Tumour bed delineation for partial breast/ breast boost radiotherapy: what is the optimal number of implanted markers?

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Abstract

Purpose: International consensus has not been reached regarding the optimal number of implanted tumour bed (TB) markers for partial breast/ breast boost radiotherapy target volume delineation. Four common methods are: insertion of 6 clips (4 radial, 1 deep and 1 superficial), 5 clips (4 radial and 1 deep), 1 clip at the chest wall, and no clips. We compared TB volumes delineated using 6, 5, 1 and 0 clips in women who have undergone wide-local excision (WLE) of breast cancer (BC) with full-thickness closure of the excision cavity, in order to determine the additional margin required for breast boost or partial breast irradiation (PBI) when fewer than 6 clips are used.

Methods: Ten patients with invasive ductal BC who had undergone WLE followed by implantation of six fiducial markers (titanium clips) each underwent CT imaging for radiotherapy planning purposes. Retrospective processing of the DICOM image datasets was performed to remove markers and associated imaging artefacts, using an in-house software algorithm. Four observers outlined TB volumes on four different datasets for each case: 1) all markers present (CT_{6M}); 2) the superficial marker removed (CT_{5M}); 3) all but the chest wall marker removed (CT_{CW}); 4) all markers removed (CT_{0M}). For each observer, the additional margin required around each of TB_{0M} , TB_{CW} , and TB_{5M} in order to encompass TB_{6M} was calculated. The conformity level index (CLI) and differences in centre-of-mass (COM) between observers were quantified for CT_{0M} , CT_{CW} , CT_{5M} , CT_{6M} .

Results: The overall median additional margins required to encompass TB_{6M} were 8mm (range 0-28mm) for TB_{0M} , 5mm (range 1-13mm) for TB_{CW} , and 2mm (range 0-7mm) for TB_{5M} . CLI were higher for TB volumes delineated using CT_{6M} (0.31) CT_{5M} (0.32) than for CT_{CW} (0.19) and CT_{0M} (0.15).

Conclusions: In women who have undergone WLE of breast cancer with full-thickness closure of the excision cavity and who are proceeding to PBI or breast boost RT, target volume delineation based on 0 or 1 implanted markers is not recommended as large additional margins are required to account for uncertainty over true TB location. Five implanted markers (one deep and four radial) are likely to be adequate assuming addition of a standard 10-15mm TB-CTV margin. Low CLI values for all TB volumes reflect the sensitivity of low volumes to small differences in delineation and are unlikely to be clinically significant for TB_{5M} and TB_{6M} in the context of adequate TB-CTV margins.

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 external beam partial breast irradiation (PBI) is accurate localization of the TB, for which many oncologists are using CT imaging. However, CT imaging alone has been found to be associated with significant interobserver variability (IOV) (6-8) particularly in patients with low-volume seroma (6). Full-thickness apposition of tumour cavity walls following wide local excision is an increasingly common surgical practice based on evidence that it reduces the risk of post-operative infection (9), increases the sensitivity of mammography to detect local recurrence (9), and reduces exposure of cavity walls to potentially tumorigenic wound fluids (10). Full-thickness apposition of cavity walls is likely to decrease the incidence of seroma formation and to increase uncertainty over TB localization using CT-imaging alone. Furthermore, seroma alone may underestimate the true TB volume and misrepresent its shape (11, 12). Markers implanted in surgical cavity walls provide additional localization information compared to kV-CT-imaging alone (13), such that CT and marker-based TB delineation has been recommended as the current gold standard (14). Despite this, the use of implanted fiducial markers is still not widespread.

Where markers are in use, the optimal number of implanted markers remains unclear. Evidence suggests that the use of CT plus fewer than three clips is likely to significantly underestimate the extent of the TB (13, 15). A UK protocol recommends that paired clips be inserted into the four radial, the deep and the superficial margins of excision

(16) but, having established that clips do not migrate, more recent studies recommend placement of six markers (four radial, a chest wall and a superficial marker) (17). Many surgeons however prefer not to place a superficial clip due to concerns over marker mobility, cosmesis and marker palpability.

Within-patient comparison of TB volumes delineated using different numbers of markers would be valuable in illustrating the clinical implications of using fewer than six TB markers. Such a comparison has only recently been made possible through development of computer software capable of removing markers from CT images. This study compares TB volumes delineated by four observers using CT plus 0 (TB_{0M}), 1 (TB_{1M}), 5 (TB_{5M}), or 6 (TB_{6M}) markers in a population of breast cancer patients who have undergone WLE with full-thickness closure of the tumour cavity. For each observer, the additional margin required around each of TB_{0M} , TB_{1M} , and TB_{5M} in order to encompass TB_{6M} is calculated. It is hypothesised that progressively larger margins will be required as the number of markers decreases. In addition, the conformity level index and differences in centres-of-mass (COM) between observers' volumes are calculated for each of 0, 1, 5, and 6 markers. It is hypothesised that conformity level indices will decrease and that differences in COM will increase with decreasing numbers of markers.

Methods

Eligibility

Eligible patients were recruited via an ethically-approved study in which wide local excision of invasive ductal carcinoma of the breast was followed by placement of six titanium clips according to a national protocol (17), one at each of the four radial, the deep and the superficial excision margins. All patients had undergone full-thickness closure of the tumour cavity.

Imaging

All patients underwent kV-CT-imaging for radiotherapy in a supine position with the arms extended and abducted over the head, immobilised on a semi-supine breast board. All imaging datasets were graded for seroma visibility by observer AK using a cavity visualisation score (CVS) which ranges from 1 (cavity invisible) to 5 (cavity borders clearly identifiable) (6). Four anonymised copies were made of each dataset. One dataset per patient was left unaltered and labelled CT plus 6 markers (CT_{6M}).

On the remaining three datasets, markers were removed from CT images by a single independent radiation oncologist (RJ) using the following algorithm. The CT data was displayed as a grey scale image to the user, with a cross hair to identify the location of the marker to be removed (the “target”). The user identified a second region in the CT which had approximately the same structure as the tissue around the target. By sampling from this region, the user was able to gradually replace the target with tissue of a similar density to that surrounding the target. The algorithm is similar to the 'Clone-stamp' tool found in popular image processing algorithms such as Adobe Photoshop™ (Adobe Systems, San Jose, California, USA), but coded to operate on the Hounsfield Unit (HU) values in the CT dataset rather than the grey scale representation. The algorithm was used to remove TB markers, and to remove any local streaking artefacts in the region of the markers.

Using this software on the second dataset, only the most superficial marker was removed from the dataset. This dataset was labelled CT plus 5 markers (CT_{5M}). On the third dataset, all markers except that closest to the chest wall were removed. This dataset was labelled CT plus chest wall marker (CT_{CW}). On the fourth dataset, all markers were removed and this was labelled CT with 0 markers (CT_{0M}). Data before and after clip removal is shown in figure 1.

TB delineation

Four separate observers (observers 1-4, all radiation oncologists) outlined TB volumes on all four datasets for each of the ten patients. All observers were given guidelines for TB delineation as follows: using CT alone, observers were advised to include as TB any visible seroma and associated changes in tissue architecture. Using CT and markers, observers were advised to include as TB any visible markers, together with any visible seroma or change in the surrounding tissue architecture. All delineation was performed with a fixed window level of 0 HU and width of 500 HU. In each case, observers outlined CT_{0M} first, followed by CT_{CW} , then CT_{5M} and finally CT_{6M} . Observers were blinded to the delineated TB volumes of other observers. All observers had outlined a single test case which was reviewed prior to commencing the study to ensure that guidelines were being followed. An independent observer was asked to define marker position on CT_{0M} of cases 1-3 in order to test the axiom that markers were satisfactorily obscured.

Clinical and planning target volume (CTV) definition

Based on the UK IMPORT LOW trial protocol (18), clinical target volumes (CTV) were created by adding a uniform 15mm margin to each TB in 3-dimensions, limited deeply by chest wall and superficially by 5mm beneath skin surface. Planning target volumes

were created by expanding the CTV by a 10mm 3-dimensional margin (limited by 5mm from skin).

Analysis

For each observer, the additional margin required around each of TB_{0M} , TB_{CW} , and TB_{5M} in order to encompass that observer's TB_{6M} was calculated for each of the ten cases in each of the medial, lateral, anterior, posterior, superior and inferior directions (see figure 2). Median additional margins were calculated for each of TB_{0M} , TB_{CW} , and TB_{5M} . If TB_{6M} was encompassed by any of the other TB volumes in any direction, this margin was set to zero. Differences in centres-of-mass (COM) between TB_{6M} and each of the other TB volumes were calculated.

TB volumes were quantified. The conformity level index (CLI) for each dataset was calculated according to methodology defined by Kouwenhoven et al (19). The conformity level index is a variation on the conformity index (defined as the ratio of common volume to encompassing volume). The CLI performs pairwise comparisons, expressing the sum of all pairwise overlaps as a fraction of the sum of all encompassing volumes. The CLI is independent of the number of observers and is therefore considered more suitable for comparison between studies using different numbers of observers. CLI calculations were carried out using a modified version of software for comparison of multiple radiotherapy contours (COAST (Cambridge Outline Analysis and Scoring Tool) (20)).

Results

Ten patients were recruited, all of whom had undergone full-thickness closure of the tumour cavity with insertion of one clip at each of the four radial, the deep and the superficial margins. Median age was 54 years (range 41-65 years). Five patients had CVS= 1 and five had CVS= 2. Examples of TB contours are displayed in figure 3.

Table 1 details the additional margins that would have been required around TB volumes delineated using fewer than 6 clips in order to encompass TB_{6M}. There was no overlap at all between TB_{0M} and TB_{6M} for case 1 (observers 3 and 4), case 7 (observer 1), and case 9 (observer 2). For all other comparisons, there was some overlap between TB volumes. The overall median additional margin required was 8mm (range 0-28mm) for TB_{0M}, 5mm (range 1-13mm) for TB_{CW}, and 2mm (range 0-7mm) for TB_{5M}.

Table 2 displays median differences in TB COM. Median CLIs for each of the delineation methods are displayed in table 3. Median TB volumes for each observer are listed in table 4. Observers 1 and 2 outlined significantly larger volumes than observers 3 and 4. The independent observer was unable to locate any markers on obfuscated datasets. Her best guesses did not match with marker location on any of the three datasets analysed suggesting that markers had been satisfactorily removed from CT datasets.

Discussion

This study set out to compare tumour bed (TB) volumes delineated using 0, 1, 5 and 6 clips in women who have undergone wide-local excision (WLE) of breast cancer (BC), in order to determine the additional margin required when fewer than 6 clips are used. When TB volumes were outlined using no clips or a single chest wall clip, median additional margins of 8mm and 5mm respectively were required in order to encompass

TB_{6M}. Indeed, 4/10 TB_{0M} completely geographically missed TB_{6M}. This finding appears to be independent of observers as each observer geographically missed one TB using CT alone. Such uncertainty over TB location means that TB delineation using CT alone cannot be recommended for PBI. Where breast boost radiotherapy is being planned without TB markers, our study found that additional margins of up to 28mm and 13mm for TB_{0M} and TB_{CW} respectively would have been required in order to encompass the true marker-defined TB_{6M}. Differences in centres-of-mass reflected and supported the margin findings, being greatest (up to 37mm difference) for TB_{0M} versus TB_{6M}. The additional margins would translate to a significant increase in breast boost field size with implications for late side-effects. For example, Cox et al (21) found that for every 5mm increase in CTV-PTV margins, there was a 15% increase in the mean ipsilateral breast dose, and that for a 10mm increase in CTV-PTV margins, the mean heart dose doubled (from 23-43cGy) and mean lung doses tripled (from 61 to 180cGy). In short, TB delineation for either PBI or breast boost radiotherapy using CT alone or a single chest wall marker cannot be recommended as, without an additional margin, accuracy is compromised and, with an additional margin, normal tissue doses are significantly increased.

Where TB volumes were outlined using five clips (the most superficial having been removed from the CT images), the differences between TB_{5M} and TB_{6M} were, as expected, negligible in all but the anterior direction. (Previous work suggests that a median difference between observers of around 1-2mm is an acceptable level of variation between expert observers (22)). The median additional anterior margin required was 4mm (maximum 7mm). This is unlikely to be clinically significant in the context of mini-tangential field arrangements for PBI, as these usually splash the skin surface. However, where more conformal field arrangements are used, an additional

small margin (4-5mm) to ensure adequate coverage of the anterior aspect of target tissue may be advisable.

The methodology of performing the margin analyses within each observer's own volumes was designed to distinguish differences between TB delineation methods from differences between observers. Interobserver variability (IOV) however also reflects uncertainties in target volume delineation and should be accounted for in CTV-PTV margins. Hurkmans et al (23) previously reported conformity indices (Col) of between 0.11 and 0.52 for ten TB volumes outlined by four different observers. These Col's were low in comparison to the Col of 0.8 that is suggested to be an acceptable level of variation amongst expert observers (22). Patients in Hurkmans' study (23) did not have TB markers but, judging from the high average initial TB volume (40cm^3), tumour cavities had been closed only superficially such that CVS is likely to have been high on initial CT scanning. IOV has been reported to increase with decreasing visibility of the tumour cavity (6), Landis et al having found a median percentage PTV overlap of 57% for cavities with CVS=2 versus 87% for cavities with CVS=5. It has been hypothesised that TB markers might reduce IOV although Struikmans et al (8), who reported IOV between five observers outlining 17 cases, found no difference in conformity indices for patients with clips ($n=8$, $\text{Col}=0.56$) and without clips ($n=9$, $\text{Col}=0.55$). CVS was not measured in this study.

Our study did find a relationship between markers and conformity level indices (CLI). CLI were almost double for TB volumes delineated using 5 or 6 markers than for those delineated using 1 or 0 markers suggesting that markers do reduce uncertainty in target volume delineation. That said, CLI were low even for $\text{TB}_{6\text{M}}$ in comparison to those previously reported (6, 8, 23). Table 4 demonstrates that there were significant differences in median TB volumes between observers. Observers 1 and 2 outlined, on average, larger TB volumes than did observers 3 and 4. The reasons for this are

unclear. All observers followed the protocol and no significant volumetric differences were detected on the test case. Qualitative review of TB volumes suggests that observers 3 and 4 conformed much more tightly to TB markers than did observers 1 and 2. Interestingly, observers 1 and 2 worked at one institution and observers 3 and 4 at another. Observers 1 and 2 had more experience with gold seeds (which generate more artefact and therefore more uncertainty as to their boundaries) and with superficially-closed cavities whilst observers 3 and 4 had more experience with titanium clips and full-thickness closure of cavities.

Limitations of this study are as follows. Firstly, all cases had undergone full-thickness closure of the excision cavity as reflected by the low CVS. This accounts for the very low CLI for cases with 0 or 1 markers. The conclusions of this study are therefore only applicable to this patient group and cannot be applied to patients who have undergone superficial cavity closure, in whom seroma is likely to be more easily visualised and more consistently outlined. It is likely that in such patients, the risk of geographical miss without TB markers would be much lower. Secondly, large volumetric differences exist between observers. These have resulted in universally low CLI but are unlikely to have affected conclusions regarding margins. Thirdly, it is likely that differences in TB volumes will be greater than differences between clinical target volumes given that volumes are truncated at the peripheries of breast tissue. A similar comparison of differences in CTV_{0M} , CTV_{CW} , CTV_{5M} and CTV_{6M} would be of interest. Fourthly, the markers may have been inadequately obscured on the CT datasets although this seems unlikely given that the independent observer failed to identify any markers on obscured datasets, and that each observer completely geographically missed one TB volume using CT alone. Finally, sample size was small. Ten further cases with full-thickness closure are currently being processed alongside ten cases with superficially-

closed cavities. This will improve confidence in the findings as well as broadening their applicability.

In conclusion, in women who have undergone WLE of breast cancer with full-thickness closure of the excision cavity and who are proceeding to PBI or breast boost RT, target volume delineation based on 0 or 1 implanted markers is not recommended as large additional margins would be required to account for uncertainty over true TB location. Five implanted markers (one deep and four radial) are likely to be adequate for the purposes of TB delineation for partial breast/ breast boost radiotherapy using tangential fields. Six implanted markers are preferable where more conformal techniques are employed.

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Figure legends

Figure 1. Axial CT image from a single case a) before and b) after removal of tumour bed titanium clips

Figure 2. Diagram illustrating methodology for margin calculations (by convention, margin =0mm where TB_{0M} is outside TB_{6M})

Figure 3. Equivalent axial and sagittal CT slices from a single patient demonstrating the four observers' outlines (red, yellow, green & blue) for a) TB_{0M} , b) TB_{CW} , c) TB_{5M} , 4) TB_{6M} demonstrating increased conformality between observers as number of markers increases.

Figure 1.

Figure 2.

Figure 3.

Table 1: Median additional margins required to encompass TB_{6M} (mm) (range)

	Right	Left	Anterior	Posterior	Inferior	Superior
TB_{0M}	6 (1-10)	7 (3-13)	5 (0-11)	8 (1-14)	6 (1-19)	14 (4-28)
TB_{CW}	4 (1-12)	3 (1-5)	6 (1-13)	3 (1-8)	6 (2-13)	5 (3-10)
TB_{5M}	1 (0-3)	1 (0-3)	4 (0-7)	0 (0-1)	2 (1-3)	1 (0-4)

Table 2: Differences in centres-of-mass compared to TB_{6M} (mm) (range)

	Right-left	Anterior-posterior	Inferior-superior
TB_{0M}	7 (3-24)	4 (2-22)	11 (1-37)
TB_{CW}	5 (1-10)	4 (1-6)	6 (2-13)
TB_{5M}	2 (1-7)	2 (1-5)	3 (1-6)

Table 3: Median conformity level indices between tumour bed volumes defined using different numbers of markers (range)

	Median conformity level index (range)
TB_{0M}	0.15 (0.04-0.27)
TB_{CW}	0.19 (0.05-0.27)
TB_{5M}	0.32 (0.25-0.41)
TB_{6M}	0.31 (0.19-0.40)

Table 4: Median TB volumes by observer (cm³) (range)

	Observer 1	Observer 2	Observer 3	Observer 4	p
TB_{0M}	10.0 (2.2-30.5)	10.3 (2.6-42.2)	2.5 (0.7-10.0)	3.9 (0.7-8.3)	<0.001
TB_{CW}	20.7 (2.1-68.8)	7.8 (1.0-48.4)	3.0 (1.2-7.3)	4.3 (2.2-14.0)	0.002
TB_{5M}	13.6 (10.0-48.0)	7.9 (4.5-42.2)	5.6 (3.4-14.1)	5.2 (3.2-14.9)	<0.001
TB_{6M}	18.1 (10.0-61.0)	11.9 (3.5-44.8)	5.2 (1.8-9.7)	7.1 (4.8-9.0)	<0.001