RPM Inspiration Gating: Improving Radiotherapy for Left Breast Cancer Patients with Anterior Heart Position

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ABSTRACT: **Background:** Adjuvant radiotherapy for breast cancer reduces local recurrence and improves survival. In patients with left sided breast cancer, anterior heart position or medial tumor location may cause inadequate breast coverage due to heart shielding. Respiration gating using the Real-time Position Management (RPM) system enables pushing the heart away from the tangential fields during inspiration, thus optimizing the treatment plan.

Objectives: To compare breathing inspiration gating (IG) techniques with free breathing (FB), focusing on breast coverage.

Methods: The study comprised 49 consecutive patients with left sided breast cancer who underwent lumpectomy and adjuvant radiation. RPM was chosen due to insufficient breast coverage caused by an anterior heart position or medial lumpectomy cavity. FB and IG computed tomography simulations were generated for each patient. Breast (PTVbreast) and lumpectomy cavity (CTVlump) were defined as the target areas. Optimized treatment plans were created for each scan. A dosimetric comparison was made for breast coverage and heart and lungs doses.

Results: PTVbreast V95% and mean dose (Dmean) were higher with IG vs. FB (82.36% vs. 78.88%, $P = 0.002$; 95.73% vs. 93.63%, $P < 0.001$, respectively). CTVlump V95% and Dmean were higher with IG (98.87% vs. 88.92%, $P = 0.001$; 99.14% vs. 96.73%, $P = 0.003$, respectively). The cardiac dose was lower with IG. The IG left lung Dmean was higher. No statistical difference was found for left lung V20.

Conclusions: In patients with suboptimal treatment plans due to anterior heart position or medial lumpectomy cavity, RPM IG enabled better breast/tumor bed coverage and reduced cardiac doses.

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KEY WORDS: adjuvant radiotherapy, breast cancer, inspiration gating (IG), Real-time Position Management (RPM), respiration gating

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It is well established that radiotherapy for breast cancer following breast conserving surgery reduces local recurrence and improves survival [1,2]. However, breast radiation has also been shown to result in long-term cardiac toxicity and increased rates of cardiac death [3,4]. Due to these concerns, various strategies to reduce heart dose in patients with left sided breast cancer have been studied, including the use of a three-dimensional conformal radiotherapy heart block, intensity-modulated radiotherapy [5,6], prone breast technique [7,8], and respiratory gating.

In some patients with left sided breast cancer, anterior heart position causes inadequate breast coverage due to heart shielding. Other anatomical characteristics, such as medial lumpectomy cavity, contralateral breast form, or breast reconstruction can also compromise coverage. In such cases, using an inspiration gating (IG) system can help separate the heart from the chest wall during inspiration, thereby allowing treatment plan optimization and increased target coverage.

At the Sheba Medical Center, the Varian Real-time Position Management (RPM) system has been used since April 2009 for left sided breast cancer patients. While other common gating systems require breath hold (i.e., ABC system and SDX), RPM also enables respiratory phase-dependent irradiation while the patient is breathing. It measures the patient's respiratory pattern and range of motion by using an infrared tracking camera and a reflective marker, which is placed on the patient's chest. The gating threshold is then set according to the breast position in relation to the patient's respiratory cycle.

In this study, we compared left breast radiation using RPM free breathing IG with a free breathing (FB) technique, focusing on breast and lumpectomy cavity coverage, as well as comparing normal tissue doses to the heart and the lungs.

PATIENTS AND METHODS

PATIENTS

Between 2009 and 2012, 129 patients with left sided breast cancer at the Sheba Medical Center were treated with adjuvant radiotherapy following breast conserving surgery using the

RPM gated breathing technique. From this cohort, patients who received post-mastectomy radiation or regional nodal irradiation were excluded, leaving 49 consecutive patients with stage 0–2 left breast cancer who underwent breast conserving surgery and received adjuvant radiotherapy to the left breast only. All patients signed informed consent and the study was approved by the institutional review board. In all patients, RPM technology was chosen due to either an anterior heart position, which led to insufficient left breast (planning target volume, [PTVbreast]) coverage on FB-computed tomography (CT)-based treatment plan due to heart blocking or very medial lumpectomy cavity.

SIMULATION AND DELINEATION

Each patient underwent two CT simulations: a conventional FB-CT simulation and a simulation with Varian RPM gated breathing. All scans were conducted on a breast board with 3–5 mm cuts with both arms raised above the head. Following FB simulation, and after detailed explanation and instructions (written and verbal), a gated breathing simulation was performed. The patient, set on the breast board, was given audio instruction for breathing rate. Both inspiration and expiration lasted 6 seconds each. The gating window (the period in which the treatment is given) was set at the level of 70%–100% of the highest inspiration-expiration wave phase.

During simulation, catheters were placed to define the clinical borders of the left breast: the medial border at the patient midline, the lateral border at the mid-axillary line, the superior border at the inferior aspect of the clavicular-head, and the inferior border 1.5 cm below the inframammary fold. The PTVbreast was delineated on axial CT cuts using the clinical borders as guides. The anterior border was defined 0.5 cm inside the external body contour. The posterior border was defined by connecting a point 5 mm lateral to the medial catheter, 5 mm medial to the lateral catheter, and subsequently editing the volume back to the muscle-rib interface to exclude lungs and ribs. The lumpectomy cavity clinical target volume (CTVlump) was delineated on all axial cuts, including all clips and seromas seen on the CT. The whole heart was contoured according to a heart atlas described by White et al. [9]. In brief, the superior contour was placed below the left pulmonary artery and continued inferiorly to include the pericardium down to the level of the diaphragm, excluding the superior vena cava (SVC) where the SVC was clearly visible. The lungs were contoured using automated density gradient tracking and were then reviewed and edited as necessary.

The volumes of the PTVbreast, CTVlump, and heart in both plans (with and without gating) were measured and compared to ensure acceptable similarity, which was defined as a maximal difference of 10%.

The delineation and treatment planning were completed by the same physician (MAB) for all patients to retain consistency.

TREATMENT PLANNING

Treatment plans were designed and calculated for both FB-CT and RPM IG-CT scans. All planning and dosimetric evaluations were generated by the ECLIPSE V.11 TPS system (Varian Medical Systems, Palo Alto, CA, USA).

The primary planning objective was to optimize PTVbreast coverage while completely avoiding the heart or contralateral breast tissue in the radiation fields. For the purpose of this dosimetric study, the prescription dose was 50 Gy in 25 fractions to the whole breast only, using 3D treatment planning with tangential fields technique; 0.5 cm MLC were used as needed for heart blocking, as were field-in field techniques to maximize homogeneity; 6–15 MV photon energy was used. The constraints used to optimize the PTVbreast dose were according to the ICRU 50, 95%–107% dose.

For each pair of plans, dose volume histograms (DVH) were generated and compared for the PTVbreast, CTVlump, heart, and lungs.

All patients were treated according to the IG plan using the Varian RPM system. Following the adaption breathing training period and adjustment, the radiation therapist initiated the treatment, with 7–10 breathing cycles for each field.

STATISTICAL ANALYSIS

The following values were compared and analyzed using standard 2-sample *t*-test: V5, V10, V20, mean dose (Dmean), maximal dose (Dmax) to the left lung and to both lungs; V1, V2, V5, Dmean and Dmax to the heart; V80%, V90%, V95%, V100%, V105%, Dmean, and Dmax to the PTVbreast; V90%, V95%, V98%, V100%, Dmean, and Dmax to the CTVlump.

Two sided P value < 0.05 was considered as statistically significant.

Maximal dose for each of the examined tissues was defined as the maximal dose received by 1% of the organ volume.

RESULTS

PATIENT CHARACTERISTICS

The mean patient age was 53.1 years (range 30–80 years), three patients were BRCA carriers, and one patient had previous breast augmentation. Patient and tumor characteristics are presented in Table 1.

PULMONARY VOLUMES

The mean total left lung volume was elevated by 66% in the RPM IG simulation CT scan, compared with FB [Table 2].

TARGET DOSIMETRY

The volume of PTVbreast receiving 80%, 90%, and 95% of the prescribed dose was higher with IG compared to FB. No significant difference was found in V100%. Dmean was higher

Table 1. Patient characteristics

		Number of patients	%
Stage	0 I II	4 28 17	8.2 57.1 34.7
Histology	IDC ILC DCIS	42 2 5	85.7 4.1 10.2
Chemotherapy	Yes No	27 22	55.1 44.9
ER status	Positive Negative	38 11	77.6 22.4
HER2 status (for IDC/ILC)	Positive Negative	19 25	43.2 56.8
Menopause	Pre Post	21 28	42.9 57.1

DCIS = ductal carcinoma in situ, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma

Table 2. Pulmonary volumes

	FB		IG		*P* value
	Mean	Range	Mean	Range	
Left lung, cm^3	1044.9	668.3–1461.0	1734.7	1009.5–2382.2	< 0.001
Both lungs, cm^3	2274.1	1612.6–3205.5	3788.5	2445.1–5330.7	< 0.001

FB = free breathing, IG = inspiration gating

with IG (95.73% vs. 93.63%, $P < 0.001$). V105% and maximal doses were similar in both plans.

CTVlump coverage was statistically significantly higher using IG for every dose percentage including V100% compared to FB. Dmean with IG was higher (99.14% vs. 96.73%, $P = 0.003$) [Table 3].

CARDIOPULMONARY DOSIMETRY

All heart doses were lower with IG vs. FB treatment planning [Table 4]. The heart Dmean was 2.36 Gy vs. 2.91 Gy, $P < 0.001$; heart Dmax was 15.31 Gy vs. 23.91 Gy, $P < 0.001$; and heart V5 was 2.34% vs.3.72%, $P < 0.001$.

No statistical difference was found for ipsilateral left lung V20 between techniques. Ipsilateral lung V5, V10 and mean lung dose were all higher when using IG.

DISCUSSION

Breast radiotherapy has been shown to improve locoregional control and breast cancer-specific mortality. However, breast radiation has also been shown to increase cardiopulmonary morbidity and mortality. The meta-analysis from the Early Breast Cancer Trialists' Collaborative Group [3] showed that breast cancer patients who received radiotherapy had an increased rate of death from heart disease with a ratio of 1.27. Furthermore, Darby and colleagues [4] found that women with left sided breast cancer were at increased risk for major coronary events including myocardial infarction, catheterization and death from cardiac disease. The authors found that rates of coronary events increased linearly by 7.4% for every increase in 1 Gy in mean heart dose and that increase in coronary events can occur within 5 years of radiation. As a result, various techniques have been studied to determine if the heart dose can be reduced during left breast radiation.

Table 3. Target dosimetry

	FB (mean)	IG (mean)	*P* value
PTVbreast			
V80%	92.0	94.97	< 0.01
V90%	87.63	90.69	< 0.01
V95%	78.88	82.36	0.002
V100%	35.27	37.99	0.230
V105%	2.17	2.64	0.304
Dmean	93.63	95.73	< 0.001
Dmax	105.25	103.55	0.428
CTVlump			
V90%	94.73	99.89	0.009
V95%	88.92	98.87	0.001
V98%	55.83	66.78	0.01
V100%	22.91	30.71	0.044
Dmean	96.73	99.14	0.003
Dmax	101.65	102.64	0.005

FB = free breathing, IG = inspiration gating

Table 4. Cardiopulmonary dosimetry

	FB (mean)	IG (mean)	*P* value
Heart			
V1 Gy	40.66%	36.26%	< 0.001
V2 Gy	17.59%	14.62%	< 0.001
V5 Gy	3.72%	2.34%	< 0.001
Dmean	2.91 Gy	2.36 Gy	< 0.001
Dmax	23.91 Gy	15.31 Gy	< 0.001
Left lung			
V5 Gy	20.49%	23.33%	0.01
V10 Gy	14.11%	15.65%	0.022
V20 Gy	10.55%	11.63%	0.059
Dmean	12.10 Gy	13.28 Gy	0.027
Dmax	88.0 Gy	90.35 Gy	0.126
Both lungs			
V5 Gy	9.23%	10.61%	0.001
V10 Gy	6.32%	7.11%	0.011
V20 Gy	4.71%	5.28%	0.031
Dmean	5.51 Gy	6.11 Gy	0.013
Dmax	81.8 Gy	87.07 Gy	0.025

Our study is one of few to evaluate target coverage benefits of RPM IG versus FB in left breast cancer patients, and to the best of our knowledge, first for pre-selected cases due to an anterior heart position and/or medial CTV on FB-CT simulation. Most previous dosimetric studies regarding respiratory gating with RPM focused on the deep inspiration breath hold (DIBH) technique (as opposed to free breathing IG) and anticipated cardiopulmonary toxicity. It has been demonstrated that DIBH reduces cardiac and lung radiation doses [10-14] and complication probability [15,16] in patients with left sided breast cancer. Recently, Joo et al. [17] also showed cardiac radiation dose and major coronary events probability reduction using DIBH. Korreman [18] and co-authors compared DIBH with IG and demonstrated similar reduction in cardiopulmonary doses in both techniques.

DIBH using RPM was also compared to prone position FB, showing equal PTVbreast coverage with lower cardiac, left anterior descending coronary artery, and contralateral breast doses for DIBH, but higher lung doses [7].

In our study, significantly better PTVbreast and CTVlump coverage were produced with RPM IG compared with FB plans (82.36% vs. 78.88%, $P = 0.002$ for PTVbreast V95%; 98.87% vs. 88.92%, $P = 0.001$ for CTVlump V95%, respectively). Dosimetric planning and treatment with RPM gating during the inspiration phase (in which the heart separates from the chest wall), allowed for treatment plans to encompass the target breast tissue better (with heart avoidance), by including medial and lateral portions that were previously compromised. We present no difference in maximal doses received by RPM IG PTVbreast compared with FB (V105% was 2.64% vs. 2.17%, $P = 0.304$; Dmax 103.55% vs. 105.25%, $P = 0.428$, respectively), resulting in no higher probability for breast tissue toxicity.

In concordance with Korreman and colleagues [15], reduction of cardiac doses was also demonstrated in our study with RPM IG. The volume of heart receiving 5 Gy was only 2.34% using RPM IG vs. 3.72% with FB ($P < 0.001$). Mean dose and maximal dose were also significantly lower (2.36 Gy vs. 2.91 Gy, $P < 0.001$; 15.31 Gy vs. 23.91 Gy, $P < 0.001$, respectively). This reduction is of clinical value in light of the research by Darby and colleagues [4] who demonstrated a linear connection between major coronary events and mean heart dose in women after radiotherapy for breast cancer, even for low radiation doses.

In contrast to previous studies [11,14,16,18,19], we found a slight increase in pulmonary doses while using RPM IG. The left lung mean dose was higher with IG (13.28 Gy vs. 12.1 Gy, $P = 0.027$) as well as V5 and V10, but no difference was observed for left lung V20. The dose reduction presented by others referred to decreased lung portion in the tangential field as the whole lung volume increases during inflation. This discrepancy may be explained by patient pre-selection according to the anterior heart position. In those patients, the relative lung portion within the tangential field may paradoxically increase during inflation, as the lung could enter the field where the heart was previously attached to the chest wall. The heart separation with IG allowed better PTVbreast coverage but also a greater lung portion within the field. It is important to note that pulmonary doses with RPM IG in our report were still below accepted lung dosimetric parameters associated with radiation pneumonitis risk [20,21].

RPM IG does not require the use of facial devices as opposed to other techniques such as ABC or SDX and therefore has the advantage of potentially superior patient comfort. In fact, in our study all patients successfully completed RPM IG simulation and treatment.

Due to superior dosimetry, all study participants were treated using RPM at our institution**.** Future research regarding disease recurrence as well as late toxicities is anticipated.

LIMITATIONS

Our study was carried out in a single institution and the treatment plans were retrospectively evaluated (although prospectively compared) and were not compared to DIBH technique treatment plans. Only patients with early stage cancer were included; therefore, internal mammary lymph node coverage and cardiopulmonary doses in node-positive patients were not studied.

CONCLUSIONS

In left breast cancer patients with suboptimal FB treatment plans due to anterior heart position or very medial CTVlump, IG using the RPM system enables better breast coverage, excellent CTVlump coverage, and reduced cardiac doses.

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Capsule

A broader repertoire for MHC molecules

A subset of T cells can present microbial ligands using MR1, a nonconventional major histocompatibility complex (MHC) molecule. MR1 is known to present metabolites from microbes such as *Mycobacterium tuberculosis*, but the breadth of the MR1 ligandome is not well understood. **Harriff** et al. used mass spectrometry and molecular networking to identify MR1-presented ligands from two divergent microbes, *Escherichia coli* and *Mycobacterium smegmatis*. MR1 could present a surprisingly broad array of ligands for both microbes, and ligands could be distinguished by different T cell receptors on MR1-restricted T cells exerting inhibitory or activating effects. Thus, MR1 is a critical molecule for presenting microbial ligands to the immune system.

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Eitan Israeli

Capsule

Emergence of carbapenemase-producing enterobacteriaceae, south-central Ontario, Canada

Kohler and colleagues analyzed population-based surveillance data from the Toronto Invasive Bacterial Diseases Network to describe carbapenemase-producing *Enterobacteriaceae* (CPE) infections in 2007–2015 in south-central Ontario, Canada. The authors reviewed patient medical records and travel histories, analyzed microbiologic and clinical characteristics of CPE infections, and calculated incidence. Among 291 cases identified, New Delhi metallo-β-lactamase was the predominant carbapenemase (51%). The proportion of CPE-positive patients with prior admission to a hospital in Canada who had not received healthcare abroad or traveled to high-risk areas was 13% for patients with oxacillinase-48, 24% for patients with New Delhi metallo-β-lactamase, 55% for patients with *Klebsiella pneumoniae* carbapenemase, and 67% for patients with *Verona integron*-encoded metallo-β-lactamase. Incidence of CPE infection increased, reaching 0.33 cases/100,000 population in 2015. For a substantial proportion of patients, no healthcare abroad or high-risk travel could be established, suggesting CPE acquisition in Canada. Policy and practice changes are needed to mitigate nosocomial CPE transmission in hospitals in Canada.

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Eitan Israeli