1   **Title:** Characterisation of target volume changes during breast radiotherapy using
2   implanted fiducial markers and portal imaging

3

4   **Contact details:**

5   Institute of Cancer Research, Joint Department of Physics, Cotswold road, Sutton,
6   SM2 5PT, U.K.

7   Tel:++44 208 6613478

8   Fax:++44 208 6433812

9

10   **Email:**eharris@icr.ac.uk

11

12   Emma J. Harris^a (corresponding author) PhD., Ellen M. Donovan^a PhD, John R.
13   Yarnold^b M.D., Charlotte E. Coles^c M.D. and Philip M. Evans^a D.Phil., On behalf of
14   the IMPORT Trial Management Group

15   a -Joint Department of Physics, Institute of Cancer Research and Royal Marsden
16   Foundation Trust, Sutton, SM2 5PT, U.K.

17   b -Department of Clinical Oncology, Royal Marsden Foundation Trust, Sutton, U.K

18   c -Department of Oncology, Cambridge University Hospitals NHS Foundation Trust,
19   Cambridge, U.K.

20   **Conflicts of interest:** None

21   **Acknowledgments:** IMPORT and Institute of Cancer Research are funded by Cancer
22   Research UK.

23   **Running Title:** Excision cavity changes

24   **Keywords:** Excision cavity; Partial breast irradiation; fiducial markers; shape
25   analysis; breast radiotherapy.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

ABSTRACT

Purpose: To determine target volume changes using volume and shape analysis for patients receiving radiotherapy following breast conservation surgery. To compare different methods of automatically identifying changes in target volume, position, size and shape during radiotherapy for use in adaptive radiotherapy.

Methods and Materials: Eleven patients undergoing whole breast radiotherapy had fiducial markers sutured into the excision cavity at the time of surgery. Patients were imaged using CT (for planning and at the end of treatment) and during treatment using portal imaging. A marker volume (MV) was defined using the measured marker positions. Changes in both the individual marker positions and in the MV were identified manually and using six automated similarity indices. Comparison of the two types of analysis (manual and automated) was undertaken to establish whether the similarity indices can be used to automatically detect changes in target volumes.

Results: Manual analysis showed that 3 patients had significant marker volume reduction. This analysis also showed significant changes between planning CT and start of treatment for 9 patients, including single and multiple marker movement, deformation (shape change) and rotation. Four of the six similarity indices were shown to be sensitive to the observed changes.

Conclusions: Significant changes in size, shape and position occur to the fiducial marker defined volume. Four similarity indices can be used to identify these changes and a protocol for their use in adaptive radiotherapy is suggested.

1. INTRODUCTION

Radiotherapy of the breast following breast conservation surgery is adjuvant treatment as the gross tumour volume has been excised leaving possible microscopic disease. Standard breast radiotherapy treats the whole breast, but the region with the highest risk of tumour recurrence is proximal to the excision cavity and this may be treated with a higher dose of radiation. The excision cavity may be localised using imaging techniques to visualise seroma (1,2), changes in tissue architecture (3,4) or fiducial markers implanted into the breast at the time of surgery (5). The commonest method uses a combination of fiducial markers (typically surgical clips) and soft tissue changes imaged using computed tomography (CT) to localise the excision cavity and margins to encompass possible sub-clinical spread of disease are added to create the clinical target volume (CTV). Using fiducial markers, the Centre of Mass (CoM) of the markers at the time of treatment can be compared to the CoM at the time of planning to calculate daily shifts in the position of the excision cavity (6,7). In addition, changes in marker positions may arise due to deformation or volume change of the excision cavity (3) and fiducial marker migration (8,9) which will lead to changes in the size, shape and measured CoM of the measured volume.

Deformation may result in underdosing of the CTV or overdosing of healthy adjacent tissues. Marker migration will change the shape of the measured volume and its CoM, consequently these may differ from the shape and CoM of the excision cavity as defined at the initial CT planning scan. Measurement and characterisation of changes in marker positions during treatment may help to:

- identify time trends in changes of the excision cavity,
- characterise deformation and

- 1   • identify marker migration.

2   Using this information, strategies may be developed so that a response to changes in
3   the excision cavity may be made and the treatment tailored to the individual patient.

4

5   The aims of this study were:

6   1. To manually analyse target volume, shape and position with time, based on
7   implanted fiducial markers imaged using projection x-rays to determine what
8   changes occur.

9   2. To investigate automated methods of comparing target volumes and positions
10   using similarity indices to automatically detect changes in volume position,
11   shape and orientation.

12   3. To recommend an IGRT protocol for breast radiotherapy incorporating the use
13   of similarity indices.

14

15   **2 MATERIALS AND METHODS**

16   The measured positions of implanted fiducial markers were used to define the marker
17   volume (MV) which acts as a surrogate for the excision cavity which cannot be
18   visualised using portal imaging (PI). This was based on the envelope of the markers
19   to obtain the maximum coverage of the target volume; illustrated in figure 1. We
20   evaluated changes to the MV. Four methods (resulting in six possible similarity
21   indices) were used to compare the MV defined using CT at the time of planning
22   (volume A) with that defined during treatment, imaged using PI (volume B). The first
23   method uses the positions of the fiducial markers and the other 3 use the MV. The
24   methods used were:

- 1   1. Analysis of the second order moments of the positions of markers in A and B:
2   in the three spatial dimensions (first order moment gives the CoM and has
3   been studied by Coles *et al.* (6)).
- 4   2. Volume analysis, including the measured volume of A and B and a volume
5   index which gives the fractional change in the volume of the MV between
6   planning and treatment images.
- 7   3. The Jaccard Index (JI) which describes the volume overlap of A and B.
- 8   4. The Minkowski Index (MI) which is sensitive to changes in volume shape
9   only.

10   If the CoMs of A and B are shifted to a common origin the analysis will be
11   independent of any translation between the two volumes. For methods 1(second order
12   moments), 2 (volume analysis) and 4 (MI) a CoM shift was applied prior to the
13   analysis. For method 3 (JI), the analysis was performed before (JI1) and after (JI2)
14   CoM shift.

15

16   2.1   Patient study

17   At The Royal Marsden Hospital, 11 patients gave informed consent to be entered into
18   the National Cancer Research Network multi-centre GOLDSEED feasibility study
19   evaluating the use of implanted fiducial markers for IGRT in patients with early breast
20   cancer (5). Following wide local excision of the primary tumour, gold fiducial
21   markers were sutured around the excision cavity following a strict surgical procedure.
22   The markers were gold rings, 3mm in diameter, with a 1mm central hole and 1mm
23   thickness. The intended number of markers was 6 but this was less in some patients
24   due to re-excision or surgeon preference, therefore of the 11 patients recruited, 7 had

1 6 markers inserted, 4 had 5 markers inserted and one patient had 4 markers sutured
2 into the cavity.

3

4 All patients were CT scanned prior to treatment (CT1) and in the last week, or just
5 after, the end of their treatment (CT2). The CT axial slice separation was 1.25mm.
6 The CT images were exported to the Pinnacle Treatment planning system (Phillips
7 Medical Systems, Milpitas, CA, USA). The marker positions relative to the treatment
8 isocentre were identified by manually locating the centre of each of the markers on
9 the treatment planning system. The median time between surgery and CT1 was 88
10 days (range 30 – 169 days). Three of the patients received Chemotherapy, the time
11 between surgery and CT1 for these patients was 155, 157 and 169 days. Ten patients
12 received hormonal therapy.

13

14 The patients were treated under 3 fractionation regimens. These were the current
15 international standard of 50Gy in 25 fractions, and two regimes from randomised
16 controlled trials - 30Gy in 5 fractions and 40Gy in 15 fractions. No changes were
17 made to their treatment based upon the fiducial markers.

18

19 Portal images were acquired on the first treatment day and between 4 and 13
20 subsequent treatment days. The median time between CT1 and the first day of
21 treatment was 13 days. The images were acquired using an Elekta iViewGT EPID.
22 Two orthogonal portal images were acquired to locate the markers in 3D. One image
23 was acquired using the anterior tangential treatment beam. The second image was
24 acquired with the gantry placed orthogonal to this beam (using 1MU). Examples of

1 orthogonal portal images of the implanted fiducial markers are shown in figure 2.
2 Each marker position was calculated using triangulation with in-house software.

3
4 Observer errors associated with the measurements were evaluated by 3 physicists
5 locating the markers 3 times each with both CT and PI and using statistical methods
6 outlined by Bland and Altman (10). Changes in the MVs throughout treatment were
7 made by analysing the patient data manually. These observed changes were used as
8 the gold standard with which we compared the changes identified using the similarity
9 indices.

10
11 Translation was measured using the CoM shifts. A significant translation is defined as
12 a shift greater than 5mm (the local set up tolerance). The median magnitude of
13 rotation was 5° hence this was used as threshold to identify MVs with large rotation.
14 Significant volume reduction is defined as a volume reduction outside the 95% C.I.s.
15 Single marker movement is identified if a single marker has moved more than 2.5 mm
16 (3 times the mean total observer error) with respect to its CT1 position. Multiple
17 marker movement is defined as the movement of two or more markers by the same
18 distance. A change was defined as being characteristic for a patient's MV if observed
19 in more than 50% of cases.

20

21 2.2 Comparison methods

22 2.2.1 Second order moment analysis

23 The second order central moment of a distribution of N points is its variance and is
24 given by:

$$\mu_2 = \frac{1}{N} \sum_{i=1}^N (d_i - \mu_1)^2 \quad (1)$$

Where d_i is the position of point i and μ_1 is the centre of mass (CoM), given by:

$$\mu_1 = \frac{1}{N} \sum_{i=1}^N (d_i) \quad (2)$$

The position of d_i is specified in each of the three spatial directions: left-right (LR), superior-inferior (SI) and anterior-posterior (AP), allowing μ_2 to be determined in each direction (to limit the number of variables, cross-moments were not considered). Two methods of comparing volumes A and B were considered: firstly comparison of the whole volume and secondly pair-wise comparison of markers.

For the first method the variance index, m , was defined:

$$m = \frac{\mu_2(B)}{\mu_2(A)} \quad (3)$$

where $\mu_2(A)$ and $\mu_2(B)$ are the variance in marker positions in A and B respectively. m was evaluated in each direction (LR, SI and AP). This is expected to be sensitive to changes in rotation and deformation.

For the pair-wise comparison of the marker positions, by subtracting marker positions in volume B from those in volume A the movement of the markers, δ_i , was measured. If we replace d with δ in equations 1 and 2 we may calculate the variance in the marker movements, $\mu_2(A-B)$ and define similarity index Δm , to be:

$$\Delta m = \mu_2(A-B) + 1 \quad (4)$$

(where the addition of 1 is used to ensure Δm is 1 if the volumes are identical). This pair-wise approach was adopted to detect changes in the position of a single marker

1 between images of A and B as an indication of single marker migration. As with m
2 this may be calculated in each spatial direction.

3

4 2.2.2 Volume analysis

5 MVs were calculated for all scans. We define the volume index (VI). For the two
6 volumes $V(A)$ and $V(B)$ this is given by:

$$7 \quad VI(A, B) = \frac{V(A) - V(B)}{V(A)} + 1 \quad (5)$$

8 (as with eq. 4, the addition of 1 ensures identical volumes have an index of 1). VI is
9 constructed to be sensitive to change in volume only.

10

11 2.2.3 Jaccard Index

12 The Jaccard Index (JI) is defined as the intersection divided by the union of two
13 sample sets. For the volumes A and B :

$$14 \quad JI(A, B) = \frac{|A \cap B|}{|A \cup B|} \quad (6)$$

15 JI measures the overlap of the two volumes and a JI of unity indicates that the two
16 volumes are identical in size, shape, position and orientation (14) and will be less than
17 unity if any of these parameters differ i.e. the ideal value of the JI is 1. JI was
18 evaluated both before (JII) and after ($JI2$) the CoM of the markers in volumes A and
19 B were shifted to a common origin. JII measured the differences in volume overlap
20 between CT and PI volumes without set-up correction. Values of JII of less than 1
21 may be due to translational shifts and changes in size, shape and orientation whilst $JI2$
22 measure changes in size, shape and orientation of the volumes only. Neither of these
23 indices can be used to determine specific changes only to indicate that one of these
24 changes has occurred.

1

2 2.2.4 Minkowski Index

3 The Minkowski Similarity Index (*MI*) measures the similarity in shape of two
4 volumes (A and B) and is given by (11):

$$5 \quad MI(A,B) = \frac{V(B)^{\frac{2}{3}} V(A)^{\frac{1}{3}}}{V_m(A,B)} \quad (7)$$

6 where $V_m(A,B)$ is the Minkowski mixed volume for volumes A and B (12). Volumes
7 A and B are corrected for any difference in position or orientation: volume B is
8 rotated until it's orientation matches that of A as closely as possible. *MI* is sensitive to
9 differences in shape only and therefore can be used to distinguish between changes in
10 shape and other changes that occur. If no shape change has occurred *MI* will be equal
11 to 1.

12

13 2.3 Model analysis

14 The effects of stochastic variations in measured marker positions due to observer
15 variability were modelled to:

- 16 • calculate the resulting uncertainty in the volumes and similarity indices
17 measured for the patient data and
- 18 • evaluate confidence intervals to represent threshold values for each of the
19 indices for each patient MV; we define no change as a value of similarity
20 index that lies within the confidence 95% interval.

21

22 For each patient MV, 10000 sample volumes were generated by adding total observer
23 error to each marker position in the LR, SI and AP directions. Observer errors were
24 generated by randomly sampling a normal distribution with standard deviation equal

to the total observer error (10). Similarity indices were calculated for the 10000 new volumes. The distribution of the index values was non-normal and therefore the distribution was transformed by evaluating the cubed root of the index values. The resulting 95% confidence limits of this distribution were then found. Confidence limits were transformed back to give the 95% C.I. for each similarity index.

3. RESULTS

3.1 Observer error

The coefficients of repeatability (standard deviation $\times$ 1.96) in each direction are given in table 1 for both CT and PI for each observer (intra-observer) and all observers (inter-observer). The total coefficient of repeatability (CT+PI) is used to calculate error in the similarity indices evaluated for measured MVs.

3.2 Patient MVs and volume changes during treatment

The implanted markers did not define a regularly shaped MV as shown for patients 3 and 6 in figures 3(a) and 3(b). For patient 3, the outer 4 markers describe the largest MV and therefore 2 markers lie completely inside the MV (c.f. fig 1c). The MV(CT1) for patient 6 is an example of an MV which is formed from all six markers. It can be seen that the MV surface comprises a set of triangular faces, MVs can be described using the greatest width and length of the largest face and the distance of the marker furthest from this face. The dimensions of the MV(CT1) and the number of markers implanted for each patient are given in table 2.

Five types of change were observed:

1

2 1. translation

3 2. rotation

4 3. volume change

5 4. single marker movement

6 5. multiple marker movement (two or more markers)

7

8 The observed MV changes between CT1 and a) first day of treatment (PI first) and b)

9 all MVs measured during treatment are summarised in table 2. Column 5 of table 2,

10 gives changes observed between CT1 and PI first. The maximum measured values are

11 given if rotation, marker movement or volume change are observed. Column 6 of

12 table 2 gives changes for all the MVs measured during treatment. In column 6, values

13 given are maximum values for all portal imaging and CT2 MVs. Translations were

14 observed in the majority of patient MVs. These were excluded from further analysis

15 as they may be corrected using couch shift.

16

17 Two patients (4 and 11) had no substantial change between CT1 and treatment, one

18 patient (patient 6) had rotation only and the remaining patients all had some marker

19 movement. MVs for patients 1 and 10 were almost planar with thicknesses of less

20 than 1mm.

21

22 Figure 4 gives MV as a function of time. 95% confidence intervals are shown as error

23 bars for the MV measured for CT1 and CT2 (indicated using larger data points) and

24 on the first and last PI days. With the exception of patient 9 who had a large MV,

25 observer error produces large uncertainty in the measured volumes because of the

1 relatively small volume of the MVs compared to the magnitude of the observer errors.
2 There was significant ($P < 0.05$) change in volume size between CT1 (day 0) and the
3 first day of treatment for patients 5, 8 and 9. Patient 9's MV reduced between CT and
4 treatment by 47% and by a total of 65% by the end of treatment. This patient had a
5 large specimen size (100g) and large volume of seroma is visible in CT1 (this patient
6 did not receive a second CT scan). The MVs of patients 5 and 8 shrink in volume by
7 the end of treatment by 60% and 30% respectively.

8

9 Patient 2 had a very thin volume which shows a large fluctuation (to below 60% of
10 CT1 on days 10, 21 and 38 (CT2)). This was a result of the movement of the most
11 superior marker in the SI direction by 2mm. This is shown in figure 6.

12

13 3.3 Similarity indices for patient data

14 Similarity indices have been calculated between MV(CT1) and treatment MVs for all
15 patients. Values for the first PI, last day of PI and CT2 are given in figure 5. m and
16 Δm) were calculated in all 3 spatial directions and only the spatial direction the
17 greatest change is given. Patients are grouped by type of MV change. We define a
18 significant change in index value (i.e. significantly different from 1) if it lies outside
19 the 95% C.I.. There is good agreement between CT2 and the last days of treatment,
20 indicating no systematic difference between the two imaging methods. Table 3 gives
21 the percentage of MVs with “true-results” for each of the patients, where “true-
22 results” are defined as correct prediction of a change or no change using the similarity
23 index and “false-results” give an incorrect prediction. We now consider each of the
24 indices in turn.

25

1   *Variance index, m*

2   m indicates marker movement and volume change. From figure 5 m indicates change
3   for MV(PI first), MV(PI last) and MV(CT2) for all patients where this happens. m
4   gives false positive results for patient 11 (PI first) and false negative results for
5   patients 2 (PI first, PI last and CT2) and 3 (PI first) both of which have single marker
6   movement. m also gives false results for patients 8 and 10 (table 3). In the case of
7   patient 2 single marker movement has been identified (table 2) however, this marker
8   lies within the MV and as a consequence, variance, shape and volume do not change.
9   For patient 3 the marker movement is in the direction of the largest dimension and the
10   variance is not affected until one marker moves more than 5mm.

11

12   *Marker movement index, Δm*

13   Δm should also indicate marker movement or volume change. This index indicates
14   changes for all MVs shown in figure 5 with the exception of patient 6. False positive
15   results are given for patients 2, 4, 6 and 11.

16   *Jaccard Index, $JI1$ and $JI2$*

17   The Jaccard index should indicate translation, deformation, volume change or
18   rotation. All patients had true positive results for $JI1$. From figure 5 $JI2$ indicates
19   change for MV(day1) for patient1, this is in agreement with observed rotation. $JI2$
20   also correctly indicates no change for patients 4 and 11. False negatives were seen for
21   patients 2, 3, 4, 6 and 8 (table 3). For patient 2 the single marker movement is inside
22   the MV and hence does not change the volume. Hence this single marker movement
23   was not detected. From the manual analysis patient 3 has a high incidence of multiple
24   marker movement, which was not detected by $JI2$. This was also the case for

1 MV(CT2) for patient 4. For patient 6, rotations 6.2° and 6.3° were not detected. For
2 patient 8, single marker movement of 2.55mm was not detected for one MV only.

3

4 *Volume Index*

5 The volume index gives an incidence of true results of 100% for all patients.

6

7 *Minkowski Index, MI*

8 *MI* should indicate shape change only. For all patients except 2 and 3 *MI* gives an
9 incidence of true results of 100%. False negative results for patient 2 occurred due to
10 single marker movement inside the MV (as described above). Marker movement for
11 patient 3 was also not detected by the Minkowski index because the shape does not
12 change significantly.

13

14 From the above analysis, a single index cannot distinguish between single marker
15 movement and deformation. It has been seen that in some cases *JI2* and the *MI* do not
16 indicate marker movement where the MV shape does not change. However, these
17 changes can be detected by Δm .

18

19 **DISCUSSION**

20 Significant reduction in the size of the MV was observed for 3 patients. Other studies
21 have measured reduction of the volume of excision cavity during breast radiotherapy
22 for a larger proportion of patients. Using CT scanning, Jacobson *et al.* (3) found that
23 of 20 patients, 16 had a greater than 20% decrease in excision cavity volume 4 to 5
24 weeks into radiotherapy. Oh *et al.* (13) performed a similar analysis for 31 patients
25 and found a mean reduction of 22.5% in the excision cavity volume. In both studies,

1 excision cavities were defined using surgical clips, seroma and anatomical changes
2 seen in the CT. The mean marker volumes measured by Jacobson and Oh and in this
3 study were 36.1cm^3 , 36.6cm^3 and 3.12cm^3 respectively. Median time between CT1
4 and surgery was 88 days for this study and 60.9 for the Oh et al study (this data is not
5 given by Jacobson et al.) and therefore shrinkage over this greater time period may
6 account for the difference in volume. However, due to the magnitude of the
7 difference in volume (greater than a factor of 10) it is more likely that we have
8 measured smaller volumes because we use only the marker positions to define volume
9 and not seroma. Furthermore, our surgeons aim to obliterate the excision cavity to
10 reduce seroma, thus we would expect the marker volumes to be small. Observer error
11 in marker location using portal imaging was found to be less than 1mm, however the
12 small dimensions of the MVs (2 - 60mm) means that this error creates large
13 uncertainties in volume measurement and in the evaluation of the similarity indices.
14 Therefore, in this study, uncertainties in measured marker volume are of the order of
15 20% and so volume reduction for some patients may be undetectable. However, it is
16 possible that the volumes used in this study do not tend to decrease by significant
17 amounts as they are not defined using seroma, the volume of which we would expect
18 to decrease with time post surgery. In our study we use treatment PIs to measure the
19 marker positions. Our treatment PIs had an acquisition time of 4.56s which is on the
20 order of one breathing cycle and therefore any error in marker position measurement
21 due to infraction motion is included in the observer error (markers were slightly
22 blurred in the images). If shorter PI acquisition times are used it will be necessary to
23 consider intrafraction motion in the estimation of measurement errors.
24 Migration of surgical clips has previously been identified in two studies (7,8) however
25 this feasibility study is the first to use markers that are sutured into the excision cavity

1 wall. If we consider that the greatest amount of single marker movement detected was
2 7mm for patient 2 and multiple marker movements of up to 13.3mm were also
3 observed it is reasonable to assume that the single marker movement observed for
4 patient 2 is due to anatomical changes and not due to marker migration. Large volume
5 fluctuations observed for patient 2 were not a result of the 7mm marker movement
6 (this marker was inside of the MV) but for the 2mm movement of the most superior.
7 This marker moved back and forth in the SI direction during treatment. This motion
8 may be due to slight changes in the patient's arm position.

9

10 In practice, the CTV will be derived from the MV, seroma and any anatomical
11 changes evident on CT. However, the MV can be used in conjunction with the
12 similarity indices to indicate anatomical changes. With the exception of m , similarity
13 indices agreed well with the observed changes. JII was found to be very sensitive to
14 shifts in patient position. These shifts can also be measured using the CoM. In some
15 cases, marker movements may not be indicated by $JI2$ or MI . However, Δm will be
16 sensitive to these changes and alert to changes in the CoM. MI identifies shape change
17 only. These methods will not allow automatic distinction between single and multiple
18 marker movement. To apply these techniques to adaptive radiotherapy, we suggest the
19 verification protocol presented in figure 7. Interventions are shown by grey trapezoids
20 and include repositioning, investigation into the need to re-plan a treatment and
21 possible marker migration and/or a CoM changes. After initial corrections for CoM
22 shifts and rotations, VI is used to detect volume change, $JI2$ is used to detect changes
23 in rotation or shape, MI detects shape change (if $JI2$ is positive and MI is negative
24 then changes in $JI2$ must be due to rotation) and finally Δm is used to detect marker
25 movement and therefore possible migration.

1

2   **CONCLUSIONS**

3   Significant changes in size, shape and position occur to the fiducial marker defined
4   volume during radiotherapy. We have shown that using a combination of similarity
5   indices we can identify when changes in size and shape have occurred and devised a
6   protocol to use these methods for adaptive radiotherapy.

7

8   **REFERENCES**

- 9   1. Ringash J, Whelan T, Elliott E, *et al.* Accuracy of ultrasound in localization of
10   breast boost field. *Radiother. Oncol.* 2004;72:61-66.
- 11   2. Wong EK, Truong PT, Kader HA, *et al.* Consistency in seroma contouring for
12   partial breast radiotherapy: Impact of guidelines. *Int. J Radiat. Oncol. Biol.*
13   *Phys.* 2006;66:372-376.
- 14   3. Jacobson G, Betts V, Smith B. Change in volume of lumpectomy cavity
15   during external-beam irradiation of the intact breast. *Int. J Radiat. Oncol. Biol.*
16   *Phys.* 2006;65:1161-1164.
- 17   4. Goldberg H, Prosnitz RG, Olson JA, *et al.* Definition of post lumpectomy
18   tumour bed for radiotherapy boost field planning: CT versus surgical clips. *Int.*
19   *J Radiat. Oncol. Biol. Phys.* 2005;63:209-213.
- 20   5. Coles CE, Wishart G, Donovan E, *et al.* The IMPORT gold seed study:
21   Evaluation of tumour bed localisation and image-guided radiotherapy for
22   breast cancer. *Clin. Oncol.* 2007;19:S26-S27.
- 23   6. Coles CE, Wishart GC, Fairfoul J, *et al.* Implanted gold seeds for tumour bed
24   localisation and image-guided radiotherapy. *EJC Supplements* 2007;6-6.

- 1   7. Coles CE, Cash CJC, Treece GM, *et al.* High definition three-dimensional
2   ultrasound to localise the tumour bed: A breast radiotherapy planning study.
3   *Radiother. Oncol.* 2007;84:233-241.
- 4   8. Kass R, Kumar G, Klimberg VS, *et al.* Clip migration in stereotactic biopsy.
5   *Am. J. Surg.* 2002;184:325-331.
- 6   9. Tersteeg JHA, Roesink JM, Albregts M, *et al.* Changes in excision cavity
7   volume: Prediction of the reduction in absolute volume during breast
8   irradiation. *Int. J Radiat. Oncol. Biol. Phys.* 2007;69:S209-S210.
- 9   10. Bland JM and Altman DG. Applying the right statistics: Analyses of
10   measurement studies. *Ultras. Obstet. Gynecol.* 2003;22:85-93.
- 11   11. Tuzikov AV, Roerdink J, Heijmans H. Similarity measures for convex
12   polyhedra based on Minkowski addition. *Pattern Recognition* 2000;33:979-95.
- 13   12. Klain DA. The Minkowski problem for polytopes. *Advances in Mathematics*
14   2004;185:270-288.
- 15   13. Oh KS, Kong FM, Griffith KA, *et al.* Planning the breast tumor bed boost:
16   Changes in the excision cavity volume and surgical scar location after breast-
17   conserving surgery and whole-breast irradiation. *Int. J Radiat. Oncol. Biol.*
18   *Phys.* 2006;66:680-686.

19

14. Figures

1. Schematic 2D diagram of the excision cavity boundary (dashed lines) and 6 fiducial markers (circles) showing the variation in excision cavity volume contained within the MV. (a) and (b) show two possible MVs, (c) shows the MV containing the excision cavity volume which was chosen for this work.
- (a) Right anterior oblique portal image and (b) left anterior oblique portal image (1MU). The portal images were acquired at orthogonal angles.
3. Schematic diagrams of implanted fiducial marker positions and MVs for (a) patient 3 and (b) patient 6. Rings represent the fiducial markers and the lines show the boundaries of the MVs. Shadow projections of the MVs are shown.
4. Volume of patient MVs as a function of time. Error bars show 95% C.I. for CT1(day 0), MV(PI first), MV(PI last) and CT2 (large data points).
5. Similarity index values for MVs on the first (PI first) and last day of treatment (PI last) and for CT2. The Δm bars correspond to the right hand axis. All other index values correspond to the left hand axis. Error bars indicate uncertainty in measurement due to observer error. Solid black boxes indicate index values that lie outside the threshold values (95% C.I.).
- (a) Left anterior oblique DRR (patient 2) from CT1 and portal images of markers acquired 8 (b) and 10 (c) days after CT1. Implanted fiducial markers are circled. The change in the most superior marker is seen.
7. Work flow diagram representing suggested protocol for use of similarity indices VI , $JI2$, MI and Δm in an adaptive radiotherapy scheme.

1   **Tables**

- 2   **1.** Observer Coefficients of repeatability for CT and PI measurements.
- 3   **2.** Description of patient MV(CT1) and observed changes between CT1 and
- 4   treatment and during treatment.
- 5   **3.** Percentage of true results obtained using similarity indices for MVs. 100%
- 6   indicates that all MV changes were correctly identified by the similarity index.

7

8