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ORIGINAL ARTICLE

Intrafractional baseline drift during free breathing breast cancer radiation therapy

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ABSTRACT

Background: Intrafraction motion in breast cancer radiation therapy (BCRT) has not yet been thoroughly described in the literature. It has been observed that baseline drift occurs as part of the intrafraction motion. This study aims to measure baseline drift and its incidence in free-breathing BCRT patients using an in-house developed laser system for tracking the position of the sternum.

Materials and methods: Baseline drift was monitored in 20 right-sided breast cancer patients receiving free breathing 3D-conformal RT by using an in-house developed laser system which measures one-dimensional distance in the AP direction. A total of 357 patient respiratory traces from treatment sessions were logged and analysed. Baseline drift was compared to patient positioning error measured from in-field portal imaging.

Results: The mean overall baseline drift at end of treatment sessions was −1.3 mm for the patient population. Relatively small baseline drift was observed during the first fraction; however it was clearly detected already at the second fraction. Over 90% of the baseline drift occurs during the first 3 min of each treatment session. The baseline drift rate for the population was -0.5 ± 0.2 mm/min in the posterior direction the first minute after localization. Only 4% of the treatment sessions had a 5 mm or larger baseline drift at 5 min, all towards the posterior direction. Mean baseline drift in the posterior direction in free breathing BCRT was observed in 18 of 20 patients over all treatment sessions.

Conclusions: This study shows that there is a substantial baseline drift in free breathing BCRT patients. No clear baseline drift was observed during the first treatment session; however, baseline drift was markedly present at the rest of the sessions. Intrafraction motion due to baseline drift should be accounted for in margin calculations.

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Introduction

Breast cancer radiation therapy (BCRT) is transitioning from offline in-field portal imaging to online volumetric imaging. Differences in target position between planning computed tomography (CT) and treatment can be accounted for by adding safety margins [1,2]. Margin reduction in radiation therapy could enhance the therapeutic ratio by reducing normal tissue doses [3–5]. Online imaging using cone beam computed tomography (CBCT) has the potential to reduce margins, but might increase the overall treatment time thereby resulting into greater intrafraction movement. The transition from offline in-field portal imaging to online pretreatment imaging also changes the timing of the image acquisition. Intrafraction movement should therefore be accounted for.

Geometrical uncertainties in BCRT are mostly due to setup errors, and the internal motion is not well described yet. A number of studies have quantified the setup errors in BCRT, but few include intrafraction errors [6,7]. Baseline drift is not regularly monitored during non-gated treatments and this might lead to unrecognized geometrical misses.

Baseline drift occurs probably due to muscle relaxation in the shoulder region, and the drift is differentiated from baseline shifts that probably happen due to patient movement during treatment. There are some studies that have evaluated baseline drift for breast, liver and lung cancer [8–12]. To our knowledge there are no studies describing the baseline drift within each fraction and for all treatment sessions for a large population of breast cancer patients.

The aim of this study was to measure baseline drift and its incidence in free-breathing BCRT patients using an in-house developed laser system for tracking the position of the sternum [13]. The in-house system was developed as a tool for deep inspiration breath hold (DIBH) BCRT, nonetheless in this study it was used to unveil patients with large baseline drift during conventional BCRT. Our hypothesis was that patients would exhibit different baseline drifts throughout the course of treatment, as a result of tension during the first treatment sessions. A secondary aim was to investigate if the

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Supplemental data for this article can be accessed here.

position of the patients' sternums measured with the laser system correlated with the calculated offsets from the portal images.

Material and methods

Patient selection

Patients referred to Ålesund Hospital for free-breathing (right-sided) BCRT were eligible for the study. A total of 20 patients were recruited; 11 patients received hypofractionation for breast only and nine patients received normofractionation for locally advanced breast cancer. Hypofractionation was given as 40.05 Gy in 15 fractions, while normofractionation as 46 Gy in 23 fractions to the breast and regional lymph nodes, plus 4 Gy in two fractions to breast only. An eventual boost to the tumor bed of 16 Gy in eight fractions was additionally prescribed and administered to some of the patients in accordance to national procedures. All recruited patients were asked for consent to participate in the Regional Ethics Committee approved protocol. There were no limitations regarding age or other diseases. The patients had a median age of 55 (range 30–89) years. The 20 patients were recruited consecutively during the period from October 2014 to March 2015. The treating physician informed the patient about the study and written consent was collected before acquiring the planning CT.

Treatment set-up

All patients were immobilized with a WingSTEP® (IT-V, Innsbruck, Austria) breast board in the supine position, no tilt was used, as the small bore opening of our CT-scanner could not accommodate this.

An in-house developed laser system was used to measure the position of the sternum [13]. The laser was attached to a flexarm (Jysk Handi, Hornslet, Denmark), and was pointed at a flat part of the sternum. The patient was aligned to the localization lasers, and then the in-house system started logging the position of the sternum. The system measures with a frequency of 10 Hz, and the baseline was established as the mean distance from the first 5 s of measurements as this corresponds to 1–2 breathing cycles. This relatively short measuring time was necessary in order not to conceal the initial baseline drift. The personnel left the room and treatment was initiated approximately 40–60 s after the logging of the sternum had begun.

Treatments were delivered by Elekta Synergy or Elekta Precise machines, both of them equipped with an 80 leaves MLC and an amorphous-silicon flat panel portal imaging system (iView GT 3.4, Elekta, Crawley, UK). Patient treatments comprised 4–11 fields, and the treatment was performed within 10 min treatment slots, only the first session required a double slot due to the extra time used for storing the table positions in our record and verifying system Mosaiq (Elekta, Crawley, UK), field and flash verification, manual loading of each treatment field as well as image acquisition during the first treatment fraction.

All patients followed an offline stereoscopic portal imaging protocol, in which the patients were imaged on day 1–3 and then weekly.

Data analysis

Patient respiratory traces from 357 fractions in total were investigated, as 15 respiratory traces were missing and the traces from the last two fractions of the normofractionated treatments were not measured. Due to breathing motion in the measurements, smoothing of the baseline measurements using a 20-s moving average with 10-s interval was calculated. Baseline drift was defined as the change in vertical position of the mean respiratory cycle, and the maximum upward or downward drift was calculated from the respiratory traces. For the calculation of the total baseline displacement of the patient population at the end of the treatment session a 30-s moving average with 30-s interval was calculated. The intrafraction drift was evaluated, for each patient and for the whole population sample. The incidence of different baseline shifts and the drift rate were also calculated.

The chest wall and ribs were outlined and two perpendicular fields were used to match the portal images to the digitally reconstructed radiographs from the CT-scan. Localization offsets were calculated after the third fraction and systematic positioning errors were corrected. Weekly patient positioning errors of less than 5 mm were accepted thereafter; in case of having deviations over 5 mm new images were acquired and a new trend was calculated. The average of the individual systematic setup-up error for the population (μ), the standard deviation of the individual systematic set-up errors for the population ($\sum$), and the average of the individual random set-up error for the population (σ) was calculated in accordance with the formalism proposed by van Herk et al. [1,2]. Using this formalism, the necessary margins to ensure that 90% of the patients would have 95% dose coverage to the CTV were estimated. In 3D, the PTV margins are determined using the formula $M = 2.5\sum + 0.7\sigma$ which has been widely used for margin calculation in BCRT [6,14,15].

The position of the patient's sternum measured with the laser system at the time of portal imaging was compared to the calculated offsets from matching the digital reconstructed radiographs with the portal images.

Statistical analysis

The results were analysed using a two-tailed paired student *t*-test and considered significant if p was less than 0.05. Simple linear regression was used for correlation tests. All statistical analysis and calculations were executed using SPSS version 23 (IBM, Armonk, NY, USA).

Results

The baseline drift of the patients as a population is shown in Figure 1. There was close to no baseline drift during the first fraction, whereas a significant baseline drift in the posterior

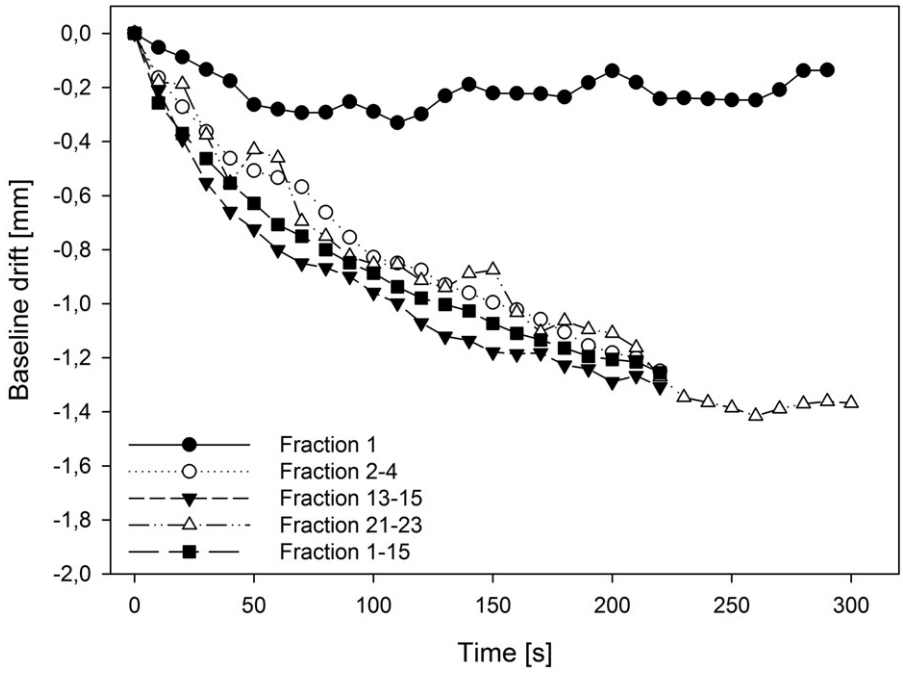

Figure 1. Baseline drift for the patient population as a function of time. Solid circles indicate the baseline drift during the first fraction; open circles represent the mean baseline drift for the 2nd, 3rd, and 4th fraction; solid reversed triangles show the mean baseline drift for the 13th–15th fraction; open triangles depict the mean baseline drift for the last three fractions of patients treated with the normofractionated regime; and solid squares indicate the average baseline drift for the first consecutively 15 fractions in both patient groups. Error bars not shown for readability.

direction was observed in the patient population at the 15th fraction. This baseline drift was already present at the second fraction and it was found that the mean baseline drift of fractions 2–4 was representative for fractions 13–15. The negative sign indicates a displacement towards the posterior direction. Error bars are not displayed for readability purposes (included in Supplementary Figure S1); however the maximum standard deviation was 1.2 mm after 220 s.

The baseline drifts for two patients displaying opposite behavior are shown in Figure 2. The patient shown in Figure 2(A) exhibited a large baseline drift in the posterior direction, whereas the patient shown in Figure 2(B) moved towards the anterior direction. It was found that 18 of the 20 patients exhibited a tendency of baseline drifts towards the posterior direction throughout the treatment sessions.

Figure 3 shows the total displacement of the baseline at the end of each treatment session for all patients. Baseline drift for the first fraction is represented by solid triangles. Only small displacements were observable during the first fraction. Nearly all baseline drift happened early in the treatment sessions, and then it reached a stable position over time.

The drift rate of the baseline position for the patient population is shown in Figure 4. The drift rate was more accentuated during the first minute, and a gradual decline in the drift rate was observed after the second minute. Over 90% of the baseline drift occurs during the first 3 min of each treatment session, and the rate of the baseline drift for the studied patient population is -0.5 ± 0.2 mm/min in the posterior direction the first minute after localization.

The incidence of baseline drifts of different magnitudes throughout the treatment sessions is presented in Figure 5. The incidence of baseline drift above 3 mm for all sessions was 10.2% three minutes after patient positioning, and only a small increase was observed from there on. After 6 min, a baseline drift of more than 3 mm was observed in 15.1% of the patient treatments. Baseline drifts of more than 5 mm, 5 minafter patient positioning were only found in 4.3% of the treatments. Treatment times were in the range of 3–12 min.

The baseline data was used to estimate the difference in AP position between the timing of an online pretreatment and offline in-field technique. In an online imaging protocol images are typically acquired approximately 60 s after initiating baseline logging, while portal images in this study were captured up to 292 s after patient was aligned to localization lasers. Baseline differences for 98 imaging sessions were calculated. Statistical significance was found for the mean difference of 0.5 ± 0.8 mm in the posterior direction ($p < .001$).

Portal imaging

A total of 238 portal images from 20 breast cancer patients were analysed. The overall mean setup-deviation μ was smaller than 0.1 mm in all directions. The systematic error $\sum$, and random error σ, were of the same order of magnitude in all directions ($\sum$AP $=1.6$ mm; $\sum$LR $=2.2$ mm; $\sum$SI $=1.7$ mm; σAP $=2.7$ mm; σLR $=2.5$ mm and σSI $=3.0$ mm).

PTV margins were calculated according to the systematic and random errors. Using van Herk's formula the margins were found to be 5.9 mm in the AP direction, 7.3 mm in the LR direction and 6.4 mm in the SI direction.

Taking the final baseline position into account, the PTV margins require an expansion in the AP direction. The mean baseline position of the patient population at end of treatment in the AP direction was -1.3 mm. About 18 out of

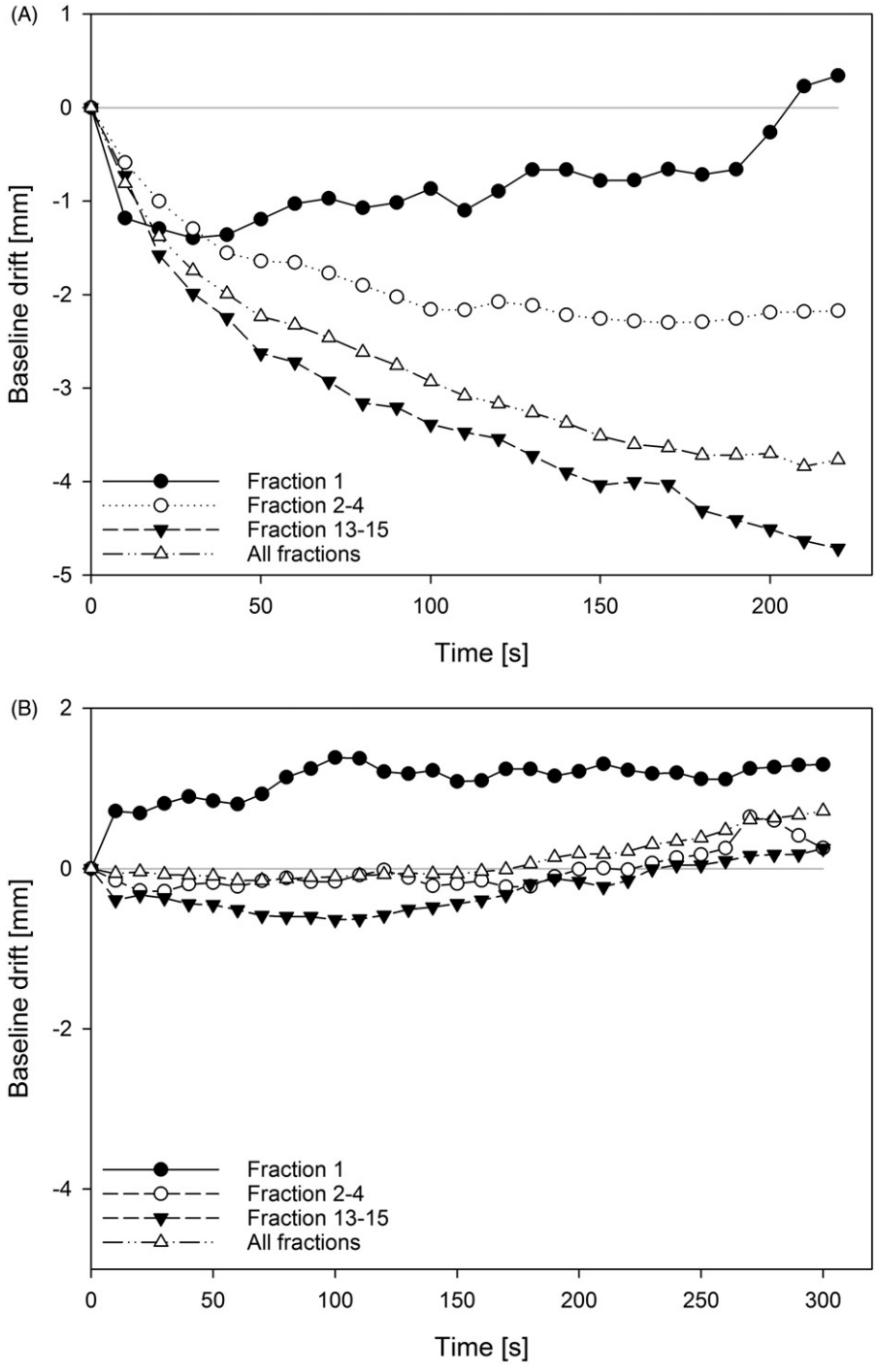

Figure 2. Measured baseline drift for two patients displaying opposite behavior: (A). Patient with relatively large baseline drift in the posterior direction, and (B). Patient showing baseline drift towards the anterior direction.

20 patients had a mean baseline drift over all fractions in the posterior direction. The systematic error $\sum$AP was 1.1 mm, and the random error σAP was 1.5 mm. This implies that if only intrafractional baseline drift is taken into consideration, a margin of 3.8 mm in the AP direction would be required. However, because the offline approach is used in this study, this group of patients would need a total margin of 7.0 mm in the AP direction.

It was also evaluated if the baseline position at the time of portal imaging correlated with the localization offset in the AP direction, and a weak correlation ($R = .26$) was found. The mean time from the positioning of the patient until portal images were acquired was 207 s, ranging from 94 to 292 s.

Discussion

The in-house system measured the displacement of the sternum as a surrogate for baseline drift. This is a one dimensional measurement and previous studies have found a good correlation between an external fiducial or breast surface and

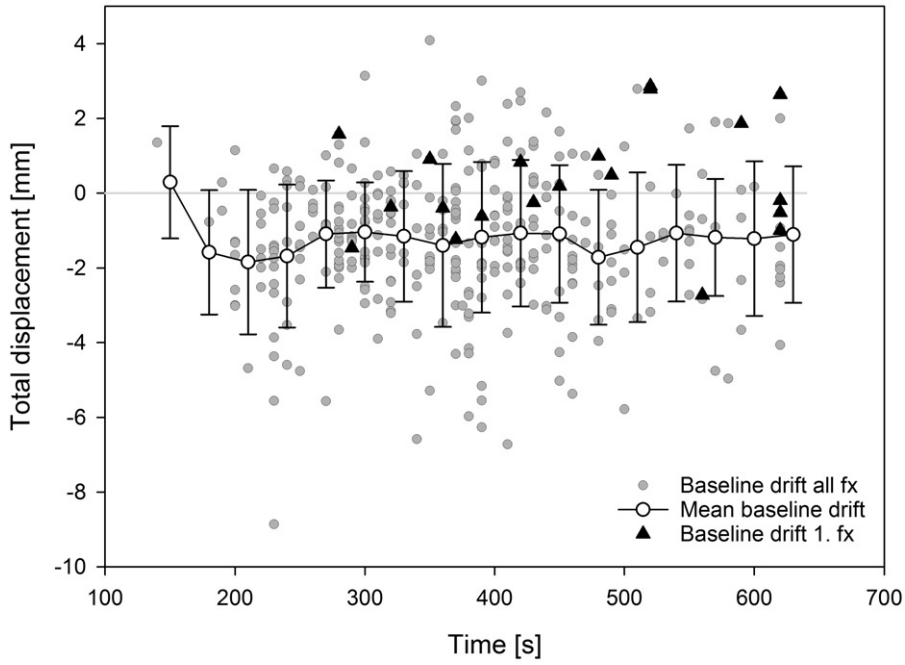

Figure 3. Total baseline displacement at the end of the treatment session. Open circles represent the mean baseline drift of the patient population at the end of all fractions; error bars indicate ±1 standard deviation. Solid circles depict the baseline drift for all patients and each fraction, and the solid triangles represent the total baseline drift of each patient at the first fraction.

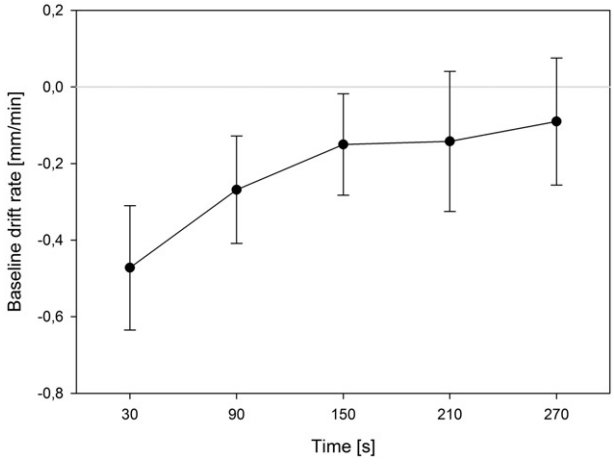

Figure 4. Baseline drift rate of the patient population for all fractions. Error bars indicate ±1 standard deviation.

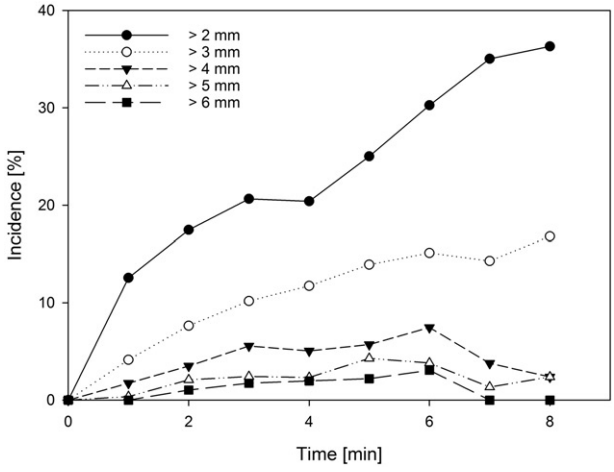

Figure 5. Incidence of baseline drift above different displacement levels as a function of elapsed treatment time.

the position of the breast [16–19]. All patients were immobilized with a WingSTEP® (IT-V, Innsbruck, Austria) breast board without tilt. We have previously reported that patients might slide down a breast board if an angle is used [20]. It is therefore assumed that there should be minimal patient movement in the SI direction as there was no breast board tilt in our study. Immobilization techniques can influence both inter- and intrafraction errors. A review by Michalski et al. [21] tried to assess the effect of different immobilization techniques, but the included studies only described interfractional error results. To our knowledge there are no studies investigating intrafractional baseline drifts for different immobilization techniques.

Kinoshita et al. [11] used a fluoroscopic real-time tracking system to monitor the position of a fiducial marker on the breast during the first minute of irradiation and only 4 out of 17 patients had baseline drift of more than 1 mm in the AP direction, this is compatible with our results. However they did not specified when the 1 minute tracking was initiated during the treatments sessions. Fein et al. [12] used tangential portal imaging to assess patient movement during treatment, and found motion tangential to the beam axis of 2.1 mm, but because of the imaging technique it is not possible to know the contribution from the AP direction. Quirk et al. [8] analysed 120 lung, liver and abdominal patients weekly determining the extent of vertical motion. Relatively large baseline drift was found in their study (>5 mm in 40% of the patients), however the measuring point was situated between the xiphoid process and the umbilicus. No obvious trend of increasing or decreasing baseline drift over the course of treatment was observed, and this is in line with the results in our study excluding the first fraction.

In our clinic, we have transitioned from offline in-field portal imaging to online pretreatment CBCT. We hypothesized

that extended treatment time would lead to increased intrafractional baseline drift. At our clinic it has been measured that online CBCT prolongs the treatment time between 120 and 240 s, depending upon the experience of the radiation technologist performing the match, and the complexity of it. The results show however that most of the baseline drift occur early during the treatment session and this extra time will not yield much to intrafraction errors.

Online pretreatment imaging is typically acquired 60 s after the patient is aligned according to the localization lasers, and the study showed that the portal images where acquired 207 ± 53 s after alignment. The mean baseline difference between imaging at 60 and 207 s was calculated to be only 0.5 ± 0.8 mm in our patient cohort. We could only find a weak relationship between the portal imaging and the measured baseline drift. A possible reason for this could be the rather large uncertainty in patient positioning. Patients are aligned to skin tattoos, which are susceptible to random errors due to loose skin. An online approach would reduce interfraction uncertainties, nevertheless uncertainties in accuracy of automatic table movement, kV versus MV isocenter position and intrafraction movement would still require a substantial target margin. At our clinic, interfraction uncertainties contribute to around 70% of the margin expansions when using an offline in-field imaging protocol, but an online protocol would lower systematic and random errors, thereby reducing our margins by 30%. A recent American survey found that even though the use of IGRT was increasing, there was no clear relation between the frequency of pretreatment imaging and the PTV expansion [22]. This indicates that the potential to enhance the therapeutic ratio is not being exploited.

It has been assumed that the DIBH technique could contribute to reduced PTV margins since patients usually are presented a 2 mm gating window inside which the sternum must remain during irradiation of each treatment field [23]. To date, there are no studies that have confirmed this, possibly because the intrafraction motion in free breathing BCRT patients is not large enough to establish a significant difference in small patient cohorts or since patient localization imaging is performed early in the treatment session without taking baseline drift into account. We found that for the patient population in this study, the overall mean intrafraction baseline drift was −1.3 mm, which indicates that the baseline drift might not be large enough to establish a significant difference in margins between patients presented with DIBH and those without it. Our group has recently submitted a paper that reports only a moderate non-significant margin reduction in the AP direction between DIBH patients and those without. We did however find that some patients had a substantial baseline drift that would compromise the margins typically used in BCRT. The largest baseline drift at end of treatment was close to 8 mm, and 17 out of 357 (∼5%) of the sessions exhibited a baseline drift larger than 5 mm.

The first fraction showed a different pattern than subsequent sessions for most patients. There was close to no baseline drift during the first fraction, even though the total treatment time was significantly longer than the rest of the fractions. One reason for this could be stress-related muscular tension during the first radiotherapy treatment session, which leads to limited muscle relaxation during the session. Already at the second fraction there was a marked difference in the baseline drift and this remains throughout the rest of the treatment sessions.

A limitation of our study is that the in-house laser system only tracks the position of the sternum in one dimension and therefore we are only able to describe the intrafraction movement in the AP direction. Most of the intrafraction movement due to muscle relaxation would occur in the AP direction, however, other authors have also described presence of intrafraction movement in the SI direction, which could be a consequence of the immobilization used [10,11].

It is not possible to avoid intrafractional movement during RT completely; however, it might be possible to compensate some of the displacements without significantly increasing the target margins. Some treatment planning systems include a robustness feature which calculates dose for different scenarios, each of this with the target and the organs at risk (OAR) at different possible positions, i.e., organ positions during a breathing cycle. This yields to lower dose to normal tissue when compared to using margins generated from overlapping all possible target positions, without compromising dose to the target. This technique has been compared to other possible solutions for accounting displacement of the target, and it has been proven to be superior [24].

A possible solution to improve intrafraction variability would be to reposition patients that exceed a threshold for baseline drift. This would remove the outliers and improve treatment for these patients. In our cohort only 17 out of 357 treatments sessions exhibited a baseline drift of more than 5 mm and this could be used as a threshold that would be sustainable in the clinic. Another suggestion to reduce the influence of baseline drift is to add a delay between patient alignment and patient imaging when using an online correction protocol.

A further possibility to reduce baseline drift is to monitor the sternum position of the patients and let them control it themselves. DIBH patients are presented with their breathing curve where they must keep the position of the sternum inside a target window in order to be irradiated, thereby limiting the baseline drift and possibly reducing the necessary margins to the target. The study by Essers et al. is so far the only study using DIBH for right sided BCRT, but they did not report inter- or intrafraction stability [25]. To our knowledge no studies have used active feedback for right sided BCRT patients in order to improve intrafraction stability.

In conclusion, this study shows that there is a substantial baseline drift in free breathing BCRT patients. An all-fraction mean baseline drift in the posterior direction in free breathing BCRT was observed in 18 of 20 patients. Overall, the baseline drift will account for roughly a third of the expansion of margins in the AP direction. If online corrections had been performed before treatment, the baseline drift in the studied group of patients would become the largest contributor to PTV margins in the AP direction, it is therefore essential that baseline drift is taken into account for margin calculations. The study shows that the first fraction is not

representative for baseline drift for the rest of the treatment sessions, and that it is possible to differentiate patients with large baseline drift that might compromise target coverage early in the treatment series. Baseline drift larger than 5 mm after 5 minutes was observed in 4% of the treatment sessions.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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