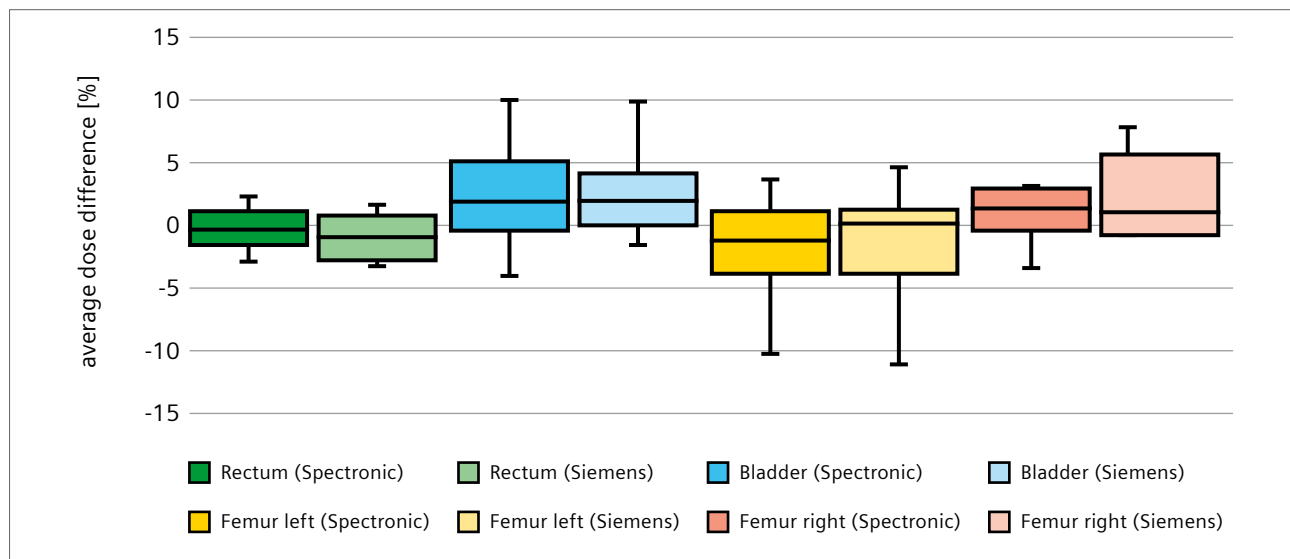
7 Boxplots of the mean dose difference of considered OARs. Representation of the dose differences to pCT, each in comparison to sCT.
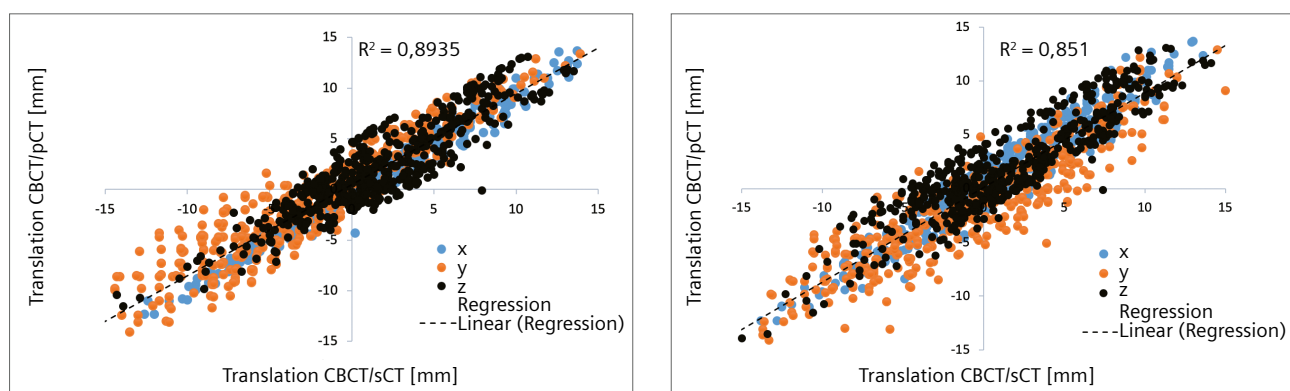
8 Scatterplot showing the translations from CBCT to pCT and from CBCT to sCT, for Spectronic (left) and Siemens (right) (n = 513 CBCTs). Estimations of the coefficient of determination considering all directions as independent values. Each direction is represented by a different color: blue = x, lateral; orange = y, vertical; black = z, longitudinal.

Discussion

In order to integrate the MR-only workflow into our clinical routine we had to develop a new CarePath (ARIA, Varian). For this, the existing workflow has been extended by adding the MRI simulation, including the sCT generation, as new task. This modified workflow comprises the pCT scan acquisition, followed by MRI acquisition when the MRI scanner was available. Afterwards, the standard clinical workflow was carried out. During the validation phase of this study, pCT images were used as basis for

contouring, dose calculation, and IGRT. In the analysis, the results from sCT are compared with pCT as a reference.

The MR-only workflow eliminates the error introduced in the standard MR/CT workflow when doing image registration. Patient positioning during CT and MRI acquisition may be different. Moreover, scans are taken at different times, which can produce different internal geometry (for example bladder filling).

The standard simulation timeslot required for MR only is 45 minutes, independent of the chosen solution for sCT generation. The sequences required for sCT generation and
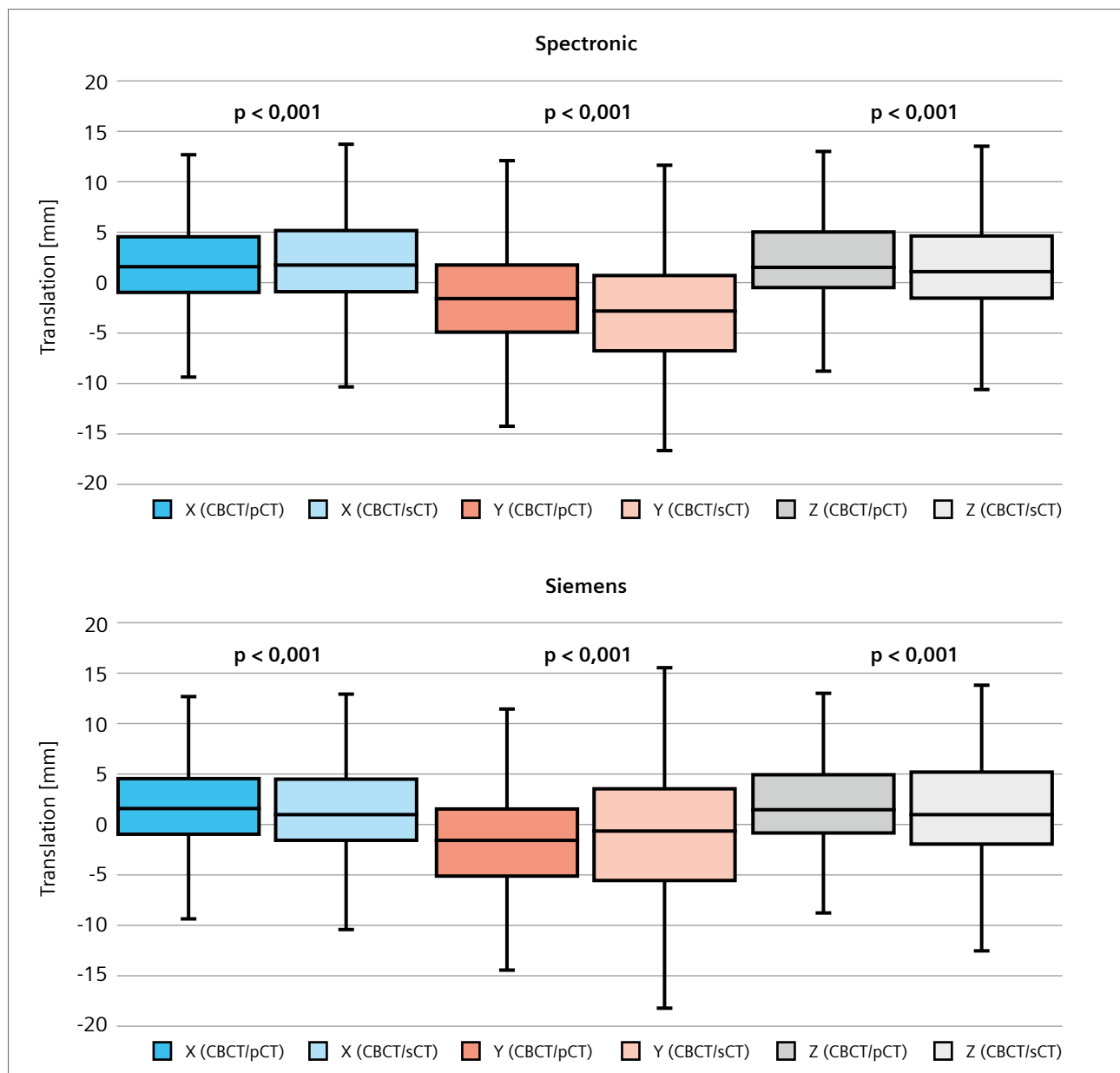
9 Boxplots of the translations of the CBCT registration to pCT, sCT (Spectronic) and sCT (Siemens).
blue = x-direction, orange = y-direction, grey = z-direction.

also the diagnostic images for staging are taken at this time. If diagnostic images are already available, the timeslot is shortened to 20 minutes to acquire T2- and T1-Dixon sequences for contouring, and generate sCT images. The advantage of the quick T1-Dixon sequence from the Siemens solution is reduced when considering that a T2 sequence is normally needed for contouring. However, an important advantage of the quick acquisition is that motion artifacts are less prominent compared with those from a long sequence acquisition for sCT generation.

All 15 patients included in the implementation phase received a daily image-guided radiotherapy treatment in the prostate region at the Halcyon linear accelerator. A total of 513 CBCT images were compared with pCT and sCT images to calculate the translation. The values were significantly different when comparing the results from pCT (reference) images to the results from sCT images. The correlations ($R^2 = 0.85–0.89$) from CBCT/pCT and CBCT/sCT images demonstrate the difficulty when comparing the translation values from pCT and sCT images because of changes in geometry between pCT and MRI (sCT) scans taken at different times. The mean differences are smaller than 1.1 mm, and therefore not clinically relevant for daily IGRT on the Halcyon. They are, moreover, in accordance with already published studies [4].

IGRT based on sCT can therefore be performed on the Halcyon-System and allows the replacement of the conventional workflow using pCT as reference imaging for online matching. For the considered OARs the dose calculations based on sCT image sets from Siemens and Spectronic show small mean differences and dose distributions.

The GRADE Phantom, adapted to MRI, allows to scan a large field of view, comparable to the field of view used for a pelvis patient. The mean distortion value measured in a clinically relevant field of view (150–200 mm from magnet isocenter) is 0.76 mm.

Conclusion

The MR-only workflow with the 1.5T MAGNETOM Aera has been successfully implemented. High contrast images for prostate contouring, and the immediate availability of the radiological report integrated in the ARIA OIS are helpful features that will lighten the daily workload in a busy clinical environment. The daily IGRT using the sCT image generated with the solution either from Siemens or Spectronic as reference CT can be performed on the Halcyon-system and allows the replacement of the conventional workflow using a pCT. The "pay-per-use"-model offered by Spectronic allows costs to be assigned to patients. The advantage of a license-based model as offered by Siemens is the unlimited and real-time availability of sCT.

References

1   Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany, editors. Cancer in Germany for 2015/2016, 12th edition. Berlin, 2019.
2   Nyholm T, Nyberg M, Karlsson MG, Karlsson M. Systematisation of spatial uncertainties for comparison between a MR and a CT-based radiotherapy workflow for prostate treatments. Radiat Oncol. 2009; 4(1): 54. doi:10.1186/1748-717X-4-54.
3   Siversson C, Nordström F, Nilsson T, Nyholm T, Jonsson J, Gunnlaugsson A, Olsson LE. MRI only prostate radiotherapy planning using the statistical decomposition algorithm. Med. Phys. 2015; 42(10): 6090-6097. doi:10.1118/1.4931417.
4   Chen S, Quan H, Qin A, Yee S, Yan D. MR image-based synthetic CT for IMRT prostate treatment planning and CBCT image-guided localization. J Appl Clin Med Phys. 2016; 17(3): 236–245. doi:10.1120/jacmp. v17i3.6065.

Contact

Mandy Zimmermann M.Sc.
Medical Physics
Radiologische Allianz Hamburg
Mörkenstraße 47
22767 Hamburg
Germany
Tel.: +49 (40) 325552-598
mandy.zimmermann@radiologische-allianz.de

Left to right: M.Sc. Marcello Sabatino, Dr. Matthias Kretschmer, M.Sc. Mandy Zimmermann, Dr. Christian Giro