How does imaging frequency and soft tissue motion affect the PTV margin size in partial breast and boost radiotherapy?

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Purpose: This study investigates (i) the effect of verification protocols on treatment accuracy and PTV margins for partial breast and boost breast radiotherapy with short fractionation schema (15 fractions), (ii) the effect of deformation of the excision cavity (EC) on PTV margin size, (iii) the imaging dose required to achieve specific PTV margins.

Methods and Materials: Verification images using implanted EC markers were studied in 36 patients. Target motion was estimated for a 15 fraction partial breast regimen using imaging protocols based on-line and off-line motion correction strategies (No Action Level (NAL) and the extended NAL (eNAL) protocols). Target motion was used to estimate a PTV margin for each protocol. To evaluate treatment errors due to deformation of the excision cavity, individual marker positions were obtained from 11 patients. The mean clip displacement and daily variation in clip position during radiotherapy were determined and the contribution of these errors to PTV margin calculated. Published imaging dose data were used to estimate total dose for each protocol. Finally the number of images required to obtain a specific PTV margin was evaluated and hence, the relationship between PTV margins and imaging dose was investigated.

Results: The PTV margin required to account for excision cavity motion, varied between 10.2mm and 2.4mm depending on the correction strategy used. Average clip movement was 0.8mm and average variation in clip position during treatment was 0.4mm. The contribution to PTV margin from deformation was estimated to be small less than 0.2mm for both off-line and on-line correction protocols.
Conclusion: A boost or partial breast PTV margin of ~10mm, is possible with zero imaging dose and workload, however, patients receiving boost radiotherapy may benefit from a margin reduction of ~4mm with imaging doses from 0.4cGy to 25cGy using an eNAL protocol. PTV margin contributions from deformation errors are likely to be small in comparison to other sources of error, i.e., set up or delineation.

Keywords: partial breast radiotherapy; fiducial markers; imaging dose; verification protocols; image-guided radiotherapy.
Introduction

Typical radiotherapy regimens for patients undergoing breast conservation therapy are 45 to 50 Gy delivered to the whole breast in daily 1.8 to 2 Gy fractions over 5 or 6 weeks with or without a boost dose to the excision cavity. There is increasing evidence to support the introduction of strategies to tailor patients’ treatment to their risk of local recurrence. Excision cavity boosts have been shown to reduce the risk of recurrence and in patients of high risk of recurrence simultaneous integrated boost (SIB) to the excision cavity is appropriate (1). For patients at low risk of recurrence, modest dose reduction to non-target tissue away from the excision cavity is expected to reduce complications without compromising tumour control because the risk of recurrence is highest in the index quadrant (1). Furthermore, the observation that a modest increase in fraction size accompanied by a decrease in total dose is likely to result in equivalent local control (2) has led to the re-introduction of hypofractioned breast treatment. Accelerated partial breast irradiation (APBI) delivered in 10 fractions is currently being investigated in the NSABP/RTOG-0413 phase-III trials in the United States and in the UK, the IMPORT phase III trials (3) are exploring the effects of reducing radiation dose to low risk volumes in both high and low risk patients groups using a 15 fraction regime (3).

Work by de Boer et al (4, 5) has shown that it is possible to reduce set up errors without the need for daily imaging. They introduced imaging verification protocols (No Action Level and extended No Action Level) that only require between 3 and 9 images for a 35 fraction treatment thus decreasing both concomitant dose and workload to acceptable levels. Markers implanted into the breast at lumpectomy reduce patient motion errors for the partial breast or boost PTVs and hence improve accuracy of treatment. Depending on the availability of imaging equipment and type of markers used, gold seeds or surgical clips, marker-based image guidance may require 3D imaging which will impart higher concomitant doses.
Despite the improvements afforded by marker-based IGRT, deformation of the excision cavity is of particular concern in partial breast and breast boost radiotherapy where the PTV is determined by the addition of margins to the excision cavity delineated at the time of planning. We and other authors (6-8) have reported on changes in size and shape of the excision cavity that occur during treatment. These studies have measured the changes but have not investigated how these changes could reduce treatment accuracy and if so how PTV margins should be adjusted accordingly to account for this type of target motion, which this study attempts to do.

The purpose of this work is to investigate the following:

- The effect of using established imaging verification protocols on PTV margins in a 15 fraction treatment regimen.
- The effect of deformation on margin size
- The variation of PTV margin size with imaging dose

Methods

Fifty-three patients were recruited from four UK radiotherapy centres (centres A, B, C and D) for the Gold Seed feasibility study; a full description of this study is given by Coles et al. (9). Briefly, following wide local excision of the primary tumour, patients received six gold markers (diameter 3mm; thickness 1mm: hole diameter 1mm). Markers were sutured onto walls of the excision cavity (medial, lateral, superior and inferior aspects) prior to any breast remodelling. In this work two subsets of these data were used. The first was a subset of 36 patient datasets from patients who received a minimum of 12 imaging sessions. This enabled imaging verification protocols to be simulated by sampling from the measured data and then using the whole data set to assess the net effect of the protocol. The second subset of patients datasets were those patients who were treated at centre C, a total of 11 patients. The names of the radiotherapy centres, the number of patients included are provided in Table 1. Of these
11 patient, 4 had visible or highly visible seroma (9) and two had large volume changes (greater than 30% shrinkage) (6).

**Verification Imaging**

Patients were immobilised using a breast board, buttock support and arms were raised behind the head. Prior to imaging, patients were set-up using orthogonal laser-alignment with medial and lateral skin tattoos marked at the time of planning, and any isocentre shift was applied. Verification imaging was carried out for each patient to a maximum of 15 fractions of the total course. Each centre had different verification equipment. B used kilovoltage (2D on-board kV imager), whereas A, C and D used 2D MV imaging. The 2D MV imaging used a pair of images at each imaging fraction: one using the treatment beam and one using a 10x10cm² field with the gantry positioned orthogonal to the treatment beam. For 2D kV imaging orthogonal anterior and lateral images were acquired. Centres, A, B and D determine the movement of the gold marker using matching software that compared the position of the markers in the verification images with that in DRRs generated from the planning CT or simulation images. For centre C, in-house software (6) allowed the user to identify the position of each marker in the orthogonal images and calculate their 3D position using triangulation. The imaging equipment and analysis software used is given in Table1. Their centre of mass position was compared with that in the planning CT. All systems delivered an output which was the 3D daily displacement of the gold markers (representing excision cavity displacement) from the reference position at planning, hence the effective systematic and treatment execution (random) motion errors per patient as a function of time could be calculated. Daily positions of individual markers were determined for the subset of 11 patients using the in-house software described above.
Target motion

Target motion data for the group of 36 patients were measured in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions respectively. Each patient dataset consisted of at least 12 displacements: 4 patients had 12, 1 patient had 13, 6 patients had 14 for and 25 had 15. Shapiro-Wilk test was used to check that data were normally distributed. An ANOVA test was used to test for differences between data from each centre. There was no evidence that the distributions were significantly different, therefore the data were pooled to create a single dataset of 36 patients.

The following correction protocols were modelled retrospectively to the measurement data from the 36 patients:

- No correction
- No Action Level (NAL) (4): mean set up error is determined from a fixed number of fractions.
- Extended No Action Level (eNAL) (5): includes addition imaging fractions at regular intervals.
- Daily on-line correction

A measurement fraction is defined as one which is used to calculate a correction value. The whole patient dataset was then used to assess the effect of this correction.

No correction

No correction was applied based on the measurement data.

NAL Protocol
The correction value $C_{NAL}$ was the mean of the displacements measured at the first $N_m$ fractions and applied on all subsequent fractions i.e. from fraction $N_m+1$. We investigated $N_m$ values of 3, 4 and 5 (Table 2). For $N_m$ values of 4 and 5, a correction based on the first 3 measurements was always applied on fraction 4 and updated after each additional measurement fraction. This rolling adjustment to the NAL protocol was necessary because of the relatively small number of treatment fractions ($N_i$). If the proportion of uncorrected fractions ($N_m/N_i$) becomes higher than ~0.3 systematic errors are expected to increase (4).

**eNAL Protocol**

The eNAL approach started in the same way as the NAL protocol but the corrections $C_{eNAL}$ were updated at subsequent measurement fractions. They are summarised in table 2, where images are acquired for the first 3 fractions and $\Delta f_{rep}$ is the interval between subsequent measurement fractions and $N_{tot}$ is the total number of imaged fractions (5).

**On line Correction**

All measurement data were used and each measurement fraction was corrected for the measured motion for that fraction.

Post correction, a residual error, $\sigma_r$, is expected to remain due to factors such as the finite accuracy with which the correction was applied, surrogate error (i.e., error in cavity position after perfect set-up to clips), and the effects of breathing variations (the internal margin). From the literature (10,11) we have estimated $\sigma_r$ to have a random error component of 2mm (standard deviation); we assume that the systematic component of
\( \sigma_r \) is zero. \( \sigma_r \) will act to increase the day to day variation in post-correction patient displacements. For each corrected fraction we added a correction error which was randomly sampled from a normal distribution with zero mean and 2mm standard deviation using Matlab (Mathworks, USA).

The impact on margins of correction protocols was evaluated using distributions of the patient motion errors post correction in each direction of motion. Both effective systematic (\( \Sigma_{\text{mot}} \)) and treatment execution errors (\( \sigma_{\text{mot}} \)) were calculated (6).

**Deformation of the excision cavity**

The magnitude of deformation of the excision cavity was estimated using the marker positions from 11 patients. In the first instance the centre of mass (COM) of the markers at planning (day 0) and all imaging days (\( n = 1, \ldots, N_{\text{tot}} \)) was calculated. Then COM correction was performed for all imaging days. Displacements \( \delta(LR) \), \( \delta(SI) \) and \( \delta(AP) \), between day 0 and day N were measured for each individual marker. Marker movement toward the COM was recorded as a negative displacement and movement away from the COM as a positive displacement. Further detail on these measurements is included an e-appendix.

Following the same formulism as for treatment errors the following population variables were defined to describe the distribution of errors due to deformation:
• Patient-specific deformation, $\mu_{\text{def}}$: all ($\mu_{\text{def(all)}}$) and positive ($\mu_{\text{def(\text{+ve})}}$) mean marker displacements averaged across all imaging days and all markers.

• Patient-specific day-to-day deformation, $\Delta_p$: the mean daily variation in marker position averaged across all markers ($\Delta_p(\text{all})$) and those with positive mean displacements only ($\Delta_p(\text{+ve})$). The daily variation of a marker was defined as the standard deviation in marker displacement across all imaging days.

• Effective systematic treatment error, $\Sigma_{\text{def}}$: the standard deviation of all $\mu_{\text{def}}$.

• The treatment execution error, $\sigma_{\text{def}}$: the mean of all $\Delta_p$.

**Effect of Correction Protocols on PTV Margins**

Calculated motion errors post correction were used to estimate a margin, $M_{\text{mot}}$ for different correction protocols. $M$ was defined using (12):

$$M_{\text{mot}} = 2\Sigma_{\text{mot}} + 0.7\sigma_{\text{mot}}$$  \hspace{1cm} (1)

Additional total motion margin estimations ($M_{\text{TM}}$) which include the effect of deformation were also determined. Total effective systematic and treatment execution errors were determined by adding motion and deformation errors in quadrature. Thus, $M_{\text{TM}}$ is found using:
\[ M_{TM} = 2 \sqrt{\Sigma^2_{mot} + \Sigma^2_{def(+ve)}} + 0.7 \sqrt{\sigma^2_{mot} + \sigma^2_{def(+ve)}} \]

(2)

We use the treatment errors derived using clips with positive mean displacements only, mean negative displacements are set to zero.

**Imaging Dose Data**

Estimates for the dose delivered were collated from published data (13-15). Doses given in the literature were measured using a variety of methods and measurement points. MVCT doses were derived from the number of monitor units delivered (13) and related to the calibration of the treatment machine typically 1cGy/MU at depth \( D_{\text{max}} \). Doses chosen from the literature for other imaging modalities were those measured at the surface of the patient (14) or phantom (15) as this was the closest measurement point to \( D_{\text{max}} \). The range of clinically used MVCT doses are reported to be 2 -10cGy by Morin et al. (13), however, to assess dose to specific organs they use a minimum exposure of 5cGy and therefore we have used this value.

For planar imaging doses we use data from Walter et al.(14) who present surface doses measured for anterior and lateral views. We have taken the mean dose of the two views. Published MV planar imaging doses were based on 5MU/image, we have adjusted the dose assuming 1MU/image which was used in the Gold Seed study (9). Table 3 summaries the dose per image used in this study.
Results

Analysis of the uncorrected patient data (Table 4) showed that the population effective systematic error ($\Sigma_{\text{mot}}$) was ~ 4.0 mm and the treatment execution error ($\sigma_{\text{mot}}$) ~ 2.7 mm. The effect on $\Sigma_{\text{mot}}$ of the different correction protocols is seen in Table 5 with an on-line protocol producing the greatest reduction. Off-line protocols reduced effective systematic errors to between 2.0 and 1.3 mm depending upon the imaging frequency. Lower effective systematic errors were obtained using the eNAL rather than the NAL protocol however increasing the number of imaging days, $N_{\text{tot}}$, from 5 to 8 gave a relatively small reduction in $\Sigma_{\text{mot(avg)}}$ of 0.3 mm.

Table 4 shows data relating to the deformation of the excision cavity. When all displacements (towards and away from the COM) are considered the mean deformations $\mu_{\text{def(all)}}$ are negative indicating that on average movements are toward the COM. Both $\Sigma_{\text{def}}$ and $\sigma_{\text{def}}$ are smaller (less than 0.4 mm) when only positive motions only are considered. For the 11 patients, 61 markers were investigated, of these 45 had mean positive displacements in at least one direction and 26 had greater than 2mm 3D movement (i.e., the magnitude of the displacement vector). Table 5 gives margin estimations for motion and total motion per correction protocol. The effect of deformation and rotation is to increase the margins by 0.2 mm when on-line imaging is used. This addition is ~ 0.1 mm if an off-line protocol is employed due to larger residual systematic motion error post corrections.

Figure 1(a) shows the relationship between dose and $M_{\text{mot}}$ and $M_{\text{TM}}$. To achieve a specific margin, a higher number of images and hence a higher imaging dose is required
to account for deformation. Figure 1(a) shows the relationship between mean total motion margin size (averaged over the three directions, see Table 3) and imaging dose for the different imaging systems when the range of error correction protocols was applied. The total imaging dose increased with complexity of correction, although not exceeding 2% of a typical 45Gy dose to the treated breast, even for the highest estimated dose. A margin of less than 6mm could be achieved post correction using the eNAL protocol. However, increasing $N_m$ from 6 to 8 and hence increasing dose by 33% afforded little reduction in margin size.

11 Discussion
12 This study has shown that pre-correction effective systematic motion errors are approximately 4.0 mm in all directions which are similar to another study by Tolpolnjak et al.(16) who reported systematic errors of 3.0 mm, 3.8 mm and 2.7 mm in the left-right, superior-inferior and anterior-posterior directions. PTV motion margins pre-correction are ~10.2 mm. The average estimated motion margin offers an indication of the relative decease in volume of normal tissue irradiated using the different correction protocols. An on-line protocol reduced the margins to less than 3 mm, at a cost in time and imaging dose however, this imaging dose can be as low as ~1.5cGy if kilovoltage 2D planar imaging is used.

21 Penninkhof et al. (17) reported mean clip displacement during treatment of 0.9mm and average intrafraction motion 0.5mm and Topolnjak (18) found average clip motion from CT to end of treatment to be -1.4 ± 1.5 mm. These values are for the magnitude of the 3D vector from the clip to the centre of mass. We found similar values for average displacements, -0.6, -0.8 and -0.5 mm and mean intrafraction variation 0.7, 0.6 and 0.8
mm in the LR, SI and AP directions respectively. Of our 11 patients 4 had seroma clarity score (SCS) > 2, Topolnjak et al. reported 3/21 with SCS > 2 (18). Based on the assumption of a convex excision cavity, the negative sign implies shrinkage of the cavity (see e-appendix). Weed et al. (7) showed that, despite an overall shrinkage of the excision cavity deformation led to a proportion of the volume (defined during or after treatment) to fall outside of the volume defined at planning. Our estimation of suitable deformation errors used only those clips with positive mean displacements. If negative mean displacements are included the errors are greater (see table 4) however, these negative deformations will not lead to an underdosage of the target volume and should not act to increase the margin. Only positive displacements lead to underdosage of the target volume.

Study Limitations:

Set-up data were acquired using 2D imaging technologies. Others (19, 21) have found set-up errors measured using 2D imaging can be smaller than those measured using 3D imaging. The difference has been mainly attributed to poor visibility of the matching structure in portal images and the use of different parts of the anatomy for matching for the 2D and 3D techniques. For centres A, C and D the visualisation of gold marker in EPID images may be difficult if the markers overlay the rib cage and may have led to conservative set-up error estimation. However, no difference in set-up errors were observed for centre B (kV imaging) in comparison to the other centres. Penninkhof et al. (17) have compared 2D planar set-up errors with CBCT errors both based on clip match, the greatest difference was 1.1 mm in the AP direction, consequently we would not expect set-up errors of markers measured using 3D imaging to differ greatly from what we have observed.
Delineation errors are not included in our margin calculation. Other authors have proposed the inclusion of an error term in the margin formula to account for the variation in clinician delineation of the target volume (21). In this patient group, large clinician variation was observed (9) and distances between delineations exceeded 10mm. We have included surrogate errors in our estimation of residual errors from the literature (10). Studies by Topolnjak et al. (18) and Weed et al. (7) show that markers are a good surrogate for the excision cavity, however, Topolnjak et al. reported residual systematic and treatment executions errors of ~1mm. Clearly, both delineation and surrogate errors are likely to be equally if not more important than deformation errors.

Rotations are not treated separately in this analysis. Where rotational set-up errors can be measured, i.e., using 3D imaging, local practice is to correct for large rotations (>5°) by repeating laser set-up. Rotations are not explicitly corrected i.e, there is no method available to rotate the patient. Clip motion due to rotation has been included in the deformation analysis. If small rotations could be accurately corrected for, these could be removed from the analysis and would have the effect of decreasing deformation errors.

It is important to note that the imaging systems’ dose values from the literature are not specific for the case of breast irradiation and are measured in different ways, but they do provide an indication of the magnitude and range of the likely doses. The information available in a 2D image is inevitably less than that in a 3D image; a 3D image dataset may be used to track excision cavity soft-tissue deformation with time compared to the pre-treatment shape and size.

Margins were used as an indication of treatment accuracy only. Most margin models assume motion errors are normally distributed (21). When using an off-line protocol, the
patient motion set up error distribution has a step function because of the first 3 fraction correction. The margin formula used does not take into account that a proportion of the boost or partial breast dose may be delivered using the whole breast field. This will reduce the contribution of treatment execution errors to the required margin; the reduction being dependent on the specific treatment (21). The analysis used is a simplification of how deformation will affect the CTV dose coverage. A more accurate estimation of motion margins would employ a model of treatment dose distribution, motion errors and a more accurate description of deformation. It is our intention to make a more precise estimate of the boost margins required once this data has becomes available from the IMPORT trial.

Clinical relevance: It appears from our data that a modest level of verification imaging (e.g. a NAL protocol with 3 imaging sessions) would achieve the aim of checking the set up with a low concomitant imaging dose. This may benefit patients at low risk of recurrence who have a very good prognosis so imaging doses to non-target tissue should be kept as low as possible. Patients at high risk of recurrence may benefit from a dose escalation to excision cavity. Simultaneous integrated boost (SIB) is an obvious way to achieve this, but PTV margins probably need to be kept very small (in the region of 5 mm) to prevent excessive damage to normal tissues. In this patient group, a higher imaging dose may be accepted in order to achieve safe dose escalation to excision cavity. We have shown that an eNAL protocol with a total of 5 imaging sessions would enable a excision cavity margin of approximately 6mm, with an estimated total imaging dose of ~0.4cGy for a kV planar imaging system or ~25cGy using MVCT (Figure 1). To achieve a margin of less than 5 mm on-line imaging is required. This study has shown
that deformation errors are small and further studies are required to measure delineation errors which are likely to be the greatest source of error.
Conclusion

This work has shown the relationship between PTV margin and estimated total dose from concomitant verification imaging, and their dependence on verification strategy for a cohort of breast cancer patients. The deformation of the excision cavity requires a larger number of imaging days to reduce systematic errors to a given level however, deformation errors are small (less than 0.4mm). A boost or partial breast PTV margin of ~10 mm, is possible with zero imaging dose and workload, however, high risk patients receiving simultaneous integrated boost radiotherapy with steep dose gradients, may benefit from a margin reduction of ~4mm with imaging doses from 0.4 cGy to 25 cGy using an eNAL protocol with $\Delta f_{rep} = 4$ (a total of 5 imaging sessions). A NAL protocol with 3 measurements gave an estimated margin of ~ 6 mm and may be suitable for low risk PBI patients.
References


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Figure 1: (a) Relationship between motion margin ($M_{\text{mot}}$) and total motion margin ($M_{\text{TM}}$) in the LR, SI and AP directions. Doses are based on kV-CBCT. (b) Relationship between average $M_{\text{TM}}$ (averaged over all directions) and dose per imaging modality.