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Active Breathing Coordinator Reduces Radiation Dose to the Heart and Preserves Local Control in Patients with Left Breast Cancer: Report of a Prospective Trial

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Abstract

Purpose—Incidental radiation dose to the heart and lung during breast radiotherapy (RT) has been associated with an increased risk of cardiopulmonary morbidity. We conducted a prospective trial to determine if RT with the Active Breathing Coordinator (ABC) can reduce the mean heart dose (MHD) by 20% and dose to the lung.

Methods & Materials—Patients with Stages 0-III left breast cancer (LBC) were enrolled and underwent simulation with both free breathing (FB) and ABC for comparison of dosimetry. ABC was used during the patient's RT course if the MHD was reduced by 5%. The median prescription dose was 50.4 Gy plus a boost in 77 patients (90%). The primary endpoint was the magnitude of MHD reduction when comparing ABC to FB. Secondary endpoints included dose reduction to the heart and lung, procedural success rate, and adverse events.

Results—112 pts with LBC were enrolled from 2002 to 2011 and 86 eligible patients underwent both FB and ABC simulation. Ultimately, 81 pts received RT using ABC, corresponding to 72% procedural success. The primary endpoint was achieved as use of ABC reduced MHD by 20% or greater in 88% of patients ($p < 0.0001$). The median values for absolute and relative reduction in MHD were 1.7 Gy and 62%, respectively. RT with ABC provided a statistically significant dose reduction to the left lung. After a median follow up of 81 mos., 8-year estimates of locoregional relapse, disease-free, and overall survival were 7%, 90%, and 96%, respectively.

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Conclusions—ABC was well tolerated and significantly reduced MHD while preserving local control. Use of the ABC device during RT should be considered to reduce the risk of ischemic heart disease in populations at risk.

INTRODUCTION

Adjuvant radiotherapy (RT) is essential in the treatment of breast cancer. In the setting of breast conservation therapy (BCT) for invasive cancer and post-mastectomy radiotherapy (PMRT) for high-risk disease, RT reduces the risk of local-regional recurrence (LRR) and improves overall survival (OS) [1, 2]. However, incidental radiation dose to the heart and lung during RT has been associated with an increased risk for ischemic heart disease (IHD) and lung cancer, particularly in women with left-sided breast cancer (LBC) [3-4]. For example, a recent population-based study noted that the excess risk of IHD is proportional to mean heart dose (MHD), is apparent within four years of RT, and persists for decades [4].

There is considerable interest in validating treatment techniques that minimize exposure to organs at risk (OAR) since it is known that radiation-related adverse effects are related to the dose and irradiated volume. Such practices have the potential to improve the therapeutic ratio [5] and include techniques like prone positioning, intensity-modulated radiotherapy (IMRT), and proton therapy. Another promising technique is moderate deep inspiration breath hold (mDIBH) with the Active Breathing Coordinator (ABC) device. ABC allows for reproducible immobilization of the chest wall by monitoring the patient's breathing cycle and implementing a breath hold at a predefined lung volume. By optimizing the distance between the heart and chest wall, this maneuver can shift OAR volume out of the RT field while still allowing for therapeutic irradiation of breast tissue.

Early published data using ABC for thoracic RT demonstrated it to be safe and feasible to use, but data in breast RT was limited at the time this study commenced [6]. This prompted the design of a prospective, controlled trial using the ABC device in women with LBC to determine if the technique is able to reduce heart and lung dose without the use of IMRT. We hypothesized that use of the ABC device would reduce MHD by 20% or greater. Since initiation of this trial, dosimetric data with the ABC device have been reported [7-9], but data from prospective trials remains limited [10, 11] and long-term oncologic outcomes are unknown. We present the dosimetric endpoints and long-term clinical outcomes.

METHODS & MATERIALS

Women were enrolled from October 2002 through August 2011 and all signed informed consent for participation in this Institutional Review Board-approved trial. Eligible patients required adjuvant RT to the breast or chest wall, could tolerate mDIBH, and had greater than 5 cc heart within the tangential field. Patients were ineligible if they were unwilling to undergo device training or were unable to perform a breath hold for 20 seconds. Patients who were non-English speaking or who had poor hearing were ineligible due to concerns that they would not understand breath hold instructions during treatment.

Patients underwent training with the ABC device (Elekta Oncology, Stockholm, Sweden), during which lung capacity, optimal breath hold length and level, and patient comfort and

compliance were assessed. Patients were positioned supine for computed tomography (CT) simulation with the ABC device and while free breathing (FB). The increased exposure to ionizing radiation was justified because patients were likely to have lower dose to the OAR with trial participation. A reference axial plane was identified on the FB scan at the level of the areola and the posterior borders of standard tangents were visually estimated from radiopaque field borders. If less than 5 cc heart was present in the field, simulation with ABC was not performed.

Target volumes and OARs were delineated on each CT scan. The heart contour included the cardiac skeletal muscle and pericardial sac. RT planning was performed with XiO Planning System (Elekta, Maryland Heights, MO) and dose-volume histograms (DVH) were generated for comparison of FB and ABC dosimetry. Heart blocking with the multi-leaf collimator was permitted. Initially, dose distributions were calculated using wedged, tangential, 6-10 MV photons to achieve a $\pm 5\%$ dose gradient. After it became apparent that patients could tolerate repeated breath holds, hypofractionated RT, multi-field plans, and forward-planned, “field-in-field” techniques were permitted.

ABC was used during RT if the MHD was reduced by 5% or greater. Dedicated therapists specifically trained in the mDIBH technique performed daily checks for device functionality and were present at each treatment. A separate breath hold was used for treatment of each field. In our clinical practice, there is heterogeneity in the use of sequential tumor bed boost, boost dose, and boost technique. Due to this heterogeneity, an unclear clinical benefit, and concerns for poor reproducibility during electron set-up, mDIBH was not used during the delivery of boosts.

Acute toxicity was scored weekly using the Common Terminology Criteria for Adverse Events v3.0. Following completion of RT, patients were seen in routine follow-up every 3 months for the first 6 months and every 6-12 months thereafter. Annual diagnostic mammography was performed in women with BCT. Additional diagnostic testing was performed as clinically indicated due to signs and symptoms of disease.

At the time the trial was initiated, it was evident from early studies that the ABC device would provide some reduction in OAR dose, but the magnitude was unknown [6]. Therefore, the primary goal was to determine the magnitude of reduction in MHD when comparing ABC to FB. A reduction of 5% in OAR dose was considered to be of minor clinical value while a reduction of 20% or more was thought to be of considerable value and would justify routine use of ABC in our practice. A sample size of 112 patients was needed to detect a 20% reduction with 80% power ($\alpha=0.05$). In order to test the null hypothesis that mDIBH reduces MHD by less than 20%, the Wilcoxon signed rank test was performed using individual patients as internal controls. To corroborate data, binomial proportions (BP) with confidence intervals (CI) were determined using SAS (SAS Institute Inc., Cary, NC) and the Clopper-Pearson method.

Secondary endpoints included procedural success rate, adverse events, and reduction in OAR dosimetric parameters. Procedural success was defined as the proportion of patients who could perform the mDIBH technique and derived a dosimetric benefit. The Wilcoxon

Signed Rank test was performed for paired data and survival times were analyzed using the Kaplan-Meier method. LRR included recurrence within the ipsilateral chest wall, breast, or draining lymphatics. Disease free survival (DFS) was calculated based on time from the start of RT until recurrence or death. Patients alive without disease were censored at the date of last clinical follow-up.

RESULTS

One hundred twelve women with LBC were enrolled but 26 (23%) patients were found to be ineligible for trial participation (Figure 1), including: 21 (19%) patients who could not tolerate mDIBH, four (4%) patients with less than 5 cc heart within the field, and one (1%) was lost to follow-up prior to RT initiation. FB and ABC simulations were performed in 86 (77%) patients.

Table 1 summarizes baseline patient characteristics. Thirty-four (40%) patients had comorbidities that might affect cardiopulmonary reserve, but were able to perform the mDIBH technique. Modest heterogeneity was present among stage, receptor status, and systemic treatment (Tables 1&2).

Dosimetry

For all parameters evaluated, mDIBH with ABC significantly reduced dose to the heart. MHD was reduced by 20% or greater with use of ABC ($p<0.0001$): the median value for FB was 2.7 Gy (range, 0.9 to 8.6) compared to 0.9 Gy (range, 0 to 4.5) for ABC (Table 3). The median absolute and relative reduction in the MHD was 1.7 Gy (range, -2.8 to 6.2 Gy) and 62% (range, -9 to 94%), respectively. The BP for 20% reduction in MHD was 0.88 (95% CI 0.78-0.95, $p<0.0001$). Maximum heart dose was also effectively reduced with ABC (50.4 Gy vs. 27.9 Gy, $p<0.0001$). A physiologic decrease in heart volume was noted during mDIBH (590 vs. 531 cc, $p<0.001$).

Statistically significant reductions in left lung dose were also observed including: mean lung dose, volume receiving 20 Gy (V20 Gy), V10 Gy, and V5 Gy (Table 3). The relative reduction in dose to the left lung ranged 9-13% among the parameters. For total lung dosimetry, the V20 Gy and V10 Gy were also significantly reduced with ABC. Use of ABC did not compromise target coverage, as indicated by clinical target volume receiving 95% of the prescription dose (V95%) and V100%.

Toxicity and Adverse Events

There were no grade 3 or higher toxicities. Acute skin and soft tissue toxicity was grade 1 in 59 (69%) and grade 2 in 27 (31%) patients. There were no acute pulmonary or cardiac toxicities. Late skin and soft tissue toxicities were grade 1 in 34 (40%) and grade 2 in 3 (3%) patients.

Procedural Success and Clinical Outcome

Ultimately, 81 (94%) patients received RT with the ABC device (Figure 1), corresponding to a 72% procedural success rate (81/112). Nineteen percent of weekly portal images required repeat imaging and 96% of final images were approved for treatment.

After a median follow-up of 81.3 months (range, 1.5-131.7), 5-year rates of LRR, DFS, and OS were 3.7%, 95.1%, and 95.7%, respectively. Similarly, 8-year estimates of LRR, DFS, and OS were 7.2%, 89.8%, and 95.7%, respectively. Two patients treated with the ABC device have developed isolated LRR in the index quadrant of the primary tumor. A third patient treated with mDIBH developed a multicentric ipsilateral breast recurrence with synchronous axillary recurrence. A fourth patient who was not treated with mDIBH developed a LRR. Two patients treated with mDIBH developed isolated distant relapse.

DISCUSSION

Consensus guidelines recommend that the volume of heart receiving radiation should be minimized as much as possible without compromising target coverage [12], but few controlled trials have validated cardiac-sparing techniques for breast cancer. Our findings indicate that most (81%) women with LBC tolerated the mDIBH technique with the ABC device. When this technique was implemented into clinical practice for eligible patients, nearly all (88%) achieved at least a 20% reduction in the MHD with no appreciable compromise in coverage of target tissues. The magnitude of relative reduction in the MHD (62%) is consistent with retrospective studies in which the value ranged 40% to 62% [7-9]. Our dosimetric findings may generalize to other mDIBH devices like the SDX system (Dyn'R, Toulouse, France) as previously demonstrated [10]. The Real-time Position Management (RPM) system (Varian, Palo Alto, CA) has also been demonstrated to provide significant reduction in cardiac dose; however, in a comparison of RPM with ABC, Giraud *et al.* demonstrated greater lung inflation and lower heart V 40 Gy, maximum heart dose, and MHD with ABC [10].

The cardiac doses noted in the present study are lower than in other series, including some in which IMRT was used [7, 13]. This may be due to differences in contouring, elective coverage of lymph node basins, or the degree of cardiac blocking accepted at various institutions. It is notable that these low doses were achieved without the use of inverse-planned IMRT, which is typically more costly than 3D conformal RT [14]. However, there may be costs associated with acquiring the ABC device and for simulations with respiratory motion management.

In addition to financial considerations, implementation of the ABC device into clinical practice may increase clinic workload, particularly at the time of simulation and treatment. Currently, physicians and radiation therapists at our center require several supervised training sessions prior to independent use of ABC in practice. Additionally, when CT simulation with the ABC device is planned, the allotted time is increased from 45 to 60 minutes. Similarly, the allotted time for daily treatment is increased from 20 to 30 minutes for patients treated with segmented fields or even up to 40 minutes if regional nodal irradiation is performed. A similar increase in daily clinic workload was recently described

by Comsa *et al.* Despite the use of mDIBH in 20% of their breast cancer patients, their center was still able to meet provincial efficiency standards of 3.4 fractions treated per hour. Furthermore, after the first few fractions per patient, the daily treatment time was reduced by several minutes due to increased patient comfort with the device and therapist familiarity with patient-specific set up details [9]. When all of the facts are considered, the marked reduction in cardiac dose owed to mDIBH justifies the utilization of clinic time and resources in our department.

As DFS in women with breast cancer continues to improve, minimization of late toxicity is increasingly important in order to advance the therapeutic index. This is particularly essential in patients with pre-existing cardiac risk factors or who receive systemic therapies with the added potential for cardiac toxicity, including taxanes, anthracyclines, and trastuzumab. In a recent study of breast cancer survivors in Europe, Darby *et al.* found that the risk of IHD was linearly dependent on MHD at a rate of 7.4% per Gy with no apparent threshold [4]. Similar dose-response rates for late circulatory disease have been reported for patients exposed to cardiac doses comparable to patients treated with mDIBH, with alternate estimates of 10.2% per Gy MHD [15, 16]. In accordance with the Darby model, the median reduction in MHD of 1.7 Gy owed to mDIBH (0.9 Gy equivalent dose delivered in 2-Gy fractions) may afford a 63% relative reduction in the excess risk of IHD in the two decades following RT.

A small series by Korreman *et al.* also estimated the reduction in cardiac complication probability with mDIBH in 16 patients using the relative seriality model. When compared to FB technique, mDIBH reduced the cardiac mortality normal tissue complication probability from 4.8% to 0.1% [17]. Importantly, these risk estimates remain unverified and with specific limitations. The 10-year risk of IHD for women ages 50 to 79 years approaches 4% [18], so the absolute risk reduction from RT with mDIBH techniques may be small. However, findings remain clinically significant given the high incidence of breast cancer—207,000 new cases each year in the United States alone.

Radiation may contribute to IHD through microvascular injury to myocardial capillaries or macrovascular injury to the coronary arteries [19]. As such, an alternative hypothesis is that other dose metrics, such as dose to the left anterior descending artery (LAD), are more relevant than MHD for predicting IHD [20]. The coronary arteries may be considered a serial structure, such that RT-induced damage to any portion can result in occlusive disease [12]. Due to poor visibility on simulation images and error associated with contouring small structures, segmentation of the LAD was not standard practice at the time of trial initiation, and this missing information may be considered a limitation. Prior studies have demonstrated significant reductions in dose to the LAD with use of mDIBH techniques [19].

Radiation dose to the lungs is also a meaningful endpoint when considering toxicities like pneumonitis or radiation-related lung cancer. As with previous studies [7-10], the mDIBH technique modestly reduced dose to the left lung by inflation so that less tissue remained within the tangential field. The clinical significance of this finding, if any, is not understood at this time.

Ultimately, the success of mDIBH with ABC requires that there be no compromise of local control during cardiac-sparing efforts. However, there are limited data reporting outcomes following cardiac-sparing RT for LBC. A non-randomized, French trial of 233 women undergoing BCT compared breast RT with mDIBH and FB techniques. After a median follow-up of 28 months, there was no apparent difference in DFS and OS in the two cohorts, although, patterns of relapse were not described [10]. Additionally, in a large series of patients undergoing breast RT in the prone position, relapse rates in the ipsilateral breast and regional nodes were 5.5% and 1.2%, respectively at 5 years [21]. While the present series is limited by sample size, our observed LRR rate of 3.7% and 7.2% at 5 and 8 years, respectively, appears similar or favorable when compared to modern trials of BCT and PMRT [1, 2]. In theory, alterations of the posterior border of tangential fields for RT with mDIBH could contribute to a geographic miss if chest wall immobilization and respiratory gating are poorly reproducible. In the present series, no definitive conclusions could be drawn regarding patterns of relapse, but future investigation is warranted.

Successful implementation of the ABC device into routine clinical practice also depends on the reproducibility of the mDIBH technique, which was not systematically assessed in this study and should be considered a limitation. However, the modest rate of repeat filming and high acceptance rate of final portal imaging suggest acceptable reproducibility. Giraud *et al.* recently demonstrated good reproducibility of the clinical target and total lung volumes with the ABC device [10]. The inter-fraction set-up variability during mDIBH has been systematically assessed in other series using 2D kV and MV image sets, cone beam CT, and 3D surface imaging, all with generally excellent registration [22, 23]. Intra-fraction cardiac motion, however, poses a unique challenge as shifts of over 5 mm can occur in LAD position and heart-to-chest wall distance. However, following dose reconstruction to account for systemic shifts in heart position, mDIBH still demonstrates excellent reduction in heart dose when compared with FB methods [23, 24].

RT with the ABC device may not benefit all patients with LBC, as some patients will have minimal heart volume within the tangential fields. In the present study, ABC was reserved for patients with greater than 5 cc of heart within the tangential fields based on visual estimates, but alternative methods may select patients who would benefit from mDIBH in a more consistent manner, such as rapid automated planning [19]. The 5 cc threshold is less stringent than used in other series [9, 19], but may approximate 5% of the left ventricular volume (mean volume 119 cc). Patients with greater than 5% of left ventricle included in the RT fields develop perfusion defects and wall motion abnormalities more frequently after RT and are more likely to benefit from mDIBH [25]. Other criteria commonly used for patient selection include 10 cc of the heart receiving more than 50% of the prescribed dose on the FB scan. Additionally, the exclusion of patients who did not speak English or with poor hearing should be considered a limitation of the study methods. Translator services and visual feedback monitors on the ABC device and others may overcome hearing and language barriers. Given the demonstrated benefits of mDIBH, this technique should be offered indiscriminately to all patients who may benefit.

In the present series, a high proportion (19%) of enrolled patients were ineligible due to poor tolerability of the device, which is a higher rate than observed in prior series [9, 10] and

suggests a role for additional cardiac-sparing techniques. In our practice, mDIBH with the ABC device remains the preferred approach for cardiac sparing, but prone positioning or IMRT are employed when mDIBH is not feasible.

This prospective trial confirms prior studies that mDIBH with the ABC device reduces cardiac dose in a clinically significant manner. The rate of LRR after long-term follow up is low, implying that local control is preserved during RT with mDIBH. According to existing radiobiologic models, this technique advances the therapeutic index of breast RT by reducing the risk of radiation-related IHD.

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomised trials. *Lancet*. 2011; 378:1707–16. [PubMed: 22019144]
2. Whelan TJ, Julian J, Wright J, et al. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol*. 2000; 18:1220–9. [PubMed: 10715291]
3. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol*. 2005; 6:557–65. [PubMed: 16054566]
4. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013; 368:987–98. [PubMed: 23484825]
5. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet*. 2005; 366:2087–106. [PubMed: 16360786]
6. Sixel K, Aznar M, Ung YC. Deep inspiration breath hold to reduce irradiated heart volume in breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2001; 49:199–204. [PubMed: 11163515]
7. Swanson T, Grills IS, Ye H, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol*. 2013; 36:24–30. [PubMed: 22270108]
8. Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. *Radiother Oncol*. 2013; 106:28–32. [PubMed: 23199652]
9. Comsa D, Barnett E, Le K, et al. Introduction of moderate deep inspiration breath hold for radiation therapy of left breast: Initial experience of a regional cancer center. *Prac Rad Onc*. 2013 doi: 10.1016/j.prro.2013.10.006.
10. Giraud P, Djadi-Prat J, Morelle M, et al. Contribution of respiratory gating techniques for optimization of breast cancer radiotherapy. *Cancer Investigation*. 2012; 30:323–330. [PubMed: 22489833]
11. Bartlett FR, Colgan RM, Carr K, et al. The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiration breath-hold in women undergoing breast radiotherapy. *Radiother Oncol*. 2013; 108:242–7. [PubMed: 23726115]
12. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys*. 2010; 76:S77–S85. [PubMed: 20171522]
13. Lohr F, El-Haddad M, Dobler B, et al. Potential effect of robust and simple IMRT approach for left-sided breast cancer on cardiac mortality. *Int J Radiat Oncol Biol Phys*. 2009; 74:73–80. [PubMed: 18973977]

14. Smith BD, Pan I, Shih YT, et al. Adoption of intensity-modulated radiation therapy for breast cancer in the United States. *J Natl Cancer Inst.* 2011; 103:798–809. [PubMed: 21525437]
15. Little MP, Kleinerman RA, Stovall M, et al. Analysis of dose response for circulatory disease after radiotherapy for benign diseases. *Int J Radiat Oncol Biol Phys.* 2012; 84:1101–9. [PubMed: 22494591]
16. Little MP, Azizova TV, Bazyka D, et al. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risk. *Environ Health Perspect.* 2012; 120:1503–11. [PubMed: 22728254]
17. Korreman SS, Pedersen AN, Aarup LR, et al. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys.* 2006; 65:1375–1380. [PubMed: 16750314]
18. Hsia J, Rodabough RJ, Manson JE, et al. Evaluation of the American Heart Association cardiovascular disease prevention guideline for women. *Circ Cardiovasc Qual Outcomes.* 2010; 3:128–134. [PubMed: 20160160]
19. Wang W, Purdie TG, Rahman M, et al. Rapid automated treatment planning process to select breast cancer patients for active breathing control to achieve cardiac dose reduction. *Int J Radiat Oncol Biol Phys.* 2012; 82:386–393. [PubMed: 21093165]
20. Darby SC, Cutter DJ, Boerma M, et al. Radiation-related heart disease: Current knowledge and future prospects. *Int J Radiat Oncol Biol Phys.* 2010; 76:656–665. [PubMed: 20159360]
21. Stegman LD, Beal KP, Hunt MA, et al. Long-term clinical outcomes of whole-breast irradiation delivered in the prone position. *Int J Radiat Oncol Biol Phys.* 2007; 68:73–81. [PubMed: 17337131]
22. Alderliesten T, Sonke J, Betgen A, et al. Accuracy evaluation of a 3-dimensional surface imaging system for guidance in deep-inspiration breath-hold radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013; 85:536–42. [PubMed: 22652107]
23. McIntosh A, Shoushtari AN, Benedict SH, et al. Quantifying the reproducibility of heart position during treatment and corresponding delivered heart dose in voluntary deep inhalation breath hold for left breast cancer patients treated with external beam radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011; 81:e569–76. [PubMed: 21531087]
24. Wang X, Pan T, Pinnix C, et al. Cardiac motion during deep-inspiration breath-hold: Implications for breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012; 82:708–14. [PubMed: 21444161]
25. Marks LB, Yu X, Prosnitz RG, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys.* 2005; 63:214–223. [PubMed: 16111592]

Figure 1.
Patient selection for radiotherapy with the Active Breathing Coordinator device.

Table 1

Patient and tumor characteristics.

Parameter	N=86 (%)
Age (years)	
Median (Range)	52 (25-80)
Karnofsky Performance Status (%)	
Median (Range)	100 (70-100)
Cardiopulmonary comorbidities	
None	52 (60)
Obesity	33 (38)
Hypertension	17 (20)
Smoker	12 (14)
Hyperlipidemia	9 (10)
Obstructive lung disease	6 (7)
Other [†]	9 (10)
Pathologic Stage	
0	19(22)
1	43 (50)
2	20(23)
3	4 (5)
Tumor stage	
pTis	19(22)
pT1 or ypT1	52 (60)
pT2 or ypT2	12 (14)
pT3 or ypT3	3 (4)
Nodal Stage	
0	70 (81)
1	14 (16)
2	1 (1)
3	1 (1)
Estrogen receptor status	
Positive	55(64)
Negative	22 (26)
Not assessed or unknown	9 (10)
Progesterone receptor status	
Positive	47(55)
Negative	29 (34)
Not assessed or unknown	10 (11)
Her-2/neu status	

Parameter	N=86 (%)
Over-expressed	19(22)
Not over-expressed	50 (58)
Not assessed or unknown	17 (20)
Surgical margins	
Negative	83 (97)
Positive	3 (3)

[†]Type II diabetes (n=3), Arrhythmia (n=3), mitral valve prolapse (n=1), coronary artery disease (n=1), congestive heart failure (n=1)

Table 2

Treatment characteristics.

Parameter	N=86 (%)
Breast conservation	
Yes	76 (88)
No	10 (12)
Systemic therapy	
Neoadjuvant chemotherapy	4 (5)
Adjuvant chemotherapy	35 (41)
Adjuvant Trastuzumab	6 (7)
Adjuvant endocrine therapy	69 (80)
None	5 (6)
Field arrangement	
Standard tangents	78 (91)
Standard tangents + supraclavicular	4 (5)
4 field	2 (2)
5 field	2 (2)
Wedge tangents	74 (86)
Field-in-field	12 (14)
Prescription dose (Gy)	
Median (Range)	50.4 (42.4-50.4)
Standard fractionation (1.8 or 2.0 Gy/day)	82 (95)
Hypofractionated (2.65 Gy/day)	4 (5)
Boost to breast or chest wall	
Yes	77 (90)
No	9 (10)
Median (range) in Gy	10 (9-16)

Table 3

Comparison of dosimetric data for free breathing (FB) and Active Breathing Coordinator (ABC) plans (n=86)

Structure	Parameter	FB Median (95% CI)*	ABC Median (95% CI)	Median Relative Reduction (%)	p value	Proportion with 5% reduction	Proportion with 20% reduction
Heart	Volume (mL)	590 (561-621)	531 (498-564)		<0.001		
	Mean dose (Gy)	2.7 (2.3-3.1)	0.9 (0.7-1.1)	62	<0.001	0.94 (0.86-0.98)	0.88 (0.78-0.95)
	Maximum dose (Gy)	50.4 (48.2-52.6)	27.9 (24.2-31.5)	40	<0.001	0.82 (0.72-0.94)	0.69 (0.56-0.82)
	V40 Gy (%)	1.0 (0.5-1.5)	0 (0-0.2)	100	<0.001	0.96 (0.86-1.0)	0.96 (0.86-1.0)
	V25 Gy (%)	2.7 (2.0-3.4)	0 (0-0.2)	100	<0.001	0.93 (0.84-0.98)	0.93 (0.84-0.98)
	V5 Gy (%)	11.1 (8.9-13.4)	3.0 (1.6-4.4)	71	<0.001	0.75 (0.63-0.85)	0.57 (0.45-0.69)
Left Lung	Volume (mL)	1145 (1093-1197)	1969 (1900-2039)	-	<0.001	-	-
	Mean (Gy)	6.4 (5.7-7.0)	5.9 (5.4-6.3)	9	0.007	0.53 (0.40-0.65)	0.31 (0.20-0.43)
	Maximum (Gy)	52.4 (51.6-53.1)	52.6 (50.8-54.4)	-	0.070	-	-
	V20 Gy (%)	12.0 (10.6-13.4)	10.4 (9.5-11.4)	10	0.002	0.56 (0.43-0.68)	0.40 (0.28-0.52)
	V10 Gy (%)	15.0 (13.4-16.8)	13.7 (12.6-14.9)	13	0.001	0.59 (0.46-0.71)	0.37 (0.25-0.49)
	V5 Gy (%)	22.9 (19.6-26.2)	20.9 (17.9-23.8)	9	0.005	0.54 (0.42-0.67)	0.32 (0.21-0.45)
Total Lung	V20 Gy (%)	5.7 (4.9-6.5)	4.9 (4.3-5.4)	11	0.025	0.56 (0.41-0.70)	0.35 (0.22-0.49)
	V10 Gy (%)	7.3 (6.4-8.2)	6.4 (5.8-7.0)	9	0.014	0.58 (0.43-0.71)	0.31 (0.19-0.45)
	V5 Gy (%)	10.0 (8.3-11.8)	9.6 (8.0-11.1)	-	0.093	-	-
CTV	Volume (mL)	765 (519-1011)	752 (531-972)	-	0.936	-	-
	V100% Rx (%)	86.3 (83.0-89.5)	86.8 (82.9-90.7)	-	0.407	-	-
	V95% Rx (%)	96.6 (95.0-98.1)	96.1 (94.3-97.9)	-	0.177	-	-

* CI=confidence interval, Gy=Gray, CTV=clinical target volume, Rx=prescription