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Original Article

Intrafraction motion during partial breast irradiation depends on treatment time

Nienke Hoekstra [a,*], Steven Habraken [a], Annemarie Swaak-Kragten [a], Mischa Hoogeman [a], Jean-Philippe Pignol [b]

[a] Erasmus MC Cancer Institute, Department of Radiation Oncology, Rotterdam, The Netherlands; [b] Dalhousie University, Department of Radiotherapy, Halifax, Canada

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ABSTRACT

Introduction: As the prognosis of early-stage breast cancer patients is excellent, prevention of radiation-induced toxicity has become crucial. Reduction of margins compensating for intrafraction motion reduces non-target dose. We assessed motion of the tumor bed throughout APBI treatment fractions and calculated CTV-PTV margins for breathing and drift.

Methods: This prospective clinical trial included patients treated with APBI on a Cyberknife with fiducial tracking. Paired orthogonal kV images made throughout the entire fraction were used to extract the tumor bed position. The images used for breathing modelling were used to calculate breathing amplitudes. The margins needed to compensate for breathing and drift were calculated according to Engelsman and Van Herk respectively.

Results: Twenty-two patients, 110 fractions and 5087 image pairs were analyzed. The margins needed for breathing were 0.3–0.6 mm. The margin for drift increased with time after the first imaging for positioning. For a total fraction duration up to 8 min, a margin of 1.0 mm is sufficient. For a fraction of 32 min, 2.5 mm is needed. Techniques that account for breathing motion can reduce the margin by 0.1 mm. There was a systematic trend in the drift in the caudal, medial and posterior direction. To compensate for this, 0.7 mm could be added to the margins.

Conclusions: The margin needed to compensate for intrafraction motion increased with longer fraction duration due to drifting of the target. It doubled for a fraction of 24 min compared to 8 min. Breathing motion has a limited effect.

Accelerated partial breast irradiation (APBI) is an alternative to whole breast irradiation after lumpectomy for low risk breast cancer patients selected according to several international guidelines [1–6]. There is a tendency to reduce the number of treatment fractions for APBI from ten to five, or even down to single fraction treatments [7–14]. Hypofractionation has the advantage of convenience both for the patient and the radiotherapy facility, but could create challenges for the treatment delivery. Due to the reduced number of fractions, there is a possibly larger impact of a geographical miss of the target, with hence a potential increase in the risk of local recurrence. Most current hypofractionated external beam APBI (EB-APBI) protocols use daily online positioning verification and correction based on cone beam CT or kV imaging, or more recently MR imaging [13,15–17]. The motion that occurs after this setup and during the treatment delivery is often not considered. It is currently unclear what the magnitude of intrafraction motion is, and thus which safety margins should be used to compensate for intrafraction motion during EB-APBI. This safety margin is used to expand the clinical target volume (CTV) and create the planning target volume (PTV) according to the ICRU report 50 [18]. In short, it is called the PTV margin.

When treating small volumes like in APBI, every additional millimeter expansion of the PTV leads to a large increase in the volume irradiated, and to a higher dose in the surrounding healthy tissues. This increases the risk of toxicity and radiation-induced mortality, partially offsetting its survival benefit [19–21]. This is especially relevant for early-stage breast cancer patients, because of their excellent long-term breast-cancer specific survival. Using a PTV margin that is as small as possible is important to reduce radiation induced mortality. On the other hand, if the PTV margin used is too small, the consequence could be a higher risk of local recurrence and eventually a higher breast-cancer mortality.

The intrafraction motion of the breast can be complex, as it is a non-rigid organ and it is affected by breathing motion as well as slight changes in arm position and patient's muscular relaxation. There are some studies comparing pretreatment and post

* Corresponding author at: Erasmus MC Cancer Institute, Department of Radiation Oncology, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail address: n.hoekstra@erasmusmc.nl (N. Hoekstra).

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treatment imaging, but these analyses do not give information on the motion during treatment delivery [22–24]. Other studies only investigated breathing motion [24–26]. There are also studies that use a superficial surrogate for the motion of the tumor bed, using surface scanning techniques or LEDs on the skin of the patient [27,28]. These studies provide information on the motion during treatment delivery, but only of these surrogates and not of the actual target, which is the tumor bed. Acharya et al. reported on MR imaging of the tumor bed during APBI delivery [29]. The cine MR imaging is 2D, which means that there is no information about the left–right motion. The calculated margins are based on the total treatment times for their patient group, and they do not provide a method to adapt the margins for a possible difference in treatment time. Treatment time influences intrafraction motion and varies substantially between techniques (e.g. flattening filter free VMAT versus pencil beam scanning protons).

In this prospective clinical study, we assessed the intrafraction motion of the tumor bed during EB-APBI, based on fiducials inside or very close to the tumor bed and using kV imaging throughout the entire fraction. To this end, we analyzed clinical data of a cohort of patients treated with Cyberknife APBI. We calculated treatment time-dependent PTV margins in 3 dimensions based on the Van Herk margin recipe and distinguished breathing motion from drift [30].

Materials and methods

Twenty-two patients treated with APBI at Erasmus MC, Rotterdam the Netherlands, were included in this study, as part of a prospective clinical trial registered in the Netherlands Trial Register under NL6802. All patients provided written informed consent and were treated with 5 daily fractions of 5.7 Gy on a Cyberknife. Eligible patients were at least 50 years of age, had a pTis, pT1 or pT2 tumor of less than 3 cm, were pN0 for invasive disease and were treated with lumpectomy with negative margins (negative at ink for invasive disease, at least 2 mm for DCIS). Patients had at least three surgical clips placed in the tumor bed made of tantalum (any size) or titanium (at least 1 cm). Exclusion criteria were lobular carcinoma, presence of lympho-vascular infiltration, extensive intraductal component, multifocal or multicentric disease, neoadjuvant chemotherapy, distant metastasis or prior thoracic radiotherapy. In addition, all patients had three gold fiducial markers of 3 mm length placed inside the breast tissue at approximately 2 cm from the tumor bed under ultrasound guidance.

Patients were positioned supine in a vacuum mattress with the ipsilateral arm raised above the head. A planning CT scan was made with 1–1.5 mm slice thickness. The tumor bed was delineated using the seroma, postoperative changes, surgical clips and preoperative information. The CTV was created applying a uniform expansion of 10 to 15 mm to the tumor bed, excluding the thoracic wall and skin. An expansion of 5 mm was used to create the PTV. Treatment plans were made following our local clinical protocol, including digitally reconstructed radiographs (DRRs) for patient positioning. Patients were treated using the Synchrony® real-time motion synchronization technology (Accuray Inc., Sunnyvale USA). The details of this imaging protocol have been published previously [31]. In brief, two orthogonal kV images are acquired to reconstruct the 3D position of fiducials. The position of the target is calculated based on the position of the fiducials. In this study, either the surgical clips or the interstitial gold markers were used. The Synchrony system tracks breathing motion using three optical markers placed on the abdomen of the patient. These markers are the termination of optical fibers that transmit the signal of LEDs. A stereo camera system measures the 3D position of the markers continuously. The Synchrony system creates a correlation model between the motion of the optical markers and the motion of the fiducials based on kV images that sample the entire breathing cycle. Throughout the entire treatment fraction, the model is updated with sets of 3 pairs of kV images at regular intervals. The imaging interval can be adapted by the RTTs during treatment delivery based on observed patient's motion and their clinical expertise. The most common interval used was 150 seconds, with the three kV images made one second apart.

We extracted the 3D position of the target center of mass at each kV image pair for all patients and all fractions. The magnitude of breathing motion was calculated from the minimum and maximum center of mass position of the images that were used for the breathing correlation model, as the system ensures that it samples the entire breathing cycle during the modelling phase. The method by Engelsman et al., which is based on the Van Herk margin recipe, was used to calculate the margin needed to compensate for breathing motion:

Margin = 0.7 * σ, with σ = 0.4 * amplitude [30,32]. To apply this method to a population instead of an individual patient, we first calculated the random error σ of breathing per patient, which is 0.4 * amplitude, and then calculated the root mean squared of all the errors for the population. This value was multiplied by 0.7 to calculate the margin.

The next step was to calculate the drift of the tumor bed during the entire treatment fraction. The mean center of mass position of the breathing model was used as the reference to calculate any displacement during the treatment fraction. The images were binned into 2 min intervals, starting at the first image pair used for the breathing model. We calculated the mean and standard deviations of the center of mass displacements of all image pairs per patient and per bin. We used this to calculate the mean of means (M), systematic error (Σ) and random error (σ). Using the Van Herk formula, we calculated the margins needed to compensate for systematic and random intrafraction motion [30]. This resulted in a margin for each time bin separately. To obtain a margin that was valid for a given fraction duration as a whole, we calculated the cumulative running average for all bins up to and including the given time bin.

The Σ and σ are used in the margin calculation, whereas M is not. We analyzed M and its standard error separately. This metric would show a trend in the drift in one direction. To calculate the standard error, we divided the standard deviation by the number of fractions with data in each bin. We did not use the number of image pairs per bin, as the measurements within one fraction are strongly correlated.

The Synchrony algorithm ensures that the entire breathing cycle is sampled throughout the fraction. This means that breathing motion is included in our analysis of the drift. We subtracted the breathing motion error from the combined error to estimate the margin for drift only. This margin would apply to techniques that account for breathing motion but not for drift, e.g. breath hold or gating techniques. We used the Van Herk formula for the combination of different random errors, which means that the different random errors were subtracted quadratically [30].

All margin calculations were done for a target surrounded by breast tissue and a prescription isodose level of 95%.

Data extraction and calculations were done in Python version 3.5 (Python Software Foundation, Beaverton, USA) with the use of the packages Numpy and Pandas.

Results

Twenty-two patients were included in this study. Table 1 shows the patient characteristics. All patients were treated with APBI in 5 fractions to a total of 28.5 Gy. For one patient, the data of one fraction

Table 1
Patient characteristics.

		Range or percentage
Age (years)	Mean 63	50–84
Body mass index	Mean 27.7	22.3–40
Breast cup size		
A	1	4
B	7	27
C	5	19
D	5	19
E or more	4	15
Tumor laterality		
Left	9	41
Right	13	59
Affected quadrant		
Upper outer	13	59
Lower outer	1	5
Upper inner	6	27
Lower inner	0	0
Multiple quadrants	2	9
Tracking method		
Surgical clips	16	73
Interstitial markers	6	27

was missing. For another patient, a fraction was delivered in 2 subfractions over 2 days. Thus, there were 110 fractions available for analysis.

The mean duration of a treatment fraction, starting from the first images, was 26 min and the median was 25 min (range 11–47 min, 5th percentile 16 min, 95th percentile 36 min). In 15 fractions, the breathing model had to be rebuild at least once, due to patient movement or technical issues. The length of time that a breathing model was in use was on average 22 min with a median of 23 min (range 3–35 min). In total, 5039 image pairs were made, giving an average of 46 images pairs per fraction.

The average amplitude of the breathing motion of the tumor bed is shown in Table 2. The breathing amplitudes of the individual patients for each fraction are available in supplementary material table S1. The breathing motion was smallest in the lateromedial direction and of similar magnitude in the craniocaudal and anteroposterior directions. Margins between 0.3 and 0.6 mm are required to compensate for breathing motion.

Fig. 1 shows the mean deviation M (Fig. 1a), systematic error Σ (Fig. 1b) and random error σ (Fig. 1c) of the motion of the center of mass per time bin. This analysis includes all intrafraction motion, so both drift and breathing motion. Interestingly, the values increased with the time elapsed since the start of the fraction, mainly for M and Σ. After more than 30 min of treatment, there was limited data, which is also reflected by the increased error bars. The margin needed to compensate for intrafraction motion, calculated per time bin, also increased with fraction duration (Fig. 2). The values of M, Σ, σ and the calculated margins per time bin can also be found in the table in supplementary material table S2.

In clinical practice, the PTV margin is defined for the entire fraction instead of being variable over time. The single PTV margin is shown in Fig. 3. It is the cumulative running average of the margins per bin up to and including the given fraction duration. The margin increases with time, from 1.0 mm if the fraction is delivered in 8 min, to 2.0 mm for a fraction of 24 min and to more than 2.5 for a fraction of 32 min or more.

Fig. 3 also shows that the margin is very similar for the craniocaudal and anteroposterior direction, but smaller for the lateromedial direction. The margin in the lateromedial direction is about half as large as the margin in the other directions.

The systematic and random errors are translated into the required PTV margin, but the overall mean M is not used in this calculation. Taking a closer look at M, Fig. 1a shows that there

Table 2
Breathing amplitudes and required margins in craniocaudal, lateromedial and anteroposterior directions.

	Breathing amplitude (mm)		Margin (mm)
	Median	Interquartile range	
Craniocaudal	1.4	1.0–2.0	0.5
Lateromedial	0.6	0.4–1.0	0.3
Anteroposterior	1.5	1.0–2.2	0.6

was a significant deviation from the zero position in all directions. On average, patients drifted 0.7 mm in the caudal direction, 0.7 mm in the medial direction and 0.8 mm in the posterior direction during treatment. This drift could be included by the addition of 0.7 mm in the caudal and medial direction and 0.8 min in the posterior direction. That would result in asymmetric margins. For example, for a treatment of 20 min the margin would be 1.8 mm cranially, 2.5 mm caudally, 1.5 mm laterally, 2.2 medially, 1.7 mm anteriorly and 2.5 mm posteriorly.

The average margin from Fig. 3 includes the compensation for breathing motion. Some radiotherapy techniques already account for breathing motion, including breath-hold irradiation and gating, but not for drift. In these situations, the breathing error can be subtracted from the total random error using the Van Herk rules for combining different random errors [30]. The results for the cumulative running average of the required margins are shown in Fig. 4. The margin excluding breathing motion is on average only 0.1 mm smaller than the margin including breathing motion, with a maximum of 0.16 mm for the longest treatment times in the anteroposterior direction.

Discussion

This study showed that the margin accounting for intrafraction motion during EB-APBI is highly dependent on treatment time. The shorter the time interval between imaging and the end of irradiation, the smaller the margin required. For a fraction of up to 8 min, a PTV margin of 1.0 mm is sufficient, whereas a fraction of 32 min or more requires a margin of 2.5 mm. This is an additional reason to keep the fraction duration as short as possible, next to patient comfort and logistical reasons.

The duration of a fraction is mainly based on two aspects, the set-up time and the treatment delivery time. The set-up time includes the time for imaging, the evaluation of the images, and the application of the calculated corrections. It depends on the protocol used, for example kV imaging or CBCT and offline or online matching. Using a less sophisticated protocol can save time, but one needs to keep in mind that it could result in a lower accuracy. The margin for interfraction motion might increase, mitigating the benefit of a reduced time for positioning. The solution could be an automated set-up calculation and correction, as this should be both accurate and fast.

The treatment delivery time depends on the planning technique and the treatment machine. Regarding the choice for a technique, there is also a trade-off to keep in mind. A more sophisticated dose plan might result in lower doses to non-target tissues. For APBI, it has been shown that a non-coplanar beam setup resulted in lower doses to surrounding organs than a coplanar beam setup [33]. On the other hand, a more sophisticated dose plan often has a longer beam-on time and a longer gantry or couch movement time. The treatment machine also has an important effect on the treatment delivery time. Pencil-beam scanning proton therapy has a relatively long treatment time, but very low doses to organs-at-risk. A conventional linac is faster with flattening filter free dose delivery than without. To combine speed with conformity, the use of non-coplanar arcs or even hyperarcs could be of great benefit.

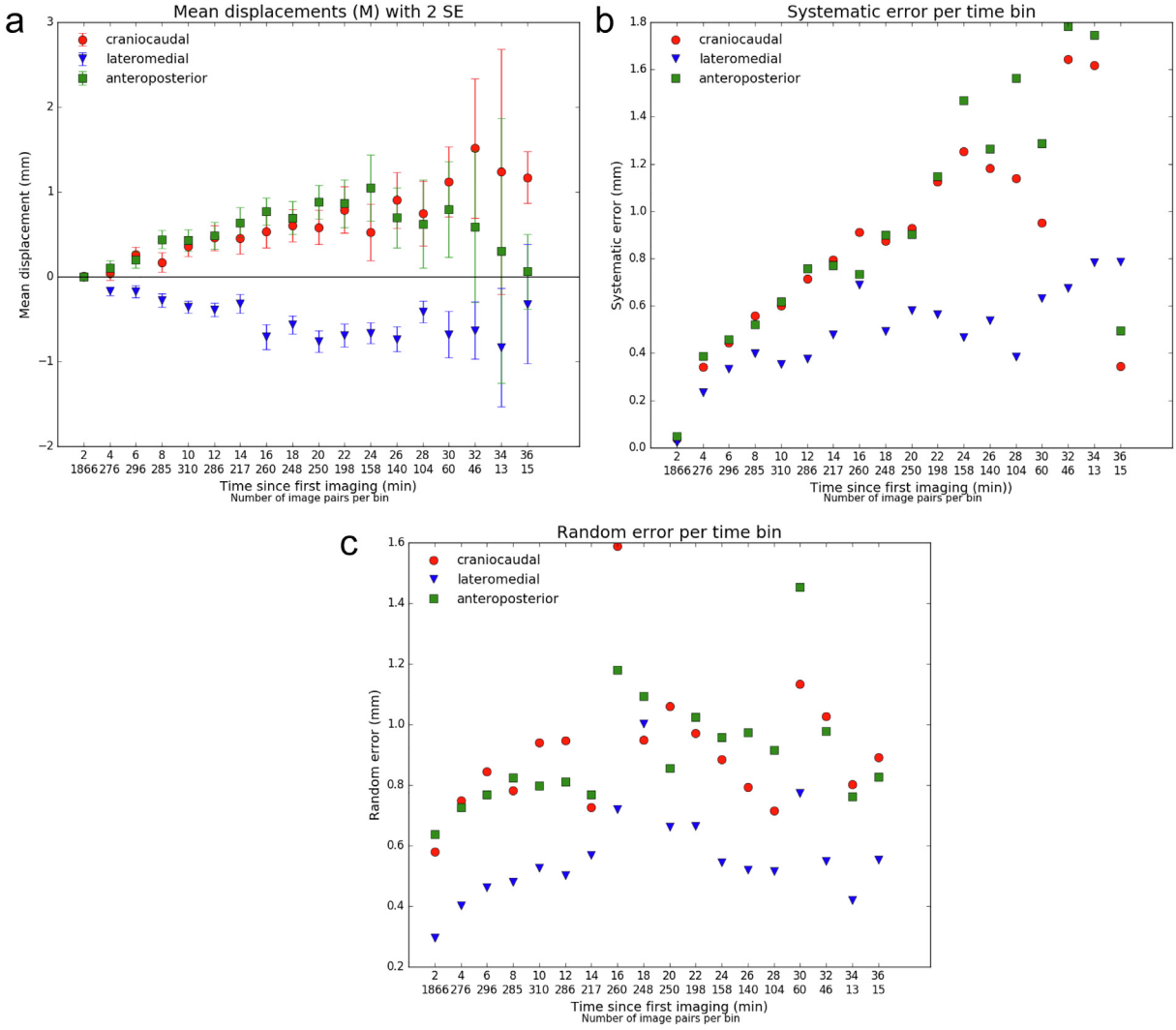

Fig. 1. Mean of means M (a), systematic error Σ (b) and random error σ (c) of the intrafraction motion for each 2-minute time bin. The bars in (a) depict 2 standard errors. A positive value in (a) is a displacement in the caudal, lateral and posterior direction. The upper row of values along the X-axis shows the time elapsed since the first imaging for set-up. The lower row shows the number of image pairs analyzed in each time bin.

The Cyberknife has a long treatment time, due to the large number of non-coplanar beams and the robot travelling time. As the Cyberknife can track and trail the target during treatment delivery, the increased drift is continuously corrected and the prolonged treatment time does not require a larger margin.

To the best of our knowledge, our study is the first to show the increase in drift over time during treatment for breast cancer patients. Lovelock et al. investigated intrafraction motion in prostate cancer patients and found an increase in margin of 2 mm per 5 min, starting from the time of the imaging procedure [34]. Wang et al. report a time-dependent increase in 3D-vector for intracranial treatments [35]. Hoogeman et al. published on both intracranial treatments and spine treatments [36]. They concluded that the systematic error of intrafraction motion depended on the time between localizations. For breast cancer patients, no other time-resolved analysis has been published.

We found a systematic drift in the caudal, medial and posterior directions. This mean deviation M is not addressed in the margin recipe as proposed by Van Herk. He assumed that M would be zero. The best way to deal with such a systematic drift would be to change the isocenter of the treatment to the new target location. Certain techniques like the CyberKnife and the MRIridian are able to track and trail the target. For techniques that cannot track the target, an additional margin is necessary. We calculated that this additional margin should be 0.7 mm in the caudal and medial direction and 0.8 mm in the posterior direction. It is unclear why this drift occurs, but it is evident that the human body is not rigid over time. During treatment delivery, patients might slide downwards in the vacuum mattress, breathe differently, relax muscles or shift the ipsilateral arm which is raised above the head. This could all influence the position of the tumor bed.

Our results do also apply to other treatments than APBI. The motion patterns will probably be the same for whole breast irradiation with a tumor bed boost. The fields or arcs of a simultaneous boost are often given after the whole breast fields, which means that the time since start of treatment is longest. Also, protons treatments are increasingly used for complex cases, often requiring whole breast irradiation, nodal irradiation and a boost on the tumor bed. The total treatment time with pencil-beam scanning is long. The margins for the PTV of the boost should take the intrafraction motion into account.

The margins reported in this study are small with differences in PTV margins in the order of one millimeter. It is unsure whether a clinical benefit could be expected from such small differences. For example, the IMPORT LOW trial, which uses a very crude way to deliver partial breast irradiation, reports good cosmetic outcomes

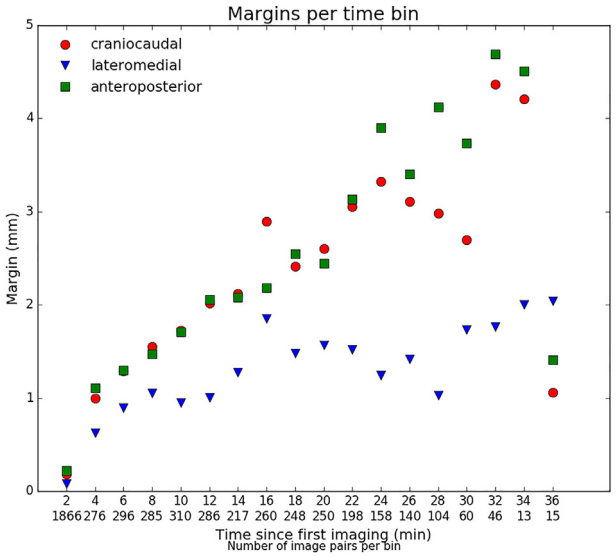

Fig. 2. Margin required for each time bin to compensate for intrafraction motion. The upper row of values along the X-axis shows the time elapsed since the first imaging for set-up. The lower row shows the number of image pairs analyzed in each time bin.

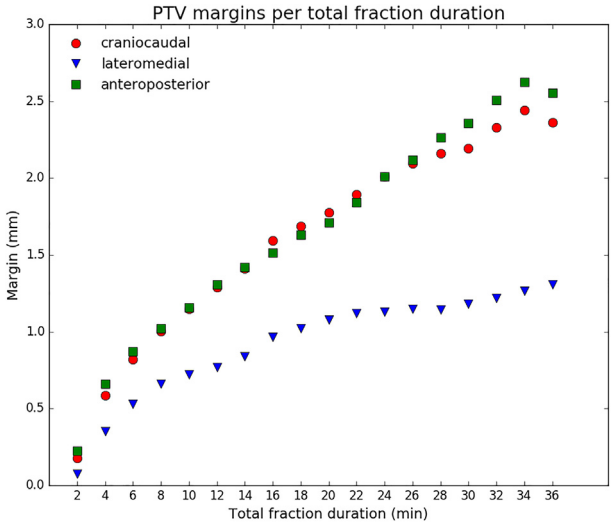

Fig. 3. Margin required per total fraction duration to compensate for intrafraction motion.

[37]. Thus, it is unclear whether a small margin reduction for a highly conformal technique could lead to a measurable benefit in a clinical trial. In the setting of a clinical trial, the number of patients and the length of follow-up are limited, so the absolute numbers of patients with long-term toxicity within a trial will be very small. After widespread adoption of APBI for this patient group with a long life expectancy, the absolute numbers will increase, making minor benefits also relevant. It is also important to see the small difference in margin in the light of the small volumes treated in APBI. For example, for a 2 cm sphere, a millimeter margin leads to a 33% volume increase in the PTV. Treating this much larger PTV will result in higher doses to the healthy tissues surrounding the target and in higher risks of long term toxicity. This may become clinically important with the more accelerated dose fractionations used in recent trials, even down to a single

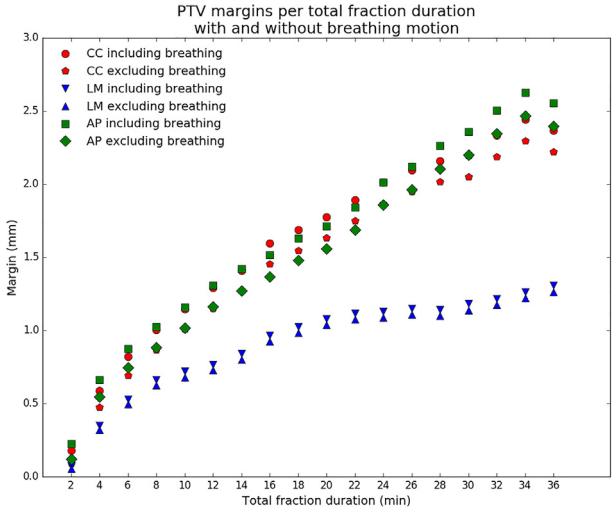

Fig. 4. Margin required per total fraction duration to compensate for intrafraction motion. CC = craniocaudal, LM = lateromedial, AP = anteroposterior.

fraction treatment [9–14]. Moreover, following the ALARA principle ("as low as reasonably achievable"), one should aim to reduce the not-target dose as much as possible.

Acharya et al. reported a study on cine MR imaging during APBI delivery [29]. They found that a margin of 0.7 mm was required to cover 90% of the cavity volume for 90% of the time. This value was an average over 30 patients. The mean treatment time in their cohort was 12.7 min. We found a margin of 1.4 mm for a treatment time of 12–14 min. The difference might be explained by a difference in margin definition. We used the formula by Van Herk, which requires at least 90% of the patients to receive at least 95% of the prescribed dose in the CTV [30]. Both the required volume and the proportion of the population are higher in our analysis than the values used by Acharya et al., namely 95% versus 90% and 90% versus 50% respectively. The average margin of 0.7 mm of Acharya et al. would result in only half of the patients meeting a minimum coverage of 90%.

Our analysis is based on the motion of fiducials that are in the tumor bed. There is a lot of debate on the accuracy of the delineation of the tumor bed. This is especially true in the case of full thickness closure. The use of MR for delineation did not improve the interobserver agreement [38]. The study by Acharya et al. defined the tumor bed motion on 2D cine MRI, while our study is an analysis of the motion of the fiducial markers in three dimensions [29]. The 3D position of the fiducials can be calculated with high accuracy. Assuming that they are good surrogates for the tumor bed within a single fraction, this results in an accurate measurement of tumor bed motion. Our study does not focus on tumor bed definition, only on its motion. A drawback of our method is that there can be motion of the fiducials relative to the tumor bed. This has been shown for the interval between simulation and the first fraction, and the magnitude of this motion is related to the length of the interval [23,39]. For the very short time scale of intrafraction motion, the displacement of fiducials with respect to the tumor bed is expected to be negligible. The analysis is done relative to the position at the start of treatment after the initial alignment. Because the patient is not repositioned during treatment, there is no influence of repositioning or interfraction motion in our analysis. To calculate a margin that compensates for both intrafraction and interfraction motion, a linear combination of these margins would result in an overestimation. The systematic and random errors of each component should be combined quadratically in the van Herk formula. The systematic and random

errors for each time bin in this study are provided in the supplementary materials.

In our study, patients were positioned in a vacuum mattress. Another option for patient positioning is the use of a chest board. The magnitude of drift can differ between different positioning devices. Hubie et al. found the accuracy of a vacuum mattress to be better than that of a chest board, but the differences were not statistically significant [40]. Thus, a definitive conclusion cannot be drawn at this point.

The median breathing amplitude in this study was small, 1.4 mm in craniocaudal direction, 0.6 mm in lateromedial direction and 1.5 mm in anteroposterior direction. This is similar to the results of other studies [25,26,28]. These studies do not report a margin for breathing motion. Applying the calculation as published by Engelsman, the margins in these studies would be similar to our results [32].

Another interesting finding of our study was that the margin for techniques that already account for breathing motion, e.g. breath hold and gating, is only 0.1 mm smaller than for techniques that do not account for breathing. The random error of breathing motion was subtracted quadratically from the total error according to the Van Herk formula, resulting in a very small difference [30]. This indicates that efforts trying to reduce intrafraction motion would better be aimed at reducing drift than at accounting for breathing motion. Still, the use of deep inspiration breath hold has other advantages than reducing breathing motion, such as a lower dose to heart and lungs.

The required margin does not linearly depend on treatment time, as can be seen in Figs. 2 and 3. After an initial steep increase, the dependence flattens. This might be explained by the patients tending to relax and settle down on the treatment couch. The time spent on the couch before the first imaging might influence the drift. This time is not included in our analysis. In 15 out of 110 fractions, the breathing model was rebuilt during treatment delivery. In some cases, the patient was repositioned and therefore we expect no difference with motion after the initial setup. In other cases, the patient was not repositioned, which could lead to a smaller drift after the model rebuild. Overall, this could lead to a slightly smaller drift calculated for the entire patient population.

The use of kV images throughout the fraction warrants a consideration of the associated imaging dose. The imaging dose of an orthogonal kV image pair is about 0.01 cGy [41]. With an average number of image pairs per fraction of 46, the total imaging dose is below 0.5 cGy. With a prescription dose of 5.7 Gy per fraction, the imaging dose contribution is only 0.01%. Also, a decrease in margin will result in lower doses in surrounding tissues, and the benefit is expected to be much larger than the additional imaging dose. The steepness of the drift is highest in the first part of treatment and quite stable in the second part. It would be most efficient to use a slightly shorter imaging interval in the first part of treatment, but imaging throughout the fraction will remain necessary.

Conclusion

For APBI, the CTV to PTV margin is strongly influenced by the target drifting over time. The margin required to compensate for intrafraction motion increases from 1.0 mm for a fraction of 8 min, to more than 2.5 mm for a fraction of 32 min. We recommend to keep the time between set-up and end of treatment as short as possible to avoid geographical miss. If a short treatment time is not feasible, the margin should be increased or the drifting should be corrected for. Therefore, it is important to consider treatment time when developing and implementing more conformal irradiation techniques. Breathing motion has a limited influence on the intrafraction motion.

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Conflicts of interest

Dr. Hoekstra reports grants from Accuray Inc., Sunnyvale, USA, during the conduct of the study. Prof. Hoogeman has been member of the Clinical Advisory Board of Accuray Inc., Sunnyvale, USA. The other authors report no conflicts of interest.

Erasmus MC Cancer Institute has research collaborations with Accuray Inc., Sunnyvale, USA, and Elekta AB, Stockholm, Sweden.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.03.029.

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