Utility of Deep Inspiration Breath Hold for Left-Sided Breast Radiation Therapy in Preventing Early Cardiac Perfusion Defects: A Prospective Study

Timothy M. Zagar, MD,* Orit Kaidar-Person, MD,* Xiaoli Tang, PhD,† Ellen E. Jones, MD,* Jason Matney, MS,* Shiva K. Das, PhD,* Rebecca L. Green, MS,* Arif Sheikh, MD,‡ Amir H. Khandani, MD,§ William H. McCartney, MD,§ Jorge Daniel Oldan, MD,§ Terence Z. Wong, MD, PhD,§ and Lawrence B. Marks, MD*

Departments of *Radiation Oncology, and §Radiology, University of North Carolina, Chapel Hill, North Carolina; †Memorial Sloan Kettering Cancer Center, West Harrison; and ‡Department of Radiology, Columbia University; New York, New York

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Summary

To evaluate radiation-induced cardiac toxicity after left breast/chest wall adjuvant radiation in the setting of Vision RT-based deep inspiration breath hold, we performed a prospective single-institution single-arm study. Our results suggest that Vision RT-based deep inspiration breath hold for patients receiving adjuvant tangential radiation for left-sided breast cancer is an effective method for reducing radiation-induced cardiac toxicity.

Purpose: To evaluate early cardiac single photon computed tomography (SPECT) findings after left breast/chest wall postoperative radiation therapy (RT) in the setting of deep inspiration breath hold (DIBH).

Methods and Materials: We performed a prospective single-institution single-arm study of patients who were planned for tangential RT with DIBH to the left breast/chest wall (± internal mammary nodes). The DIBH was done by use of a controlled surface monitoring technique (AlignRT, Vision RT Ltd, London, UK). The RT was given with tangential fields and a heart block. Radiation-induced cardiac perfusion and wall motion changes were assessed by pre-RT and 6-month post-RT SPECT scans. A cumulative SPECT summed-rest score was used to quantify perfusion in predefined left ventricle segments. The incidence of wall motion abnormalities was assessed in each of these same segments.

Results: A total of 20 patients with normal pre-RT scans were studied; their median age was 56 years (range, 39-72 years). Seven (35%) patients also received irradiation to the left internal mammary chain, and 5 (25%) received an additional RT field to supraclavicular nodes. The median heart dose was 94 cGy (range, 56-200 cGy), and the median V25Gy was zero (range, 0-0.1). None of the patients had post-RT perfusion or wall motion abnormalities.

Reprint requests to: Timothy M. Zagar, MD, Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC. Tel: (984) 974-0400; E-mail: zagar@med.unc.edu

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Introduction

The risk of radiation therapy (RT)-associated cardiovascular disease in women with breast cancer has been a concern for decades (1). Many patients are also treated with systemic agents that may be cardiotoxic (eg, anthracyclines and trastuzumab), which magnifies these concerns (2, 3). Improvements in RT techniques over the past several decades (eg, 3-dimensional treatment planning, the movement away from anterior photon fields directed at the internal mammary nodes, [IMN]) have likely reduced the risk of RT-associated cardiotoxicity (1, 4). More recently, additional approaches are being used to further limit cardiac exposure (eg, respiratory gated techniques, deep inspiration breath hold [DIBH]) (5-7). However, inasmuch as RT-associated heart disease is often not manifested clinically until many years after RT, the clinical effectiveness of these approaches is less certain.

Several studies suggest that RT-associated abnormalities in cardiac perfusion can be detected by single photon emission compound tomography (SPECT) imaging within several months to years after RT for breast cancer (8-10). In a prospective study of 114 women irradiated for left-sided breast cancer, 27% had new perfusion defects and 16% had wall motion defects on cardiac SPECT scan 6 months after RT. At 24 months after RT, these rates were 42% and 7%, respectively (9). Although the clinical significance of these SPECT-based abnormalities is unclear, it is reasonable to consider them as short-term surrogates for RT-associated cardiotoxicity (eg, given that previous studies demonstrated a dose-volume dependence of both RT-associated SPECT abnormalities and clinical cardiac events) (9, 11-13).

We herein report the results of a prospective study to assess the utility of DIBH by use of a controlled surface monitoring technique (AlignRT, Vision RT Ltd, London, UK) as a means to prevent incidental cardiac irradiation in patients receiving tangential photon irradiation for left-sided breast cancer, with the use of cardiac SPECT as a surrogate biomarker.

Methods and Materials

Study design

The study was designed as a prospective nonrandomized, single-institution, single-arm, observational pilot study and was approved by the institutional review board.

Patients

The eligibility criteria included patients aged 18 years or older with histologically confirmed left-sided breast cancer after lumpectomy or mastectomy with or without lymph node involvement who were planned for DIBH-RT. Eligible patients who were planned for the use of DIBH and tangents to the left breast/chest wall RT, with the intention of totally excluding the heart from the primary RT beam, were offered the opportunity to participate in the study. Adjuvant chemotherapy, with or without trastuzumab as indicated was allowed.

The exclusion criteria included patients who were not planned for DIBH during RT. Patients with cardiac perfusion defects at baseline were also excluded. In addition, patients with a medical history of active cardiac disease, arrhythmias, myocardial infarction, congestive heart failure, or any other cardiac condition, and patients treated previously with mediastinal RT, were excluded.

Eligible patients were identified by their providers and were approached by a study coordinator for counseling and to obtain written informed consent.

The data collected from patients’ medical files included demographic information, comorbidities considered as cardiovascular disease risk factors (eg, smoking history), chemotherapy exposure, and (if available) cardiac functional assessments (eg, echocardiography) or clinical cardiac toxicity (eg, acute myocardial infarction).

Treatment simulation and RT technique

Enrollment on this trial did not affect the therapy decisions. All patients included in the study were scanned in the supine position and immobilized with a Vaclok cradle (CIVCO medical solutions, Kalona, IA). The Pre-RT treatment simulation CT was performed for each patient and included free breathing and breath hold scans. These allowed the physician to assess whether the patient could benefit from the use of DIBH during RT. Care was taken to assure that target coverage was not compromised by fully excluding the heart.

All patients were treated to the left breast or chest wall with tangential photon beams, with beams shaped to totally exclude the heart from the primary radiation beam. If the IMN were targeted, typically the upper 3 intercostal spaces, were included in the tangent fields. Patients received either 2.67 Gy/fraction for 16 fractions for a total dose of 42.72 Gy, or 2 Gy/fraction for 23 to 25 fractions to a total dose of 46 to 50 Gy. Most commonly, patients received a boost to the lumpectomy bed with the use of en face
electrons. Patients were treated once per day, 5 days per week, over 3 to 6 weeks depending on the fractionation and the use of a lumpectomy/scar boost. For patients who also received irradiation to the supraclavicular nodes, an anterior-medial oblique field was typically used.

**Three-dimensional radiation dose calculation**

Breath hold CT images were used to calculate 3-dimensional radiation dose distribution throughout the chest. In-house (Plan-UNC, Chapel Hill, NC) or commercial (Raystation, RaySearch Laboratories, Stockholm, Sweden) treatment planning systems were used to plan beams and calculate dose. Dose calculation was performed with a collapsed cone convolution superposition algorithm. All treatments were forward planned by use of a mixed-energy field-in-field tangential technique to improve dose homogeneity and cover the ipsilateral breast/chest-wall tissues (and regional nodes when indicated).

**Positioning and reproducibility and DIBH**

Before the first treatment, portal images (medial and lateral tangential) were taken of the treatment fields during DIBH as part of the pre-RT quality assurance day. The images were compared by a radiation oncologist with digitally reconstructed radiographs to determine whether the patient alignment was correct. The AlignRT system was used to verify that the patient surface matched that of the planned skin surface during which the portal image was acquired. If the patient needed to be shifted after a review of portal images, a new reference image of the patient’s skin surface was acquired and used for subsequent alignment. For all subsequent treatment days, the same setup procedure was taken to verify that the skin surface during DIBH matched the reference images taken on the quality assurance day (14).

**Quantitative cardiac assessments**

The method used to perform cardiac perfusion SPECT, using iv 10 mCi for a rest-only study, 128 x 128 matrix, 17 stops at 30 seconds each, iterative reconstruction has been previously described (9). Patients had a pre-RT resting cardiac perfusion SPECT scan, with repeat SPECT scanning done at 6 months after RT. This interval was chosen because the majority of the RT-associated SPECT abnormalities in prior studies were detected by this time (9).

In both visual and computer-based evaluation, wall motion abnormalities were recorded in each cardiac segment. When present, wall motion abnormalities were classified as hypokinetic, akinetic, or dyskinetic (16). The extent of wall involvement (small or large portion) was described as mild or severe.

The RT associated changes were assessed by comparing the pre-RT and 6-month post-RT SPECT-SRS scores, both scoring systems being taken into consideration.

In cases of discrepancy between the computer score and visual score, the scans were reviewed again by a senior nuclear medicine radiologist, whose reading superseded the automated score; this procedure is similar to what is done in daily practice.

**Statistical considerations**

The goal of this pilot study was to estimate the 6-month rate of post-RT cardiac perfusion defects. We hypothesized that the defect rate would be $\leq 10\%$ (down from $\sim 27\%$ without DIBH) (9). On the basis of this difference, assuming an observed rate of 10%, a sample size of 20 was chosen; the corresponding exact binomial 95% confidence interval would be 1.2%, 31.7%.

**Results**

From 2014 to 2015, a total of 25 patients were enrolled. Five were excluded from the final analysis: 4 because of abnormal pre-RT SPECT scans and 1 patient who chose not to return for the 6-month post-RT scan. The baseline characteristics of the evaluable 20 patients are summarized in Table 1. All 20 patients completed left-sided breast/chest wall irradiation without interruption. The radiation doses and treatment volumes are summarized in Table 2, and the dosimetric parameters of selected organs of interest are presented in Table 3. None of the treatment plans included any portion of the heart within the primary RT beam. The average minimal distance from the heart to the field edge, as measured in the treatment plan, was 9 mm (range, 0-20 mm). The pre-RT and 6-month post-RT cardiac parameters are presented in Table 4. There were 2 patients with a pre-RT computer-based SRS of 1, and these 2 patients had post-RT SRS of 1 and 2, respectively. Two patients with pre-RT SRS of zero had a
post-RT computer-based SRS of 2 and 4, respectively. All of these images were reviewed again by a senior nuclear medicine radiologist (T.W.), who regarded these scans as normal (subtle areas of decreased activity were attributed to attenuation or technical artifact), and no changes were seen between the pre-RT and post-RT scans. No scan had any evidence of a pre-RT or post-RT wall motion abnormality. All of the other SPECT scans had a computer-based score of zero, and these scans were also visually reviewed by the nuclear medicine physicians, who concurred with the normal findings.

None of the patients reported cardiac symptoms during RT or after RT at 6 months. Post-RT echocardiography was available for only 3 of these patients (it was not part of the study protocol), and ejection fractions were within the normal range.

### Discussion

Radiation therapy–associated cardiac injury in women with breast cancer has been recognized for decades. It remains a concern, especially because many patients are often also treated with systemic therapies (such as anthracyclines and trastuzumab) that may contribute to cardiac toxicity (2, 3). Current data supporting the use of regional nodal irradiation (RNI) will make this an ongoing concern because targeting of the IMN increases the risk for incidental irradiation of the heart (17-19). Even if the cardiac risks are modest, they might be clinically significant because the absolute benefit of the RT (or RNI) is often modest as well; therefore, the therapeutic ratio might somewhat narrow (4, 19).

The RT techniques have evolved to reduce the heart dose. This can be done by maneuvers to increase the distance of the heart from the chest wall or from the target volume (eg, timing RT with the breathing cycle, prone position), limiting the dose to the heart (eg, heart blocking, protons, intensity modulated RT), changing the target volume, and using technologies to improve the accuracy of the RT planning and delivery.

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics (n = 20)</th>
<th>Number (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis (y)</td>
<td>56 (39-72)</td>
</tr>
<tr>
<td>Ethnicity (white/African-American)</td>
<td>18/2</td>
</tr>
<tr>
<td>Menopausal (pre/post)</td>
<td>5/15</td>
</tr>
<tr>
<td>Median heart volume (cc)</td>
<td>437 (256-780)</td>
</tr>
</tbody>
</table>

Cardiac risk factors:
- Median body mass index (kg/m²) 28 (22-43)
- Coronary artery disease 2
- Hypertension 9
- Hyperlipidemia 6
- Diabetes mellitus 2
- Active smoker 0
- Past smoker 8

Tumor/treatment-related factors:
- Histology (DCIS/invasive carcinoma) 4/16
- Pre-RT hormone therapy 0
- Pre-RT Adriamycin 7
- Pre-RT trastuzumab 2
- Surgery (mastectomy/lumpectomy) 2/18

*Abbreviations: DCIS = ductal carcinoma in situ; RT = radiation therapy.
* Calculated from computed tomography used for treatment planning.

### Table 2 Radiation doses and target volumes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prescribed dose (cGy) (fraction number)</td>
<td>10</td>
</tr>
<tr>
<td>4272 (16)</td>
<td>10</td>
</tr>
<tr>
<td>4600 (23)</td>
<td>6</td>
</tr>
<tr>
<td>5000 (25)</td>
<td>4</td>
</tr>
<tr>
<td>Prescribed boost dose (cGy) (fraction number)</td>
<td>11</td>
</tr>
<tr>
<td>1000 (5)</td>
<td>11</td>
</tr>
<tr>
<td>1200 (6)</td>
<td>2</td>
</tr>
<tr>
<td>1600 (8)</td>
<td>6</td>
</tr>
<tr>
<td>Internal mammary chain RT (superiorly placed nodes)</td>
<td>7</td>
</tr>
<tr>
<td>Supraclavicular RT field</td>
<td>5</td>
</tr>
<tr>
<td>Whole axillary RT field</td>
<td>0</td>
</tr>
</tbody>
</table>

* To whole breast/chest wall
† Tumor bed/sar. In 18 patients an electron boost was used; in 1 patient photon boost was used.

### Table 3 Dosimetric parameters of radiation therapy (RT) plans

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median % D95 tumor bed</td>
<td>100.8 (92.3-102.4)</td>
</tr>
<tr>
<td>Median mean heart dose (cGy)</td>
<td>94 (56-200)</td>
</tr>
<tr>
<td>Median heart V25Gy</td>
<td>0 (0-0.1)</td>
</tr>
<tr>
<td>Median ipsilateral lung V20Gy</td>
<td>15 (4-31)</td>
</tr>
</tbody>
</table>

* Minimum dose to the “hottest” 95% of the tumor bed, in patients with intact breast.

### Table 4 Cardiac parameters before radiation therapy and 6 months afterward

<table>
<thead>
<tr>
<th>Cardiac parameter evaluated</th>
<th>Average (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechemotherapy echocardiography-based EF (n=3)</td>
<td>73% (66-83)</td>
</tr>
<tr>
<td>Postchemotherapy/pre-RT echocardiography-based EF (n=18)</td>
<td>62% (57-68)</td>
</tr>
<tr>
<td>Pre-RT wall motion score* (n=20)</td>
<td>0</td>
</tr>
<tr>
<td>Pre-RT perfusion SPECT summed-rest score (n=20)</td>
<td>0</td>
</tr>
<tr>
<td>Post-RT echocardiography-based EF (n=18)</td>
<td>63% (53-85)</td>
</tr>
<tr>
<td>Post-RT wall motion score*</td>
<td>0</td>
</tr>
<tr>
<td>Post-RT perfusion SPECT summed-rest score (n=20)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Wall motion score determined by cardiac SPECT.

Abbreviations: EF = ejection fraction; RT = radiation therapy; SPECT = single photon emission computed tomography.

Echocardiography was not required as part of the study but was often obtained as part of the patient’s regular medical care.
were not planned with the intention of having their fields. The ABC/DIBH patients in the study by Zellars et al defined perfusion defects were still seen in the DIBH cohort had IMNs included in the RT tangential fields (Table 3). In our study patients, even though 7 of 20 of our patients reported in prior dosimetric studies (7), post-RT SPECT-doses, compared with their non-DIBH cohort, and as re-

Whereas ABC/DIBH appeared to effectively reduce heart treatment with the use of DIBH versus free breathing. Perfusion defects. Their patients were randomized to left-sided RT for breast cancer failed to prevent cardiac SPECT. This rate of cardiac perfusion abnormalities after RT is lower than the 27% rate reported by Marks et al (9) (used as our historical control during protocol design) and is also lower than the rates reported by others (8, 11, 12).

The incidence and severity of new perfusion defects appear to depend strongly on the percentage of left ventricle within the primary RT field. In the series by Marks et al (9) abnormalities were seen at 6 months after RT in 4% of the patients planned to have 1% or less of the left ventricle in the RT field, and up to 50% of the patients with 5% to 10% of the left ventricle planned to be in the RT field. In the present study, and in the DIBH cohort in the series by Chung et al (20), where the heart was systematically excluded from the primary RT beams, the incidence of new post-RT perfusion defects was zero. In the series by Zellars et al (12), where DIBH was used to reduce cardiac exposure but where the heart was not systematically excluded from the RT field (so the degree of left ventricle exposure was low, but not necessarily zero), modest changes in perfusion after RT were detected.

Deep inspiration breath hold displaces the heart posteriorly, medially, and inferiorly: ie, away from the breast and away from the deep border of the tangential fields. This is reflected by the low mean heart doses and heart V25Gy seen in our study patients, even though 7 of 20 of our patients had IMNs included in the RT tangential fields (Table 3).

Nevertheless, DIBH and cardiac blocking are not synonymous. Consider the report from Zellars et al (12), who observed that active breathing control (ABC)-based DIBH (to 80% of the maximal tidal volume) in patients receiving left-sided RT for breast cancer failed to prevent cardiac perfusion defects. Their patients were randomized to treatment with the use of DIBH versus free breathing. Whereas ABC/DIBH appeared to effectively reduce heart doses, compared with their non-DIBH cohort, and as reported in prior dosimetric studies (7), post-RT SPECT-defined perfusion defects were still seen in the DIBH cohort within cardiac segments likely to be included in tangential fields. The ABC/DIBH patients in the study by Zellars et al (12) were not planned with the intention of having their heart fully excluded from the RT beam. Thus the accordance of some RT-associated perfusion defects is not that surprising. Rather, the concerning finding is that the ABC/DIBH cohort had a greater degree of interval change (pre-RT vs post-RT SRS scores) than did their free-breathing cohort. However, interpretation of these data is confusing because the DIBH cohort had a lower rate of pre-RT SPECT-scan abnormalities than did their free-breathing cohort. It is possible that systematic differences in the daily setup accuracy for patients with ABC-based DIBH versus free breathing may also explain these findings. For example, the accuracy of daily setup (quantified by the differences between the weekly portal films and the planning images) has been linked to the rate of RT-associated cardiac perfusion defects in patients with breast cancer; with greater rates of perfusion defects in patients whose RT fields, on average, were set up “too deep” (10). Thus, a possibility that might explain the findings in the study by Zellars et al (12) is that there were greater degrees of setup uncertainties in the ABC/DIBH patients than in the free-breathing patients, perhaps because of the increased complexity in the former. Furthermore, Zellars et al (12) speculated that ABC/DIBH perhaps limited the heart motion in such a manner that the heart was in the beam exposed to higher doses, compared with free-breathing patients, in whom the heart motion would have “blurred” the dose.

In the current study, we encountered a few discrepancies between the visual and computer-based scoring. Our previous study used only visual scoring to document perfusion or motion defects. The data suggest that computer-based quantitative assessment has similar prognostic and diagnostic ability to make a visual analysis (21, 22), with better reproducibility (23); however, it is unable to account for artifacts, and thus it is used mostly in an advisory role in clinical practice. Therefore, in cases of discrepancy the score given by the senior nuclear medicine radiologist was used as the final score, as is the case in routine clinical practice.

Our results suggest that DIBH with the AlignRT 3-dimensional surface matching system with conformal cardiac blocking can successfully eliminate meaningful cardiac exposure. However, is it necessary to completely eliminate incidental cardiac irradiation? In some settings the target coverage might require that a portion of the heart be included in the primary beam. Obviously, there is a balance of competing risks. Interestingly, the target volumes in the postlumpectomy and postmastectomy settings are both generous, and the data suggest that treatment of less than the entire breast is acceptable in some settings (6). Thus, it might be acceptable and prudent to completely block the heart from the primary beams in most patients, even if that means excluding part of the traditional target tissues. On the other hand, if the tissues most at risk are in or near the portion of target excluded by blocking the heart, blocking those tissues may lead to an increased risk of local failure, as we experienced when we first started to routinely use heart blocks (24). Fortunately, most breast cancers are in the superior aspect of the breast, and thus the most at-risk...
tissues might be relatively far from the breast tissue in the shadow of the heart block. In addition, an electron patch can be added to the medial/inferior aspect of the breast/chest-wall to cover these “shadowed” tissues if desired. Taken from this perspective, DIBH is merely a technique to enable a larger fraction of the traditional large target volume to be included in the tangential RT fields while at the same time minimizing the degree of cardiac exposure. The balance between target coverage and cardiac sparing is patient specific. Indeed, as part of preparing this report for presentation, we calculated the percentage of the RTOG-defined breast/chest-wall volume that received 90% of the prescribed dose (clinical target volume \( \text{CTV} \) V90%); as estimated by retrospective image segmentation (and with full acknowledgement that CTV definition is somewhat imprecise and subjective). Even though the degree of breast/chest-wall coverage was not mandated in this protocol, the CTV V90% was between 84% and 99% (an average of 92.6%). The finding that more than 90% of the breast/chest wall CTV received 90% of the prescribed dose shows that this method of DIBH allows for both good target coverage and cardiac sparing. Moreover, the tumor bed, determined on the basis of the radiologic abnormality and surgical clips, was well within the tangent fields, with 100% coverage as noted in Table 3.

Our study has several limitations. First, the sample size is modest. Nevertheless, we did not note any post-RT SPECT scan abnormalities in any of our study patients, and thus a study of additional patients would be unlikely to markedly alter our results. Second, the follow-up duration of 6 months is relatively short. However, in our prior studies, 6 months was ample time for RT-associated SPECT scan abnormalities to develop, and indeed essentially many of the post-RT defects were manifest by this time (9). Others have similarly noted perfusion defects relatively soon after RT (12, 25). Thus, further study of our cohort at a longer post-RT follow-up interval is also unlikely to alter the results and conclusion.

Third, the clinical implications of SPECT scan abnormalities are unknown. A clinical endpoint (coronary disease, angina, acute myocardial ischemia) would be preferable. However, the latency period between RT and the associated clinical cardiac events can be years to decades; thus, prospective assessment of DIBH to prevent clinical cardiac events is impractical (26). Cardiac perfusion SPECT is a widely used and sensitive method to detect and monitor non-RT–associated cardiac disease (27–29), appears to be able to detect RT-associated subclinical abnormalities in perfusion/function relatively soon after RT (8, 10, 12), and thus might be a reasonable surrogate for longer-term events.

Fourth, the use of both visual and computer-based scoring systems adds some uncertainty. Prior studies assessing RT-associated cardiac perfusion defects relied only on visual scoring, and that has been the criterion standard. Computer-aided scoring is relatively new, and its utility is unclear. Thus, our use of visual scoring to address discordant readings by an experienced radiologist is reasonable.

In conclusion, our results suggest that DIBH with the use of a controlled surface monitoring technique and conformal heart blocking for patients receiving tangential radiation for left-sided breast cancer is an effective means to avoid RT-associated cardiac perfusion and wall motion defects.

References


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