A new strategy for online adaptive prostate radiotherapy based on cone-beam CT

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Received 11 February 2009; accepted 28 May 2009

Abstract

Purpose: *Interfractional organ motion and patient positioning errors during prostate radiotherapy can have deleterious clinical consequences. It has become clinical practice to re-position the patient with image-guided translational position correction before each treatment to compensate for those errors. However, tilt errors can only be corrected with table corrections in six degrees of freedom or ''full'' adaptive treatment planning strategies. Organ shape deformations can only be corrected by ''full'' plan adaptation. This study evaluates the potential of instant treatment plan adaptation (fast isodose line adaptation with real-time dose manipulating tools) based on cone-beam CT (CBCT) to further improve treatment quality.*

Methods and Materials: *Using in-house software, CBCTs were modified to approximate a correct density calibration. To evaluate the dosimetric accuracy, dose distributions based on CBCTs were compared with dose distributions calculated on conventional planning CTs (PCT) for four datasets (one inhomogeneous phantom, three patient datasets).*

To determine the potential dosimetric benefit of a ''full'' plan adaptation over translational position correction, dose distributions were re-optimized using graphical ''online'' dose modification tools for three additional patients' CT-datasets with a substantially distended rectum while the original plans have been created with an empty rectum (single treatment fraction estimates).

Eine neue Strategie zur "Online"-adaptiven Strahlentherapie beim Prostatakarzinom basierend auf "cone-beam-CT"

Zusammenfassung

Einleitung: *Interfraktionäre Organbewegungen und Patientenpositionierungsfehler während der Strahlentherapie des Prostatakarzinoms können sich negativ auf die Behandlungsqualität auswirken. Eine Patientenrepositionierung vor jeder Behandlung auf der Basis einer bildgestützten linearen Translationskorrektur des Isozentrums zur Kompensation dieser Fehler hat Einzug in die klinische Routine gehalten. Rotationsfehler können jedoch nur mit Tischbewegungen in sechs Freiheitsgraden oder adaptiven Bestrahlungstechniken korrigiert werden. Organdeformationen lassen sich jedoch nur durch eine Anpassung des Bestrahlungsplanes ausgleichen. In dieser Arbeit wurde das Potential einer unmittelbaren Bestrahlungsplan-Adaption (schnelle Isodosenanpassung mit „Echtzeit"-Dosis-Manipulationswerkzeugen) basierend auf ''cone-beam CT'' (CBCT) untersucht, um die Behandlungsqualität noch weiter zu verbessern.*

Material und Methoden: *Mit Hilfe von Softwareeigenentwicklungen wurden die CBCT-Datensätze modifiziert, um eine korrekte Dichtekalibrierung zu erhalten. Zur Bestimmung der dosimetrischen Genauigkeit wurden die berechneten Dosisverteilungen auf Basis von*

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Results: *Absolute dose deviations of up to 51% in comparison to the PCT were observed when uncorrected CBCTs were used for replanning. After density calibration of the CBCTs, 97% of the dose deviations were ⩽3% (gamma index: 3%/3 mm).*
Translational position correction restored the PTV dose (D_{95}) to 73% of the corresponding dose of the reference plan. After plan adaptation, larger improvements of dose restoration to 95% were observed. Additionally, the rectal dose (D_{30}) was further decreased by 42 percentage points (mean of three patient datasets).

Conclusions: *An accurate dose calculation based on CBCT-datasets is possible when density distributions are corrected. The presented adaptive strategy has the potential to reduce dose delivery errors due to organ deformations to a minimum.*

Keywords: Image guided radiotherapy, adaptive radiotherapy, cone-beam CT, prostate radiotherapy

CBCT mit Dosisverteilungen basierend auf einem konventionellen Planungs-CT von vier Datensätzen miteinander verglichen (ein inhomogenes Beckenphantom, drei Patientendatensätze).
Zur Abschätzung der dosimetrischen Überlegenheit eines „voll" adaptierten Bestrahlungsplanes gegenüber einer translatorischen Positionskorrektur wurden die Dosisverteilungen mit Hilfe von grafischen "online"-Dosismodifikationswerkzeugen bei drei weiteren Patienten-CT-Datensätzen mit übermäßig erweitertem Rektum re-optimiert, während der Originalplan mit leerem Rektum erstellt wurde (Abschätzungen für Einzelfraktionen).

Ergebnisse: *Wenn unkorrigierte CBCTs zur Re-Planung verwendet wurden, konnten absolute Dosisabweichungen bis zu 51% im Vergleich zum Planungs-CT beobachtet werden. Nach einer Kalibrierung der CBCTs waren 97% der Dosisabweichungen ⩽3% (Gammaindex: 3%/3 mm).*
Eine Translationskorrektur des Isozentrums führte zu einer Wiederherstellung der PTV-Dosis (D_{95}) auf 73% der korrespondierenden Dosis im Referenzplan. Die Planadaption führte zu einer weitaus besseren Wiederherstellung der Dosis auf 95% der Ausgangsdosis. Zusätzlich verringerte sich die Rektumdosis um 42 Prozentpunkte (Mittelwert aus drei Patientendatensätzen).

Schlussfolgerung: *Eine genaue Dosisberechnung auf der Basis von CBCT-Datensätzen ist möglich, wenn die Dichteverteilungen korrigiert werden. Die hier vorgestellte adaptive Strategie hat das Potential, Dosisapplikationsfehler aufgrund von Organdeformationen auf ein Minimum zu reduzieren.*

Schlüsselwörter: Bildgestützte Strahlentherapie, adaptive Strahlentherapie, cone-beam CT, Prostatastrahlentherapie

Introduction

The traditional practice of using the same treatment plan for the entire radiotherapy course can lead to clinically relevant deficiencies. Inter- and intrafractional organ movements or positioning errors can cause substantial dose deviations in the patient [1]. Recently, several advances in radiotherapy improved the accuracy of dose delivery by incorporating patient image feedback obtained during the course of treatment. One such new paradigm is image-guided radiation therapy (IGRT), especially kilovoltage cone-beam computed tomography (kV-CBCT) [2]. With this new technology it is possible to acquire 3D X-ray volumetric images with soft-tissue definition of patients at the time of treatment. In current clinical practice, the treatment plan is generated on planning CT (PCT) images [3]. However, the tumour geometry and location acquired from these images at a single time point may not represent the actual situation during the whole treatment. The variability of prostate position has been assessed using periodic computed tomography (CT) scans during the treatment course [4]. Determining prostate position before and possibly during each treatment fraction is critical to exploit the full potential of intensity modulated radiotherapy (IMRT) and a reduction of safety margins [5]. If the prostate or the organs at risk (OAR) are not in the correct position during treatment, the dose distribution will be different from the treatment plan. This can result in a loss of tumour control probability by several percent despite generous margins

[6] and may be even more when margins are reduced. Today IGRT allows the detection of changes in organ position or shape and enables an image-guided translational and maybe also limited rotational position correction to improve the accuracy of dose delivery [7–9]. But there are instances, when substantial weight loss, shrinkage or non-linear deformation of tumour and healthy tissues are observed during radiotherapy. Developing a second modified radiation treatment plan on the basis of new anatomic information may then be better than mere translational position correction only. This practice is generally known as "adaptive radiation therapy" (ART) [10]. The prerequisites for this approach are daily imaging providing a basis for replanning and interfractional setup error correction, reliable Hounsfield units for accurate dose calculations and a fast plan adaptation. So far the quality of CBCT imaging is still not comparable with the quality of a conventional PCT. Artefacts (e.g. ring, streak and cupping) and increased scatter contribution to the CBCT image obviate obtaining reliable density distributions (Hounsfield units [HU]) of the patient, which is essential for replanning [11,12].

The purpose of this study is to propose and evaluate an integrated workflow for prostate ART. It presents a proof of principle for a new method to modify the kV-CBCT images for dosimetric calculations and replanning with a special emphasis on clinical evaluation of a commercially available real-time dose manipulating tool for a fast "online" re-optimization process.

Methods and Materials

Workflow for plan adaptation

The PCTs for the *reference plans* were acquired with a Brilliance Big Bore CT-scanner (Philips, Hamburg, Germany). The IMRT treatment plans were created with the Corvus 6.2 treatment planning system (TPS) (NOMOS, Cranberry Township, PA, USA). The dose distributions were calculated using the finite size pencil beams algorithm available in the TPS. The Synergy®/XVI® system (Elekta, Crawley, United Kingdom) was used to acquire pre-treatment CBCT-datasets (Elekta standard preset: "pelvis", M20 filter, 360° scan, 120 kV). The lack of true HU information in the CBCT images and artefacts often obviates their suitability for planning. Therefore the CBCT-datasets had to be modified before planning becomes possible.

In this study, we have proposed a strategy (shown in Fig. 1) to adapt the treatment plan to the changing anatomy of the patient before each treatment. After acquiring the kV-CBCT images, the workflow involves contouring of the external surface of the patient's body, PTV and OARs in the Corvus TPS. With the help of an in-house software, the CBCTs were modified with a multilevel-threshold algorithm to approximate the correct electron density/HU conversion. The initial patient treatment plan was copied to the *modified* CBCT images (*m*CBCT). Copying a plan means transferring the initial patient plan from the PCT to the CBCT preserving the same number of monitor units and beam geometry. The Active-Rx™ module (research version of the Corvus TPS), a tool that enables manual intuitive isodose shaping, can be used on the existing plan (*m*CBCT) for conforming the dose to the tumour with tight margins. Finally the adapted treatment plan is exported from the TPS to the treatment machine for irradiating the patient. Thus, a 'plan of the day' for patient specific variation is possible for a particular treatment fraction.

Modification of CBCT-datasets

The main idea of our strategy was to segment different homogeneous structures in the CBCT images and assign reasonable averaged HU to them which were derived from the PCT. For segmentation a multi-level-threshold algorithm was written in Mathematica 5.2 (Wolfram Research Inc. Champaign, IL, USA). It is a pixel-based method which classifies all CBCT pixels with similar HUs into three different segments due to the introduction of predefined HU ranges. Each segment is automatically homogeneous in the sense that all of its pixels have the same HU. This algorithm splits the image 'R' into disjoint segments R_i, i.e., $R = \cup_{i=1}^{x} R_i, R_i \cap R_j = \emptyset,\ i \neq j$. These regions R_i could be either air/gas inside the patient (e.g.

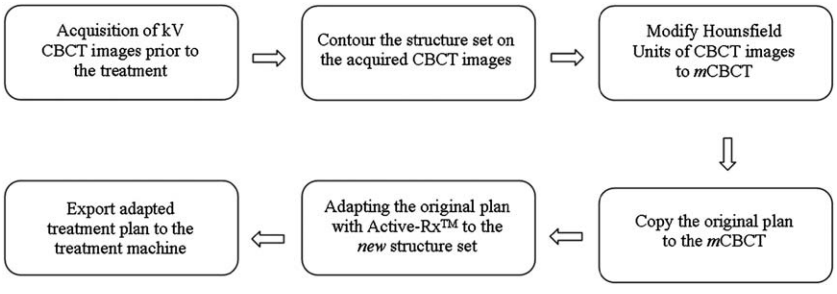

Figure 1. Workflow of the proposed ART.

in the rectum), bone or soft-tissue and are characterized by their individual HU interval. The HUs $g(x,y)$ of the resulting *m*CBCT image were generated according to the following equation:

$$g(x,y) = \begin{cases} A_{PCT} & if \quad T_{Gas\_\min} \leqslant f(x,y) \leqslant T_{Gas\_\max} \\ B_{PCT} & if \quad T_{Bone\_\min} \leqslant f(x,y) \leqslant T_{Bone\_\max} \\ ST_{PCT} & if \quad T_{Gas\_\max} < f(x,y) \; T_{Bone\_\min} \end{cases}, \tag{1}$$

A_{PCT}, B_{PCT}, and ST_{PCT} are the averaged HU of *air/gas, bone* and *soft tissue* in the PCT

T_{Gas_min}, T_{Gas_max}, T_{Bone_min} and T_{Bone_max} are the threshold value to separate *air/gas, bone* and *soft tissue* in the CBCT

$f(x,y)$ is the unmodified CBCT image.

$g(x,y)$ is the modified CBCT image.

The threshold values ($T_{min/max}$) of these intervals were chosen according to the underlying image histogram. The threshold values in the patients CBCT-datasets for each segment were: air/gas (−500 to 75) HU, soft tissue (76 to 561) HU and bone (562 to 1080) HU. After assigning fixed HU to these structures, the modified images (*m*CBCTs) contained the following values: air/gas −1006 HU, tissue −4 HU and bone 776 HU [13].

In total, this manuscript includes five CBCT image datasets. Four (one inhomogenous pelvis phantom and three patient datasets) were used exclusively for testing the accuracy of the proposed algorithm for modifying the HUs. The remaining one CBCT-dataset was used as an example for ActiveRx study where the isodose lines were adapted to the deformed anatomy.

Evaluation of accuracy of dose calculations based on CBCT/*m*CBCT

To analyze the reliability of the density/HU distribution of the CBCT, we compared it with the HU distribution of the PCT. Therefore a calibration phantom (CIRS, Norfolk, VA, USA) with five different tissue equivalent rods of known electron densities was used. Two sets of images of this phantom were acquired, one in PCT and the other in CBCT. The HU of the five tissue inserts were measured and the two HU-electron density calibration curves of PCT and CBCT were compared.

To evaluate the dose calculation accuracy achieved with CBCT in combination with the multi-level-threshold algorithm (*m*CBCT), several treatment plans and dose distributions were calculated for an inhomogeneous pelvis phantom and also for three prostate cancer patient datasets (these were used as an example for less homogeneous distributions of HUs) and compared with the dose calculation based on PCT.

Inhomogeneous pelvis phantom datasets

Images of an inhomogeneous pelvis phantom were acquired from both PCT and CBCT. Using the threshold algorithm, Voxel data values of a given tissue type in CBCT were replaced by the mean HUs of the same tissue type of PCT which lead to a *m*CBCT.

An IMRT prostate treatment plan (nine beams) was created on PCT and transferred (same monitor units (MUs) and beam geometry) to both the CBCT (unmodified) and the *m*CBCT (modified). The calculated dose distributions were evaluated and compared with OmniPro I'mRT® software (IBA Dosimetry/Scanditronics-Wellhoefer, Schwarzenbruck, Germany).

Patient datasets

Additionally, the dose distributions of three patient datasets (CBCT-1, CBCT-2 and CBCT-3) were compared in a similar manner. For two patient datasets (CBCT-1, CBCT-2) the anatomy and the outline was nearly identical on both datasets (PCT and CBCT). In the third dataset (CBCT-3) the outline and anatomy showed major differences.

To validate the dose calculations performed on CBCT/*m*CBCT a complete quantitative evaluation was performed in the region of interest (enclosing planning target volume (PTV) and OAR, excluding border areas). We analyzed gamma index distributions with general criteria of 3% in dose and 3 mm in distance to agreement as well as 5% and 5 mm in OmniPro I'mRT software.

Tools of Active-Rx™ Module

Active-Rx™ Module [14] contains a set of real time dose modification tools used for "fine tuning" an existing IMRT plan by improving the dose conformity to the organs of interest. The most common tools being used in our study were *"dose drag" (moving the isodose lines),* "*dose sculpting" (drawing/reshaping the isodose lines), and "hot/cold spot eraser" (removal of over/under dose areas).* The function of these tools is confined to 2-dimensional planes of the whole volume i.e. locally modifying the dose distribution on each CT slice. Apart from these there are various volumetric tools which shows effect on the whole plan. Usage of these tools will result in the re-weighting of the pencil beams in the fluence map. The re-optimization of pencil beam weights of Active-Rx™ tools employs a sophisticated dose-sampling algorithm which uses fewer dose-sampling points than the main dose calculation of the Corvus TPS.

Dosimetric influence of plan adaptation with Active-Rx^{TM}

It is our institutional policy to prepare the patients for the PCT with an enema to empty the rectum. A distended rectum during single treatment fractions can lead to an under-dosage of the tumour and an increased rectal dose if no position correction is performed before the treatment session [7,8]. Two patients (patient-A and patient-B) had a considerably distended rectum during an initial PCT in spite of the enema (Fig. 2(b), (c), (d), (f), (g), (h)). This PCT was not used for clinical treatment planning and afterwards a second PCT was acquired with an empty rectum (few or no faeces or gas) (Fig. 2(a), (e)). Additionally we selected a patient (patient-C) who had a distended rectum during CBCT acquisition (Fig. 2(j), (k), (l)). Thus patient-A and patient-B were scanned twice with PCT whereas patient-C was scanned with PCT at the time of treatment simulation and later with CBCT at the time of treatment delivery. The CBCT was modified according to the proposed method to validate for dose calculation, thus was implemented for plan adaptation purpose.

To evaluate the dosimetric effects of translational isocenter correction and "full" plan adaptation with Active-Rx^{TM} the dose distributions for the three patients were calculated and analyzed *with* and *without* distended rectum on image datasets acquired at different time points. The choice of these sample patients was made to assess and illustrate the potential of Active-Rx^{TM} to act over different shapes and sizes of PTV and OAR.

On each patient dataset four plans were created, namely:

(1) Reference Plans (original plan): They include plans generated on the images with *empty rectum* taken at time of PCT that were used for treating the patients (Fig. 2(a), (e), (i)). The reference IMRT plans were calculated with Corvus TPS. Prostate and seminal vesicles were chosen as clinical target volumes. To compensate for setup errors and organ motion, anisotropic safety margins (12 mm anterior, superior and lateral and about 8 mm posterior and inferior) around the prostate and seminal vesicles were chosen. The prescribed fractional dose for the PTV was 2 Gy. A beam energy of 6MV and nine non-opposing coplanar gantry angles were chosen. The plan was normalized to the median dose in the target volume.

(2) Uncorrected Plans: They comprise copies of the *reference plans* on the corresponding pre-treatment CT-dataset with *distended rectum* of each patient (second PCT

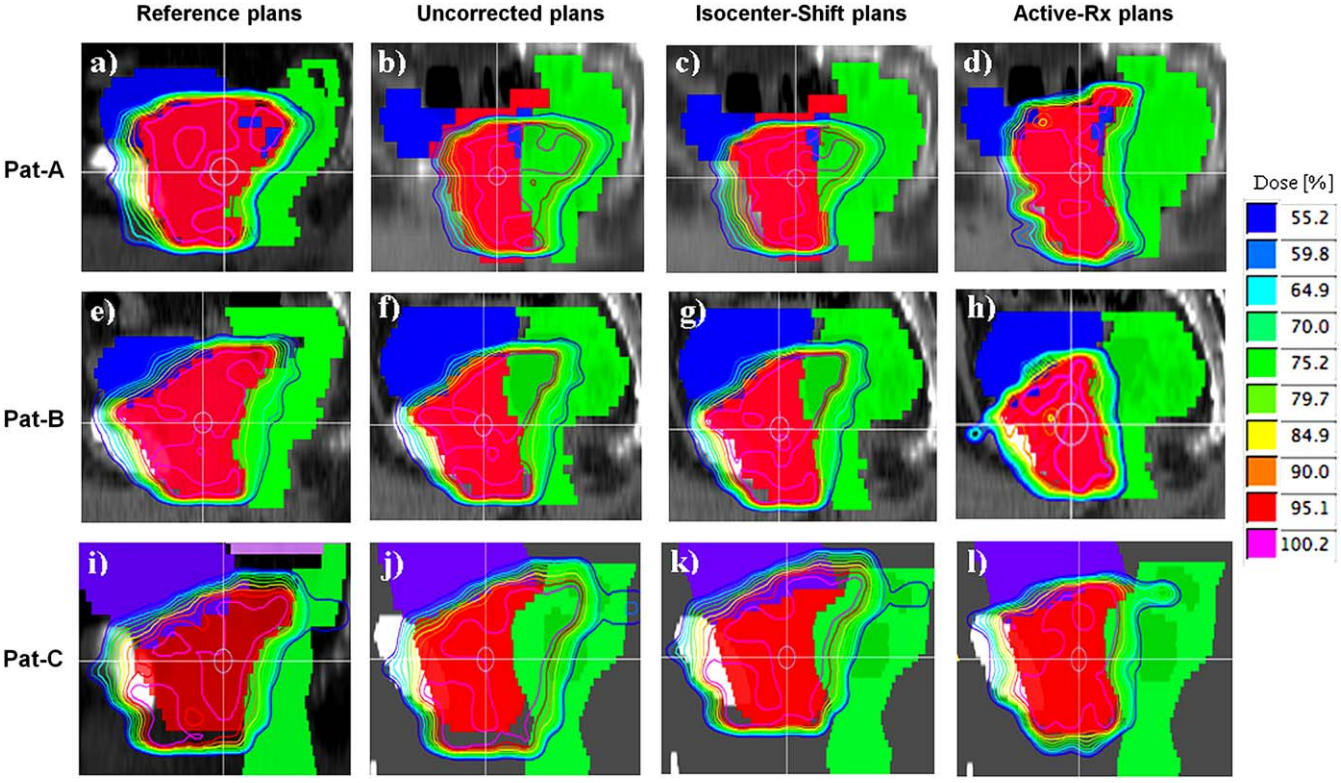

Figure 2. (a), (e), (i): *Reference plans* calculated on the CT with e*mpty rectum,* (b), (f), (j): dose distributions *without a position correction* (*uncorrected plans*) calculated on the CT with *distended rectum*, (c), (g), (k): dose distributions *with isocenter correction* (*Isocenter-Shift plans*) based on the CT with *distended rectum,* (d), (h), (l): dose distributions of *re-optimized plans* (*Active-Rx plans*) based on the CT with *distended rectum.* For patient-C the dose distributions in (j), (k) and (l) were calculated on a modified CBCT.

of patient-A, patient-B and *m*CBCT of patient-C) using the same treatment isocenter like in the *Reference plans* based exclusively on the bony landmarks (Fig. 2(b), (f), (j)).

(3) Isocenter-Shift Plans: In these plans, the treatment isocenter of the *uncorrected plans* was moved to a new location that would have resulted from a simulated translational isocenter correction based on image guidance techniques (ultrasound, CBCT, etc) (Fig. 2(c), (g), (k)). The *uncorrected & Isocenter-Shift Plans* have same MUs, segments, and beam geometry as the *Reference plans*.

(4) Active-Rx plans: They involve the treatment plans that were modified by applying Active-Rx^{TM} tools on the *Uncorrected plans*. In these plans, 'the treatment isocenter' remains the same but the MU and segments were altered (Fig. 2(d), (h), (l)).

The *Uncorrected plans, Isocenter-Shift Plans* and *Active-Rx plans* share the same image datasets for each individual patient.

Quantitative analysis

Comparison of the dose volume histograms (DVHs) between the *Reference plans* and the other plans was performed to quantify the deviations from the intended dose distribution. The criteria chosen for the comparison were PTV-D_{95} (dose delivered to at least 95% of the PTV), D_{30} & D_{60} (dose delivered to at least 30% & 60% of the rectal volume) and the mean dose to the bladder.

Table 1 gives an overview of the different patient datasets used in this manuscript for the analysis of dose calculation accuracy and dosimetric influence of plan adaptation.

Table 1
Overview of the different patient datasets used in the manuscript for the analysis of dose calculation accuracy and dosimetric influence of plan adaptation.

To test the accuracy of dose calculation based on CBCT	To demonstrate the functionality of Active-Rx tools for the adaptation of isodose lines
CBCT-1	Patient-A
CBCT-2	Patient-B
CBCT-3	Patient-C

Results

Evaluation of accuracy of dose calculations based on CBCT/*m*CBCT

The comparison between the HUs of the unmodified CBCT and the PCT showed large deviations. Therefore the correlations between relative electron density and HU were very different for the two CT-datasets (Fig. 3).

Inhomogeneous pelvis phantom

The comparison between the dose calculations based on CBCT and PCT (reference) showed large deviations when the CBCT was ***not modified***. Absolute dose deviations of up to 50% were observed. The maximum absolute dose deviation (mean of 10 slices) between PCT and uncorrected CBCT was (41.2±4.1)%. Only (68.9±5.5)% of the pixels passed the gamma test for 3%/3 mm and only (82.2±8.6)% for 5%/5 mm (see Table 2a).

When the CBCT's HUs were ***modified*** (*m*CBCT) the dose deviations were substantially reduced. The maximum absolute dose deviation was reduced by 39 percentage points (%-p) to 11% and the number of pixels which fulfil the gamma test for 3%/3 mm increased by 28%-p to

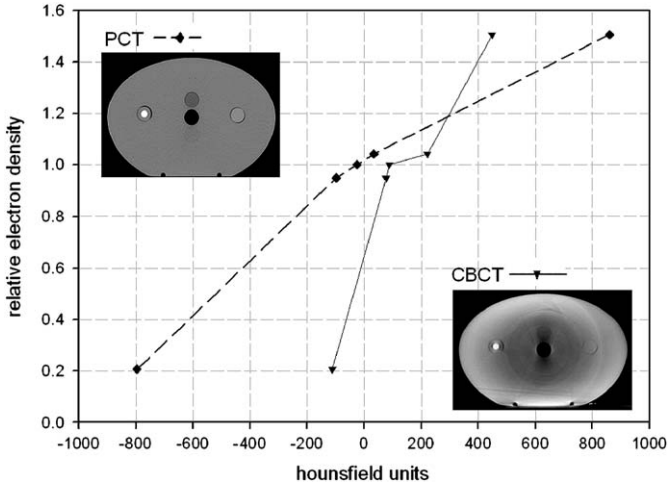

Figure 3. Representative axial CT images of PCT and CBCT and their electron density calibration curves: PCT (dashed line) and kV-CBCT (solid line). Because of the large differences, a dose calculation based on an unmodified CBCT seems to be not advisable.

Table 2
Evaluation of dose calculation accuracy based on (a) cone-beam CT (CBCT) and (b) Modified CBCT by comparing with planning CT (PCT). It could be shown that a software based first order modification of the CBCTs can improve dose calculation accuracy substantially and thus allows an implementation of CBCTs for replanning purposes.

Dose deviations between PCT and unmodified/modified CBCT datasets.

a) Dose deviations PCT vs. Unmodified CBCT (10 representative slices, 4 datasets)

	QA-Phantom (inhomogeneous pelvis phantom) mean ± SD (min .. max)	CBCT-1 (similar anatomy and outline) mean ± SD (min .. max)	CBCT-2 (similar anatomy and outline) mean ± SD (min .. max)	CBCT-3 (different anatomy and outline) mean ± SD (min .. max)
gamma 3/3 passing [%]	68.9 ± 5.5 (57.7 .. 76.1)	19.6 ± 11.3 (9.29 .. 48.7)	60.9 ± 12.2 (33.4 .. 73.1)	20.3 ± 15.8 (3.7 .. 47.1)
gamma 5/5 passing [%]	82.2 ± 8.6 (62.7 .. 92.4)	38.1 ± 16.1 (23.7 .. 76.1)	87.8 ± 8.0 (67.3 .. 94.4)	46.7 ± 21.7 (20.2 .. 80.6)
max. absolute differences [%]	41.2 ± 4.1 (33.6 .. 49.5)	45.8 ± 3.4 (40.3 .. 50.9)	11.7 ± 2.1 (8.1 .. 15.6)	42.3 ± 9.3 (22.2 .. 49.9)

b) Dose deviations PCT vs. Modified CBCT (10 representative slices, 4 datasets)

	QA-Phantom (inhomogeneous pelvis phantom) mean ± SD (min .. max)	CBCT-1 (similar anatomy and outline) mean ± SD (min .. max)	CBCT-2 (similar anatomy and outline) mean ± SD (min .. max)	CBCT-3 (different anatomy and outline) mean ± SD (min .. max)
gamma 3/3 passing [%]	97.2 ± 0.7 (96.4 .. 98.7)	95.8 ± 4.5 (84.5 .. 100.0)	96.3 ± 4.5 (89.0 .. 99.9)	86.3 ± 5.4 (79.9 .. 95.3)
gamma 5/5 passing [%]	99.7 ± 0.1 (99.5 .. 99.9)	99.9 ± 0.1 (99.7 .. 100.0)	99.9 ± 0.3 (99.2 .. 100.0)	99.0 ± 0.9 (97.0 .. 100.0)
max. absolute differences [%]	8.2 ± 2.0 (5.1 .. 10.9)	10.4 ± 2.1 (7.9 .. 13.8)	9.4 ± 2.5 (5.3 .. 13.5)	27.8 ± 5.5 (15 .. 33.3)

97%. Almost all pixels (99.7%) passed the gamma test for 5%/5 mm after correction (see Table 2b).

Patient datasets

For the three patient datasets the maximum absolute dose deviations of up to 51% were in the same range as the dose deviations for the phantom when the CBCT was ***not modified.*** The average absolute dose deviations between PCT and unmodified CBCT was (33.3 ± 18.8)% and only (33.6 ± 23.6)% of the pixels passed the gamma test for 3%/3 mm and only (57.5 ± 26.6)% the gamma test for 5%/5 mm (mean value of the three patient datasets). The dose deviations of each single patient are shown in Table 2a.

When the CBCT was ***modified*** (*m*CBCT), the dose deviations were substantially reduced for the patient dataset. Especially for the two patient datasets with nearly identical outline (CBCT-1, CBCT-2) the maximum absolute dose deviation were reduced to approximately 14%. Almost all pixels (96%) fulfilled the gamma 3%/3 mm criteria and almost 100% (99.9%) of the pixels passed the gamma test for 5%/5 mm. The patient dataset (CBCT-3) with large differences in outline, as expected, showed slightly worse results. Here, maximum absolute dose deviations of up to 33% were observed for some pixels even if the CBCT was modified (see Table 2b).

Only few pixels (less than 5%) did not pass the gamma test for 3%/3 mm (phantom and patients with similar outlines) after the CBCT had been modified which were mainly detected in regions with steep dose gradients and beam edges. The maximum absolute dose deviations of these pixels were smaller than 14% for the phantom and the two patient datasets with similar outlines.

Figures 4 and 5 show sample axial dose slices for accuracy of dose calculations based on CBCT/*m*CBCT as analyzed for one of the phantom plans and one of the patient plans (CBCT-1) respectively, together with representative dose profiles and calculated gamma indices.

Dosimetric influence of plan adaptation with Active-Rx™

Without applying any corrections (isocenter shift, isodose line adaptation), the analysis of the three patient datasets showed substantial dosimetric changes between single treatment fractions due to a distended rectum and internal organ movement and deformation. Figure 6 shows the individual DVHs for each single case and additionally the mean value DVHs for PTV and rectum.

PTV

Table 3 lists the PTV-D_{95} for all patient datasets. In the *Uncorrected plan* of 'patient-A' the PTV-D_{95} was 80.4% lower in comparison to *Reference plan.* With a translational isocenter correction (*Isocenter-Shift Plans*) only a slight improvement of 11.1% over *Uncorrected plan* was observed. A larger benefit was noticed after replanning with Active-Rx™ as it decreased the difference between *Uncorrected plan* and *Reference plan* from 80.4% to less than 6.0%, showing a remarkable

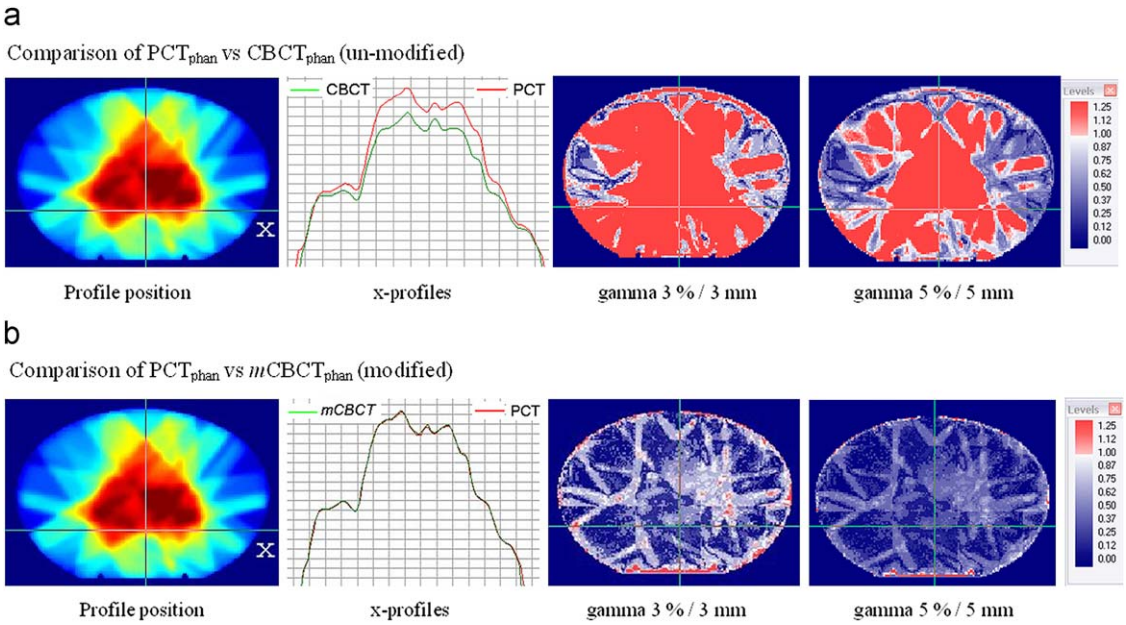

Figure 4. Accuracy of dose calculations based on CBCT vs. *m*CBCT for *PHANTOM dataset*. Dosimetric comparison between the dose calculations performed on planning CT (PCT) and CBCT, (a) unmodified CBCT and (b) modified CBCT (CBCT-1). After the modification of Hounsfield units in the CBCT the dose calculations showed good agreement in the analyzed profiles as well as for the gamma test.

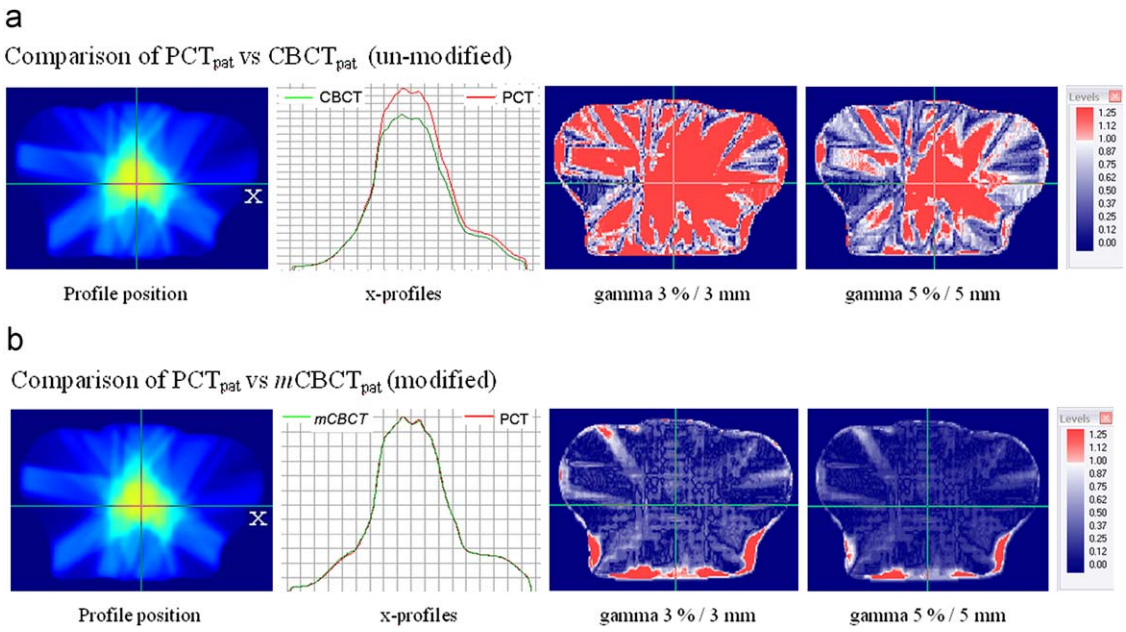

Figure 5. Accuracy of dose calculations based on CBCT vs. *m*CBCT for *PATIENT dataset*. Dosimetric comparison between the dose calculations performed on planning CT (PCT) and CBCT, (a) unmodified CBCT and (b) modified CBCT. Correcting the CBCT images lead in the patient to appropriate Hounsfield units and thus to a good dosimetric agreement.

improvement of 74.4%-p in increasing the dose to the tumour.

The PTV-D_{95} in the 'patient-B' was decreased by 12.8% and in 'patient C' it was decreased by 10.6% in the *Uncorrected plans* when compared to *Reference plans* respectively. For 'patient-B' in the *Isocenter-Shift Plans,* the dose was decreased by 6.4% in comparison to the *Reference plan* whereas for 'patient-C' a slight over

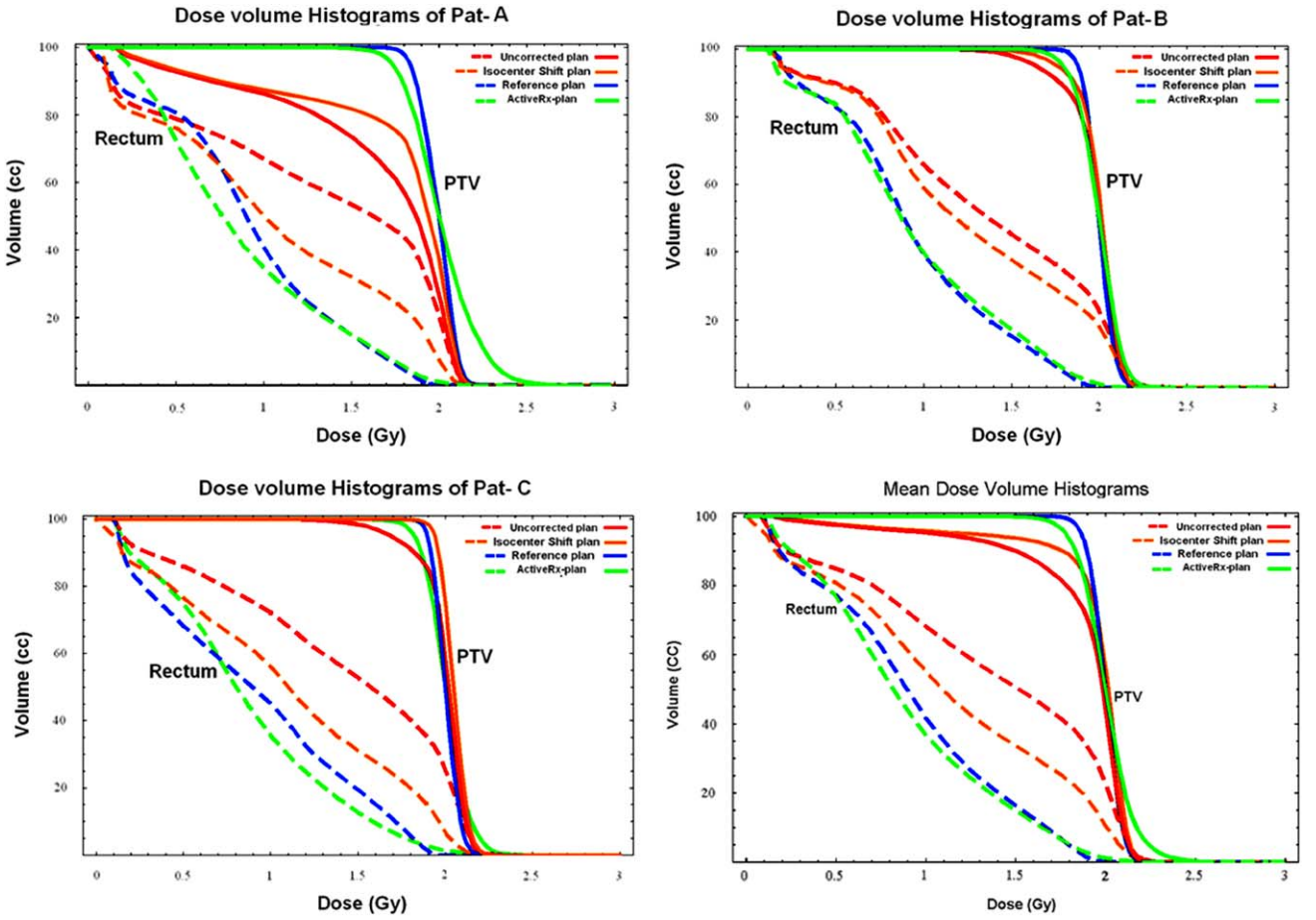

Figure 6. Comparison of individual and mean dose volume histograms for rectum and PTV for various plans: *Reference-Plan* (empty rectum), *Uncorrected-plan* (*distended rectum*), *Isocenter-Shift-Plan* (isocenter correction) (*distended rectum*), *Active-Rx-plan* (adapted plan) (*distended rectum*). It is illustrated that the *Active-Rx plans* shows better dose coverage in the PTV while substantially decreasing the dose in the rectum when compared to *Uncorrected-plans* and *Isocenter-Shift plans*.

Table 3
Overview of PTV-D_{95} (dose to 95% of the PTV) for all of the analyzed patient datasets. It is shown that a plan adaptation with real-time dose modification tools results in further improvements in dose coverage than a translational isocenter correction.

Dose delivered to 95% of the Planning Target Volume in Gray for various plans

	Reference plan	*Uncorrected plan*	*Isocenter-Shift Plans*	*Active-Rx plan*
Patient-A	1.84	0.36	0.40	1.73
Patient-B	1.88	1.64	1.76	1.80
Patient-C	1.89	1.69	1.94	1.82

dosage of 2.6% was calculated to the PTV when compared to the *Reference plan*. Finally, the PTV-D_{95} in the *Active-Rx plans* there is an improvement of 9.8% and 7.7% over *Uncorrected plans* restoring PTV-D_{95} to 95.7% and 96.3% for both 'patient-B and patient-C' respectively.

The mean DVHs (mean of the three patients) in Figure 6 showed that *Uncorrected plans* were only able to achieve 65.7% of the prescribed dose to the PTV-D_{95} of the *Reference plans*. The dose homogeneity in the PTV volume is completely lost because of severe cold areas and this can also be attributed to the degradation of the coverage aspect of the PTV. With simulated translational isocenter correction (*Isocenter-Shift Plans*), PTV-D_{95} was restored on average moderately to 73.1% of the *Reference plans*. PTV-D_{95} showed an average improvement of 7.4%-p over *Uncorrected plans*. There is a substantial improvement in the *Active-Rx plans,* which is superior in comparison to the *Uncorrected plans* and *Isocenter-Shift Plans* regarding dose uniformity and coverage. The PTV-D_{95} improved on an average of approximately 45.0% and 30.5% over *Uncorrected plans* and *Isocenter-Shift Plans*

respectively, while restoring to 95.4% of the dose of the *Reference plans*.

Rectum

For all of the patient datasets an undesired additional rectal exposure was observed when no correction was performed (*Uncorrected plans*). These differences were reduced with simulated translational isocenter correction for all patients (*Isocenter-Shift Plans)*. Using Active-Rx^{TM} the dose to the rectum could be even further reduced for all patients (*Active-Rx plans*). For 'patient-B and patient-C' the dose to the rectum was even smaller than in the *Reference plan* showing a much better sparing of rectum. Table 4 summarizes the results for the dose to the rectum for each individual patient.

On investigating the mean DVHs of the three patient datasets for rectum (Fig. 6) it was remarkable, that in the *Reference plans* D_{30} and D_{60} were 1.2Gy and 0.8Gy (mean of all three patients) respectively whereas in the *Uncorrected plans* D_{30} and D_{60} were 1.9Gy and 1.2Gy which is clinically unacceptable. There was a noticeable improvement for the *Isocenter-Shift Plans* in sparing the rectum, with D_{30} and D_{60} being on average 1.6Gy and 0.9Gy. In the *Active-Rx plans* the average doses for D_{30} and D_{60} were, with 1.1Gy and 0.7Gy respectively, well within the acceptable levels.

Bladder

When compared to the *reference plan* in patient-A, the mean dose to the bladder was decreased by 39.0% in the *Uncorrected plan*, 22.0% in the *Isocenter-Shift Plan* and increased by 15.9% in *Active-Rx plan*. In case of Patient-B, the mean dose was reduced by 41.4% (*Uncorrected plan*), 36.5% (*Isocenter-Shift Plan*) *and* 30.8 (*Active-Rx Plan*) in comparison to the *reference plan.* In Patient-C, the mean dose decreased by 15.0% (*Uncorrected plan*) and 3.8% (*Active-Rx Plan*), but increased in *Isocenter-Shift Plan* by nearly 44% when compared to *reference plan*. (Table 5 shows the individual mean dose values for each single case for bladder).

Table 4
Illustrates the dose information for various patient plans in respect to D30 and D60 (dose to 30% and 60% of the rectum). It presents that the dose in the rectum can sufficiently be decreased to reach or even fall below the doses in the reference treatment plans by adjusting the isodose lines.

Dose delivered to 30%/60% of the Rectal Volume in Gray for various plans

	Reference plan	*Uncorrected plan*	*Isocenter-Shift Plans*	*Active-Rx plan*
Patient-A	1.15/0.80	1.94/1.24	1.57/0.83	1.09/0.63
Patient-B	1.15/0.80	1.90/1.12	1.72/0.98	1.18/0.77
Patient-C	1.25/0.67	1.96/1.30	1.53/0.92	1.09/0.69

Table 5
Overview of the dose information for various patient plans in respect to mean dose to the bladder. The dose to the bladder was less than in comparison to the *reference plans* except for Patient-A, where a slightly higher dose could be observed.

Dose information of Bladder (mean dose) in Gray for various plans

	Reference plan	*Uncorrected plan*	*Isocenter-Shift Plans*	*Active-Rx plan*
Patient-A	1.036	0.630	0.807	1.201
Patient-B	1.284	0.752	0.815	0.888
Patient-C	0.571	0.485	0.824	0.549

Discussion

Interfractional organ motion, setup errors and organ shape deformations during radiotherapy can have negative clinical consequences. In our study we showed as a "proof of principle" that our proposed online adaptive replanning approach based on CBCT has the potential to improve the dose distribution in the patient fundamentally for certain treatment fractions. Prerequisites for this strategy are a reliable HU correction of the CBCTs and fast and accurate real-time isodose modification tools for a fast plan adaptation.

Evaluation of accuracy of dose calculations based on CBCT/*m*CBCT

The relationship between HUs and relative electron densities plays a crucial role for the treatment planning process. The HUs in the unmodified CBCT-dataset were quite different in comparison to the HUs measured in the PCT. The reasons for those deviations are mainly artefacts in the CBCT and very inhomogeneous HU distributions even in homogenous areas due to the lack of appropriate scatter corrections algorithms and overexposure effects in the detector. However, the stability and reproducibility of the HUs seem to be suitable (within 1.5% with maximal deviation of 21 units during three months) [15]. Dose calculations on different CBCT systems were previously reported by different authors [11,12,16–18]. They demonstrated that an accurate dose calculation (1–3%) is possible when the HU distribution is reliable.

Different CBCT vendors have different strategies to calibrate and correct their images. Sometimes hardware

filters (e.g. ''Bowtie'') are used or scatter correction algorithms are applied to acquire an improved image quality. However, each of these systems has to be evaluated separately because there can be major differences between them.

Based on our evaluation we could clearly show that our unmodified CBCT was not suitable for accurate dose calculations. Dose deviations of up to 51% in comparison to PCT could be observed. The developed algorithm to modify the CBCTs allowed a relatively simple and fast first order correction of the HU distribution of a CBCT-dataset by replacing the ''uncalibrated'' HUs with correct HUs from the PCT.

To avoid dosimetric errors between CBCT and PCT when validating the algorithm for patient datasets, the image datasets were chosen where the anatomy of the patient was almost similar. Otherwise, different anatomy between CBCT and PCT might have caused dose differences not attributable to CBCT-specific problems.

We showed that by segmentation and assigning of only three appropriate HU levels it was possible to reduce the negative effects of artefacts and wrong HUs and to achieve enough accuracy in the dose calculation which is in general comparable with the accuracy of the earlier studies described above. Our method allows a fast, robust and simple first order correction of CBCT-datasets without using complex scatter-correction algorithms or additional hardware filters.

For the phantom study around 97% of the pixels fulfilled the gamma 3%/3 mm criteria. Only very few pixels (0.3%) showed dose deviations larger than 5% (up to 11%), mainly in regions with steep dose gradients where small geometric matching errors can lead to larger dose deviations. For the patient study the results were similar when the outlines were similar. If the outline was different in CBCT larger dose deviations of up to 33% could be observed because of the changed radiological depths.

Dosimetric influence of plan adaptation with Active-Rx^{TM}

Ghilezan et al. [9] have quantified the theoretical benefits of online image-guided IMRT (on-board CBCT) with reduced safety margins. They reported that with image guidance 32% of the patients had a significant benefit ($>15\%$–41%) in terms of dose increment of corrected vs. uncorrected position. Previous studies from our group [7,8] assessed the clinical benefits during prostate radiotherapy as a consequence of an image guided translational isocenter correction. When a large displacement of the prostate occurred, a linear translation correction became insufficient. The rotational offsets and the deformation of the organs became more relevant. The problems caused by the change in prostate shape (i.e. deformation) can only be resolved by means of ''full'' adaptive radiotherapy, which prompted the current project reported here.

Strategies to address these issues have been published previously. A study [19] presented an offline strategy with an adaptive algorithm for inverse planning based on observations with portal imaging and CT imaging. With this information the initial plan was modified accordingly for following fractions. Similarly, the studies of Mackie et al. [20] and Keller et al. [21] presented other off-line strategies where corrections were applied to following fractions by applying an ''individualized PTV-margin''. A first online plan re-optimization technique based on deformable image registration and automated re-optimization of fluence maps with linear programming has been reported by Wu et al. [22].

Our strategy differs from the previous studies because we aim to use a pre-existing treatment plan, generate a new dose distribution on the new image datasets and adapt the dose with fast visual interactive dose modifications tools.

For all the three patients, with translational isocenter correction the average under-dosage of the PTV-D_{95} relative to the *Reference Plans* got reduced on average from approximately 34.3% (*uncorrected plans*) to 26.9% (for individual results, please refer to Table 3 and Fig. 6). This agrees with our previous report [8]. A further remarkable improvement from 34.3% (*uncorrected plans*) to 4.6% was observed after using the Active-Rx^{TM} module.

Similarly, the dose to rectum (D_{30} and D_{60}) was decreased on average from 58.3% and 50.0% (*uncorrected plans*) to 33.3% and 12.5% (*Isocenter-Shift Plans*). Using Active-Rx^{TM} the dose could further be decreased to -8.3% and -12.5% respectively and was thus even lower than in the *Reference plans*.

The mean dose to the bladder as expected showed also differences between the *Reference plans* and the other plans for all patients (patient-A, patient-B, and patient-C) which can be attributed to the organ movements and organ deformations due to the distension of the rectum.

The dose in the *uncorrected plans* was substantially less when compared to the *reference plans* because parts of the bladder volume were pressed in anterior-cranial direction outside the high dose area. Similarly, the dose in the *isocenter-shift plans* was still less compared to *reference plans* except for patient-C, where a larger iscocenter shift and thus a movement of the dose distribution towards the bladder resulted in a slightly increased bladder dose. In the *Active-Rx plans* (after plan adaptation) the dose to the bladder was less than in the *reference plans* except for Patient-A where a slightly higher dose could be observed because the bladder volume itself became smaller (less bladder filling that during reference CT). In summary the dose changes to the bladder were either beneficial or

resulted in a minimally larger bladder exposure that is clinically irrelevant, especially in comparison to the changes in rectal dose.

There are still certain limitations associated with the research version of the Active-Rx^{TM} module. Due to physical constraints of photon radiation, a local dose reshaping may be accompanied by an unwanted dose deposition outside the PTV. All slices of the patient dataset therefore have to be screened carefully after re-optimizing the dose distribution.

The timing of the individual steps of the proposed strategy for online adaptive radiotherapy (as shown in Fig. 1) are: acquisition and processing of kV-CBCT ($\leqslant$2.5 mins), contouring of structures (approximately 10 mins), modification of the HU of kV-CBCT to *m*CBCT ($\leqslant$1.5 mins), copying original plan to *m*CBCT ($\leqslant$12 mins) and finally usage of ***Active-Rx*^{TM} tools on *m*CBCT** ($\leqslant$10 mins). Although the strategy is designed as an online adaptive radiotherapy for correction of interfraction organ motion, the work presented in this paper is merely a proof-of-principle. The proposed strategy is intended as an advantage over the practice of mere couch-movement, it served our purpose of illustrating a new idea for correction of interfraction target dislocation and deformation for a particular treatment fraction. It is not intended as a report of the development of a system ready for clinical use. To realize the full potential of the proposed ART work flow for clinical routine the time frames of each step could be reduced in future when major obstacles and problems (e.g., non-automated operations (import/export), manual segmentation, calculation speed of TPS, limitations of *Active-Rx*^{TM} module, non-integrated systems, ..) are removed and solved.

For adaptive radiotherapy, it is not possible to perform the current practice of patient-specific pre-treatment IMRT-QA. Automated real-time IMRT-QA techniques are required, which utilise the entrance and exit dose information during actual treatment delivery and allow a reconstruction of patient dose for the adapted treatment [23]. Additional in vivo measurement could also be performed as an additional independent verification method for absolute dose values [1].

The only remaining possibility for patient-related dosimetric errors after a ''full adaptation'' of the treatment plan will be *intrafractional* movement. Those errors could only be further reduced with new strategies of intrafractional real-time tumor tracking. The clinical consequences of such movements, however, have yet to be determined.

Conclusion

In this study, the feasibility of an online adaptive radiotherapy strategy as a proof-of-principle is illustrated to account for inter-fraction variations of volumes, shapes and also positions of targets and critical tissues which can significantly affect treatment outcomes. Accurate dose calculation based on CBCT-datasets is now possible and yields clinically acceptable results, when a simple threshold algorithm as first order correction of the HU is applied. Re-optimization of treatment plans based on CBCT is therefore a feasible approach to further increase treatment quality. For fundamental changes in patient anatomy (e.g. due to rectum distension) image guided translational corrections are not sufficient because of increased tissue deformations. Interactive dose manipulating tools have the potential to minimize the dose deviations in the patient with respect to PTV coverage and OAR sparing. It is done by closely matching the DVH characteristics of the original IMRT treatment plan with the adapted plan. The proposed strategy might pave the way for a possible integration of ART into clinical practice, ensuring that complex radiation treatment like IMRT can be delivered safely and precisely.

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