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Clinical Investigation

A Randomized Comparison of Radiation Therapy Techniques in the Management of Node-Positive Breast Cancer: Primary Outcomes Analysis

Reshma Jagsi, MD, DPhil,* Kent A. Griffith, MS,† Jean M. Moran, PhD,* Edward Ficaro, PhD,‡ Robin Marsh, CMD,* Robert T. Dess, MD,* Eugene Chung, MD,* Adam L. Liss, MD,* James A. Hayman, MD, MBA,* Charles S. Mayo, PhD,* Kevin Flaherty, MD,§ James Corbett, MD,‡,§ and Lori Pierce, MD*

**Department of Radiation Oncology, University of Michigan, Ann Arbor; †Center for Cancer Biostatistics, University of Michigan School of Public Health, Ann Arbor; ‡Department of Radiology, University of Michigan, Ann Arbor; and §Department of Internal Medicine, University of Michigan, Ann Arbor*

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Summary

In a randomized trial in patients with left-sided node-positive breast cancer receiving regional nodal radiotherapy, we observed lower doses to the heart and lungs with intensity modulated radiotherapy and deep inspiration breath hold as compared to free-breathing three-dimensional conformal therapy. Patients

Purpose: Although inverse-planned intensity modulated radiotherapy (IMRT) and deep inspiration breath hold (DIBH) may allow for more conformal dose distributions, it is unknown whether using these technologies reduces cardiac or pulmonary toxicity of breast radiotherapy.

Methods and Materials: A randomized controlled trial compared IMRT-DIBH versus standard, free-breathing, forward-planned, three-dimensional conformal radiotherapy in patients with left-sided, node-positive breast cancer in whom the internal mammary nodal region was targeted. Endpoints included dosimetric parameters and changes in pulmonary and cardiac perfusion and function, measured by single photon emission computed tomography (SPECT) scans and pulmonary function testing performed at baseline and 1 year post treatment.

Results: Of 62 patients randomized, 54 who completed all follow-up procedures were analyzed. Mean doses to the ipsilateral lung, left ventricle, whole heart, and left anterior descending coronary artery were lower with IMRT-DIBH; the percent of left

Reprint requests to: Dr. Reshma Jagsi, MD, DPhil, Department of Radiation Oncology, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5010. Tel: (734) 936-7810; E-mail: rjagsi@med.umich.edu

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This protocol (NCT00581256) is registered with ClinicalTrials.gov and may be viewed online at https://clinicaltrials.gov/ct2/show/NCT00581256?term=NCT00581256&rank=1.

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treated with intensity modulated radiotherapy —deep inspiration breath hold experienced a lesser difference in left ventricular ejection fraction between baseline and one year. This should motivate larger studies evaluating whether such approaches may result in better preservation of cardiac left ventricular function.

ventricle receiving ≥5 Gy averaged 15.8% with standard radiotherapy and 5.6% with IMRT-DIBH ($P < .001$). SPECT revealed no differences in perfusion defects in the left anterior descending coronary artery territory, the study's primary endpoint, but did reveal statistically significant differences ($P = .02$) in left ventricular ejection fraction (LVEF), a secondary endpoint. No differences were found for lung perfusion or function.

Conclusion: The small but statistically significant benefit in preservation of cardiac LVEF observed here should motivate future studies that include LVEF as a potentially meaningful endpoint. Future studies should disaggregate the impact of IMRT from that of DIBH. Clinical practice should recognize the importance of minimizing cardiac dose, even when already low in comparison to historical levels.

Introduction

Both tumor control and normal tissue complication probabilities depend on the dose of radiotherapy. Radiation oncologists are therefore driven to explore technologies that may allow an improvement in the therapeutic index. Intensity modulated radiotherapy (IMRT) is a promising technology that allows the development of complex, conformal dose distributions that may be dosimetrically superior to conventional plans. This may yield improved tumor control due to increased target doses and/or reduced toxicity due to lower doses to adjacent normal tissues and improved dose homogeneity.

In the case of breast cancer treatment, standard radiation doses have been adequate for controlling microscopic disease in the routine adjuvant setting, and the goal of utilizing IMRT has largely been directed at minimizing treatment-related toxicities. Although radiotherapy is now firmly established as an integral part of the management of early stage breast cancer, both for patients undergoing breast-conserving therapy and for select patients after mastectomy, concerns remain regarding its potential long-term toxicities (1).

Randomized controlled trials (RCTs) have compared simple forward-planned intensity modulation to 2-dimensional treatment planning and delivery, revealing benefits in skin and soft tissue toxicity within the breast due to improved dose homogeneity (2, 3). However, modern technology now allows for considerably more complex IMRT plans than of the sort evaluated on those early RCTs.

Concerns about cardiac and pulmonary toxicity from breast radiotherapy, particularly when the targets of treatment include the regional lymph nodes, have motivated interest in evaluating the potential benefits of the more highly conformal plans that can be generated with inverse-planned, beamlet IMRT. Beamlet techniques have been developed that maintain target volume coverage with reduction in high doses to the lung, heart, and important substructures such as the left anterior descending coronary artery (4), without increasing contralateral breast dose (5). Given observational analyses that have suggested a linear dose-response relationship between mean heart dose and cardiac mortality risk (6), dosimetric improvements to minimize heart dose with IMRT have been hypothesized to result in improved clinical outcomes.

The additional geometrical advantages afforded by deep inspiration breath hold (DIBH) and the desire to limit motion in the context of the greater dose conformality with beamlet IMRT have encouraged investigation to determine whether the dosimetric improvements that can be obtained with IMRT in conjunction with DIBH yield the hypothesized improvements in clinical outcomes. Therefore, the authors conducted an RCT comparing inverse-planned beamlet IMRT with DIBH versus free-breathing forward-planned 3-dimensional conformal radiotherapy (3DCRT) in patients with left-sided node-positive breast cancer in whom the internal mammary nodal region was targeted.

Methods and Materials

Sample

After IRB approval, the authors recruited patients who presented to the University of Michigan with node-positive breast cancer in whom radiotherapy was indicated to treat the left breast or chest-wall, as well as the internal mammary, infraclavicular, and supraclavicular nodal regions. The sample size for the randomized design was selected after considering the feasibility of patient accrual, the desire to yield unbiased estimates of the treatment effect for use in future research, and the hypothesis that IMRT-DIBH would be superior to 3DCRT.

Between May 2006 and June 2012, 62 patients were randomized 1:1 (see Fig. 1) between IMRT with DIBH and 3D-CRT using blocks of size 4 and 6. Treatment assignment lists were held confidentially by the study statistician and reported to clinical personnel only after a prospective patient was determined eligible and signed informed consent. Of these, 54 completed all follow-up procedures and were eligible for analysis.

Treatment planning

The treating physician approved contours of the targets (breast/chest wall, regional lymph nodes, including