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Original Article

Fiducial marker motion relative to the tumor bed has a significant impact on PTV margins in partial breast irradiation

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ABSTRACT

Introduction: With the introduction of accelerated partial breast irradiation (APBI) and the trend of reducing the number of fractions, the geometric accuracy of treatment delivery becomes critical. APBI patient setup is often based on fiducials, as the seroma is frequently not visible on pretreatment imaging. We assessed the motion of fiducials relative to the tumor bed between planning CT and treatment, and calculated margins to compensate for this motion.

Methods: A cohort of seventy patients treated with APBI on a Cyberknife was included. Planning and in-room pretreatment CT scans were registered on the tumor bed. Residual motion of the centers of mass of surgical clips and interstitial gold markers was calculated. We calculated the margins required per desired percentage of patients with 100% CTV coverage, and the systematic and random errors for fiducial motion.

Results: For a single fraction treatment, a margin of 1.8 mm would ensure 100% CTV coverage in 90% of patients when using surgical clips for patient set-up. When using interstitial markers, the margin should be 2.2 mm. The systematic and random errors were 0.46 mm for surgical clip motion and 0.60 mm for interstitial marker motion. No clinical factors were found predictive for fiducial motion.

Conclusions: Fiducial motion relative to the tumor bed between planning CT and APBI treatment is non-negligible and should be included in the PTV margin calculation to prevent geographical miss. Systematic and random errors of fiducial motion were combined with other geometric uncertainties to calculate comprehensive PTV margins for different treatment techniques.

Adjuvant radiotherapy remains a cornerstone in the treatment of early-stage breast cancer, reducing the local recurrence risk and increasing the overall survival [1]. Hypofractionated treatment schedules result in similar local recurrence risks for early-stage breast cancer as conventional fractionation [2,3]. The reduced number of hospital visits and the shorter overall treatment time are more convenient for patients and radiotherapy institutions. The trend towards even more ultra-hypofractionated regimens is still ongoing, with trials currently investigating treatment schedules for accelerated partial breast irradiation (APBI) with a single fraction [4–8]. The first examples of single-fraction APBI (SF-APBI) techniques in clinical use were intraoperative radiotherapy and permanent seed implants [9–12]. These techniques require specialized equipment and training. External beam radiotherapy techniques have the advantage of being non-invasive and more widely available. However, the major concern with external beam SF-APBI is the accurate localization of the target during treatment. Missing the target could result in an increased risk of local recurrence, because the random errors between fractions are not averaged, but contribute to the systematic error in a single fraction treatment. Therefore, a high geometric accuracy combined with the use of an adequate margin from clinical target volume (CTV) to planning target volume (PTV) is essential.

Another challenge for the use of SF-APBI for early-stage breast cancer is the use of full thickness closure after breast-conserving surgery. While suturing the glandular tissue after tumor removal leads to a smaller seroma cavity and lower risk of complications, the smaller seroma is often not visible on the images used for patient setup and target localization for radiotherapy [13,14]. Radiopaque fiducial markers inserted in or close to the tumor bed are often used instead. However, little is known about the possibility of motion between the fiducials and the tumor bed. To avoid a geographical miss and an increased risk of local recurrence, the motion of the fiducials relative to the tumor bed should be quantified and included in the PTV margin calculation.

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The choice of a CTV to PTV margin for use in clinical practice is a trade-off between the risk of a geographical miss and the doses to surrounding healthy tissues. The balance depends on the prognosis of the treated patient group and the toxicity profile of the treatment. With the current highly conformal APBI techniques, dose to surrounding tissues is reduced and local recurrence risks are low [15–18]. Therefore, it would be interesting to see the effect of varying the PTV margin on the probability of geographical miss.

The main goal of this study is to determine adequate CTV to PTV margins for external beam APBI. The motion of surgical clips and interstitial gold markers relative to the tumor bed was measured in a large cohort of patients using in-room diagnostic quality CT scans. Next, we calculated the PTV margin needed to compensate for this motion in a single fraction treatment as a function of the risk of geographical miss. In addition, we generalized our results to comprehensive PTV margins for different APBI techniques to be used in clinical practice.

Materials and methods

Patients and procedures

Patients treated with APBI on a CyberKnife at Erasmus MC between November 2018 and March 2021 were included. Patients with at least 3 titanium surgical clips in the tumor bed were eligible for this study. The insertion of surgical clips in the walls of the tumor bed during lumpectomy is a standard procedure for all patients undergoing breast conserving surgery. The aim of the use of surgical clips is to increase the accuracy and reproducibility of the tumor bed delineation for radiotherapy. The standard surgical procedure was a closed-cavity technique. Patients were treated with 5 fractions of 5.2–5.7 Gy in one week. All patients had 2 to 3 gold markers inserted postoperatively into the breast around the tumor bed under ultrasound guidance. We refer to these as interstitial markers. The local Medical Ethics Committee of Erasmus MC, Rotterdam the Netherlands approved the exempt of ethics review and informed consent for this analysis of anonymized patient data (MEC-2020-0415).

Patients were positioned on a vacuum mattress with the ipsilateral arm raised. According to our clinical protocol, all patients had both a planning CT scan (Siemens Somatom Confidence) and a diagnostic-quality in-room CT scan (Siemens Somatom Definition AS) in treatment position before the first fraction. The in-room CT scan was acquired with a CT-on-rails scanner integrated with a CyberKnife [19]. The robotic treatment couch is shared between the CT scanner and the CyberKnife system, so that the patient can remain in treatment position on the treatment coach between image acquisition and the treatment. The obtained CT scan can be used to offset the treatment center to align with soft tissue targets, to perform online adaptive treatments, or to verify the position of implanted markers relative to e.g. the tumor bed, as done in this study. Identical acquisition parameters were used for the planning and in-room CT scans. The slice thickness was 1–1.5 mm. All CT scans were acquired during voluntary exhalation to decrease variation due to breathing motion. The tumor bed was delineated by the treating radiation oncologist bearing in mind all preoperative and postoperative information and physical examination, paying careful attention to the surgical clip positions and the postoperative changes on the planning CT scan. The tumor bed was expanded with a 10–15 mm uniform margin to create the CTV, depending on the resection margins.

CT analysis

The planning CT scan and the in-room CT scan were registered based on the delineation of the tumor bed using MIM software (version 6.9.3). A 5 mm isotropic margin was added to create the registration volume. All automated registrations were checked visually by a single trained observer. There were sufficient anatomical landmarks visible within this area to perform an accurate registration, including but not limited to seroma, postoperative changes and glandular tissue. In case of a suboptimal registration, the two CT scans were first registered on the PTV or CTV and then on the registration volume. This was repeated until an adequate registration was obtained. As quality assurance, the registration procedure was repeated with an isotropic expansion of 4 and 6 mm in a random sample of 10 patients. For this random sample, the registration procedure was repeated by a different observer using the default 5 mm expansion to quantify interobserver variation. Finally, we selected the patients with the 10% highest fiducial motion errors in the default analysis and repeated the registration procedure for these cases to test the intraobserver variability in the worst case scenario.

The fiducials were manually delineated by the observer who also performed the registrations, using a lower threshold of 400 HU. In the tumor bed aligned CT scans, we determined the distance between the fiducials in the planning CT and the in-room CT scan for each of the 3 main directions separately. Next, we calculated for each patient the residual distance of the center of mass (CoM) of all surgical clips and of all interstitial markers together. This distance is the error in patient setup for the tumor bed when it is based either on the CoM of the surgical clips or interstitial markers.

CTV to PTV margin calculation for fiducial-based patient set-up

The percentage of patients without any loss of coverage, i.e. without any deviation from the prescribed dose, was calculated as a function of the PTV margin, simulating a patient-setup based on the CoM of the surgical clips or the interstitial markers. The margin was defined as a uniform three-dimensional expansion of the CTV. Here, we calculated the margins required for the setup errors in the CoM of the surgical clips and interstitial markers relative to the tumor bed only. The common approach is to calculate the standard deviation of the error distributions and to use for example the Van Herk margin recipe, which provides a margin for adequate treatment in 90% of the patients [20]. Because the underlying assumption of a Gaussian distribution was not fully satisfied in this study and because we wanted to calculate the margin as a function of the percentage of patients without coverage loss, we used sampling of the error distributions instead. Bootstrapping with replacement was used to reduce bias in the calculation of the margins. For each percentage of patients without coverage loss, the average margin over the bootstrap samples was calculated.

Comprehensive CTV to PTV margin calculation

Next, we generalized the margin calculation by also including other error sources and calculating the single-fraction margin for two commonly used APBI techniques: 1) VMAT-APBI on a conventional radiation treatment unit with patient-setup based on surgical clips using cone beam CT and 2) CyberKnife-APBI with real-time respiratory tracking based on interstitial markers. As the real-time tracking algorithm does not reliably track most types of surgical clips, interstitial gold markers are used in our and other institutions [21–24]. To calculate the single-fraction margins for these two techniques, technique-specific systematic and random errors, expressed as 1 standard deviation of a Gaussian distribution, were taken from literature. For VMAT-APBI, these are beam isocenter accuracy, couch accuracy, and intrafraction motion (Table 1) [25–29]. For CyberKnife-APBI, this is the CyberKnife total system error, which combines imaging and beam adjustment errors. If only tolerance values were available, half the tolerance

Table 1
Overview of systematic and random errors for various geometric uncertainties of external beam APBI. Reported values are for conventionally fractionated treatments.

Geometric uncertainty		Systematic error Σ (mm)	Random error σ (mm)
Intrafraction motion	Breathing motion [25]	0.7*	0.7
	Drift [25]	0.49	0.28
Beam accuracy	Conventional treatment unit [26,27]	0.5	-
Couch accuracy	Conventional treatment couch [26,27]	0.5	0.5
Total system error	Cyberknife fiducial tracking [28,29]	0.23	-

* Applicable for the situation of a free breathing planning CT scan with a scanning time much shorter than the breathing cycle time.

value was taken as standard deviation of the error distribution. In case the error has been separated in a random and systematic component, both errors were combined by adding the standard deviations in quadrature for the single-fraction treatment margin. This is in accordance with the methodology presented by de Boer et al. to convert systematic and random errors for conventionally fractionated treatments to hypofractionated schedules [30]. To calculate the systematic margin for VMAT-APBI, the drift, beam and couch error distributions and the systematic breathing error distribution were sampled together with the error distribution of the surgical-clip-based patient setup and summed. Next, we calculated the random margin to account for intrafraction breathing motion by multiplying the random breathing error with 0.7. This describes the dose blurring by breathing motion. Following the methodology of Van Herk this random margin was added linearly to the systematic margin to calculate the total margin [20]. For CyberKnife-ABPI, a similar procedure was followed to calculate the systematic margin, but as CyberKnife compensates for breathing motion by real-time tracking, this random error was not added.

Finally, we generalized our margin calculation to fractionated treatments. Although the underlying assumption of a Gaussian distribution was not fully satisfied in this study, we calculated the systematic error (Σ) and of the random error (σ) for both fiducial-based patient-setup methods. As our results are based on a single fraction per patient, we had to estimate the contribution of systematic and random errors. We assumed an equal magnitude of systematic and random errors based on literature, so $\Sigma \approx \sigma$ [31]. Next, we converted the single fraction errors into errors of fractionated treatment using the method proposed by De Boer et al. [30].

Factors predictive for fiducial motion

We compared the distributions of the residual errors of the surgical clips and interstitial markers with the two-sample Kolmogorov Smirnov test. To assess whether there are clinical or treatment factors associated with the magnitude of the fiducial motion, we tested a possible correlation with breast size, tumor bed size and the interval between planning CT and first fraction. To this end, the Pearson correlation coefficient was calculated, after visual inspection of scatterplots to exclude other types of correlation than a linear correlation. All analyses were done with Python version 3.5. A *p*-value of <0.01 was considered significant because of multiple testing.

Results

In total, 70 patients were included in this study. Patient characteristics are shown in Table 2. Thirty-nine patients had a left-sided breast cancer and 31 patients had a right-sided tumor. The median

Table 2
Characteristics of included patients and their treatments.

	Number or median	Percentage or range
Laterality		
• Left-sided	39	56%
• Right-sided	31	44%
Interval planning – first fraction (days)	14.5	3–24
Number of surgical clips		
• 3	2	3%
• 4	13	19%
• 5	49	70%
• 6	3	4%
• 7	1	1%
• 8	2	3%
Number of interstitial markers		
• 2	2	3%
• 3	68	97%
Ipsilateral breast volume (cc)	873	166–2743
Tumor bed volume (cc)	9.5	0.9–41.1

interval between planning CT scan and first fraction CT scan was 14.5 days (IQR 11–17 days). For three patients, the anatomical changes noticed on the first fraction in-room CT images were so large that a new treatment plan was requested. The in-room CT images were used or this new plan and these three patients were treated with a delay of 3, 3 and 10 days. For each of those 3 patients, an additional in-room CT scan was acquired at the delivery of the first fraction. We used the first and second in-room CT scan for the analysis.

The median number of surgical clips was five (range 3–8). All but two patients had three interstitial gold markers inserted in the breast around the surgical cavity and the other two patients had 2 markers.

The distributions of the displacements of all individual fiducials are shown in Fig. 1. Both the one-dimensional displacements per fiducial and the combined three-dimensional displacements for the CoM per fiducial type are shown. The distributions of the 3D-displacements were statistically significantly different for the surgical clips and the interstitial markers (2-sample Kolmogorov Smirnov test $p < 0.001$). The quality assurance of the CT registration procedure showed good intraobserver and interobserver reproducibility (supplementary material Table S1). The absolute differences between the means and standard deviations of the original and quality assurance data were always smaller than 0.2 mm, and the large majority of differences was below 0.1 mm.

We calculated the PTV margin required for each percentage of patients without any CTV coverage loss based on the CoM motion of either the surgical clips or the interstitial markers (Fig. 2). To fully cover the CTV of 90% of patients, a margin of 1.8 mm was required when using surgical clips for patient positioning, and a margin of 2.2 mm when interstitial markers were used. Increasing this percentage to 95% of patients resulted in a margin of 2.4 mm for the surgical clips and of 2.6 mm for the interstitial markers.

We calculated comprehensive PTV margins for the two SF-APBI treatment techniques, VMAT-APBI and CyberKnife-APBI. In Fig. 3, the required PTV margins as a function of coverage are shown including all relevant geometric errors for both SF-APBI techniques. To ensure full coverage in 90% of patients, the margin for CyberKnife SF-APBI should be 2.3 mm and for VMAT SF-APBI 4.0 mm.

To calculate PTV margins for fractionated treatments, the systematic error Σ and random error σ of fiducial motion were calculated. For the surgical clips, Σ and σ for a conventionally fractionated treatment were 0.46 mm. The interstitial markers had larger Σ and σ of 0.60 mm. The PTV margin accounting for fiducial motion only was calculated according to Van Herk, ensur-

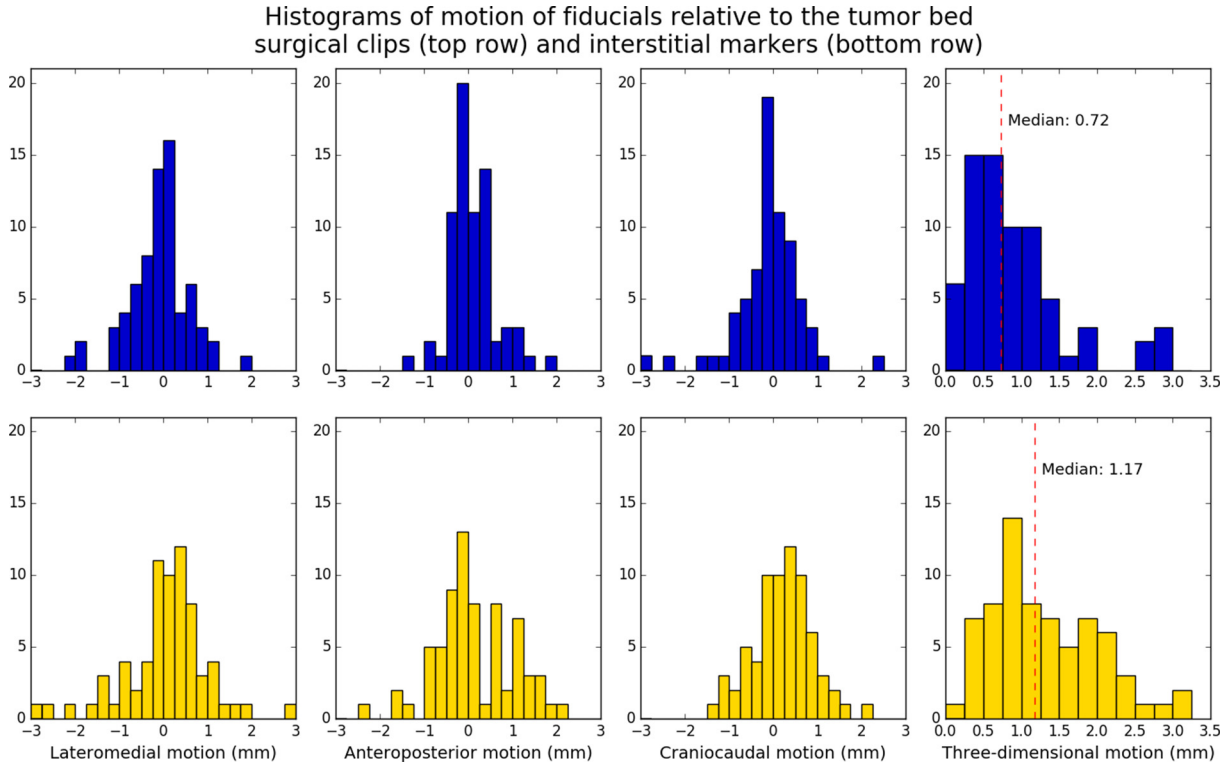

Fig. 1. Histograms of the surgical clips (top row) and interstitial markers (bottom row) center of mass displacements. Positive values for the one-dimensional displacements indicate motion in the lateral, posterior and cranial directions.

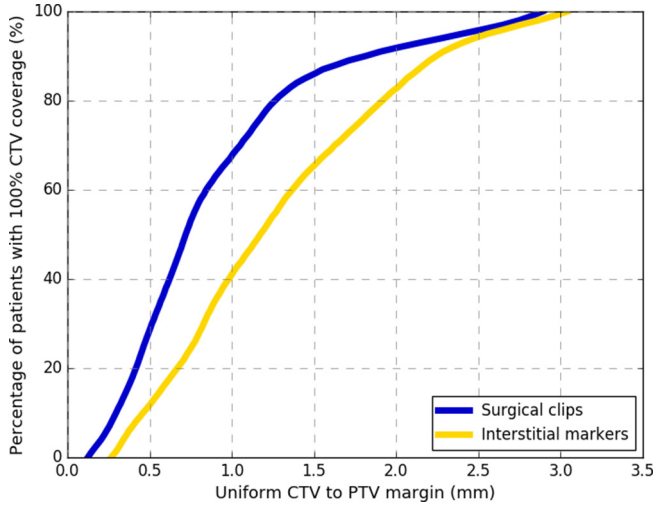

Fig. 2. Percentage of patients with 100% CTV coverage per uniform CTV to PTV margin, accounting for fiducial motion of surgical clips or interstitial markers center of mass.

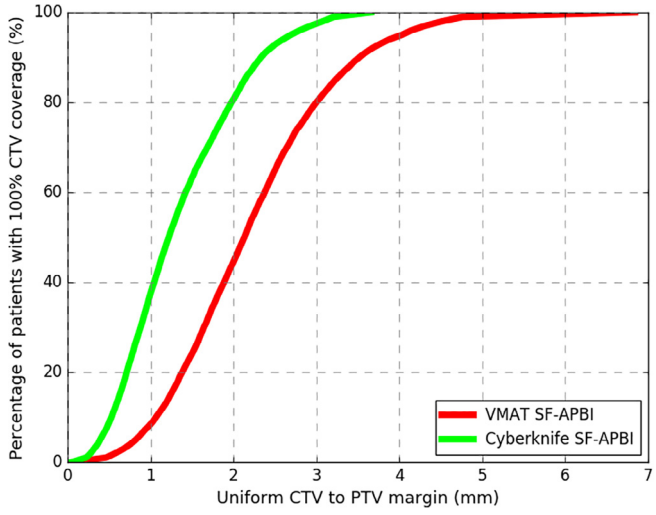

Fig. 3. Percentage of patients with 100% CTV coverage per uniform CTV to PTV margin, including all geometric uncertainties of two treatment techniques: VMAT SF-APBI on a conventional linac with positioning based on the surgical clips on cone beam CT, and CyberKnife SF-APBI with real-time tracking based on interstitial markers.

ing at least 95% CTV coverage in 90% of patients [20]. The margin should be 1.6 mm when using surgical clips and 2.1 mm when using the interstitial markers for a single-fraction treatment. These margins are slightly smaller than the margins calculated for 100% CTV coverage in 90% of patients in our single fraction analysis, which were 1.8 mm for the surgical clips and 2.2 mm for the interstitial markers (Fig. 2).

Using this calculation method, the comprehensive PTV margins for single-fraction treatment should be 3.9 mm for VMAT-APBI and 2.2 mm with CyberKnife-APBI. For a 5-fraction treatment schedule, the margins should be 3.8 mm for VMAT-APBI and 2.1 mm with CyberKnife-APBI.

There was a statistically significant but weak correlation between the distance of an individual fiducial to the tumor bed CoM and its displacement. For the surgical clips, the Pearson correlation coefficient r was 0.27 ($p < 0.001$) and for the interstitial markers, it was 0.34 ($p < 0.001$). There was also a significant but weak correlation between the length of the time interval between planning CT scan and treatment and the 3D error for the CoM of

surgical clips (Pearson's $r = 0.32$, $p = 0.007$), but not for the interstitial markers. Conversely, there was a statistically significant correlation between ipsilateral breast volume and the 3D error of the interstitial markers (Pearson's $r = 0.46$, $p < 0.001$), but not for the surgical clips. The tumor bed volume and the 3D CoM error were not correlated for either of the two types of fiducials.

Discussion

This study showed that there is significant motion of fiducials relative to the tumor bed between the planning CT and the treatment fraction. As the seroma is frequently not visible on patient or target setup imaging and the fiducials are used as a surrogate of target localization, this motion should be included in the calculation of the PTV margins to reduce the risk of geographical miss.

To generalize our results to fractionated treatment schedules, we propose a value of 0.46 mm for the systematic and random error for positioning based on surgical clips. For the interstitial markers, this value is 0.60 mm. The motion of fiducials relative to the tumor bed is only one source of uncertainty in the delivery of external beam APBI. Comparing our calculated values for fiducial motion with the other relevant uncertainties from Table 1 shows that for VMAT-APBI the surgical clip motion error is of the same magnitude as the other errors and thus should not be ignored. The interstitial marker motion is much larger than the total system error of CyberKnife-APBI and will dominate the PTV margin calculation for CyberKnife-APBI.

The values of the systematic and random errors for geometric uncertainties as shown in Table 1 and calculated in this analysis allow for the calculation of the required PTV margin for a large variety of techniques and fractionation schedules. An institution can select the uncertainties present in their treatment technique and sum them quadratically to calculate a comprehensive PTV margin. It is important to keep in mind that these values may differ between institutions and depend for example on the quality assurance program. Table 1 serves as an indication of the likely magnitude of the various errors based on literature.

The reported systematic and random errors can also be used to calculate the PTV margin for a sequentially delivered tumor bed boost if the alignment is based on fiducials. If the boost is delivered as a simultaneous integrated boost (SIB), the patient positioning is often performed on the thoracic wall or breast contour instead of on fiducials. An additional geometrical uncertainty should be included to account for the motion of the tumor bed relative to the thoracic wall or breast contour. In a review on setup using cone-beam CT, large variations are shown for the registration errors using different registration methods and different patient positioning devices [31]. The systematic error for thoracic wall and/or soft tissue registration ranged from 1.3 to 5.7 mm. For the random error, the range was 2.2–4.1 mm. These values are much larger than the values reported in Table 1 for the other uncertainties and will dominate the PTV margin calculation. Using a value of 3 mm for both the systematic and random error results in a required PTV margin of 10 mm for the tumor bed in a conventionally fractionated SIB treatment.

The range of fiducial motion in our patient cohort was large. The motion of the surgical clips CoM ranged from 0.1 to 2.9 mm. For most patients, an additional margin of 1 mm is sufficient to account for fiducial motion, while for 5% of them a margin larger than 2.5 mm is required. This suggests that the use of individualized PTV margins is warranted. Importantly, we did not find strong predictive factors for a larger CoM motion. There were some significant correlations, for the ipsilateral breast volume, the interval between simulation and treatment, and the distance between the fiducial and the tumor bed, but the predictive power was low. This means that, based on our results, it is not possible to define an individualized PTV margin for a given patient at the time of treatment planning. However, like the plan-of-the-day concept recommended for cervical and bladder cancer, a solution could be the creation of a library of plans with different PTV margins [32]. At time of treatment, the fiducial motion could be assessed based on 3D imaging for setup, and the plan with the smallest adequate PTV margin could be chosen for delivery.

If such individualized PTV margins are not practically feasible, it is necessary to define the required proportion of patients with 100% CTV coverage. In the commonly used Van Herk formula, this percentage is chosen at 90% [20]. For contemporary APBI techniques, it is important to reconsider the trade-off between the proportion of patients with 100% CTV coverage and the doses to surrounding healthy tissues. On one hand, the rate of local recurrences after APBI is low but not negligible at around 4% at 10 years [17,18,33]. The dose to surrounding tissues is dramatically reduced compared to whole breast irradiation. A millimetric increase of margins may not result in a clinically detectable increase in toxicity but could reduce the local recurrence rate. On the other hand, patients treated with APBI have a very long life expectancy and the risk of late treatment-induced mortality has become more important [34,35]. There are good salvage treatments for patients experiencing a local breast cancer recurrence, but not for radiation-induced lung cancer. Allowing for a lower percentage of patients with 100% CTV coverage might result in less treatment-related deaths. Our results enable the selection of a PTV margin for every desired percentage of patients with 100% CTV coverage. The trade-off between the percentage of patients with 100% CTV coverage and the CTV to PTV expansion is visualized in Fig. 3.

Our study shows that interstitial gold markers present a larger motion than surgical clips. The reason for this difference is unclear. The interstitial markers were inserted just outside the tumor bed, while the surgical clips are inside the tumor bed. This larger distance to the tumor bed CoM may partially explain the large difference, as there is a weak correlation between distance and the magnitude of the motion. Another possibility is that the surgical clips might be more firmly anchored in the tissue, as they are mechanically stapled into the walls of the lumpectomy cavity. Conversely, interstitial markers are inserted into fatty tissue through a needle and not firmly attached to the tissue. The surgical clips were per definition situated within the tumor bed and thus in the area used for the registration of the planning CT and in-room CT. The impact of these clips on the registration was probably small. Every registration was visually inspected for the correct alignment of the tumor bed. Also, the surgical clips represented only a small volume relative to the total registration area.

In conclusion, our study showed that the motion of fiducials relative to the tumor bed occurring between planning CT and treatment is clinically significant and should be included in the PTV margin calculation. The comprehensive PTV margin for a single-fraction treatment including fiducial motion is 2.3 mm for CyberKnife-APBI and 4 mm for VMAT-APBI.

Conflicts of interest

This study is in part funded by Accuray Inc., Sunnyvale, USA. Prof. Hoogeman has been member of the Clinical Advisory Board of Accuray Inc., Sunnyvale, USA. Prof. Pignol is currently Chief Medical and Technology Officer at Accuray Inc., Sunnyvale, USA. The work reported in this manuscript was completed before he started this position. The other authors report no conflicts of interest.

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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.2021.07.020.

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