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CLINICAL INVESTIGATION **Breast**

IMPROVEMENT IN INTEROBSERVER ACCURACY IN DELINEATION OF THE LUMPECTOMY CAVITY USING FIDUCIAL MARKERS

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Purpose: **To determine, whether the presence of gold fiducial markers would improve the inter- and intraphysician accuracy in the delineation of the surgical cavity compared with a matched group of patients who did not receive gold fiducial markers in the setting of accelerated partial-breast irradiation (APBI).**

Methods and Materials: **Planning CT images of 22 lumpectomy cavities were reviewed in a cohort of 22 patients; 11 patients received four to six gold fiducial markers placed at the time of surgery. Three physicians categorized the seroma cavity according to cavity visualization score criteria and delineated each of the 22 seroma cavities and the clinical target volume. Distance between centers of mass, percentage overlap, and average surface distance for all patients were assessed.**

Results: **The mean seroma volume was 36.9 cm^3 and 34.2 cm^3 for fiducial patients and non-fiducial patients, respectively (p = ns). Fiducial markers improved the mean cavity visualization score, to 3.6 ± 1.0 from 2.5 ± 1.3 ($p < 0.05$). The mean distance between centers of mass, average surface distance, and percentage overlap for the seroma and clinical target volume were significantly improved in the fiducial marker patients as compared with the non-fiducial marker patients ($p < 0.001$).**

Conclusions: **The placement of gold fiducial markers placed at the time of lumpectomy improves interphysician identification and delineation of the seroma cavity and clinical target volume. This has implications in radiotherapy treatment planning for accelerated partial-breast irradiation and for boost after whole-breast irradiation.** **© 2010 Elsevier Inc.**

Radiotherapy, Breast cancer, Fiducial markers, Seroma cavity, Delineation.

INTRODUCTION

Conventional breast-conserving therapy for the locoregional management of breast cancer patients has consisted of lumpectomy with axillary evaluation followed by external-beam radiotherapy (EBRT) to the whole breast (WBI) over a course of 5 to 6 weeks, with or without a boost to the tumor bed. Studies have shown that recurrence of cancer is most likely in the region surrounding the original tumor, and treatment to this specific area may be as beneficial as that to the entire breast. Accelerated partial-breast irradiation (APBI) is an alternative to WBI to highly selected patients and allows patients to receive radiotherapy to the tumor bed plus margin, thus sparing much breast tissue from receiving radiation. This allows the patient to receive treatment using hypofractionated treatment schemes, reducing treatment times and possibly leading to improved cosmetic outcomes and reduced fatigue. Furthermore, even with the specificity of APBI treatment, given the large dose per fraction, the potential long-term consequences of radiotherapy cannot be ignored (1–3). With CT-based planning, precise delineation of target structures may aid in improving the accuracy of APBI delivery.

In both APBI using EBRT and boost treatments after WBI, the lumpectomy cavity is delineated and expanded with adequate margin to form the clinical target volume (CTV). Additional margin for setup error and motion is then added to form the planning target volume (PTV). Thus, underestimation of the lumpectomy cavity will lead to possible underdosing of microscopic disease, whereas overestimation of the lumpectomy cavity will treat larger normal breast tissue volumes, possibly leading to increased skin reactions, both acute and late.

The identification of the lumpectomy cavity as defined by the presence of the seroma and possibly surgical clips is not as easy as one would think. Several studies have shown the variability in delineating the seroma cavity. Petersen *et al.* (4) examined characteristics associated with low

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interobserver concordance in target volume delineation for APBI patients and found that tissue stranding from the surgical cavity, proximity to muscle, dense breast parenchyma, and benign calcifications that may be mistaken for surgical clips were factors associated with increased interobserver variability. Weed *et al*. (5) investigated the role of surgical clips placed in the biopsy cavity during lumpectomy and concluded that surgically placed clips after lumpectomy are strong radiographic surrogates for the biopsy cavity. Dzhugashivili *et al*. (6) reported on 100 patients whose lumpectomy cavities were delineated by two physicians and reported that use of surgical clips significantly improved the ability to visualize the lumpectomy cavity. However, although clips are useful for helping visualize the seroma cavity, they are not easily identified on kilovoltage images, and it has been suggested that gold fiducial markers placed in the biopsy cavity during lumpectomy would be helpful to not only identify the cavity for treatment planning but also track the cavity during radiotherapy for image guidance (7).

Cancer Institute of New Jersey trial 040801 (CINJ 040801) is an institutional review board–approved, single-arm, prospective study investigating the utility of gold fiducial markers in APBI using three-dimensional (3D) conformal radiotherapy. At the time of lumpectomy, four to six suture-type gold fiducial markers are sutured to the walls of the surgical cavity. Although the primary endpoint of the trial is to determine whether fiducial markers improve the dose distribution in APBI, in the present study we hypothesized that the presence of gold fiducial markers would improve the inter- and intraphysician accuracy in the delineation of the surgical cavity compared with a matched group of patients who did not receive gold fiducial markers.

METHODS AND MATERIALS

Study population and seroma contouring

Twenty-two patients were identified for this study, and all of them underwent breast-conservation surgery followed by APBI between June 2006 and March 2009. Of the 22 patients, 11 received four to six gold fiducial markers (CIVCO Medical Solutions, Kalona, IA) during the definitive surgical procedure. Each gold fiducial marker is 2 mm in diameter and attached to 2/0 prethreaded absorbable suture material; these were sutured to the superior, inferior, medial, lateral, and posterior walls of the surgical cavity. Each of the 22 patients received radiotherapy to their breast according to the established partial-breast target volume guidelines set forth by the Radiation Therapy Oncology Group (8). Postoperatively, each patient underwent CT simulation to obtain 3D anatomy data for treatment planning purposes. During the simulation, each patient laid supine on a breast board, with both arms above their head on the CT couch. After the scan acquisition, images were transferred to an AcQSim workstation (Philips Medical Systems, Cleveland, OH) for isocenter placement. These data were then transferred electronically to the Varian Eclipse treatment planning system (version 7.3.10; Varian Medical Systems, Palo Alto, CA), where target delineation, beam placement, and treatment planning were performed. Normal structures were delineated and included the thyroid, ipsilateral whole breast, contralateral whole breast, lungs, and heart. Target volumes included the seroma cavity, CTV, PTV, and PTV–evaluation. These structures were drawn by three academic radiation oncologists who specialize in the treatment of breast cancer. These three radiation oncologists are labeled as Physician 1, Physician 2, and Physician 3, respectively, in the following context. In addition, fiducial marker patients are identified with an ''F'' in the following context.

All patients included in this study were treated on clinical trials. The 11 non-fiducial patients were treated on the National Surgical Adjuvant Breast and Bowel Project (NSABP) B and Radiation Therapy Oncology Group B-39, and the entry criteria have been previously reported (8). The 11 fiducial marker patients were treated on CINJ 040801, an institutional single-arm, prospective trial investigating the utility of fiducial markers and image-guided radiotherapy in APBI; patients provided informed consent before surgery for placement of fiducial markers and were enrolled on trial if results from the final pathologic review were appropriate. Eligibility criteria included age $\geq$45 years, ductal carcinoma *in situ* or invasive histologies, tumor size $\leq$3 cm, negative margins as defined by the NSABP, and delivery of APBI before any systemic therapy. Each patient received a simulation CT postoperatively, daily pre- and postradiothearpy kilovoltage images, and weekly cone-beam CT as a part of the trial.

Before defining the tumor bed, Physicians 1, 2, and 3 were required to give each tumor bed a cavity visualization score (CVS) according to guidelines established by Smitt *et al*. (9). This is a scoring system to classify seromas as follows: CVS-1, no visible cavity; CVS-2, heterogeneous cavity with indistinct margins; CVS-3, heterogeneous cavity with distinct margins; CVS-4, mildly heterogeneous cavity with mostly distinct margins; CVS-5, homogenous cavity with clearly defined margins. Each physician had the opportunity to contour the tumor bed while blind to the other physicians' contours. The physicians had the ability to adjust magnification as well as window size during contouring. Physicians also had access to all patient medical records. One author, other than the three radiation oncologists, was present during contouring to ensure that guidelines were met, as well as to load images and save coded information. Physician 1 contoured the tumor bed twice (once at time of treatment, another at time of this study), to establish intraobserver variability.

Data analysis

The contours noted above for each patient were exported in Digital Imaging and Communications in Medicine radiotherapy format from the treatment planning system to an in-house-developed software package. With the software package, a comparison of the distance between the centers of mass (DCOM), percentage overlap (PO), and average surface distance (ASD) for each set of contours for all patients was carried out.

The DCOM was defined as the Euclidean distance between the geometric centers of two 3D target volumes. The target volumes were computed numerically as binary masks in the image domain. They were generated by assigning 1 to every pixel (x_i, y_i, z_i) inside the manually drawn closed contours of the target in each axial slice, and 0 otherwise. The in-plane pixel resolution for the data sets are 0.9375 mm in both x and y axes, and the distance between slices (or the resolution in z axis) is 3 mm. The geometric center of the binary mask can be expressed as (x_c, y_c, z_c), where x_c = mean (x_i), y_c = mean (y_i), and z_c = mean (z_i).

The PO was defined as the percentage ratio between the intersection and the union of two volumes. The mathematic formulation of PO for two volumes A and B was $PO(A, B) = \frac{A \cap B}{A \cap B} \times 100\%$. Note