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Deep inspiration breath-hold technique for left-sided breast cancer: An analysis of predictors for organ-at-risk sparing

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ABSTRACT

To identify anatomic and treatment characteristics that correlate with organ-at-risk (OAR) sparing with deep inspiration breath-hold (DIBH) technique to guide patient selection for this technique. Anatomic and treatment characteristics and radiation doses to OARs were compared between free-breathing and DIBH plans. Linear regression analysis was used to identify factors independently predicting for cardiac sparing. We identified 64 patients: 44 with intact breast and 20 postmastectomy. For changes measured directly on treatment planning scans, DIBH plans decreased heart-chest wall length (6.5 *vs* 5.0 cm, $p < 0.001$), and increased lung volume (1074.4 *vs* 1881.3 cm^3, $p < 0.001$), and for changes measured after fields are set, they decreased maximum heart depth (1.1 *vs* 0.3 cm, $p < 0.001$) and heart volume in field (HVIF) (9.1 *vs* 0.9 cm^3, $p < 0.001$). DIBH reduced the mean heart dose (3.4 *vs* 1.8 Gy, $p < 0.001$) and lung V_{20} (19.6% *vs* 15.3%, $p < 0.001$). Regression analysis found that only change in HVIF independently predicted for cardiac sparing. We identified patients in the bottom quartile of the dosimetric benefits seen with DIBH and categorized the cause of this "minimal benefit." Overall, 29% of patients satisfied these criteria for minimal benefit with DIBH and the most common cause was favorable baseline anatomy. Only the reduction in HVIF predicted for reductions in mean heart dose; no specific anatomic surrogate for the dosimetric benefits of DIBH technique could be identified. Most patients have significant dosimetric benefit with DIBH, and this technique should be planned and evaluated for all patients receiving left-sided breast/chest wall radiation.

Introduction

Adjuvant radiotherapy is an integral component of multimodality management of breast cancer. Numerous randomized trials and meta-analyses have shown its effectiveness in improving locoregional control and survival in both the breast-conserving (BCT) and postmastectomy settings.[1-5] Despite these benefits, the 2005 update of the Early Breast Cancer Trialists' Collaborative Group meta-analysis showed increased rates of non–breast cancer deaths overall as well as deaths specifically due to heart disease in patients receiving radiotherapy.[1] More recently, an important study by Darby *et al.*[6] estimated a relative 7.4% increase in the rate of major coronary events per 1-Gy increase in mean radiation dose to the heart for patients with breast cancer receiving adjuvant radiotherapy from 1958 to 2001.

There are also data to suggest that more modern radiotherapy techniques may confer a lower risk of cardiac morbidity and mortality as compared with older techniques.[7] Several population-based studies of patients treated in the United States have shown that radiotherapy increased cardiac morbidity and mortality for patients with left-sided breast cancers when compared with those with right-sided cancers, presumably related to increased cardiac exposure in left-sided diseases, but this effect of laterality disappeared in patients treated after the early 1980s.[8-10] This decrease in cardiac morbidity over time is likely related to advances in radiation technique that allow for superior cardiac sparing, but it may also be influenced by the shorter follow-up times for patients treated more recently. Modern treatment with radiotherapy has allowed reductions in the volume of heart receiving radiation through a combination of factors, including

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improved visualization of the heart with the advent of computed tomography (CT)–based planning, positional aids, respiratory motion management, intensity modulation techniques, and most recently, proton therapy. Many of these techniques have been demonstrated to effectively minimize the cardiac dose, including deep inspiration breath-hold (DIBH), various intensity-modulated radiation therapy techniques, treatment in prone position, and proton therapy.[11-14] Despite these advances, the left ventricle and cardiac apex remain at risk to receive radiation in many cases.[15] Several studies have shown that the irradiated volume of the left ventricle can predict for the incidence of cardiac perfusion defects on functional imaging following radiotherapy up to 2 years after treatment,[16,17] whereas other studies have shown no changes with low-dose radiation.[18] The true clinical effect of cardiac radiation exposure with modern-era techniques remains unknown, but it is clear that minimization of radiation dose to the heart is of great importance.

Most published studies investigating respiratory motion have shown that, with DIBH, the lung volume increases and the heart moves away from the anterior chest wall, resulting in significant cardiac sparing at both high and low doses.[14,15,19-21] Although these benefits of the DIBH technique have been clearly demonstrated in the previous literature, there are limited data evaluating appropriate patient selection for this technique. We posed the question whether this approach would benefit patients being treated to different targets, including intact breast and chest wall $\pm$ regional nodes, and whether specific anatomic criteria could be identified that might independently predict for cardiac sparing. We included criteria that can be evaluated on planning CT before setting fields, in hopes that we might identify a surrogate for cardiac sparing that could serve as a simple reference to determine if a patient is likely to benefit from DIBH. We also included criteria that require setting basic fields and comparing the free-breathing (FB) and DIBH scans, to determine if these parameters, which require more effort to assess but can still be evaluated before dosimetric planning, would be predictive of organ-at-risk (OAR) sparing.

Methods

Patient selection

We retrospectively identified patients with left-sided breast cancer treated with adjuvant radiotherapy to the breast or chest wall with or without a supraclavicular field at our institution from November 2011 to September 2012. Patients were excluded from our study for the following reasons: partial breast irradiation only, use of a medial electron field for treatment of the internal mammary nodes, inverse planned intensity-modulated radiation therapy, and incomplete available image sets.

Simulation and treatment planning

Each patient underwent CT simulation using the Siemens Somatom CT with acquisition of both FB and DIBH image sets in the supine position using a supine breast board. DIBH images were acquired when the patient took a maximally comfortable inspiration. The Varian Real-time Positioning Management (RPM) system was used to monitor breathing amplitude and allow real-time respiratory tracking to facilitate a stable lung volume during acquisition of the DIBH images for each patient. All contouring, planning, and dosimetric evaluations were performed on the Varian Eclipse treatment planning system using the anisotropic analytical planning algorithm for photons and Monte Carlo for electrons. The breast and lumpectomy cavity or chest wall were contoured per the Radiation Therapy Oncology Group breast atlas; 5-mm margins were added to the breast or chest wall target for generation of the planning target volume. The cardiac structures including the heart and left anterior descending artery (LAD) were contoured per the validated University of Michigan cardiac atlas.[22] We generated 2 treatment plans for each patient using the FB and DIBH image sets. Medial and lateral nondivergent tangential fields designed to treat the entire left breast or chest wall were generated for each plan. When a supraclavicular field was employed, this was done using an anterior oblique field with a monoisocentric match line placed at the head of the clavicle. Optimization was performed using a forward planned field-in-field technique to minimize high-dose regions. Customized heart blocking (HB) with multileaf collimation was used at the treating physician's discretion with the goal of achieving the lowest heart dose possible while adequately covering the target.

A spectrum of fractionation schemes was used in this cohort, based on patient stage and at the physician's discretion. Overall, 47 patients had early-stage breast cancer, Stages 0-II, and 17 patients had either recurrent disease or Stages III-IV disease. BCT patients received either standard fractionation with 45 to 50 Gy in 25 fractions of 1.8 to 2 Gy per fraction given daily over 5 weeks or hypofractionation with 40 to 42.7 Gy in 16 fractions of 2.5 to 2.67 Gy per fraction given daily over 3 weeks. Postmastectomy radiation (PMRT) patients received 45 to 50 Gy in 25 fractions of 1.8 to 2 Gy per fraction given daily over 5 weeks, at the discretion of the treating physician. Generally low-risk patients who did not receive chemotherapy received hypofractionated regimens, whereas higher risk patients who received chemotherapy or those in whom supraclavicular fields were employed received conventionally fractionated regimens. Most patients received a boost to the lumpectomy cavity or chest wall scar of 10 to 14 Gy in 4 to 7 fractions. The boost was typically delivered using an *en face* electron beam, but in some cases, minitangential or 3-dimensional conformal photon arrangements were used based on anatomy and target location. Composite plans inclusive of boost doses were evaluated in all cases.

Goal coverage was 90% of the contoured target receiving the prescription dose. In general, the heart and lung goals were to obtain the lowest achievable doses to each structure, but more specific guidelines were to obtain ipsilateral lung $V_{20} <$ 10% in the setting of intact breast only, $<$ 20% in the setting of intact breast plus supraclavicular field, and $<$ 30% in the setting of chest wall plus supraclavicular field; heart mean dose $<$ 4 Gy (as low as possible); and heart $V_{10} \leq$ 30%.

Anatomic and treatment characteristics

We first analyzed anatomic characteristics that can either be obtained from the medical record or directly measured on each planning CT and compared before any treatment planning, including heart, lung, and LAD volumes, heart height (HH), heart-chest wall length (HCWL), chest circumference, chest depth, and body mass index (BMI), as well as the change in these parameters between FB and DIBH scans. HH was defined as the distance from the superior to inferior extent of the contoured heart. HCWL was defined as the maximum length of contact between the heart and chest wall (Fig. 1A). Chest depth was defined as the anterior-posterior thickness of the chest at the level of the maximum chest separation (CS) (Fig. 1A). Lung breath-hold volume (BHV) was defined as the proportional change in lung volume with DIBH compared with that with FB.

Additionally, we analyzed characteristics that must be measured based on the tangent fields that were set for each plan; analysis of these parameters involves a more extensive time commitment and effort as it requires fields to be set and compared between the plans, but it does not require treatment planning to be fully optimized and completed. These include the maximum CS along the central axis of the field, use of a HB, maximum heart depth (MHD), heart-chest wall distance (HCWD), heart volume in field (HVIF), and lung orthogonal distance (LOD). MHD was defined as the maximum distance from the field edge to the heart border (Fig. 1C). HCWD was defined as the distance from the maximal heart point to the chest wall (Fig. 1B). HVIF was defined as the heart volume encompassed by the 50% isodose line and is depicted in Fig. 1C. LOD was defined as the maximum distance from the field edge to the lung-chest wall interface at the level of maximum CS (Fig. 1B).

Lastly, we analyzed the entire group to identify a subgroup of patients who experienced the least benefit from DIBH. We defined “least benefit” as those patients meeting the following 3 criteria that were in the bottom quartile of the dosimetric benefits seen with DIBH: reduction of mean heart dose $\leq$ 1 Gy, absolute reduction of heart $V_{10} \leq$ 2%, and absolute reduction of heart $V_{30} \leq$ 0.75%. We attempted to identify the potential reason for minimal DIBH benefit as follows: (1) highly favorable baseline anatomy, defined as HVIF $\leq$ 1 cm^3 on the FB scan, (2) suboptimal BHV, defined as $\leq$ 150%, which is 1 standard deviation below the mean BHV for all patients in this study, or (3) other cause.

Statistical summary

Data were summarized as means and standard deviation or as percentage, as appropriate. The χ^2 test, Fisher exact test, or McNemar test was used for comparison of categorical data. For each quantitative end point, we conducted analysis as follows. Considering all patients, and grouping patients by radiation target (intact breast/BCT *vs* chest wall/PMRT), we tested whether FB technique differs from DIBH with respect to the particular variable by testing the significance of the corresponding mean difference (FB − DIBH). This analysis was performed using a paired t-test, given the correlated nature of the data. In addition, within each breathing techniques (FB and DIBH), we test whether BCT differs from PMRT with respect to the particular variable using unpaired t-test. For parameters involving 5 comparisons of interest, $p \leq$ 1% was considered significant based on adjustment by the Bonferroni method, which avoids inflation of type I error rate. The 5% significance level was used for single comparisons. The Pearson correlation coefficients were used to determine linear correlations between the changes in the