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Original Article

Both four-dimensional computed tomography and four-dimensional cone beam computed tomography under-predict lung target motion during radiotherapy

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ABSTRACT

Background and purpose: To test the hypothesis that 4DCT and 4DCBCT-measured target motion ranges predict target motion ranges during lung cancer SABR.

Materials and methods: Ten lung SABR patients were implanted with Calypso beacons. 4DCBCT was reconstructed for 29 fractions (1–4fx/patient) from a 1 min CBCT scan. The beacon centroid motion segmented for all 4DCT and 4DCBCT bins was compared with the real-time imaging and treatment beacon centroid ("target") motion range (4SDs) for each fraction. We tested the hypotheses that (1) 4DCT and 4CBCT predict treatment motion range and (2) there is no difference between 4DCT and 4DCBCT for predicting treatment motion range. Phase-wise root-mean-square errors (RMSEs) between imaging and treatment motion and reconstructed motion (4DCT, 4DCBCT) were calculated. Relationships between motion ranges in 4DCT and 4DCBCT and imaging and treatment motion ranges were investigated for the superior–inferior (SI), left–right (LR) and anterior–posterior (AP) directions. Baseline drifts and amplitude variability were investigated as potential factors leading to motion misrepresentation.

Results: SI 4DCT, 4DCBCT, imaging and treatment motion ranges were 6.3 ± 3.6 mm, 7.1 ± 4.5 mm, 11.1 ± 7.5 mm and 10.9 ± 6.9 mm, respectively. Similar 4DCT and 4DCBCT under-predictions were observed in the LR and AP directions. Hypothesis (1) was rejected ($p < 0.0001$). Treatment target motion range was under-predicted in 4DCT by factors of 1.7, 1.9 and 1.7 and in 4DCBCT by factors of 1.5, 1.6 and 1.6 in the SI, LR, and AP directions, respectively. RMSEs were generally lower for end-exhale than inhale. 4DCBCT showed higher correlations with the imaging and treatment target motion than 4DCT and testing hypothesis (2) a statistically significant difference between 4DCT and 4DCBCT was shown in the SI direction ($p = 0.03$).

Conclusion: For lung SABR patients both 4DCT and 4DCBCT significantly under-predict treatment target motion ranges.

Lung stereotactic ablative body radiotherapy (SABR) is an established treatment option achieving results comparable to surgery for non-operable non-small cell lung cancer patients [1]. It is based on the principles of irradiating small, mostly mobile lung targets to a high dose in 1–8 fractions [1,2]. Due to the conformal dose gradients, the high dose delivered per fraction and a small number of overall fractions, an accurate motion estimation and a high degree of accuracy in treatment setup and delivery are crucial.

The introduction of four-dimensional computed tomography (4DCT) played a significant role in the successful clinical implementation of lung SABR by enabling the measurement of the tumour motion for each patient ahead of treatment [3–6]. The measured motion is generally taken into account in treatment planning either via creating an internal target volume (ITV) out of the gross tumour volumes (GTVs) of the different 4DCT phases [7] or by determining the mid-ventilation position from 4DCT [8].

Nevertheless, a 4DCT scan is only a snapshot in time and several publications have shown that lung tumour motion can vary substantially inter- and intra-fractionally [9–11]. Guckenberger et al. [12] performed multiple 4DCT scans of lung cancer patients in one session and observed increased intrafractional variations in

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patients with poor pulmonary function and tumours located in the lower lobe. They suggested these patients could benefit from more than one 4D planning CT. Purdie et al. [13] have shown that the motion in the 4DCT scan may not be representative for all treatment fractions and discrepancies of up to 10 mm can be observed using a 4D reconstruction of the cone-beam CT (4DCBCT) pioneered by Sonke et al. [14] in 2004.

Today, the remaining uncertainties are usually compensated for by utilizing sufficient population-based margins. Treatment setup is generally performed based on a (3D)CBCT scan or based on 4DCBCT, which is now integrated in commercially available radiotherapy systems. 4DCBCT imaging promises a verification of tumour trajectories before each treatment fraction, and thus a reduction in geometrical uncertainties, for a more accurate patient setup.

In a previous study Steiner et al. [15] showed that the motion representation in 4DCBCT does not change significantly for different reconstruction algorithms ($p = 0.47–0.62$) or internal or external surrogates for binning ($p = 0.19–0.34$).

No study to date has quantified target motion during the three critical motion measurement processes: 4DCT, 4DCBCT and treatment. The purpose of this study was to test the hypothesis that

1) 4DCT and 4DCBCT predict motion range during treatment.

Also, we wanted to show that

2) there is no difference between 4DCT and 4DCBCT for predicting the motion range during treatment.

In addition, a possible under- or over-prediction of the treatment motion was quantified and any consistent relationships between the motion ranges in 4DCT, 4DCBCT, and the imaging and treatment motion ranges identified. Potential factors contributing to a motion range misrepresentation, such as baseline drifts and amplitude variability, were investigated.

Materials and methods

To test the hypotheses, we evaluated target motion ranges of 10 patients treated within the LIGHT-SABR clinical trial (clinicaltrials.gov: NCT02514512).

Beacon implantation

An overview of patient tumour characteristics is shown in Table 1. One week prior to treatment simulation, the patients were implanted with three Calypso lung transponder beacons (Varian Medical Systems, Palo Alto) surrounding the tumour to ensure they were an accurate surrogate of tumour motion and to confidently determine the real-time position of a soft-tissue tumour throughout the treatment fractions [16]. The Calypso beacons are visible in 4DCT and 4DCBCT and provide motion information during treatment with a temporal resolution of 25 Hz as the motion of the centroid position of 2–3 beacons with a sub-mm localization accuracy [17,18]. The Calypso motion was defined as the target motion for the later testing of hypotheses and comparison with the reconstructed motion ranges of the same beacons (Fig. 1).

CT simulation and treatment planning

The patients were positioned in a BodyFix BlueBAG (Elekta, Stockholm, Sweden) in either supine or prone position to allow the Calypso beacons to be within detectable distance (<19 cm) for the Calypso panel, which was positioned above the patient for the treatment fractions. The 4DCT scan for treatment simulation was performed with a CT Big Bore (Philips Medical Systems, Cleveland, OH) and was reconstructed based on the respiratory signal acquired with the RPM system (Varian Medical Systems, Palo Alto) for 10 phases using phase binning (Fig. 1Aa). The treatment (48 Gy/4fx or 50 Gy/5fx) was delivered as a 2-arc Volumetric Modulated Arc Therapy.

In-room imaging and image reconstruction

A half-fan, full rotation CBCT scan was performed for setup verification for each treatment fraction on a Varian Trilogy linac (Varian Medical Systems, Palo Alto) with the standard 60 s acquisition protocol (680 projections). The real-time motion signal of the implanted beacons was recorded with the Calypso system at the same time. 4DCBCT scans were reconstructed from the projections of the treatment setup CBCT using the Feldkamp–Davis–Kress (FDK) method [19] and phase-based binning for 10 phases for every fraction with a complete data set of the raw imaging data (CBCT projection images) and Calypso respiratory signal (Fig. 1Ab). The CBCT projection data could be retrieved for one fraction of patient 1 and 3–4 fractions of patients 2–10.

Motion range measurement

Calypso beacons in the 10 phases of the 4DCT scans were manually segmented in Eclipse (v.11, Varian Medical Systems, Palo Alto) as part of the clinical workflow (Fig. 1Aa). For the 4DCBCT scans, the segmentation was performed by intensity thresholding around the prior location estimated from the Calypso respiratory signal data during CBCT in MATLAB R2017b (MathWorks, Inc.) (Figure 1Ab3). The beacon centroid motion range with respect to the end-exhale reference phase was then calculated.

Root-mean-square errors (RMSEs) between the Calypso motion during imaging and treatment and the reconstructed motion in treatment planning 4DCT and the 4DCBCT of the same fraction for the 10 phases were calculated as described by Iramina et al. [20].

Table 1
Patient characteristics. Tumour volume, location (left lower lobe (LLL), left upper lobe (LUL), right lower lobe (RLL), right middle lobe (RML), right upper lobe (RUL)), treatment position, number of Calypso beacons used for tracking and treatment fractions evaluated.

Patient number	Tumour volume GTV [cc]	Tumour location	Treatment position	Beacons used for tracking	Treatment fractions evaluated
1	4.3	LUL	supine	3	1
2	3.1	RUL	prone	3	3
3	10.8	LUL	supine	3	3
4	7.3	LUL	supine	3	3
5	13.6	RLL	supine	3	3
6	5.8	LUL	prone	3	4
7	0.4	RLL	supine	2	3
8	10.3	LLL	prone	2	3
9	0.5	RML	supine	3	3
10	7.0	RLL	supine	3	3

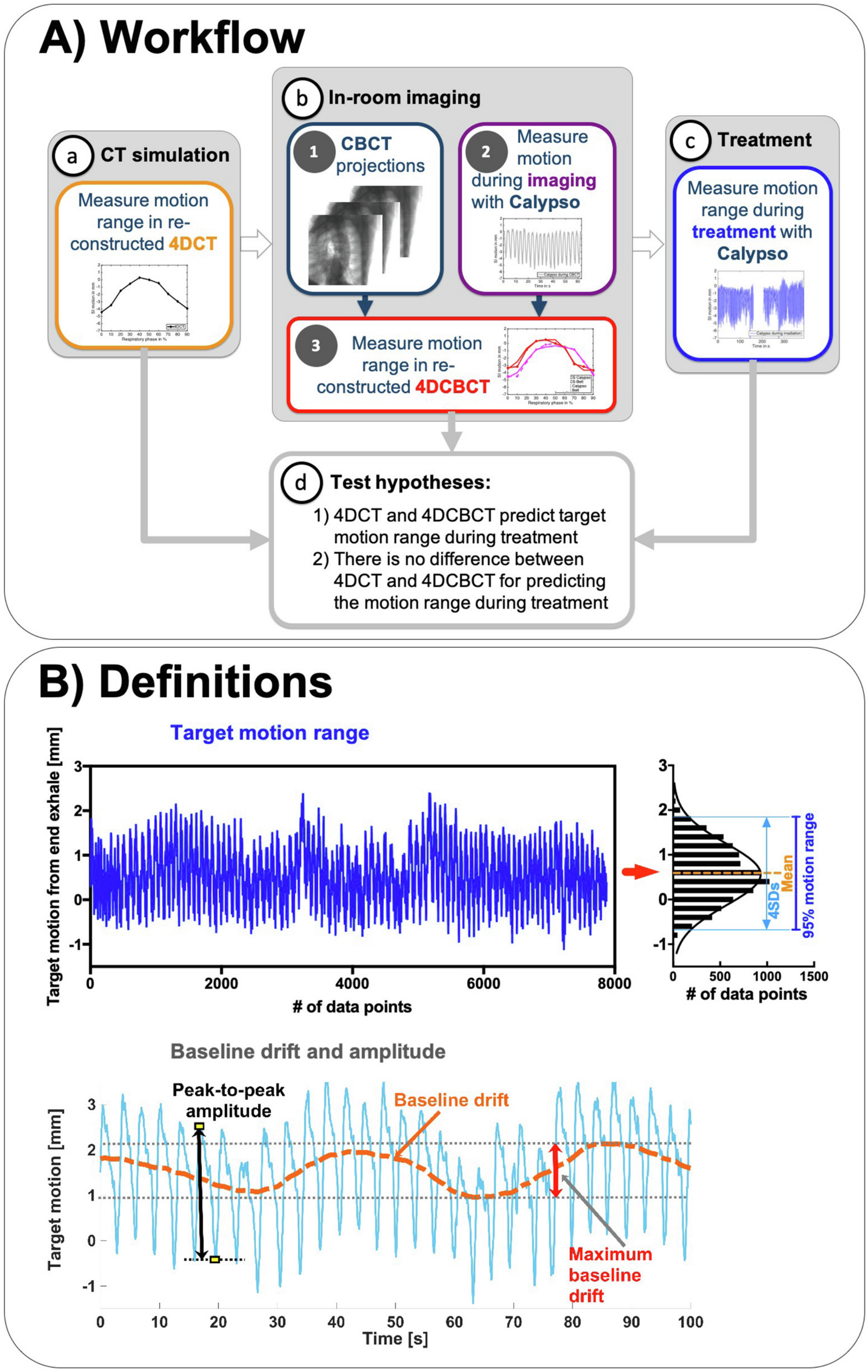

Fig. 1. (A) Workflow for the comparison of the 4DCT and 4DCBCT motion ranges with the treatment motion ranges. (B) Definitions: Note that "motion range" is the 95% range and used throughout the study for the statistical evaluations and regressions. The motion range includes cycle-to-cycle variations and baselines drifts that occur.

For the target motion range measurements during CBCT imaging (Fig. 1Ab2) and treatment (Fig. 1Ac), the motion range was calculated as 4 standard deviations (SDs) ≈ 95% of the Calypso target motion (Fig. 1B) in the superior–inferior (SI), left–right (LR) and anterior-posterior (AP) directions, to limit the effect of extreme values and will be referred to as 'imaging motion range' and 'treatment motion range', respectively.

End-exhale was aligned for 4DCT, 4DCBCT and Calypso target motion before CBCT imaging and treatment for all directions. Subsequently, the reconstructed motion ranges from the treatment planning 4DCT and the 4DCBCT scans of the same fractions were compared to the imaging and treatment motion ranges for hypotheses testing (Fig. 1Ad).

Baseline drifts and amplitude variability

To investigate how baseline drifts contribute to a motion misrepresentation in 4DCT and 4DCBCT, baseline drifts were determined for all treatment fractions as a function of the average target position (rolling average over 20 s) for all directions (SI, LR, AP) (Fig. 1B). The maximum baseline drift was defined as the range of the drift over the whole fraction.

To investigate how amplitude variability impacts a motion misrepresentation in 4DCT and 4DCBCT, for each breathing cycle of the target motion during treatment the peak-to-peak amplitudes were calculated for all directions (SI, LR, AP) and the mean amplitudes and the standard deviation (SD) of the amplitudes were calculated for each fraction. The standard deviation within one fraction was used as a measure for intrafraction variability, the range of mean amplitudes for all fractions of a patient was utilized as a measure for interfraction amplitude variability.

Statistical testing

Statistical testing was performed in Prism 7 (GraphPad, Inc.). ANOVA testing (Geissler–Greenhouse's correction, Tukey's multiple comparisons test) was used for testing both hypotheses:

1) 4DCT and 4DCBCT predict treatment motion range and
2) there is no difference between 4DCT and 4DCBCT for predicting the treatment motion range.

Additionally, two-way ANOVA testing matched for phase and patient fraction (Tukey's multiple comparisons test) was performed to identify differences in the phase-wise RMSEs between the Calypso motion during imaging and treatment and the reconstructed motion in treatment planning 4DCT and the 4DCBCT of the same fraction.

Linear regressions and Pearson's correlation coefficients between the reconstructed motion ranges from 4DCT and 4DCBCT and the imaging and treatment motion ranges were calculated and plotted for the SI, LR and AP directions.

Results

Measured motion ranges

Fig. 2A shows the measured 4DCT, 4DCBCT, imaging and treatment target motion ranges for all patients. The imaging time was always 1 min, the treatment times (time from beam-on for arc 1 to beam-off for arc 2) were 6.7 ± 2.0 min (range 4.7–13.1 min). The imaging and treatment target motion was generally under-predicted in 4DCT and 4DCBCT ($p < 0.001$ for SI, LR and AP direction), so the null hypothesis that (1) 4DCT and 4DCBCT predict the treatment motion range must be rejected. Fig. 2B shows the RMSEs for each breathing phase between the reconstructed motion in 4DCT and 4DCBCT and the imaging and treatment motion. The errors were in general smallest in the end-exhale phase and larger in the inhale phases as it was also observed by Iramina et al. [20].

Fig. 3A illustrates observed behaviour for four different patients representative for the whole population by showing the 4DCT, 4DCBCT and treatment target motion trajectories. Fig. 3B shows sample target motion in all 10 phases of 4DCT, 4DCBCT and for treatment for one patient. An overview of all patient fractions is shown in Supplementary Fig. S1.

Testing hypothesis (2) that there is no difference between 4DCT and 4DCBCT for predicting the treatment motion range, a significant difference was shown only for the SI direction ($p = 0.03$), where 4DCBCT showed less difference to the treatment motion range than 4DCT. For LR and AP directions the null hypothesis was supported ($p > 0.05$). No difference could be shown between the imaging and the treatment motion ranges (Fig. 2A).

Statistical testing of the phase-wise RMSEs between the imaging and treatment motion and the reconstructed motion resulted in a significantly lower error only for the SI direction between the imaging motion and 4DCT ($\Delta = 0.7$ mm) compared to treatment/4DCT and between the imaging motion and 4DCBCT ($\Delta = 0.8$ mm) compared to treatment/4DCBCT (both $p < 0.01$).

Fig. 4 shows the percentage of treatment time per fraction when the reconstructed motion ranges from 4DCT and 4DCBCT plus an isotropic 3 mm or 5 mm margin were exceeded by the treatment motion.

Motion range regressions

Fig. 5 shows the linear regressions and correlations between 4DCT, 4DCBCT and the imaging and treatment target motion ranges in the SI, LR and AP direction. Although a statistically significant difference in motion prediction was only found between 4DCT and 4DCBCT in the SI direction, the Pearson correlation values between the motion ranges in 4DCBCT and the imaging and treatment motion ranges were in general higher than between 4DCT and imaging and treatment for all directions.

SI treatment target motion ranges were under-predicted in 4DCT on average by a factor of 1.7 (Pearson $r = 0.93$) (Fig. 5A) and in 4DCBCT by a factor of 1.5 (Fig. 5B), where the highest correlation ($r = 0.97$) was observed.

LR and AP treatment target motion ranges were under-predicted in 4DCT by factors of 1.9 and 1.7 and in 4DCBCT by 1.6 and 1.6, respectively. The correlation to the motion ranges in 4DCT and 4DCBT was lower ($r = 0.50$–0.91) (Fig. 5C–F). Very similar trends were seen for the imaging motion ranges (Fig. 5A–F).

Impact of baseline drifts and amplitude variability

Maximum baseline drifts in the SI direction of >8 mm were observed in 10%, of 5–8 mm in 17% and of 2–5 mm in 35% of the treatment fractions. In LR direction, maximum baseline drifts of 5–8 mm were seen in 3% and of 2–5 mm in 31% of the treatment fractions. In AP direction, maximum baseline drifts of 5–8 mm were observed in 3% and of 2–5 mm in 69% of the treatment fractions. These baseline drifts can also be seen in Fig. S1.

Compared to the magnitude of baseline drifts, the magnitude of amplitude variability was smaller with a mean intrafraction variability of 1.3 ± 1.0 mm, 0.4 ± 0.4 mm and 0.6 ± 0.4 mm in the SI, LR and AP directions, respectively. An interfraction amplitude variability of 1.2 ± 0.9 mm, 0.4 ± 0.3 mm and 0.5 ± 0.5 mm was observed for SI, LR and AP direction, respectively.

Discussion

Treatment motion range variations from fraction to fraction due to baseline drifts and amplitude variability were observed. This is consistent with the data published by Shah et al. [9] and Dhont et al. [10]. Our data show that the imaging and treatment target motion range was significantly larger than predicted in 4DCT and 4DCBCT and can be used to understand the limitations of 4DCT and 4DCBCT. Ge et al. [21] found that 4DCT did not represent abdominal tumour motion and concluded "It may not be appropriate to use 4DCT without monitoring of patient motion on a regular

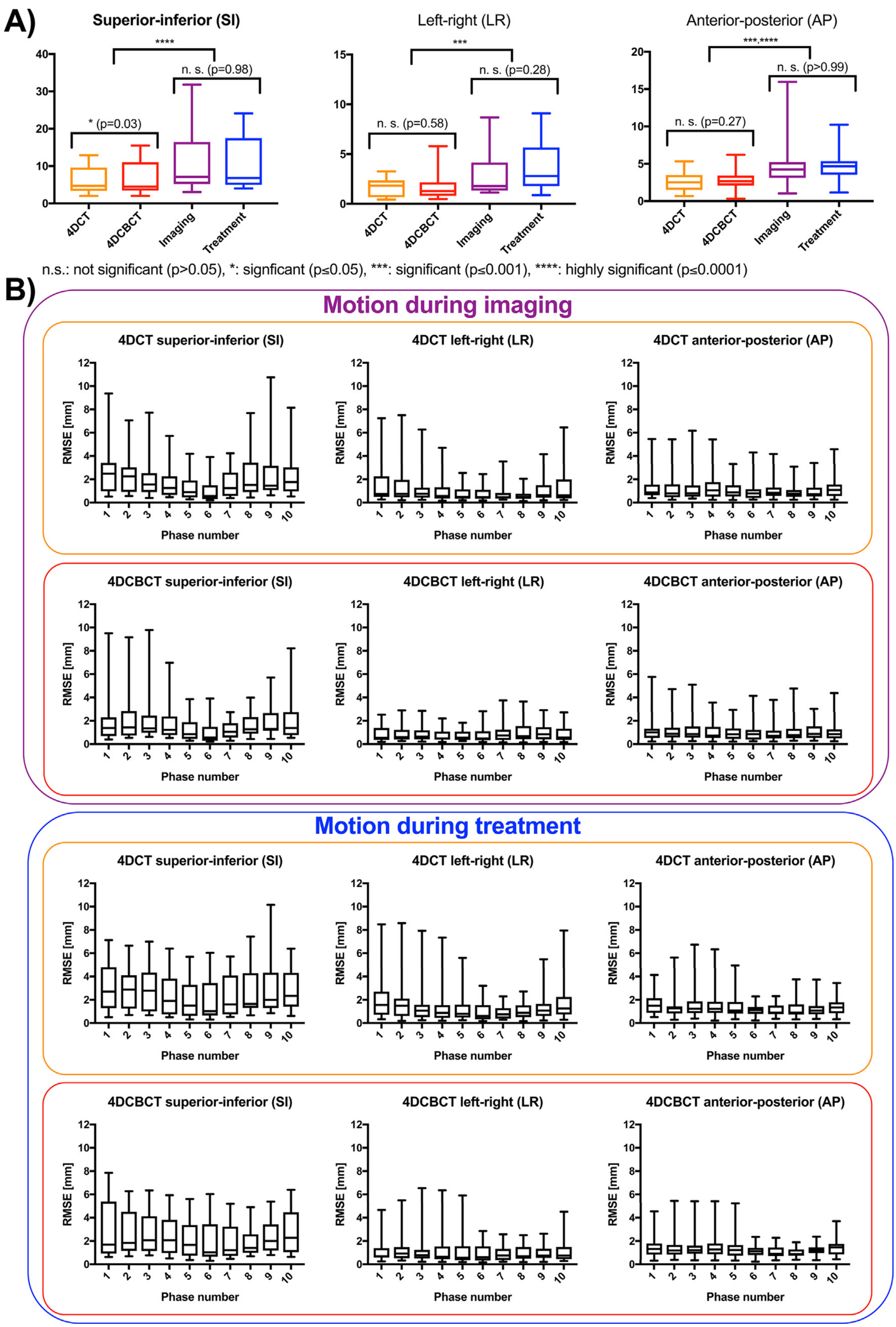

Fig. 2. (A) Boxplots of 4DCT, 4DCBCT, imaging (4 SDs) and treatment (4 SDs) motion ranges for all patients in SI, LR and AP directions. (B) Boxplots of the root-mean-square errors (RMSEs) for the different breathing phases (1–10, 6 = end-exhale) between the reconstructed target motion (4DCT, 4DCBCT) and the real-time target motion during imaging and treatment.

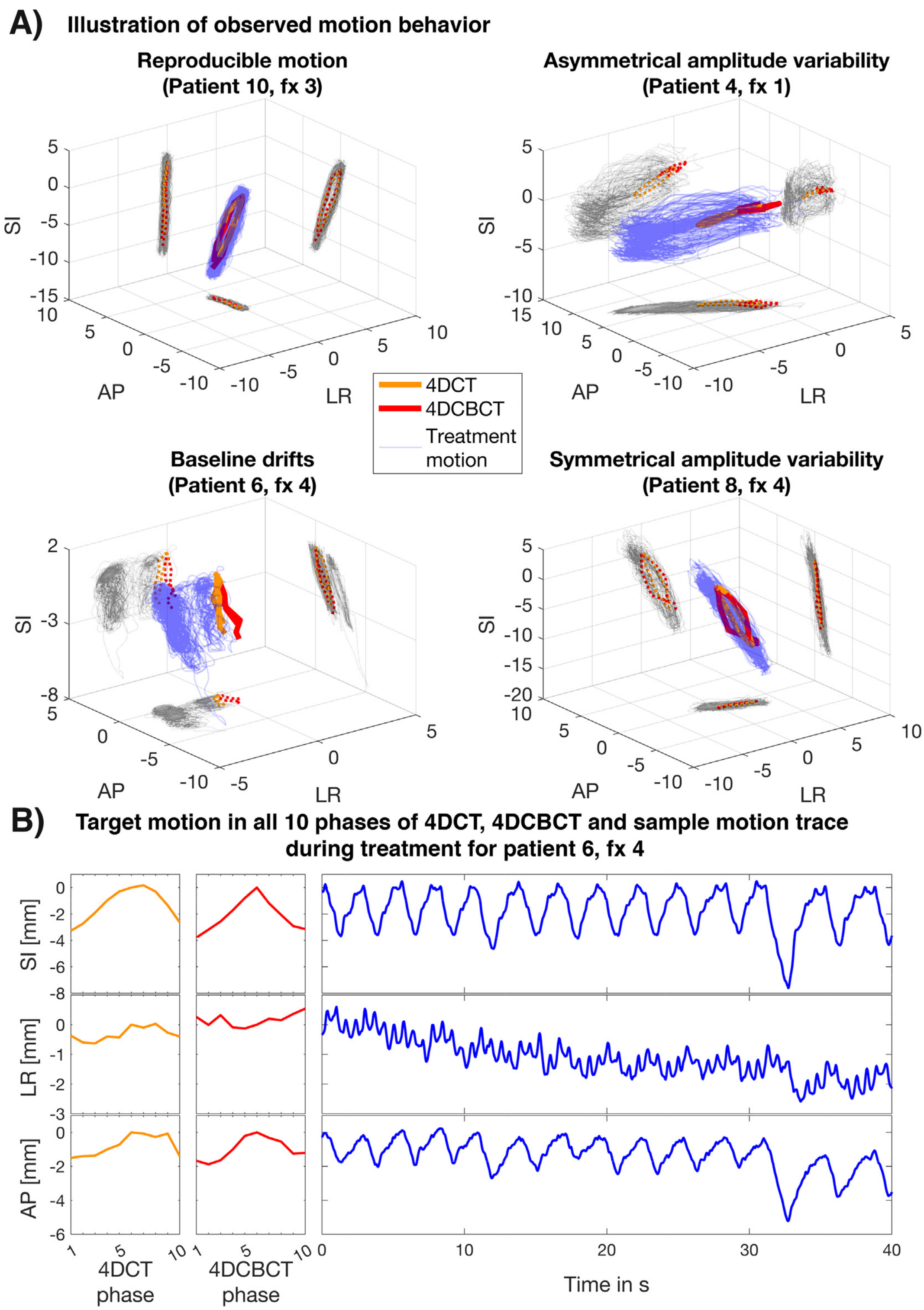

Fig. 3. (A) Illustration of observed behaviour: 4DCT (orange), 4DCBCT (red) and treatment (blue) target motion trajectories and projections (in mm) for four patients: Regular and reproducible motion, asymmetrical amplitude variability, large baseline drifts during treatment and symmetrical amplitude variability during treatment. (B) Sample target motion in all 10 phases of 4DCT, 4DCBCT and for treatment in SI, LR and AP directions.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

basis for patients with abdominal tumours, especially SBRT patients." Based on our current study, we can apply their conclusion to include both 4DCT and 4DCBCT for lung cancer SABR patients: It may not be appropriate to use 4DCT or 4DCBCT for lung cancer SABR patients without intra-treatment motion monitoring. However, the local control of lung SABR is excellent [22]; potentially because of a wider beam penumbra in the lung [16], high doses prescribed and short times of exceeding motion. The clinical

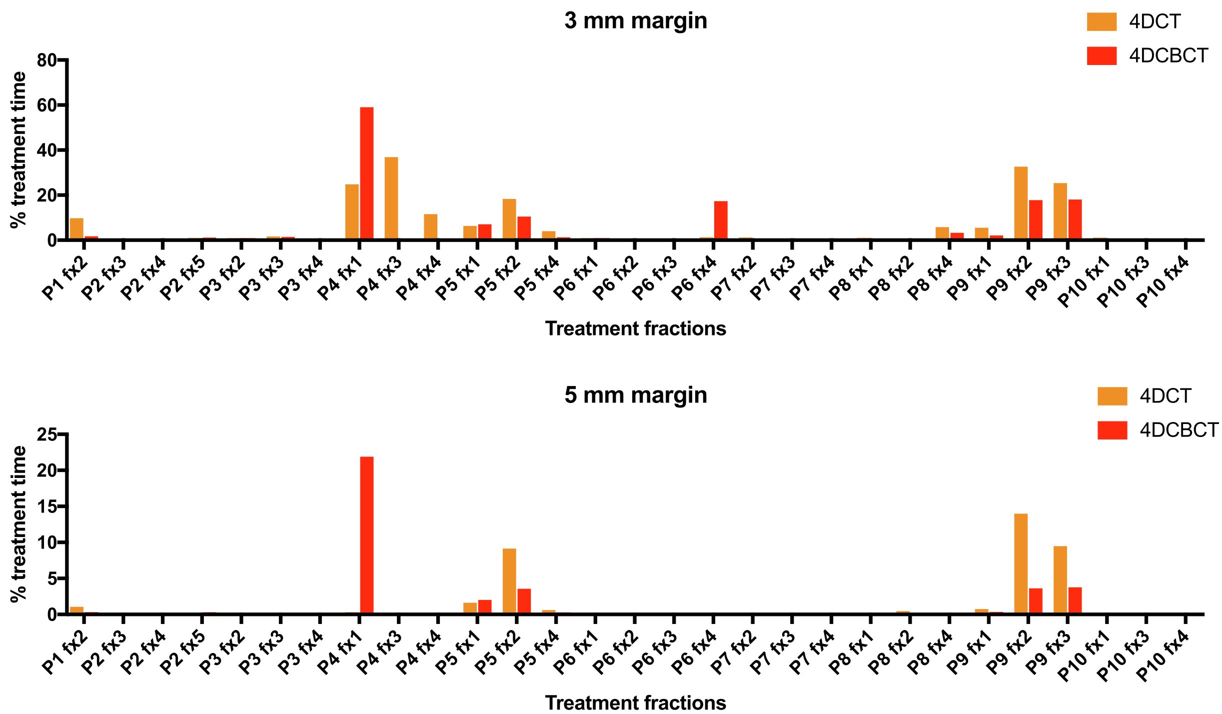

Fig. 4. Percentage of treatment time per fraction when the reconstructed motion ranges from 4DCT and 4DCBCT plus a 3 mm or 5 mm isotropic margin were exceeded in SI, LR or AP directions.

significance of the findings in this paper would need further examining in a larger study.

The motion under-prediction in 4DCT and 4DCBCT can be partly explained through the higher Calypso sampling frequency (25 Hz). Additionally, for 4DCT only one breathing cycle is recorded for the measurement of each anatomical position, while for 4DCBCT reconstruction the projection images are assigned to a discrete number of phases and the position within a phase is thus an average of the positions within the bin. One contributing factor for both, 4DCT and 4DCBT, could be the short imaging time (1 min) compared to the longer treatment time. However, the imaging motion ranges in our study were underrepresented in a similar way as the treatment motion ranges in the reconstructed 4DCBCTs and the phase-wise statistical analysis only showed relatively small effects of $\Delta = 0.7–0.8$ mm between the RMSEs of imaging and treatment motion in 4DCT and 4DCBCT in the SI direction.

Overall the 4DCBCT studies showed higher correlations with the treatment motion and smaller motion range under-predication factors than 4DCT. We showed a statistically significant difference between 4DCT and 4DCBCT motion ranges for the SI direction. High correlations ($r > 0.90$) were shown for the SI and AP directions for motion estimation from 4DCBCT and for the SI direction from 4DCT. We would expect 4DCBCT to be a better predictor for two reasons: (1) the time difference between the imaging and treatment session is minutes as opposed to days or weeks, and (2) 4DCT includes only one breathing cycle for the measurement of each anatomical position, whereas this study's 4DCBCT included 10–20 breathing cycles for each measurement.

In order to be careful with margin reduction strategies for clinical practice, the motion range under-prediction factors (Fig. 5) can help to estimate the SI and AP treatment target motion from 4DCBCT or from 4DCT, while also keeping in mind that the under-prediction errors are smaller for end-exhale than for inhale.

Baseline drifts larger than 5 mm were observed in at least one direction in 27% of the treatment fractions. The resulting uncertainties could be reduced by more frequent intrafraction imaging. Ideally, real-time motion tracking is available during treatment to monitor baseline drifts and sudden breathing pattern changes as they occur [23–25].

Overall a typical margin of 5 mm combined with a 4DCT- or 4DCBCT-based motion measurement covered for exceeding treatment motion in 76% and 83% of the treatment fractions, respectively, and the times of exceeding motion were short (1–20%, Fig. 4). This is in agreement with the data of Shi et al. [26] reporting that the tumour motion exceeded the motion estimation from 4DCT plus a 5 mm margin in up to 13% of the treatment time.

Treatment target motion amplitude variability had less effect on the motion under-prediction than the observed baseline drifts. In order to correct for amplitude variations in real-time, various options are available: multileaf collimator (MLC) tracking [23], motion tracking with CyberKnife [27], Vero [24], couch tracking [25] or gating the beam for larger amplitudes [11].

The marker segmentation error from the reconstructed 4DCT and 4DCBCT scans was estimated <1.5 mm and <1 mm based on the reconstruction voxel size of $1.2 \times 1.2 \times 1.5\ mm^3$ and $1 \times 1 \times 1\ mm^3$, respectively and therefore has only a very small effect on the presented results.

In this work, the centroid motion of the Calypso beacons served as the "target" and was used as surrogate for 4DCBCT reconstruction binning. There can be a surrogacy error between the Calypso beacon positions and the tumour centroid, but all of the motion measurements in this study were performed purely based on the beacons and thus a surrogacy error would be common to all measurements (4DCT, 4DCBCT, imaging and treatment) and is unlikely to significantly affect the results.

For lung SABR patients both 4DCT and 4DCBCT significantly ($p \leq 0.001$) under-predict imaging and treatment target motion ranges.

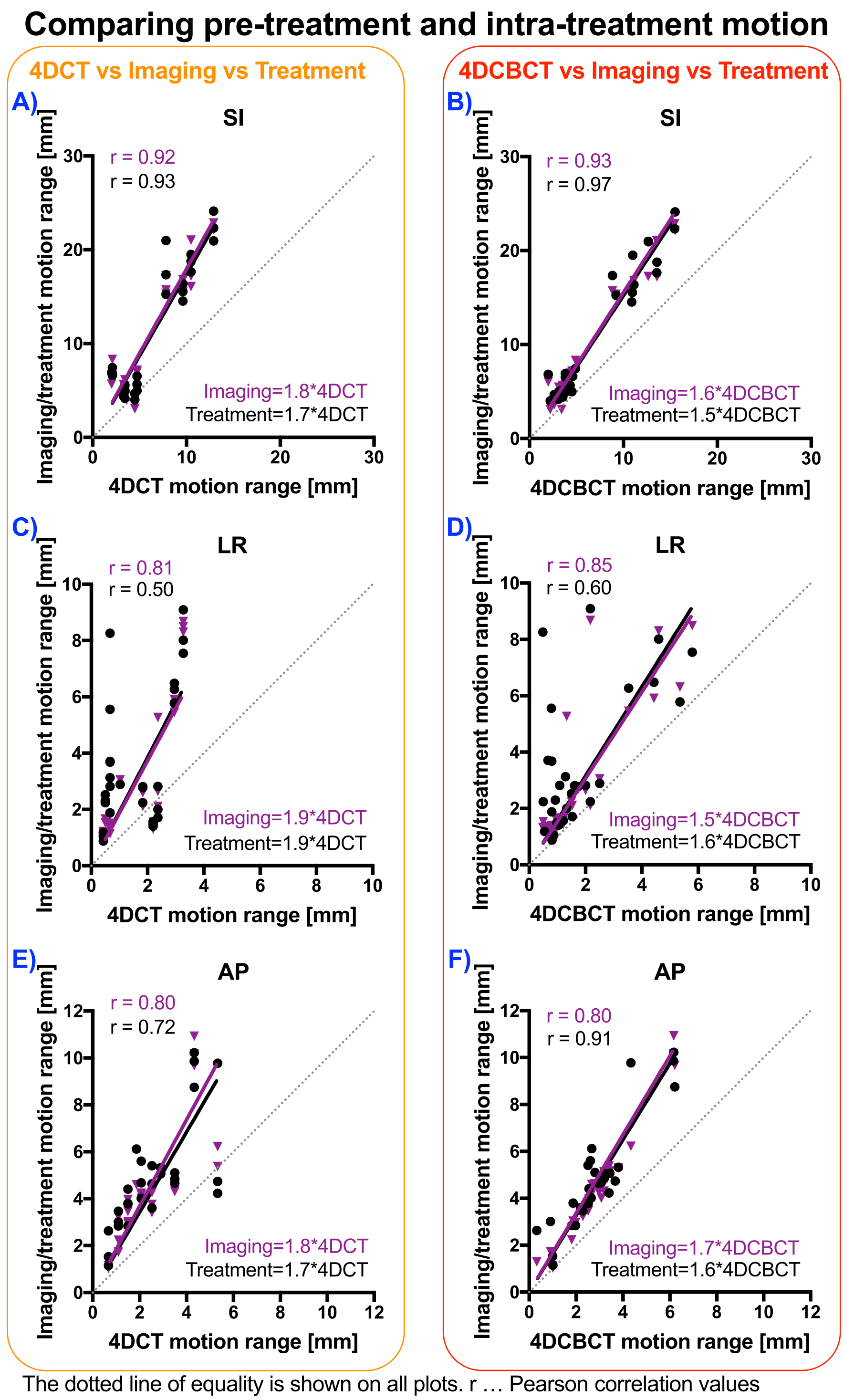

Fig. 5. Comparing pre-treatment and intra-treatment motion: Linear regressions and correlations between the SI imaging and treatment target motion ranges and (A) 4DCT and (B) 4DCBCT motion ranges; the LR imaging and treatment target motion ranges and (C) 4DCT and (D) 4DCBT motion ranges; and the AP imaging and treatment target motion ranges and (E) 4DCT and (F) 4DCBT motion ranges.

Conflicts of interest

Mr. Caillet, Dr. Booth, Mr. Briggs, Dr. Hardcastle, Dr. Jayamanne, Ms. Szymura, Dr. Eade and Dr. Keall report that Varian Medical Systems have partially funded the patient study that enabled this analysis. Dr. O'Brien and Dr. Keall hold Government and industry research grants and have other publically disclosed interests (http://sydney.edu.au/medicine/image-x/about/disclosures.php). Dr. Steiner and Dr. Shieh have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.019.

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