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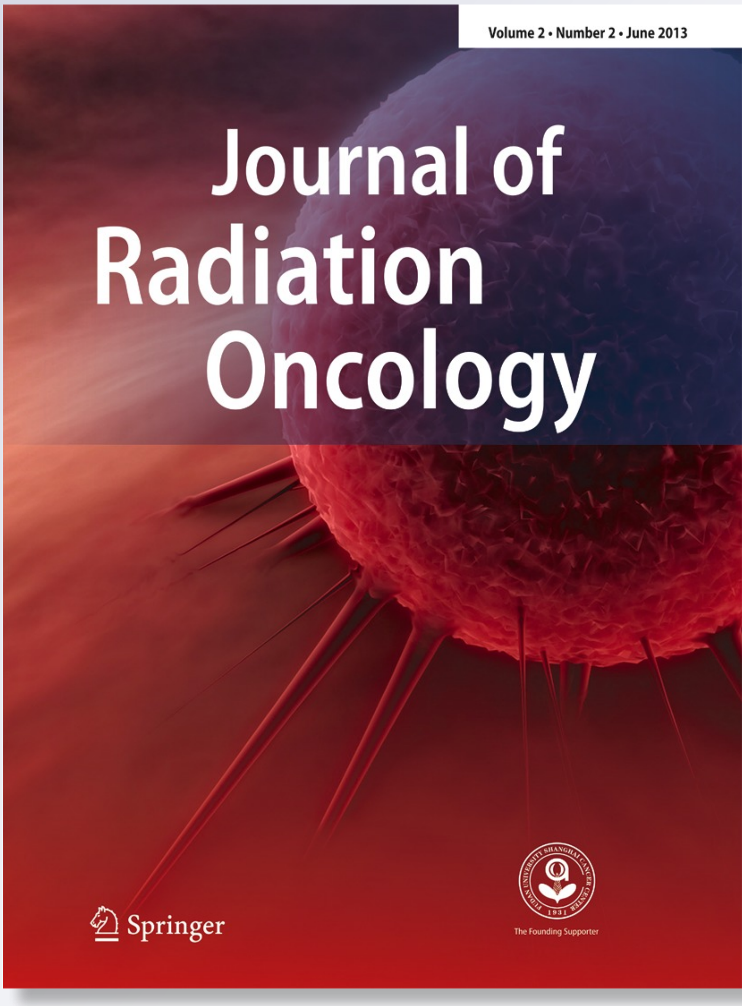

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ORIGINAL RESEARCH

Fiducial-based image-guided radiotherapy for whole breast irradiation

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Abstract

Objectives Image-guided radiation therapy (IGRT) improves setup accuracy and reduces treatment margins, potentially improving efficacy while decreasing long-term toxicity of whole breast irradiation (WBI). This study quantifies intraparenchyma fiducial motion and utility during the course of WBI.

Methods On a prospective IRB-approved protocol, textured gold fiducials were placed intraoperatively at the periphery of the surgical bed in 25 patients who then received 3D conformal conventional WBI. Free breathing and 4D CT image sets were obtained at pre-treatment simulation and at 6 weeks of treatment. Respiration-induced motion was assessed by comparing fiducials' position between inspiration and expiration. Fiducial migration and setup variation were determined by comparing the relative positions of each marker from the pre- and post-treatment megavoltage and 4D CT image sets.

Results Average intrafraction respiratory motion on 4D CT image sets was 0.1 mm. Variation in separation between fiducial pairs compared to simulation CT was on average 0.7 mm. The position of the seroma center was stable with respect to the center of mass (COM) of the fiducials throughout treatment. Based on daily megavoltage portal images, the average variation in the fiducial COM relative to the vertebral body landmark was 9.4 mm. The average variation of the seroma relative to fiducial COM from the 4D CT data was 6.2 mm.

Conclusions Fiducial position was stable during treatment, and there was minimal respiration-induced motion. Using IGRT may improve the accuracy of daily setup and reduce PTV margins in WBI. Better tumor bed localization and reduced margin size will decrease the volume of normal tissue treated, which may translate into improved outcomes and lower toxicity.

Keywords Whole breast irradiation · IGRT · Fiducials

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Introduction

Breast-conserving surgery followed by whole breast irradiation (i.e., breast-conservation treatment) has been established as an effective therapy for early-stage breast cancer [1, 2]. Conventional courses of whole breast irradiation typically involve 3 to 6 weeks of daily treatments. It is challenging to reproducibly position the breast [3], limiting the opportunity to utilize techniques which rely on accurate positioning, in particular intensity-modulated radiotherapy (IMRT). Image-guided radiotherapy (IGRT) is a method to account for target/organ motion and improve daily setup accuracy. One technique for IGRT involves the placement of intraparenchyma fiducials, although this technique has not been widely used in breast cancer patients.

Fiducial markers are typically metallic seeds implanted into target tissues. The role of fiducial markers in the treatment of breast cancer is twofold: fiducials can be used to improve accuracy in delineation of the surgical cavity [4] and for the verification of breast position during IGRT. Fiducial markers are preferred over surgical clips because they are better visualized on standard megavoltage and kilovoltage on-board imaging. Without IGRT, the planning target volume (PTV) expansion has to be large enough to cover patient setup variations and intrafraction motion. Image guidance may improve whole breast irradiation outcomes by ensuring adequate coverage of the target tissue on a daily basis while allowing smaller margins around the targets, thereby reducing exposure to lung and heart (for left sided cases).

We hypothesized that textured gold fiducial markers could be used to facilitate IGRT for external beam whole breast irradiation even when there is seroma shrinkage. In this prospective clinical trial, we evaluated intrafraction motion prior to and during treatment, as well as interfraction respiratory motion, fiducial stability, and the impact of changes in seroma on fiducial position. The relationship of fiducials to an anatomical reference was analyzed to establish PTV expansions in the event fiducial-based IGRT is not available.

Methods

Patients

Twenty-six women with early-stage breast cancer completed a prospective IRB-approved protocol, undergoing fiducial markers placement at the time of their lumpectomy, then receiving external beam whole breast irradiation between June of 2008 and August of 2010. Twenty-five patients with 80 fiducials were evaluable for the 4D analysis and the daily megavoltage image analyses. One patient had simultaneous bilateral cancers, for whom both breasts were included.

Inclusion criteria

Inclusion criteria included pathologically confirmed stage 0, I, or II unilateral breast cancer, any invasive adenocarcinoma or intraductal carcinoma, age ≥18 years and ECOG performance status ≤2, tumor size <5 cm, and axillary nodal sampling for all invasive cancers. All patients had lumpectomy with negative margins followed by radiation within 8 weeks after last surgery or last dose of chemotherapy, and a negative post-biopsy mammogram if presenting with mammographically detected microcalcifications. Patients needed to understand and be willing to sign written informed consent documents.

Patient simulation, immobilization, and treatment

Three to four textured gold fiducial markers were placed in the periphery of the tumor bed cavity by the surgeon intraoperatively [Visicoil™ (Core Oncology, Santa Barbara, CA) or X-MARK™ (ONC Solutions, Acton, MA)]. Fiducials were intentionally placed 1–2 cm into the breast parenchyma to reduce migration and positional change with seroma resorption, and were not used for target delineation.

At the time of standard CT simulation and at the end of treatment, a 4D CT scan was acquired in the treatment position, using 3-mm slice thickness and 120 kVp. Free breathing CT simulation was used for treatment planning. The whole breast was defined using the clinical reference volume of palpable breast tissue plus a 2-cm margin. The tumor bed was defined as visible seroma and other post-operative changes plus any surgical clips. Whole breast irradiation was planned using 3D conformal field-in-field technique (3D-CRT) to a total dose of 46 to 50 Gy in 2.0 Gy per fraction (N=23) or 42.46 Gy in 2.66 Gy for 16 fractions (N=3). A boost dose of 14 to 16 Gy was given in 20 patients. Regardless of fractionation, all patients underwent per protocol a 4D CT scan 6 weeks after start of treatment.

Image acquisition

Four-dimensional computed tomography

4D CT image sets at normal end-inspiration and end-expiration were imported into the Pinnacle treatment planning system (TPS; Version 9.0, Philips Medical System™, Fitchburg, WI). The tumor bed and fiducials were contoured on end-inspiration and end-expiration images on 4D CT sets acquired at the time of simulation and at 6 weeks. Standard planning tools were employed to determine the 3D coordinates of the center of each fiducial and the geometric center of the seroma. Each region of interest was represented by 3D Cartesian space in the X, Y, and Z coordinates.

2D orthogonal megavoltage images

Daily anterior–posterior (AP) and lateral (LAT) portal images were acquired using a megavoltage electronic portal imager (EPID). These images were compared to AP and LAT digitally reconstructed radiographs (DRRs) generated from the simulation CT.

Analyses

The methods for analyzing respiratory motion have been previously described [5], and are available in the "Electronic supplementary material".

Daily setup variation

Data for image analyses were obtained from the daily pretreatment megavoltage portal images. To assess fiducial positions at each fraction for each patient, a unique vertebral body bony landmark was established. Vector displacements from this landmark to the center of each fiducial were measured on AP and LAT image set using a calibrated electronic ruler. Distortions during treatment were estimated by comparing the distances between fiducial pairs on the daily megavoltage images to the corresponding distances from the pre-treatment DRRs. Of the 580 orthogonal image pairs acquired with megavoltage EPID imaging, 511 image sets were analyzable for identifying the position of the fiducial center of mass (COM), and 1,859 data points were usable for analyzing the inter-fiducial distances. Image sets were not analyzable if the bony landmark or if one or more of the fiducials could not be identified on both the lateral and AP images.

Relationship between seroma and fiducials

On the pre-treatment end-expiration image from the 4D CT, the displacement between the COM of the fiducials and the seroma was determined by calculating the vector displacement of the fiducial COM to the geometric center of the seroma. Fiducial distortion was assessed by comparing the average of fiducial separations on the expiration image of the pre-treatment and post-treatment 4D CT sets. While it was not possible to assess the intrafraction relationship of the fiducials to the position of the seroma, the process was repeated using the post-treatment (at 6 weeks) end-expiration 4D CT scan to determine if there were changes over the course of treatment.

Statistics

All statistical computations were performed with GraphPad Prism software, version 5.01 (GraphPad Software, San Diego, CA). A paired *t* test was used to determine changes in respiratory motion over the course of therapy, systemic variation between pre-treatment and post-treatment, and variations in respiratory motion.

Results

Of the 25 patients eligible for analysis, there were no reported complications from the fiducial implantation such as bleeding or infection. The 4D CT image sets were acquired on average 48.2 days apart (SD=11.3 days, range 20 to 60 days).

Respiration-induced motion

The average intrafraction respiratory motion on all 4D CT image sets based on fiducials was 0.1 mm (SD=1.1 mm, range −2.7 to 2.6 mm). The average intrafraction respiratory motion based on seroma motion was −0.4 mm (SD= 1.1 mm, range −3.4 to 1.3 mm).

Interfraction respiratory variations compared between simulation and the end of treatment for individual fiducials was 0.2 mm (SD=1.2 mm, range −2.7 to 2.7 mm), and for seroma was −0.2 mm (SD=1.3 mm, range −3.9 to 3.3 mm). The 95 % confidence intervals for interfraction variation measured before and after the treatment regimen were: −1.3 to 2.6 mm medial–lateral, −1.9 to 2.2 mm anterior–posterior, and −2.6 to 1.5 mm inferior–superior.

Fiducial migration and distortion

Using the pre- and post-treatment 4D CT data, fiducial migration, represented by the average variation in distance between fiducial pairs, was found to be −0.04 mm (SD=1.2 mm, range −3.9 to 3.1 mm; Fig. 1). Using the daily megavoltage orthogonal pairs, change in distance between fiducial pairs averaged 0.7 mm (SD=3.1 mm). The distance between fiducial pairs varied by <6.3 mm in 95 % of measurements. The average fiducial distortion was 4.0 mm closer together over the course of treatment (SD=2.8 mm, range −0.8 to −8.8 mm).

Daily setup variation

The variation in separation between fiducial pairs on post-treatment 4D CT as compared to the original separation on simulation CT was on average 0.7 mm (SD=3.1 mm, range −12.1 to 10.4 mm; Fig. 2). The mean variation of fiducial COM positions to the reference vertebral body distance compared to simulation CT was 0.4 mm (SD=4.7 mm, range −11.8 to 13.9 mm; Fig. 3).

Change in seroma volume

The change in the seroma volumes were distributed in a bimodal fashion. Median seroma volume for the whole group was 16 cm^3, (SD=16 cm^3, range=6.7 to 67 cm^3). Patients with seroma volumes >16 cm^3 (average =34 cm^3, SD=16 cm^3)

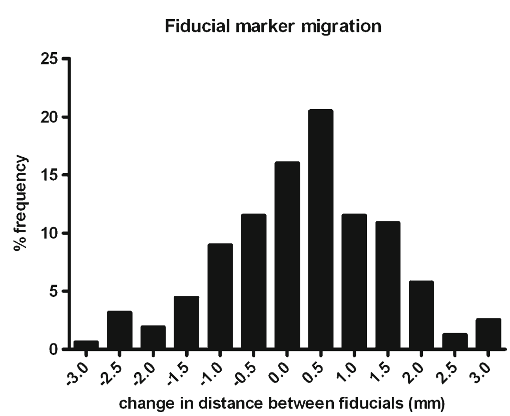

Fig. 1 Frequency of the change in fiducial positions from end-inspiration to end-expiration on 4D CTs demonstrates the average intrafraction motion

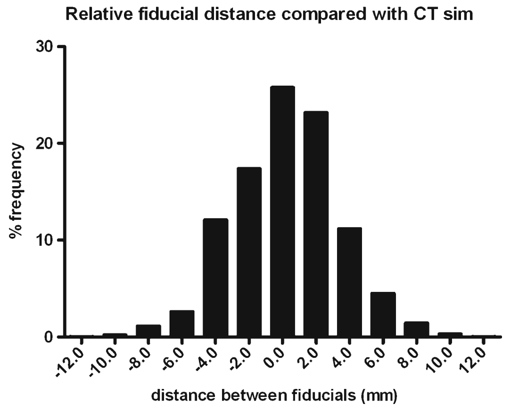

Fig. 2 Positions of each fiducial center were measured on the end-expiratory phase of the simulation CT and at 6 weeks. Figure shows the frequency of distances between fiducial pairs between the two CT sets

had an average change of volume of 12 cm^3 (SD=7.8 cm^3, range=−3.3 to 24 cm^3). Patients with seroma volumes <16 cm^3 (average=11 cm^3, SD=2.8 cm^3) had an average change of volume of 1.9 cm^3 (SD =3.7 cm^3, range=−3.8 to 12 cm^3).

Change in seroma position relative to fiducials

The position of the geometric center of the seroma relative to the fiducial COM was examined on the 4D CTs at end-expiration (Fig. 4). There was no significant difference seen in the variation in this relationship between pre- and post-treatment data sets, which was on average −0.4 mm (SD= 2.4 mm, range −4.3 to 4.2 mm). The 95 % confidence intervals for change in relative position of the seroma to the fiducial COM were as follows: −3.4 to 4.5 mm in the medial–lateral direction, −4.2 to 3.0 mm in the anterior–posterior direction, and −4.5 to 3.0 mm in the superior–inferior direction.

IGRT using bony landmarks

Based on the daily megavoltage portal image analysis of the fiducial COM (as a surrogate for breast position) relative to the vertebral body landmark, the value of 2 standard deviations of this variation (corresponding to 95 % of the treatments) was 9.4 mm, defining the margin required to account for setup variation if the patient is treated with IGRT using orthogonal images aligned to bony landmarks alone.

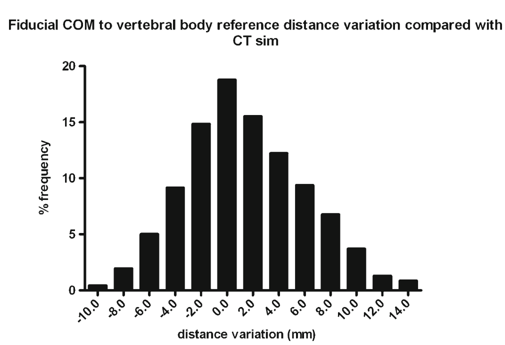

Fig. 3 Distribution of variation in distances between the fiducial COM to the reference vertebral body points as measured on daily megavoltage orthogonal films compared to the original position on DRRs generated from the simulation CT for each patient

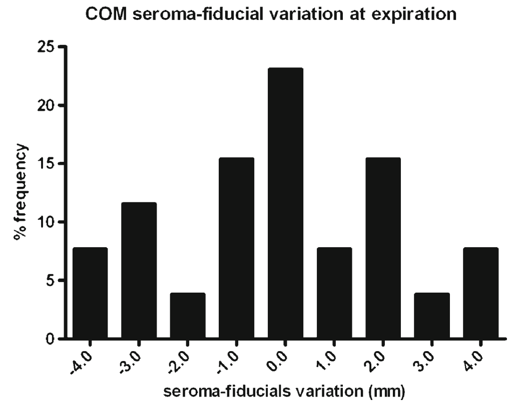

Fig. 4 The position of the geometric center of the seroma relative to the fiducial COM was measured on simulation and 6-week 4D CTs at end-expiration. Figure shows the frequency of the average variation between the two centers from pre- to post-treatment

IGRT using fiducials

The variation of the seroma relative to fiducial COM from the 4D CT data analysis, from which variation between the fiducials includes respiratory motion, fiducial migration, and variation in the seroma, is a good surrogate for the total uncertainties in fiducial-based IGRT. The PTV margin required to account for this variation 95 % of treatments (two standard deviations of the variation) was 6.2 mm. Therefore, when using fiducial-based IGRT, a margin for setup uncertainty of approximately 6 mm is recommended, indicating that the margin required to account for setup variation can be reduced when using fiducial-based alignment.

Discussion

The goal of this study was to establish the feasibility and utility of fiducial-based IGRT for whole breast radiation therapy. We previously published a concurrent cohort of patients treated on this same protocol who received one week of accelerated partial breast irradiation [5]. For this whole breast irradiation cohort, who was accrued in parallel, we were able to analyze the stability of fiducials and the impact of seroma changes on fiducial-based IGRT, as well as confirm the ability to reduce PTV margins over the much longer course of whole breast treatment. As these data demonstrate, textured fiducials remain stable in place in the breast parenchyma throughout a 6-week course of whole breast irradiation, thus can be used for IGRT aligning to fiducials. The use of IGRT allows for smaller margins around the whole breast, which will reduce the dose to normal organs. IGRT allows for more accurate daily positioning, which will facilitate the application of techniques that are highly dependent upon such accuracy, such as IMRT and simultaneous integrated boost (SIB).

Several studies have shown that larger margins are required to account for setup variation if no correction protocol is used beyond laser alignment to tattoos. Yue et al. examined positioning differences in 21 patients with sutured gold fiducials imaged with daily kilovoltage portals, comparing setup with laser tattoos and bony anatomy to the benchmark fiducial markers [6]. The mean interfractional setup error was 7.1 mm for bony anatomy and 9.0 mm for laser tattoos. Bony anatomy is less accurate than three dimensional alignment techniques. For example, Hasan et al. compared registration of CT simulation data to a second CT, comparing bony anatomy, clips and breast surface [7]. They noted improved localization of the lumpectomy cavity using either surgical clips or the breast surface over bony anatomy. Clip registration was the least sensitive to anatomic variations.

Surgical clips have been studied as potential fiducial markers for IGRT. Topolnjak et al. reported on 21 patients set up with daily cone beam CT (CBCT) retrospectively aligned to clips versus excision cavity [8]. They noted an average movement of clips towards the center of the excision cavity of 1.4 mm (maximal 5.8 mm) over the course of treatment. These authors noted importantly that the quality of the daily CBCT influenced the variability of registration to the excision cavity, and registration variation for all CBCT was up to 3.4 mm. Overall clips were a good surrogate for position verification of the excision cavity. Harris et al. examined 11 patients who had fiducials sutured into the excision cavity at the time of lumpectomy, and daily portal imaging as well as breast CT at the beginning and end of treatment [9]. The maximal single marker movement was 7 mm, with multiple marker movement up to 13.3 mm, attributed primarily to anatomic changes requiring adjustments (such as arm position). Coles et al. reported a prospective study of 42 evaluable patients using sutured gold seeds for CT-based tumor bed localization [10]. On modeling analysis, required margins around the PTV were reduced from 10.1 mm with no verification correction protocol, to 5.7 and 4.9 mm for imaging the first 3 days and then weekly, respectively, to 1.4 mm with daily imaging (using either kilovoltage on-board imager or CT).

In this study, we intentionally evaluated online megavoltage image guidance, as CBCT for IGRT is not available in all facilities, but also collected serial 4D CT data. We opted to use textured fiducial markers due to concerns about consistent visualization and possible migration of smooth sided surgical clips during a multi-week course of radiation. Our data confirm minimal fiducial migration from the time of surgery to the completion of a 6-week course of whole breast irradiation. Using the 4D CT data, we also demonstrate minimal impact of respiratory motion on fiducial and seroma position both intra- and interfractionally (<1 mm on average).

As IMRT is increasingly used for whole breast treatment, excellent outcomes must be maintained. IMRT provides better homogeneity than conventional tangential fields with wedge compensation [11], and typically less dose to organs at risk, especially the heart [12]. Hector et al. studied the effect of setup error and organ motion on conventional and forward planned breast IMRT using serial CT scans, and noted 23 % of treatments had more than 5 % of the PTV outside the 95 to 105 % isodose, and that the IMRT technique was more sensitive to patient movement and changes in breast volume during treatment [13]. Jain et al. imaged 10 patients with daily CBCT and noted that forward planned IMRT technique was more sensitive to motion and yielded more volume with mean PTV dose <95 % of the planned dose, but yielded lower volumes receiving >105 % planned dose, compared to conventionally planned tangential beams [14]. Interest is increasing in the use of a SIB to the tumor bed during whole breast treatment, which is the subject of the ongoing RTOG 1005 [15] and IMRT-MC2 [16] randomized trials. One SIB technique uses IMRT to deliver a higher dose per fraction to the tumor bed PTV while achieving conventional doses in the remaining whole breast [17, 18]. Accurate positioning and minimizing daily setup variation is required to ensure adequate target volume coverage consistently when using IMRT; IGRT provides this improved accuracy.

As IMRT techniques are being increasingly adopted, much thought has been given to standardizing breast contouring parameters. The evolving standard for whole breast contouring, as being utilized in RTOG 1005, is to use the clinically apparent breast tissue (from palpation and CT visualization) with a 7-mm PTV margin (plus 5 mm to aperture for penumbra). This likely represents smaller volume than traditionally has been treated. The RTOG protocol does not require any image guidance, only recommending that "localizing skin marks" be used for daily setup and weekly treatment images obtained.

Conclusions

Our data suggest that a 7-mm PTV margin may not be adequate without image guidance, and that even daily alignment to bony anatomy requires at least a 9-mm setup margin. While several techniques are available, fiducial-based IGRT is likely one of the least subjective IGRT techniques. As this study shows, the challenges in reproducibly positioning the breast can be minimized by integrating IGRT into the daily setup process. In a novel design utilizing 4D CT, we have demonstrated virtually no fiducial migration and minimal impact of respiratory motion. With alignment to fiducials daily, a PTV margin of 6 mm may be used.

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Conflict of interest The authors have no conflict of interest to report.

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