

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?

Kirby AM, Yarnold JR, Evans PM, Morgan VA, Schmidt MA, Scurr ED, deSouza NM

Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK

Abstract

Purpose: To investigate whether magnetic resonance imaging (MRI) data adds information leading to changes in tumour bed (TB) volume localized using CT/ titanium clips, and to evaluate the clinical significance of changes in the context of partial breast and breast boost radiotherapy.

Materials/ Methods: 30 women with G1-3 invasive ductal carcinoma or ductal carcinoma-in-situ of breast each had 6-12 titanium clips secured, at lumpectomy, in the excision cavity walls. Each woman underwent a prone CT-planning scan followed immediately by MRI in the same position. 3D-MRI datasets (T1-weighted (standard & fat-suppressed) & T2-weighted) were co-registered with CT data and matched using clips. The tumour bed (TB) was delineated separately on CT, MR, and fused-MRCT (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 by dividing volume-of-agreement by the total volume delineated by both modalities. Discordance was expressed as a geographical miss index (GMI = percentage of total delineated volume not defined by CT), and a normal tissue index (NTI = percentage of total delineated volume incorrectly defined on CT). Partial breast radiotherapy dose distributions were generated to cover CT-CTV using conventional tangential field arrangements, and the percentage of MRCT-CTV receiving >95% of the reference dose measured.

Results: Median CT- and MRCT-TB volumes were 5.7cm³ and 9.7cm³ respectively. Mean conformity indices for CT vs MRCT were 0.54 (TB), 0.84 (CTV) and 0.89 (PTV). For CT- versus

MRCT-TB, GMI was 37.1%, and NTI was 9.2%. Mean coverage of CT-CTV by the 95% isodose was 97.1% (30/30 adequately covered). Mean coverage of MRCT-CTV was 96.5% (26/30 adequately covered). Worst percentage volume coverage of MRCT-CTV was 89.0%.

Conclusions: Addition of MRI- to CT/clip-data increases TB volume by identifying additional seroma, oedema and haemorrhage. However, discordance between resulting clinical and planning target volumes is rarely significant in the context of tangential-field partial breast/ breast boost radiotherapy. CT/clip-based TB delineation is unlikely to result in a significant geographical miss and should remain the current standard.

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 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 and patient recollection of tumour location. Nowadays, localisation of titanium clips attached to excision cavity walls at surgery reduce the risks of geographical miss and unnecessary normal-tissue irradiation (6-9). Clips provide additional localization information compared to kv-CT-imaging alone, leading to modification of field borders in 43% of patients (10). The use of clips together with CT-imaging is therefore widely regarded as the current gold standard for TB localization. However, questions relating to accuracy remain unanswered. Clips only define points on the excision cavity wall [fig 1], leaving uncertainty regarding delineation of the remainder of the 3D breast tissue/excision cavity interface (11). CT has limited soft-tissue contrast making it an unreliable modality for detecting small volumes of seroma in between clips and for distinguishing TB from normal glandular breast tissue (12).

Magnetic resonance imaging (MRI), with its superior soft-tissue contrast, has the potential to differentiate more clearly between normal tissue and post-operative TB. Studies in post-operative sarcoma and prostate patients have pathologically correlated high signal-intensity on T2-weighted (T2W) images with seroma/ haematoma (13), heterogeneous signal change (hyperintense on T1-weighted (T1W) and hypointense on T2W) with organizing haematoma (14, 15) and non-enhancing low signal on T1W with fibrosis (16). The appearances of post-operative cavities following wide-local excision of breast cancer have been described, using a low-field

open MRI scanner, as heterogeneous ellipsoidal fluid-filled cavities with irregular borders (17). Coregistration of imaging datasets and direct comparison of MR- and CT/clip-defined TB 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. Prone positioning is used for diagnostic breast MRI examinations, and provides a more fruitful basis for comparison of CT and MRI.

The purpose of this study was to investigate whether or not magnetic resonance imaging (MRI) data adds information leading to a change in tumour bed (TB) volumes localized using CT/ titanium clips, and to evaluate the clinical significance of differences in the context of partial breast and breast boost radiotherapy. The hypothesis was that discordance between target volumes would not be clinically significant enough to replace CT/clips as the method of choice for external beam PBI/ breast boost target volume delineation.

Patients and methods

The study was approved by local research and ethics committees. Eligible patients were those due to undergo adjuvant breast RT following BCS for unifocal G1-3 invasive ductal carcinoma or high-grade ductal carcinoma-in-situ. Patients with claustrophobia or ferrous implants were excluded. Thirty-five patients gave written informed consent to participate.

Placement of titanium clips

Eligible patients had titanium clips placed at BCS according to a national protocol (18) 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 ≥ 2 mm 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. The distances from the patient's lateral tattoos to the surface and inferior edges 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 & photographs. Patients were imaged using T1W 3-D sequences without (TR?, TE 12ms, 192mm FOV, 1mm slice thickness, 192X192 matrix) and with (addition of 100ms inversion delay pulse) fat suppression, and using T2W sequences (TR200, TE 100ms, 192mm FOV, 2 mm slice thickness, no gap, matrix 192X192). These sequences were chosen

based on evidence from literature described above and were modified from sequences commonly used in diagnostic breast MRI. Imaging acquisition took 20 minutes.

Image transfer and fusion

MR sequences were imported into the radiotherapy-planning system (Pinnacle version 8.0, ADAC systems) and co-registered with CT images. This was achieved using regions of interest (ROI) corresponding to the midpoint of each of the surgical clips, which were manually identified on each image set and matched manually. Any 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 prone CT data by a single observer (AK) without reference to MR findings, using clips, seroma and architectural distortion. Window level and width were fixed at 0 and 500 Hounsfield Units respectively. TB was outlined on the MR dataset at least two weeks after CT-outlining by the same observer blinded to CT findings. In consensus with a consultant radiologist (NdS) beginning with the T2W-sequence and encompassing any visible seroma, fibrosis and clips. Tissue that produced heterogeneous signal on all three sequences was considered to be haemorrhage/haematoma and included as TB. Clips visualised on T1W-sequences were also included. The MR- and CT-defined TB volumes were fused to create an MRCT-defined TB. The fused volume was edited to exclude tissue that MR demonstrated to be normal breast. Theoretical CTVs were created for each of the CT, MR and fused-MRCT (MRCT) 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. PTVs were created by addition of a 10mm margin to the CTV (limited by skin).

Conformity and discordance between volumes

The volumes of each of the CT-, MR-, and MRCT-target volumes were recorded and volumes of overlap and underlap calculated. Conformity between CT- and MRCT-TB {what is this?} , CTV

and PTV, was expressed as a conformity index (CI) calculated by dividing volume-of-agreement by the total volume delineated using both modalities. Discordance was expressed as a geographical miss (GMI) and normal tissue (NTI) indices. GMI was defined as the volume of MRCT-defined seroma, haemorrhage and/or fibrosis that CT failed to visualize, and was expressed as a fraction of the total delineated volume. NTI_T {what does subscript T mean?} was the volume of CT-defined TB that MRCT identified as normal glandular breast tissue expressed as a percentage of the total-delineated-volume. [Figure 2]. Similar comparisons were done between MR- & MRCT-TBs. GMI_{MR} {what does subscript MR mean?} was the volume of MRCT-defined TB that MR {shouldn't this be CT?} alone failed to visualise expressed as a fraction of the total delineated volume (and quantified the extent to which MR alone was unable to see clips).

Radiotherapy planning

PBI dose distributions were generated with the aim of covering CT-clip-defined target volumes according to national PBI study criteria. i.e. >95% of CT-CTV 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 MRCT-CTV {what is this? MRCT-CTV has not appeared before} receiving 95% of isocentre dose was measured. Statistical analysis was performed using the two-tailed Student t-test for significance to compare the CT- and MRCT-target volumes.

CVS?

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 cup size C (range A to FF). Median time from surgery to imaging was 47 (22-210) days. The majority of patients had cavity visualisation scores (CVS) (12) of 1 (n=7) or 2 (n=16), the latter representing poorly-visualised seroma. Twenty patients had full-thickness closure of their excision cavities following lumpectomy (apposed cavities) and 10 patients did not (unapposed cavities).

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 findings of the different imaging modalities. Figure 3 illustrates these findings. The presence of seroma on MR was associated with time from surgery to scan. 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 tables 2 and 3. 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. MRCT- and CT-CTV correlate well (Pearson correlation coefficient= 0.957, $p < 0.001$). (figure 4). {is figure 4 really

needed?} (Using linear regression, $MRCT\ CTV = (1.17 \times CT-CTV) - 3.84$). Median TB volume outlined in the supine position for the same cases was 5.9cm^3 ($p=0.08$).

Table 4 summarizes values for conformity and discordance between CT- and MRCT-target volumes. Concordance between TB volumes was poor but increased for CTV and PTV due to truncation of target volumes at skin and lung. Concordance between MR and MRCT was better but there was discordance attributable to MR not being able to define all clips. Mean differences in centre-of-mass (COM) for CT- versus MRCT-TB were 1.5mm in the medial-lateral (ML) plane, 2.0mm in the anterior-posterior (AP) plane and 2.2mm in the superior-inferior (SI) plane.

Target volume coverage by standard tangential PBI plans

Median percentage volume encompassed by the 95% isodose was 97.1% for CT-CTV (range 95.3-100.0%) (30/30 cases adequately covered), and 96.5% for MRCT-CTV (range 89.0-100.0%). 26/30 MRCT-CTVs were adequately covered. In 3/4 of the inadequately-covered cases, the percentage MRCT-CTV encompassed by the 95% isodose was $>93\%$, and in the remaining case, percentage MRCT-CTV covered was 89.0%. In this case, 95% of the MRCT-CTV was covered by the 87% isodose. In 2/4 cases, MRCT-TB extended inferiorly to CT-TB such that coverage of MRCT-CTV was inadequate in this direction. 4/4 cases had tumours at the most lateral or medial aspects of breast tissue. Mean CTV CI 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 CT-TB volume (7.9 vs 8.5cm^3 , $p=0.9$) between the adequately and inadequately covered groups.

Discussion

Anna, please list for me the most important points you wish to discuss. This will help me comment. At present, it opens very abruptly and it is not very clear what direction you are leading the reader. For example, you could open with a broad statement of your findings and their implications before introducing a discussion of your specific findings in relation to the literature. The Discussion should include an analysis of the strengths and potential limitations of your work.

We have found, consistent with a previous study (20), that addition of MR- to CT/clip-data increases delineated TB volume. CT alone is only able to visualise clearly 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. 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 aside from clips. We inferred some of the apparently normal fatty tissue to be TB but could only guess {very unscientific language?} at its location on CT. In our study, MRI sequences collectively visualised seroma, haemorrhage, oedema and fibrosis extending outside CT-TB volumes in most cases resulting in a median GMI of 37%. MRI was also able to distinguish post-operative change from normal glandular breast tissue bringing the MRCT-defined volume within the CT-TB at certain points and leading to a median NTI of 7.4%. Thus, the principal cause of discordance between CT- and MRCT-TB volumes was the finding of soft-tissue abnormalities on MR in regions where CT defined nothing but fatty tissue. However, this discordance is in the context of median CT-TB volumes of $\sim 6\text{cm}^3$.

MR- versus MRCT-TB volumes were more concordant than CT- versus MRCT-TB volumes reflecting MRI's greater soft-tissue contrast. Nonetheless, there was discordance due to MRI failing to identify some clips, especially those closest to the chest wall. T1-weighted sequences without fat suppression were more sensitive than the other two sequences but still only detected 77% clips. Work towards refining MR-imaging parameters in order to improve clip visualisation is ongoing at our institutions. The clinical significance of MR failing to visualise clips was not tested in our study.

Following excision of breast cancer, the boundaries of TB, or excision cavity walls, have been defined in 3D as the interface between fluid and breast tissue (eg on CT imaging, by the change in soft-tissue density from water to breast tissue). A margin (standardly 10-15mm) is then added to TB to encompass tissue considered to be at risk of local recurrence (CTV). An increasing majority of post-excision cavities however are not fluid-filled (12) and require definition with surgical clips in order to be visualised on CT. However, the relationship of these clips to the true post-operative cavity, and therefore the delineation of the entire cavity-tissue interface is unclear. Our MR-based delineation protocol is likely to overestimate true TB by including pericavity granulation tissue, oedema and haemorrhage. The resulting volume is somewhere between TB and CTV i.e. cavity plus part of the tissue-volume at risk of microscopic spread, and has been termed by one author as a post-operative complex (17). Adding 15mm to this volume would likely overestimate CTV. However, without including post-operative haemorrhage and oedema it would have been difficult to standardise our approach to MR-delineation of TB. Apposed cavities do not have clearly visible cavity/ normal tissue interfaces on the MRI sequences employed. Also, given reports suggesting that granulation tissue may be laid down within the original excision cavity (17), 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. If we find that addition of MR does not clinically significantly increase target volumes, we can be confident that use of the CT/clip method is unlikely to result in a geographical miss.

Following expansion of TB to CTV, CIs between CT/clip and fused-MRCT volumes improved from 0.54 to 0.89 due both 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 CT-based tangential PBI fields. 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) rather than to peripheral position of the target volume. Peripherally, coverage is difficult to achieve due to the breast shape and small differences in CTV may be result in coverage that is theoretically inadequate. Differences in COM positions for CT vs. MRCT TBs agree that discordance was greatest in the SI plane (2.2mm) but such a difference in COM is minimal in the context of a TB-PTV margin of 25mm, and it is unsurprising that discordance lead to inadequate coverage in so few cases. Our finding that even with a median TB CI of 0.54, coverage of CTVs was satisfactory in 87% of patients reflects the fact that the TB-CTV-PTV margins in PBI are large enough (in relation to the dimensions of most breasts) for differences in TB to be minimised by expansion and target volume truncation at tissue boundaries.

Even in the case with least adequate coverage, 89% of the MRCT-CTV would have been adequately irradiated, and the MRCT-CTV adequately covered by the 87% isodose. Using the linear-quadratic model and assuming an α/β value for breast cancer of 4.8Gy (1), this would result in a minimum equivalent dose of 41.8Gy. From dose-response curves, this is estimated to produce a reduction in tumour control probability relative to 50Gy in 25 fractions of ~3%. Bentzen suggests, from review of trials of adjuvant RT and systemic therapy, that a 3 percentage-point decrease in local control results in a 1% decrease in 10-year survival (21). This is weighed against the extra toxicity that would be incurred inferiorly extending the radiotherapy fields.

The co-registration of CT and MR datasets is a source of error, but the use of TB clips as match

points minimized changes in breast shape from CT to MR as a variable (22). 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 (23), 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) (22). 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). Misalignment 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 a trial (IMPORT-LOW). The RT techniques used therein are simple so as to be easily undertaken by the majority of centres. Using tangents, however, any ML discordance in CTV is unlikely to cause discrepancies in target-volume coverage. In centres where intensity-modulated radiotherapy is employed to increase conformality of the irradiated volume to the target volume, ML discordance could become more relevant, although our differences in TB COM were least in the ML direction.

The fact that patients were positioned prone for our study should not alter applicability of our findings standard supine treatment. As breast tissue falls away from chest wall this could elongate TB in the AP plane, maximising differences between modalities in this plane. However, there was no significant difference in median TB volumes defined supine and prone for our patients. Moreover, the most clinically-significant discordance was in the SI plane in our study, a finding unlikely to be affected by patient position.

Conclusions

Addition of MRI- to CT/clip-data increases TB volume by identifying additional seroma, oedema and haemorrhage. However, discordance between resulting clinical and planning target volumes is rarely significant in the context of tangential-field partial breast/ breast boost radiotherapy. CT/clip-based TB delineation is unlikely to result in a significant geographical miss and should remain the current standard.

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Table 1: Comparison of findings on CT and MR sequences in 30 patients imaged prone after breast conservation surgery for early breast cancer

Feature	CT	Standard	Fat-suppressed	T2W MR
		T1W MR	T1W MR	
Seroma visible	5	0	0	18/30
Other abnormalities	Architectural distortion 23	Fibrosis 5 Oedema/ haemorrhage 26	Fibrosis 5 Oedema/ haemorrhage 26	Oedema/ haemorrhage 26
Clips visualised (out of total 195 inserted)	195	151	81	129
Clips as only defining feature	7	0	0	0

Table 2: Median target volume (range) (cm³)

	CT	MR	MRCT
TB	5.7 (2.2-31.7)	7.8 (1.7-35.8)	9.7 (1.9-37.6)
CTV	81.9 (23.4-221.1)	88.5 (42.0-236.8)	93.1 (41.9-244.1)
PTV	225.3 (109.6-432.2)	228.4 (127.3-469.7)	239.2 (127.8-489.6)

Table 3: Median volume and percentage volume increase in CT vs. MRCT-defined target volume (range)

	Volume increase (cm ³)	Percentage volume increase (%)
TB	2.7 (-2.3-19.4)	44.8 (-18.7- 186)
CTV	8.8 (-21.2-71.9)	10.3 (-33.6- 80.9)
PTV	15.1(-43.3-14.21)	7.0 (-22.0- 46.5)

Table 4: Conformity and discordance between target volumes: median values (range)

	CT vs. MRCT volumes			MR vs. MRCT volumes
	TB	CTV	PTV	TB
Conformity index	0.53 (0.23-0.83)	0.87 (0.55-0.97)	0.92 (0.65-0.96)	0.83 (0.48-0.98)
Geographical miss index (%)	36.8 (7.9-65.1)	10.9 (0.5-44.7)	7.1 (0.1-33.5)	14.9 (1.8-51.2)
Normal tissue index (%)	7.4 (0.0-28.3)	1.6 (0.0-34.0)	0.6 (0.0-22.1)	0.7 (0.0-12.3)

Figure Captions

Figure 1. Axial CT image demonstrating titanium clips in excision cavity walls.
Uncertainties remain as to how to join these to represent tumour bed.

Figure 2. Diagram demonstrating the calculation of conformity, geographical miss and discordance indices

Figure 3. Co-registered axial images of right breasts of three different cases (1-3): a= CT; b= T1-weighted MRI with fat suppression; c= T2-weighted MRI; d= T1-weighted MRI. Superimposed target volumes: blue = CT-TB; red = MRCT-TB.

Top row: Titanium clip and skin-surface markers demonstrated on all datasets. Seroma visualised on T2-sequence only. MR distinguishes TB from normal glandular breast tissue.

Middle row: T1-weighted MR sequences most clearly demonstrated titanium clips (d). Clips appear as voids and those closest to the breast/ chest wall interface are most difficult to visualise.

Bottom row: Heterogeneity corresponding to oedema/ haemorrhage is visualised on T1/T2 MR sequences (b-d). Wrap artefact at lateral edge of image can make it difficult to visualise lateral TB on MRI.

Figure 4. Correlation between CT- and MRCT-CTV

Figure 1.

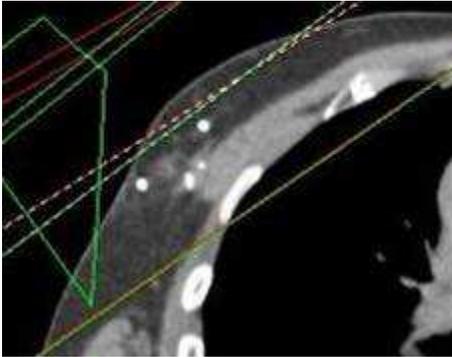


Figure 2.

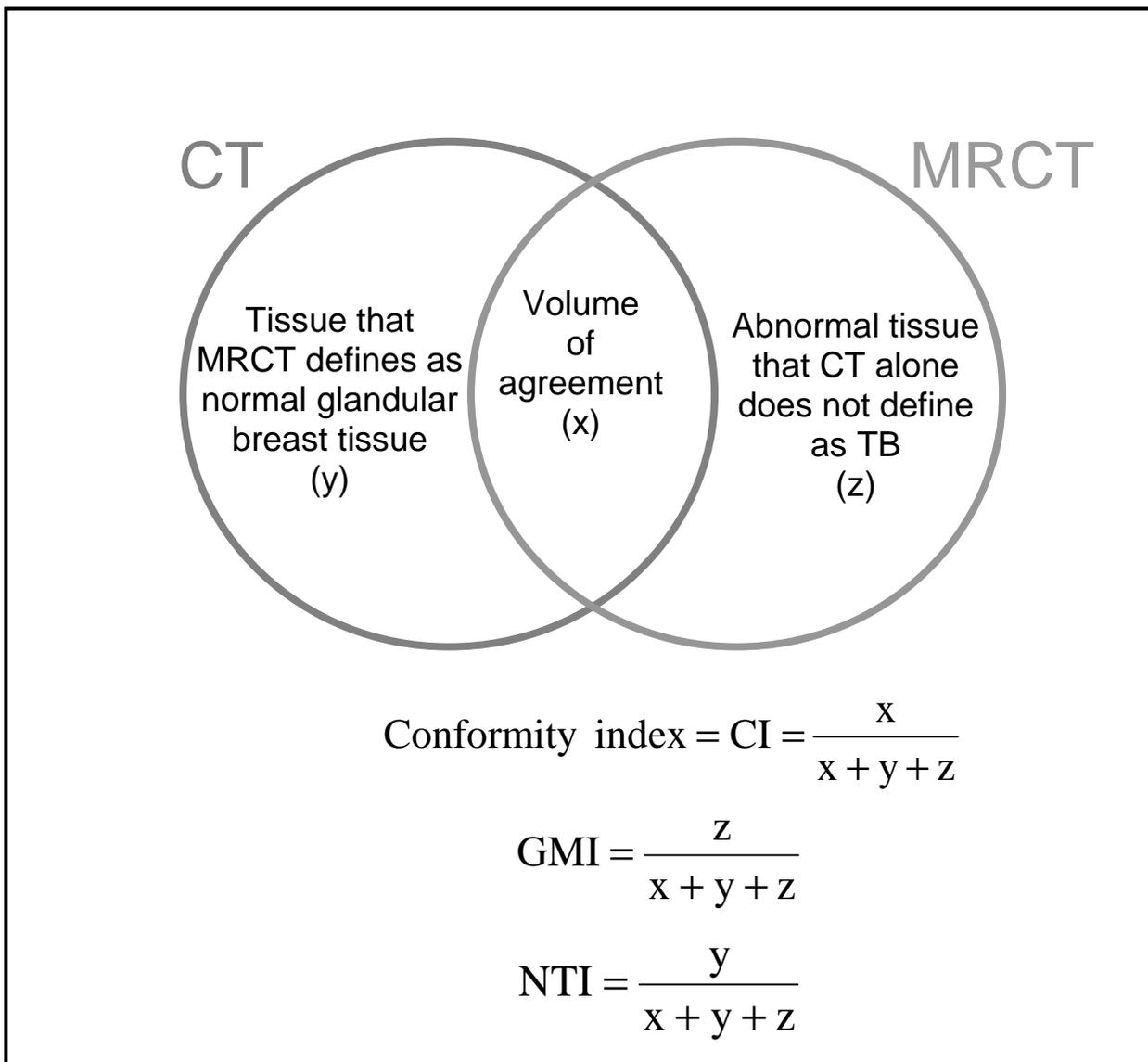


Figure 3.

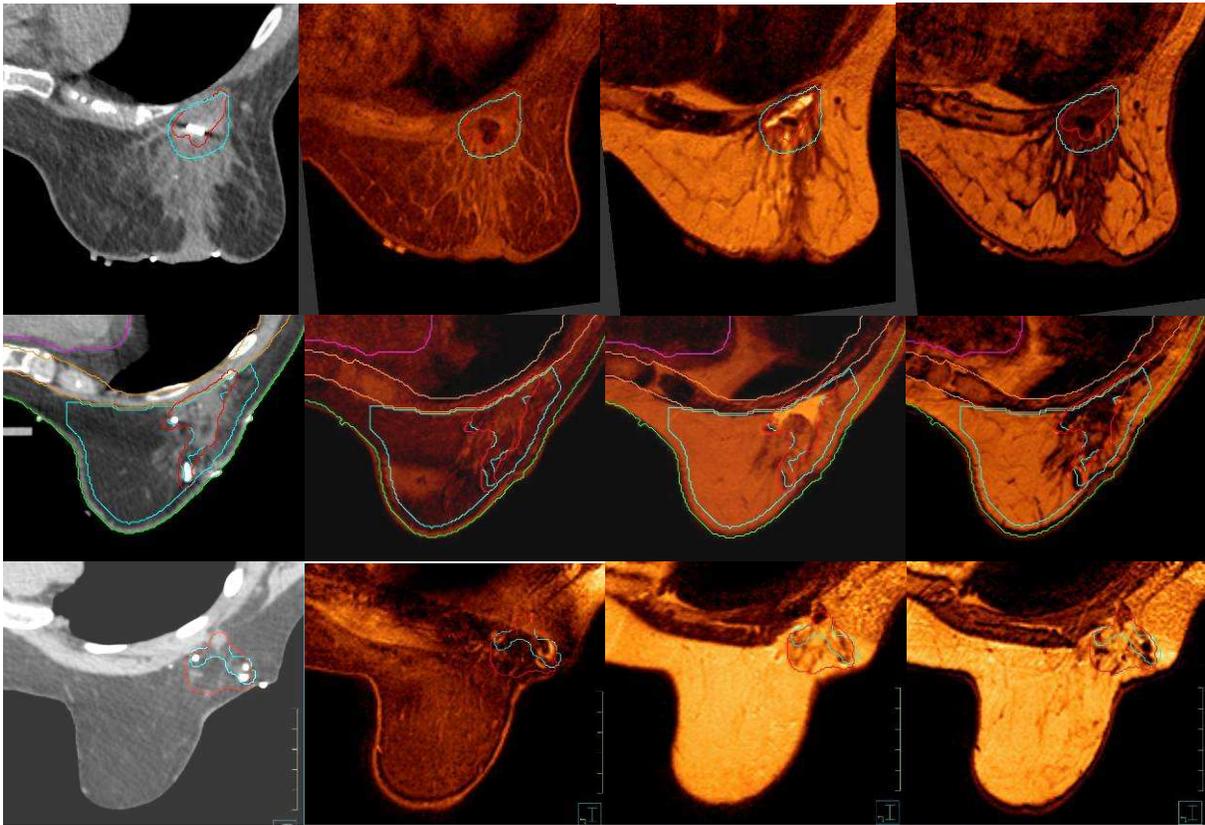


Figure 4.

