Tumour bed delineation for partial breast and breast boost radiotherapy planned in the prone position: what does MRI add to x-ray CT localization of titanium clips placed in the excision cavity wall?

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Abstract

Purpose: To compare tumour bed (TB) volumes delineated using MRI plus CT/clips (MRCT) with those delineated using CT/clips-alone in post-lumpectomy breast cancer patients positioned prone, and to determine the value of MRCT for planning partial breast radiotherapy (PBI).

Materials/Methods: 30 women with breast cancer each had 6-12 titanium-clips secured in the excision cavity walls at lumpectomy. Patients underwent prone CT-imaging followed by prone MRI (T1-weighted (standard & fat-suppressed) and T2-weighted sequences). TB volumes were delineated separately on CT and fused-MRCT datasets. Clinical (CTV=TB+15mm) and planning target volumes (PTV=CTV+10mm) were generated. Conformity indices between CT- and MRCT-defined target volumes were calculated (ratio of volume-of-agreement to total-delineated-volume). Discordance was expressed as a geographical-miss index (GMI=fraction of total-delineated-volume not defined by CT), and a normal-tissue index (NTI=fraction of total-delineated-volume designated as normal tissue on MRCT). PBI dose-distributions were generated to cover CT-defined CTV (CTV_C) with $\geq 95\%$ of the reference dose. The percentage of MRCT-defined CTV (CTV_MRCT) receiving $\geq 95\%$ of the reference dose was measured.

Results: Mean conformity indices were 0.54 (TB), 0.84 (CTV) and 0.89 (PTV). For TB volumes, GMI was 0.37 and NTI was 0.09. Median percentage-volume coverage of CTV_C was 97.1\% (range 95.3-100.0\%), and of CTV_MRCT was 96.5\% (range 89.0-100.0\%).

Conclusions: Addition of MR- to CT/clip-data generated TB-volumes that were discordant to those based on CT/clips-alone. However, clinically satisfactory coverage of CTV_MRCT by CTV_C-based tangential PBI fields provides support for CT/clip-based TB delineation remaining the method of choice for PBI/ breast boost radiotherapy planned using tangential fields.
Key words: Breast cancer; Partial breast radiotherapy; Magnetic resonance imaging; Target volume delineation; computed tomography
Introduction

Whole breast radiotherapy (WBRT) following breast-conserving surgery (BCS) improves local control and survival (1, 2) but is associated with increased non-breast-cancer-related mortality and morbidity due to irradiation of non-target tissue (2, 3). A strategy that aims to improve the therapeutic ratio in women at relatively low risk of local tumour relapse involves limiting high radiation doses to the index quadrant and reducing or eliminating dose to breast tissue remote from the tumour bed (TB) (4, 5). An essential prerequisite of partial breast irradiation (PBI) is accurate localization of the TB. Until recently, TB localization was performed using pre-operative radiological imaging, surgical annotation, clinical palpation of surgical defect, scar position, patient recollection of tumour location, and in some cases post-operative ultrasound imaging. More recently, localization of titanium clips attached to excision cavity walls at surgery has been shown to reduce risks of geographical miss and unnecessary normal-tissue irradiation (6-9). Clips provide additional localization information compared to kv-CT-imaging alone, and therefore CT/clip-based TB delineation is considered the current gold standard (10). However, clips define a limited number of points on an irregular excision cavity wall surface [see figure 1], and the complete breast tissue/excision cavity interface is derived by interpolation, taking into account tissue density and distortion (11). Moreover, CT has limited soft-tissue contrast making it an unreliable modality for detecting small volumes of seroma between clips and for distinguishing TB from normal glandular breast tissue (12).

Magnetic resonance (MR) imaging has superior soft-tissue contrast and the potential to differentiate more clearly between normal tissue and post-operative TB. Studies in post-operative sarcoma and prostate patients have correlated signal changes on T1- (T1W) and T2-weighted (T2W) images with seroma, haematoma, haemorrhage and fibrosis on the pathological specimen (13-16). Following wide-local excision of breast cancer, heterogeneous ellipsoidal fluid-filled cavities with irregular borders are commonly reported on MR (17), but there are no
studies using these data for radiotherapy planning. Direct comparison of MR- and CT/clip-defined volumes is difficult in the supine position due to the limited bore size of conventional closed MR scanners, respiratory motion artefacts, and distortion of breast tissue by overlying MR-receiver coils. These difficulties are partially overcome by use of a prone position (as per diagnostic breast MR examinations) and this position is therefore more suitable for comparison of CT and MR in the context of breast radiotherapy planning.

The purpose of this study was to evaluate the contribution of MRCT to the planning of partial breast and breast boost radiotherapy. This was done by comparing tumour bed volumes delineated using MR plus CT/clips (MRCT) with those delineated using CT/clips alone in post-lumpectomy breast cancer patients positioned prone.
Patients and methods

The study was approved by the Royal Marsden NHS Foundation Trust Committee for Clinical Research. Patients due to undergo adjuvant breast RT following lumpectomy for unifocal G1-3 invasive ductal carcinoma or high-grade ductal carcinoma-in-situ were eligible. Patients with claustrophobia or ferrous implants were excluded.

Placement of titanium clips

Patients had titanium clips placed at BCS according to a national protocol (10) in which each of the six excision cavity boundaries was defined by 1 or 2 clips. Clips were secured at the centre of the deep boundary, half-way between skin and pectoral fascia (lateral, medial, superior and inferior walls) and in subcutaneous tissue close to the suture line (anterior boundary). Where oncoplastic surgery was performed, clips were placed before re-modelling. All patients had clear margins of ≥2mm around the microscopic limits of tumour.

Patient positioning and image acquisition

Each patient underwent CT-imaging in a prone position not less than three weeks post-surgery using an in-house designed platform with an aperture through which the index breast could fall away from chest wall. The platform was compatible with both CT and MR scanners. The contralateral breast was supported on a foam wedge. Three multi-modality markers were placed at different points on the index breast surface in proximity to the scar. Patients had bilateral tattoos in the mid-axillary line (placed as part of their standard supine radiotherapy treatment-planning). The distances from each lateral tattoo to the surface and inferior edge of the prone platform were recorded. Photographs were taken of arm and head position. Non-contrast CT images were acquired in each position (slice thickness 1.5mm, from C6 to below diaphragm). Patients proceeded directly to the MR scanner where their prone position was reproduced on the same platform using measurements from tattoos and photographs. Patients were imaged using T1W 3-D sequences without fat suppression (TR 6.1ms, TE 1.7ms, flip angle 12) and with
fat suppression (TR 4.8ms, TE 2.4ms, flip angle 10, 100ms inversion delay pulse), and using T2W sequences (TR 10195ms, TE 100ms, flip angle 90). Each sequence had a field of view of 192/100mm, slice thickness 1mm, and matrix 192*192mm. Imaging acquisition took 20 minutes.

**Image transfer and fusion**

MR data was imported into the radiotherapy-planning system (Pinnacle version 8.0, ADAC systems) and co-registered with CT data. Matching was achieved using regions of interest (ROI) corresponding to the midpoint of each of the surgical clips, manually identified on each of the CT and MR datasets. Misalignment between CT and MR clips was calculated in terms of the total conjugate deviation (TCD), defined as the square root of the sum of the squares of the deviation between each pair of ROIs. The mean misalignment per clip was calculated as \(\sqrt{\text{TCD}^2 / \text{number of clips}}\) in 3-dimensions.

**Target volume definition**

TB was delineated on the prone CT data by a single observer (AK), encompassing clips, seroma and architectural distortion. Window level and width were fixed at 0 and 500 Hounsfield Units respectively. The observer was blinded to MR findings. Each CT-defined TB (TB\textsubscript{CT}) was assigned a cavity visualization score (CVS) (12) in which 1=no cavity visible, 2=heterogeneous cavity with indistinct margins, 3=heterogeneous cavity with some distinct margins, 4=mildly heterogeneous cavity with mostly distinct margins, and 5= homogeneous cavity with clearly identified margins. TB was outlined on the MR data at least two weeks after CT-outlining by the same observer in consensus with an experienced MR radiologist (NdS) (both blinded to CT findings), encompassing seroma, fibrosis and clips. Tissue that produced heterogeneous signal on all three MR sequences was considered to be haemorrhage/haematoma and was also included. The MR- and CT-defined TB volumes were fused to create an MRCT-defined TB (TB\textsubscript{MRCT}). This fused volume was edited to exclude tissue that MR did not classify as seroma, fibrosis, haematoma, or haemorrhage. Clinical target volumes were created for each of the CT
MRCT tumor bed delineation for partial breast RT (CTV<sub>CT</sub>), and fused-MRCT (CTV<sub>MRCT</sub>) datasets by adding a uniform 15mm margin to the tumour bed in 3D, limited deeply by chest wall and superficially by 5mm beneath skin surface. Planning target volumes were created for each of the CT (PTV<sub>CT</sub>) and MRCT (PTV<sub>MRCT</sub>) datasets by addition of a 10mm margin to the CTV (limited by skin). Volumes were recorded and amount of overlap and underlap between CT- and MRCT-defined target volumes calculated.

Conformity and discordance between volumes

Conformity between TB<sub>CT</sub> and TB<sub>MRCT</sub> was expressed as a conformity index (CI). Discordance was expressed as geographical miss (GMI) and normal tissue (NTI) indices. Definitions for these indices are given in figure 2. The same indices were calculated for CT- versus MRCT-defined CTV and PTV.

Radiotherapy dosimetry

PBI dose distributions were generated using multiple static tangential fields with the aim of covering CT-clip-defined target volumes according to UK IMPORT LOW (Intensity Modulated Partial Organ Radiotherapy) trial criteria (18) i.e. >95% of CTV<sub>CT</sub> should be covered by >95% of isocentre dose (50Gy in 2Gy fractions). Plans fulfilled ICRU dose homogeneity criteria (19). Based on these plans, the percentage of CTV<sub>MRCT</sub> receiving 95% of isocentre dose was measured, a value of ≥95% being deemed adequate coverage and a value of <95% being deemed inadequate coverage. Statistical analyses were performed using the two-tailed Student t-test for significance.
Results

Thirty-five patients gave informed consent to participate in the study. Two patients did not fit into the MR-scanner on the in-house platform. Three patients were unable to tolerate MR-scanning due to claustrophobia. Thirty patients had evaluable data. Median age was 54 years (range 34 to 76), and median UK cup size was C (range A to FF) (equivalent to median US cup size B (range A to G). Median time from surgery to imaging was 47 (22-210) days. Twenty patients had full-thickness closure of their excision cavities following lumpectomy (apposed cavities) and 10 patients did not (unapposed cavities). 23/30 patients had cavity visualisation scores (CVS) (12) of 1 (n=7) or 2 (n=16). 7/30 patients had more clearly-visualised cavities: CVS=3 (n=2); CVS=4 (n=3); CVS=5 (n=2).

Image fusion

Mean clip misalignment across all 30 cases was 0.8mm (medial-lateral), 0.6mm (superior-inferior) and 1.0mm (anterior to posterior). The largest mean clip misalignment seen was 2.6mm (anterior-posterior).

Comparison of findings on imaging sequences

Table 1 summarizes the features described on CT and on the individual MR sequences. These features are illustrated in Figure 3. Titanium clip and skin-surface markers were demonstrated on all datasets. Clip-related artefact was minimal on CT and did not affect visualisation of surrounding tissue. Seroma was visualised on T2-W images, enabling MR to distinguish TB from normal glandular breast tissue (figure 3a(i-iv)). T1-W MR sequences most clearly demonstrated titanium clips (figure3b(iv)). Clips appeared as voids and those closest to the breast/ chest wall interface were most difficult to visualize. Heterogeneity corresponding to haemorrhage or haematoma was visualized on T1W and T2W MR sequences (case 3, images 3b-d). Wrap artefact at lateral edge of image made it difficult to visualize lateral TB on MR in some cases (figure 3c(ii)).
The presence of seroma on MR was related to the time interval from surgery to scanning: patients with visible seroma had a median time to scan of 39 (range 22-210) days whilst those with no seroma had a median time to scan of 154 (31-196) days. The presence of fibrosis on MR was also associated with time from surgery to scan. Median time to imaging for patients with fibrosis was 154 (44-196) days and for those without fibrosis was 42 (22-210) days.

Target volumes and the differences between them are summarized in table 2. In 28/30 cases, the addition of MR to CT data increased the TB volume. Median percentage volume increases for MRCT- versus CT-defined CTV and PTV were proportionally less than for TB because these volumes are truncated at skin or lung/chest-wall interface. CTV\textsubscript{CT} and CTV\textsubscript{MRCT} correlate well (Pearson correlation coefficient= 0.957, p<0.001). (figure 4).

Table 3 summarizes values for conformity and discordance between CT- and MRCT-target volumes. Concordance between TB volumes was low but increased for CTV and PTV due to truncation of target volumes at skin and lung. Mean differences in centres-of-mass for TB\textsubscript{CT} versus TB\textsubscript{MRCT} were 1.5mm in the medial-lateral plane, 2.0mm in the anterior-posterior plane and 2.2mm in the superior-inferior plane.

**Target volume coverage by standard tangential PBI plans**

Median percentage volume encompassed by the 95% isodose was 97.1% for CTV\textsubscript{CT} (range 95.3-100.0%), and 96.5% for CTV\textsubscript{MRCT} (range 89.0-100.0%). The 95% isodose covered the CTV\textsubscript{CT} in 30/30 cases and covered the CTV\textsubscript{MRCT} in 26/30. In 3/4 cases with inadequately-covered CTV\textsubscript{MRCT}, the percentage of CTV\textsubscript{MRCT} encompassed by the 95% isodose was >93%. In the remaining case, the percentage of CTV\textsubscript{MRCT} encompassed by the 95% isodose was 89.0% (95% of the CTV\textsubscript{MRCT} was covered by the 87% isodose). In 2/4 of the inadequately-covered cases, TB\textsubscript{MRCT} extended inferiorly to TB\textsubscript{CT}, and 4/4 cases had tumours located at the extreme lateral or medial edges of breast tissue. Mean CTV conformity index of the inadequately covered cases was significantly lower than that of the adequately covered-cases (0.69 vs. 0.86, p=0.001), but
there was no difference in mean number of clips (6 in both groups), CVS (2 in both groups) or TBCT volume (7.9 vs. 8.5cm³, p=0.9) between the adequately and inadequately covered groups.
Discussion

This study found that tumour bed volumes delineated using fused MR and CT/clip data were discordant to those delineated using CT/clip alone. However, resulting clinical and planning target volumes were sufficiently concordant to ensure adequate coverage of $\text{CTV}_{\text{MRCT}}$ using $\text{CTV}_{\text{CT}}$-based tangential partial breast radiotherapy fields in most cases.

CT alone is able to clearly visualise only seromas that are large enough to be under tension, producing a convex border (equivalent to CVS 4 and 5) (12). These were an infrequent finding in our population, of whom two-thirds had their excision cavities apposed at surgery. In all of our patients, titanium clips, clearly visible on CT, defined points on the TB/ breast tissue interface. However, uncertainty remained over how to join these points together. Intervening soft tissue abnormalities, described as “architectural distortion”, were seen in 23/30 of our cases on CT. Distortion can represent post-operative change (small-volume seroma, fibrosis, haemorrhage or oedema) but is difficult on CT alone to distinguish from normal glandular breast tissue. A more common problem was that clips were separated by apparently normal fatty tissue. Indeed, 7/30 cases in our study had no abnormalities at all on CT apart from clips. We assumed that tissue in between clips was TB but could not with any certainty decide on the true location of the excision cavity wall between clips. MR imaging, on the other hand, visualised seroma, haemorrhage, haematoma and fibrosis in association with titanium clips. The $\text{TB}_{\text{MRCT}}$ extended outside the $\text{TB}_{\text{CT}}$ in most cases resulting in a median GMI of 0.37. This finding agrees with previous work reporting MR-defined TB volumes to be larger than those defined on CT (20). MR was also able to distinguish post-operative change from normal glandular breast tissue, albeit with a median NTI of only 0.07. Thus, the principal cause of discordance between $\text{TB}_{\text{CT}}$ and $\text{TB}_{\text{MRCT}}$ volumes was the finding of soft-tissue abnormalities on MR in regions where CT defined apparently normal tissue. Although MR identified a larger volume of abnormal tissue than CT, it was difficult on MR imaging alone to identify clips close to the breast tissue/ chest wall interface. T1-weighted
sequences without fat suppression were better than the other two sequences, as the signal voids left by clips were more clearly visible against the high-signal fat, but still only detected 77% of clips. Inclusion of gradient echo sequences might improve clip visualisation in future studies.

Following expansion of TB to CTV, CI between CT- and MRCT-defined volumes improved from 0.54 to 0.89 due to the size of the margin in relation to the magnitude of discordance and to limits on expansion presented by skin, chest wall and breast tissue boundaries. In the majority of cases, the addition of MR to CT/clip-data generated target volumes which were adequately encompassed by tangential PBI fields based on CTV_{CT}. In only 4/30 cases was coverage inadequate according to our criteria, and in only two of these was inadequate coverage due to discordance between volumes, both inferiorly. In the other two cases, inadequate coverage was related to the target volumes being located at the peripheries of breast tissue where coverage is difficult to achieve due to the complex 3-dimensional shape of breast tissue. Differences in COM positions for TB_{CT} versus TB_{MRCT} confirmed that discordance was greatest in the SI plane (2.2mm) but were again small in the context of a TB-PTV margin of 25mm, thus explaining why coverage of TB_{MRCT} by the 95% isodose was achieved in such a high proportion of cases.

Even in the case with the least adequate coverage, 89% of the CTV_{MRCT} was encompassed by the 95% isodose, and 95% of the CTV_{MRCT} was covered by the 87% isodose. A recent large study of dose-fractionation in breast radiotherapy has found the gradient (γ value) of the dose-response curve (measured as the percentage increase in effect per percentage increase in total dose delivered in 2Gy fractions) to be only 0.2 (1). Assuming this γ value to be correct, a 13% underdosage of 11% of the partial breast CTV would not be expected to impact measurably upon local tumour control.

One criticism of this study is that the different imaging modalities are delineating different targets. Following excision of breast cancer, the boundaries of TB have been defined in 3D as the interface between fluid and breast tissue, demonstrated on CT by a change in soft-tissue...
density. A margin (standardly 10-15mm) is then added to encompass tissue considered to be at risk of local recurrence (CTV). Our MR-based delineation protocol is likely to overestimate the true TB by including haematoma and haemorrhage that is not necessarily within the cavity itself but may instead represent pericavity post-operative changes. The resulting "post-operative complex" (17) would therefore include part of the tissue-volume at risk of microscopic spread and adding 15mm to this structure would likely overestimate CTV. However, without including post-operative haemorrhage and haematoma it would have been difficult to standardise our approach to MR-delineation of TB. Two-thirds of our study population underwent full-thickness closure of excision cavities, decreasing the volume of intra-cavity fluid, and resulting in a cavity-tissue interface that was difficult to define, even on MR. Also, reports suggest that granulation tissue may be laid down within the original excision cavity (17), and we did not want to underestimate TB on MR by only outlining seroma. Our approach of including any tissue on MR that might be part of the cavity/tissue interface produced a "worst case scenario" by which to test the current CT/clip-based method. Our finding that addition of MR to CT/clips did not significantly increase target volumes is reassuring that use of the CT/clip method is unlikely to result in a geographical miss.

The co-registration of CT and MR datasets is another potential source of error, but the use of TB clips as match points minimized changes in breast shape from CT to MR as a variable (21). Clips had other advantages over chest wall as a matching structure: they overcame the problem of accurately identifying bony boundaries on MR, the smaller field-of-view required reduced system-related image distortion (22), and clips were within the region that we were interested in matching most accurately. Previous work suggests that, for fusion to be considered satisfactory, the total conjugate deviation should be <3mm (consistent with a mean misalignment between imaging modalities of <1.74mm for each clip) (21). Our mean misalignment was better than this. Only 3/30 cases had mean misalignment in a single plane of >2mm (none of whom had
inadequate MRCT-coverage). The fact that only 77% of clips were visible on MR did not compromise co-registration as the “missing clips” on MR were those closest to chest wall or in close proximity to neighbouring clips. Misalignment between imaging modalities may have contributed to some TB discordance but, in the context of 25mm margins would not have affected our conclusions regarding clinical significance. The limited misalignment is due to difficulties in exactly reproducing the position of an amorphous soft-tissue structure, and does not provide any support for the hypothesis that clips migrate.

The applicability of our findings to other patient populations will depend upon local RT practices. External beam PBI is currently only available in the UK in the context of the IMPORT-LOW trial. The RT techniques used therein are simple so as to be easily undertaken by the majority of centres. Using tangents, however, any medial to lateral discordance in CTV is unlikely to result in discrepancies in target-volume coverage. In centres where intensity-modulated radiotherapy is employed to increase conformality of the irradiated volume to the target volume, medial-lateral discordance could become more relevant, although our differences in TB centre-of-mass were least in the medial-lateral direction.

We believe the results of our prone CT versus MRCT comparison to be applicable to patients planned in the supine position. In the prone position, breast tissue falls away from chest wall under gravity and may tend to elongate the TB in an anterior-posterior plane. In the supine position, breast tissue tends to fall laterally in relation to chest wall, particularly in women with larger breasts, such that the TB might be elongated in a lateral plane. However, the most clinically-significant discordance between CT versus MRCT-defined volumes in our study was in the superior-inferior plane, a finding unlikely to be affected by patient position.

Conclusions

Addition of MR- to CT/clip-data in the context of cavity-wall clips delineates TB volumes that are discordant to those based on CT/clips alone. However, resulting clinical and planning target
volumes are sufficiently concordant that coverage of $\text{CTV}_{\text{MRCT}}$ by $\text{CTV}_{\text{CT}}$-based tangential partial breast radiotherapy fields is satisfactory in most cases. CT/clip-based TB delineation is unlikely to result in a significant geographical miss and should therefore remain the current method of choice for TB delineation in patients treated with partial breast and breast boost radiotherapy using tangential fields. A comparison of CT and MRCT in the context of more sophisticated beam arrangements would be of interest.
References


Figure Captions

Figure 1. Axial CT image of breast tissue demonstrating titanium clips (placed in excision cavity walls at surgery). The location of the cavity/breast tissue interface in between clips is not clearly defined on CT alone.

Figure 2. Diagram demonstrating the definitions of conformity, geographical miss (GMI) and normal tissue (NTI) indices.

Figure 3. Co-registered axial images of right breasts of three different cases (a-c): (i)=CT; (ii)= T1-weighted MRI (T1W) with fat suppression; (iii)= T2-weighted (T2W) MRI; (iv)= T1-weighted (T1W) MRI. Superimposed target volumes: blue = CT-defined tumour bed; red = MRCT-defined tumour bed.

Figure 4. MRCT-defined clinical target volume (CTV_{MRCT}) plotted against CT-defined clinical target volume (CTV_{CT}).