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CLINICAL INVESTIGATION

# Factors Associated With Cardiac Radiation Dose Reduction After Hypofractionated Radiation Therapy for Localized, Left-Sided Breast Cancer in a Large Statewide Quality Consortium

Daniel J. Herr, MD, PhD,[*] Alexander Moncion, PhD,[*] Kent A. Griffith, MS, MPH,[†] Robin Marsh, CMD,[*] Margaret Grubb, MS,[*] Amit Bhatt, MD, PhD,[‡] Michael Dominello, DO,[§] Eleanor M. Walker, MD,[‖] Vrinda Narayana, PhD,[¶] Eyad Abu-Isa, MD,[¶] Frank A. Vicini, MD,[#] James A. Hayman, MD,[*] and Lori J. Pierce, MD[*] on behalf of the Michigan Radiation Oncology Quality Consortium

[*]*Department of Radiation Oncology and;* [†]*School of Public Health, University of Michigan, Ann Arbor, Michigan;* [‡]*Department of Radiation Oncology, Karmanos Cancer Institute at McLaren Greater Lansing, Lansing, Michigan;* [§]*Department of Radiation Oncology, Karmanos Cancer Institute, Detroit, Michigan;* [‖]*Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, Michigan;* [¶]*Department of Radiation Oncology, Ascension Providence Hospital, Southfield, Michigan; and* [#]*MHP Radiation Oncology Institute/GenesisCare USA, Farmington Hills, Michigan*

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**Purpose:** Limiting cardiac radiation dose is important for minimizing long-term cardiac toxicity in patients with left-sided early-stage breast cancer.

**Methods and Materials:** Prospectively collected dosimetric data were analyzed for patients undergoing moderately hypofractionated radiation therapy to the left breast within the Michigan Radiation Oncology Quality Consortium from 2016 to 2022. The mean heart dose (MHD) goal was progressively tightened from ≤2 Gy in 2016 to MHD ≤ 1.2 Gy in 2018. In 2021, a planning target volume (PTV) coverage goal was added, and the goal MHD was reduced to ≤1 Gy. Multivariate logistic regression models were developed to assess for covariates associated with meeting the MHD goals in 2016 to 2020 and the combined MHD/PTV coverage goal in 2021 to 2022.

**Results:** In total, 4165 patients were analyzed with a median age of 64 years. Overall average cardiac metric compliance was 91.7%. Utilization of motion management increased from 41.8% in 2016 to 2020 to 46.5% in 2021 to 2022. Similarly, use of prone positioning increased from 12.2% to 22.2% in these periods. On multivariate analysis in the 2016 to 2020 cohort, treatment with motion management (odds ratio [OR], 5.20; 95% CI, 3.59-7.54; $P < .0001$) or prone positioning (OR, 3.21; 95% CI, 1.85-5.57; $P < .0001$) was associated with meeting the MHD goal, while receipt of boost (OR, 0.25; 95% CI, 0.17-0.39; $P < .0001$) and omission of hormone therapy (OR, 0.65; 95% CI, 0.49-0.88; $P = .0047$) were associated with not meeting the MHD goal. From 2021 to 2022, treatment with motion management (OR, 1.89; 95% CI, 1.12-3.21; $P = .018$) or prone positioning (OR, 3.71; 95% CI, 1.73-7.95;

Corresponding author: Lori J. Pierce, MD; E-mail: ljpierce@med.umich.edu

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Data Sharing Statement: We are not authorized to share MROQC data. The data are individually owned by the member institutions of MROQC.

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*P* = .0008) was associated with meeting the combined MHD/PTV goal, while larger breast volume (≥1440 cc; OR, 0.34; 95% CI, 0.13-0.91; *P* = .031) was associated with not meeting the combined goal.

**Conclusions:** In our statewide consortium, high rates of compliance with aggressive targets for limiting cardiac dose were achievable without sacrificing target coverage. 

## Introduction

Cardiac exposure during radiation therapy for early-stage breast cancer is associated with increased rates of future cardiac events.[1,2] Prior work has estimated the magnitude of this increase in relative risk ranging from 7.4% to 16.5% per gray (Gy) of mean heart dose (MHD), with no known safe level of exposure.[3-5]

Advances in knowledge about the importance of cardiac radiation exposure during radiation therapy for breast cancer treatment have spawned a multitude of efforts aimed at reducing cardiac dose without sacrificing oncologic control. These include the use of field-in- field or intensity modulated radiation techniques,[6-8] proton therapy,[9] deep-inspiration breath hold,[10,11] and prone positioning,[12,13] among others. Although these efforts have greatly expanded the tools available to facilitate cardiac dose reduction, refining the factors associated with successful cardiac dose reduction is critical to the successful application of these techniques.

We previously demonstrated that an emphasis on cardiac dose reduction within a continuous quality initiative (CQI) framework is associated with progressive reduction in MHD over time for patients undergoing radiation therapy for breast cancer.[14] Here, we sought to expand upon this finding by examining the dosimetric outcomes associated with further tightening of heart dose goals and the factors associated with meeting these goals in patients with early-stage left-sided breast cancer undergoing hypofractionated radiation therapy to the whole breast.

## Methods and Materials

The Michigan Radiation Oncology Quality Consortium (MROQC) is a collaborative effort among 27 academic and community radiation oncology centers in the state of Michigan that prospectively collects dosimetric, demographic, and acute treatment-related toxicity data from patients undergoing definitive intent radiation therapy for breast, lung, and prostate cancer, as well as the palliative treatment of bone metastases. This information is used to formulate quality improvement metrics that are propagated across the consortium with the goal of improving the safety and efficacy of radiation therapy for all patients treated within MROQC.

Quality improvement metrics related to cardiac radiation dose exposure in the setting of radiation therapy for breast cancer have been included for patients undergoing treatment since 2012 and have previously been demonstrated to be associated with a reduction in median MHD in these patients over time.[14] Beginning in 2016, the cardiac dose metric for patients with early-stage breast cancer with left-sided disease undergoing radiation therapy to the whole breast without regional nodal irradiation has undergone multiple revisions with the goal of further lowering cardiac dose exposure without sacrificing tumor coverage. In 2016, the goal MDH from the composite whole breast radiation therapy and lumpectomy cavity boost plans was ≤2 Gy. In 2018, this metric was lowered to a goal MHD of ≤1.2 Gy. In 2021, the cardiac metric further tightened to a goal of MHD ≤ 1 Gy and was refined to include a composite planning target volume (PTV) coverage goal of ≥95% of the lumpectomy cavity PTV receiving ≥95% of the prescription dose. This combined metric was also adjusted to be calculated from solely the whole breast radiation therapy plan, excluding dose contribution from the boost plan, if present.

The percentage of plans meeting target quality metrics is reported annually for each site participating in MROQC. The raw percentage of plans meeting the cardiac metric in place in each given year was calculated as a simple proportion of the total number of patients treated each year within MROQC with left-sided, node negative disease. Multivariable logistic regression models were used to determine the association between patient disease and treatment characteristics with metric compliance. Separate models were developed for patients treated from 2016 to 2020, when the cardiac metric focused on MHD alone, and from 2021 to 2022, when the composite metric including both MHD and PTV coverage was in place. Covariates included age, treatment position (supine without motion management vs supine with motion management vs prone), treatment technique (3-dimensional conformal radiation therapy [3D-CRT] vs intensity modulated radiation therapy [IMRT]), presence of boost (for the 2016-2020 analysis), year of treatment, patient body mass index (BMI), breast volume, heart volume, treatment at an academic versus community center, receipt of chemotherapy, and receipt of hormone therapy. Motion management was defined as treatment with deep inspiratory breath hold or respiratory gating. Consistent with our prior work, IMRT was defined as either inverse-planned cases or cases using highly segmented forward planning using ≥5 segments per any unique gantry angle for the primary breast plan.[15] All statistical analyses were performed using SAS version 9.4. This study was considered institutional review board−exempt because of the nature of MROQC as a quality assurance/quality improvement initiative.

## Results

### Patient and disease characteristics

A total of 4165 patients who underwent whole breast moderately hypofractionated irradiation without regional nodal irradiation were included in this analysis. Of these patients, 2830 underwent treatment during the era in which the MHD-only goal was in place (2016-2020), and 1335 underwent treatment during the time period when the composite MHD and PTV coverage goal were in place (2021-2022). Patient and disease characteristics did not differ substantially between these 2 periods. Mean patient age was 63.5 years for the patients treated 2016 to 2020 versus 63.3 years for those treated 2021 to 2022. In both periods, most patients were White (79.7% vs 79.1%), had T1 disease (60.8% vs 61%), did not receive chemotherapy as part of their breast cancer treatment (83% vs 81.4%) but did receive hormone therapy (65.6% vs 65.5%) (Table 1). The majority of patients were treated supine during both periods (87.2% vs 77.7%), but utilization of motion management increased from 41.8% in 2016 to 2020 to 46.5% in 2021 to 2022. Deep inspiratory breath hold was the most commonly used motion management technique, accounting for 90% of patients treated with motion management in the 2016 to 2020 cohort and 88% in the 2021 to 2022 cohort. The remainder of cases treated with motion management used respiratory gating. Similarly, use of prone positioning increased from 12.2% in 2016 to 2020 to 22.2% from 2021 to 2022. Lumpectomy cavity boost was administered in 69.7% of patients treated 2016 to 2020 compared with 64.2% of patients treated 2021 to 2022 (Table 1).

## Compliance with cardiac metric over time

In order to determine whether changes in the cardiac quality metric over time affected the ability to meet cardiac dose goals, we examined the proportion of plans meeting the cardiac goals in each year from 2016 to 2022. Despite tightening of the MHD goals during the 2016 to 2020 period, the proportion of plans that successfully achieved doses below the goal threshold in place at the time of treatment ranged from 86.5% in 2019 to 94.6% in 2020 (Fig. 1). Even after incorporation of the composite MHD and PTV coverage goal in 2021, compliance with the cardiac quality metric remained very high at 95.8% in 2021 and 90.3% in 2022.

## Factors associated with meeting the cardiac metrics

We next performed multivariable analyses to examine which patient and treatment characteristics were associated with metric compliance or noncompliance during the periods 2016 to 2020 and 2021 to 2022. For patients treated 2016 to 2020 when the cardiac quality metric was based on MHD alone, treatment with motion management (odds ratio [OR], 5.20; 95% CI, 3.59-7.54; $P < .0001$) or prone positioning (OR, 3.21; 95% CI, 1.85-5.57; $P < .0001$) were associated with meeting the MHD goal, whereas receipt of boost (OR, 0.25; 95% CI, 0.17-0.39; $P < .0001$) and omission of hormone therapy (OR, 0.65; 95% CI, 0.49-0.88; $P = .0047$) were associated with not meeting the MHD goal.

**Table 1 Patient demographic, disease, and treatment details**

| Variable | 2016-2020 (N = 2830) | 2021-2022 (N = 1335) |
|---|---|---|
| Age (mean, y) | 63.5 | 63.3 |
| Race (n, %) | | |
| White | 2255 (79.7) | 1056 (79.1) |
| Black | 395 (14.0) | 185 (13.9) |
| Other | 180 (6.3) | 94 (7.0) |
| Body mass index (n, %) | | |
| Underweight/normal: <25 | 689 (24.4) | 254 (19.0) |
| Overweight: 25 to <30 | 875 (30.9) | 378 (28.3) |
| Obesity I: 30 to <35 | 674 (23.8) | 332 (24.9) |
| Obesity II: 35 to<40 | 334 (11.8) | 217 (16.3) |
| Obesity III: >40 | 246 (8.7) | 149 (11.1) |
| Unknown | 12 (0.4) | 5 (0.4) |
| Breast volume (n, %) | | |
| ≤690 cc | 783 (27.7) | 321 (24.0) |
| 690.1-1015 cc | 702 (24.8) | 323 (24.2) |
| 1015.1-1440 cc | 667 (23.5) | 342 (25.7) |
| ≥1440.1 cc | 678 (24.0) | 349 (26.1) |
| T-stage (n, %) | | |
| $T_{is}$ | 700 (24.7) | 331 (24.8) |
| T0 | 26 (0.9) | 21 (1.6) |
| T1 | 1721 (60.8) | 813 (61.0) |
| T2 | 373 (13.2) | 161 (12.1) |
| T3-4 | 9 (0.3) | 5 (0.4) |
| Unknown | 1 (<0.1) | 4 (<0.1) |
| Chemotherapy | | |
| Yes | 471 (16.6) | 217 (16.3) |
| No | 2348 (83.0) | 1087 (81.4) |
| Unknown | 11 (0.4) | 31 (2.3) |
| Hormone therapy | | |
| Yes | 1858 (65.6) | 874 (65.5) |
| No | 961 (34.0) | 426 (31.9) |
| Unknown | 11 (0.4) | 35 (2.6) |
| Lumpectomy cavity boost | | |
| Yes | 1971 (69.7) | 857 (64.2) |
| No | 859 (30.3) | 478 (35.8) |
| Treatment position | | |
| Supine without motion management | 1285 (45.4) | 417 (31.2) |
| Supine with motion management | 1184 (41.8) | 621 (46.5) |
| Prone | 345 (12.2) | 296 (22.2) |
| Unknown | 16 (0.6) | 1 (<0.1) |

(*Continued*)

**Table 1** (*Continued*)

| Variable | 2016-2020 (N = 2830) | 2021-2022 (N = 1335) |
|---|---|---|
| Treatment technique | | |
| 3D-CRT | 1692 (59.8) | 789 (59.1) |
| IMRT | 1127 (39.8) | 538 (40.3) |
| Not reported | 11 (0.4) | 8 (0.6) |
| Treatment setting | | |
| Academic | 884 (31.2) | 212 (15.9) |
| Community | 1946 (68.8) | 1123 (84.1) |
| Heart volume (median [IQR], cc) | 602.6 (520-696) | 599.6 (522-687) |

*Abbreviations:* 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

In comparison with the smallest quartile of heart volume, heart volume in the second quartile (520.1-600 cc) was also associated with not meeting the MHD goal (OR, 0.57; 95% CI, 0.38-0.86; *P* = .007), but this effect did not persist with larger heart volumes in the third (600.1-690 cc: OR, 0.92; 95% CI, 0.60-1.42; *P* = .71) or fourth (>690 cc: OR, 0.99; 95% CI, 0.64-1.52; *P* = .949) quartiles. Treatment technique (IMRT vs 3D-CRT: OR, 0.77; 95% CI, 0.57-1.04; *P* = .09), year of treatment, BMI category, treatment at an academic center, and receipt of chemotherapy were not associated with either meeting or not meeting the MHD goal (Fig. 2).

During the era including composite heart dose and PTV coverage goals (2021-2022), treatment with motion management (OR, 1.89; 95% CI, 1.12-3.21; *P* = .018) or prone positioning (OR, 3.71; 95% CI, 1.73-7.95; *P* = .0008) were associated with meeting the combined goal, whereas breast volume in the third quartile (1015.1-1440 cc: OR, 0.40; 95% CI, 0.17-0.97; *P* = .04) or fourth quartile (>1440 cc: OR, 0.34; 95% CI, 0.13-0.91; *P* = .031) and treatment at an academic center (OR, 0.36; 95% CI, 0.22-0.67; *P* = .0009) were associated with not meeting the combined goal. Treatment technique (IMRT vs 3D-CRT: OR, 0.80; 95% CI, 0.48-1.33; *P* = .39), receipt of chemotherapy (OR, 0.84; 95% CI, 0.046-1.56; *P* = .58), hormone therapy (OR, 0.81; 95% CI, 0.46-1.35; *P* = .42), BMI category, and heart volume quartile were not associated with either meeting or not meeting the combined metric (Fig. 3). Lumpectomy bed boost was not included in this analysis as the composite metric goals during this period were based on the whole breast plan alone.

## Discussion

In this analysis, we found high compliance with aggressive cardiac dose goals in the treatment of early-stage left-sided breast cancer within our CQI framework despite tightening

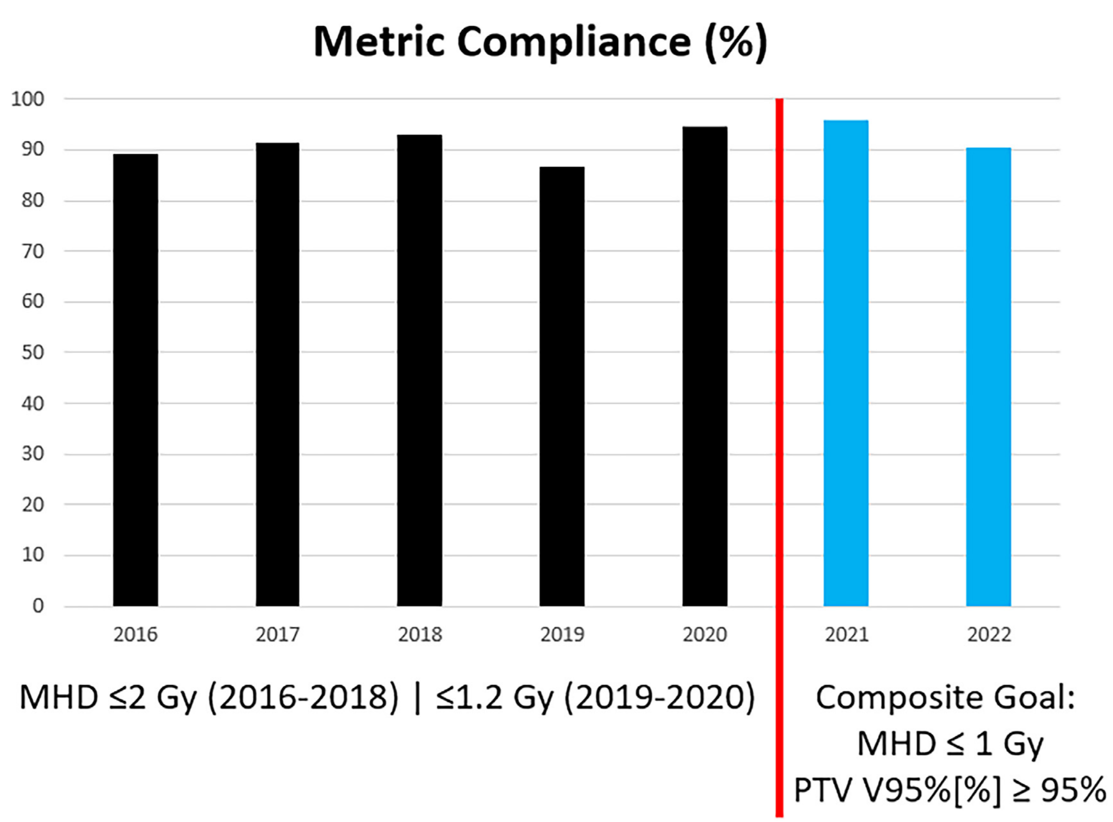


**Fig. 1.** Annualized compliance rates with cardiac dose goal for treatment plans from 2016 to 2022. Red bar indicates transition from mean heart dose to composite mean heart dose and planning target volume coverage goals.

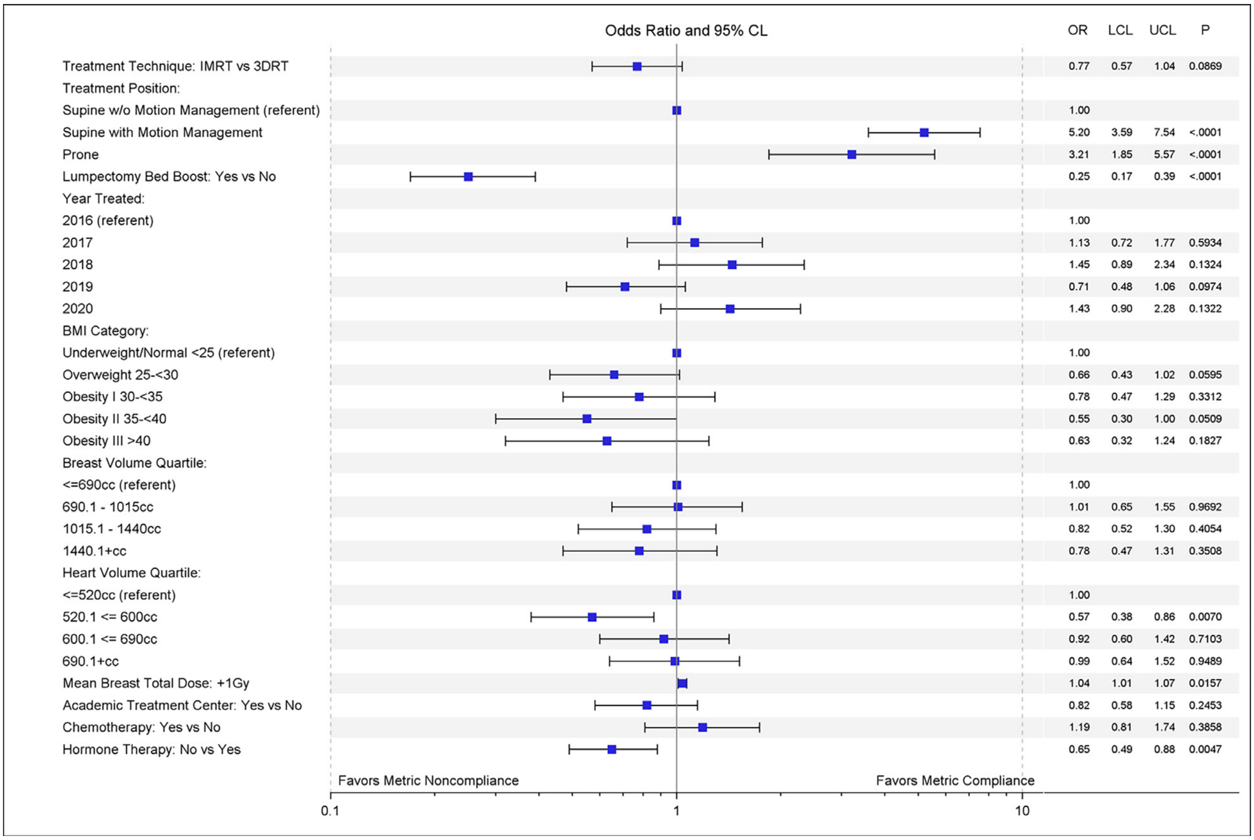


**Fig. 2.** Forest plot demonstrating covariates associated with meeting or not meeting the mean heart dose goals in place from 2016 to 2020.

of these goals and addition of a concurrent PTV coverage goal over time. Treatment using motion management or prone positioning were associated with meeting the cardiac dose goals in both periods analyzed. To our knowledge, this is the largest study to demonstrate feasibility of attaining such aggressive cardiac dose goals while maintaining target coverage.

Cardiac radiation exposure during the treatment of breast cancer has decreased over time with increasing awareness of the increased risk of cardiac events after radiation therapy. For instance, older studies estimated MHDs as high as 10 Gy for patients with left-sided disease and unfavorable anatomy.[3] This has improved substantially in more contemporary cohorts. One recent systematic literature review of studies performed from 2010 to 2015 demonstrated an average MHD of 4.4 Gy,[4] and another detailed single institution series in a similar timeframe reported a median MHD of 2.37 Gy.[5] Our own analysis of cardiac dose exposure for patients treated within MROQC revealed improvement of median MHD from 2.19 Gy in 2012 to 1.65 Gy in 2015 for left-sided node negative cases,[14] forming the basis for our cardiac dose constraint of an MHD < 2 Gy for left-sided cases beginning in 2016. This was subsequently tightened to <1.2 Gy in 2018 without a decrement in compliance. The high compliance rates for these aggressive MHD goals suggest that MHDs substantially lower than historical benchmarks are often achievable with contemporary treatment techniques. Data from our multivariable analyses suggest that increasing utilization of prone positioning and breath hold techniques are highly useful for attaining these more aggressive cardiac goals. Interestingly, in this cohort of patients the absence of planned adjuvant hormone therapy was associated with not meeting the MHD goal, possibly indicating a subset of patients with more aggressive, hormone receptor−negative disease where the risk-benefit calculation may have favored more aggressive whole breast coverage at the expense of cardiac exposure.

In order to optimize the balance of tumor coverage and cardiac dose reduction, our continuous quality initiative goal for cardiac dose exposure was updated in 2021 to a combined MHD and PTV coverage goal, as detailed in the Methods and Materials section. Similar to the MHD-only goal, use of breath-hold technique and prone positioning was associated with meeting the combined MHD/PTV goal. Factors generally associated with more complicated patient populations (ie, patients with the highest breast volumes or those treated at academic centers) were associated with not meeting the combined MHD/PTV coverage goal. However, despite further restricting the MHD goal to ≤1 Gy and incorporation of a 95% PTV coverage goal, compliance remained very high, with >90% of plans meeting these goals in both 2021 and 2022.

Although the dosimetric data included herein were prospectively collected, some inherent limitations to population-based data exist in this analysis. One such limitation is

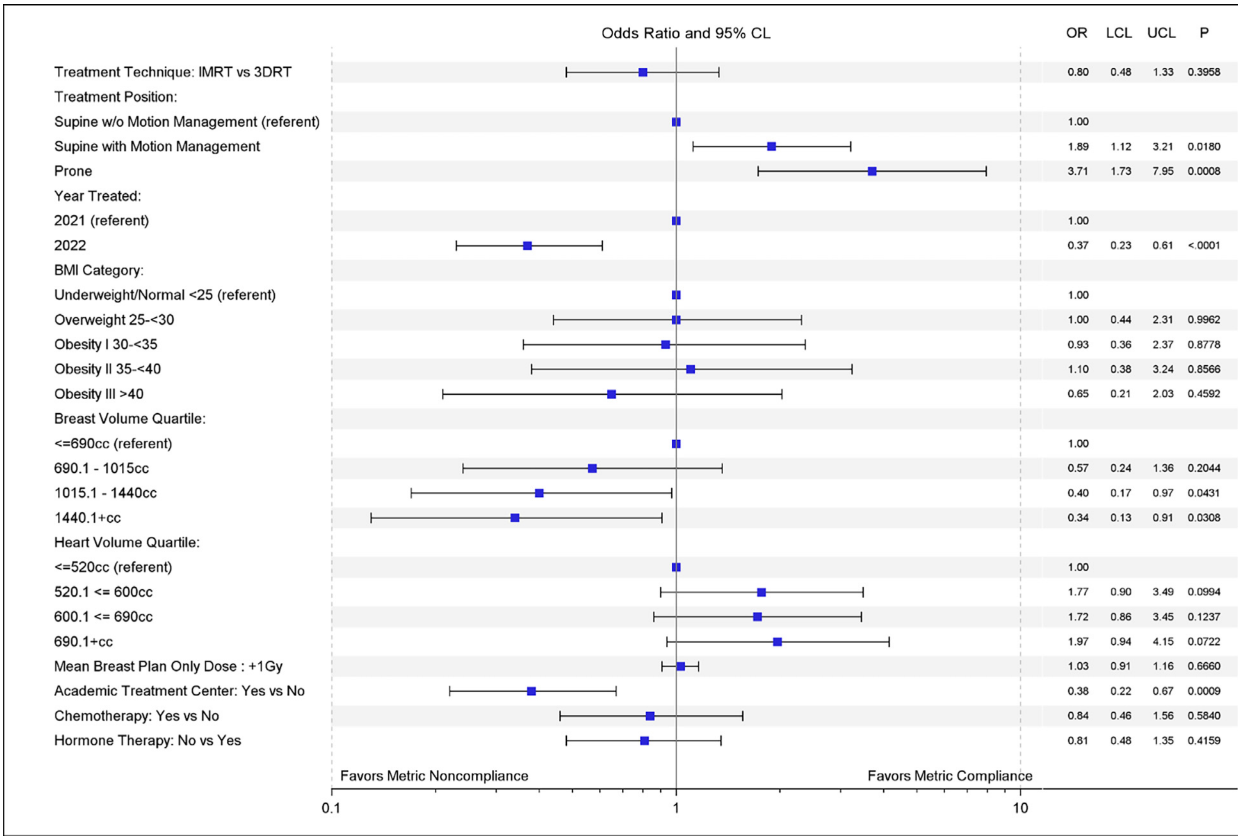


**Fig. 3.** Forest plot demonstrating covariates associated with meeting or not meeting the composite mean heart dose and planning target volume goals in place from 2021 to 2022.

the lack of details regarding the rationale for specific trade-offs during treatment planning for individual treatment plans that were unable to meet planning goals. However, this was only the case for <10% of treatment plans. Another limitation is that long-term follow-up for major adverse cardiac events or oncologic outcomes is not feasible to collect within MROQC. Both the long-term oncologic outcomes of treatment for early-stage breast cancer and the dose-response relationship between MHD and future risk of cardiac events are well defined elsewhere and unlikely to differ substantially in this population of patients. Additionally, although our multivariable models accounted for a wide range of variables that may influence outcomes, it remains possible there are unknown confounders that remain unaccounted for, as is the case with all population-based data. Finally, although this study focused on MHD, discussions are underway with member institutions regarding the possibility of future studies focused on analyzing dose to cardiac substructures.

As data from contemporary clinical trials mature, a more nuanced understanding of the well-established association between cardiac dose and clinical cardiac endpoints is likely to emerge. For instance, Radiation Therapy Oncology Group (RTOG) 1005 included an endpoint directed at describing cardiac events posttreatment, reporting of which will likely also involve careful description of cardiac exposure in these patients. Similarly, NRG BR007 is collecting prospective data on heart dose, including standardized contouring of the heart and protocoled cardiac constraints of MHD $\leq$ 1.6 Gy and V16 Gy(%) $\leq$ 5% for left-sided cases, as well as encouraging respiratory management techniques for left-sided cases and scheduled cardiac toxicity assessment for the first 5 years of follow-up. Additionally, the United Kingdom FAST-FORWARD trial reported planning constraints of V2 Gy(%) $\leq$ 30% and V10 Gy(%) $\leq$ 5% for the control arm and V1.5 Gy (%) $\leq$ 30% and V7 Gy(%) $\leq$ 5% for the experimental arm, raising the possibility of a future report describing the cardiac dose exposure in these patients. Importantly, as our understanding of the effects of cardiac radiation exposure continues to evolve, it is becoming increasingly apparent that even very low cardiac dose exposure may have adverse consequences,[16] emphasizing the critical importance of future studies on this topic and the importance of efforts focused on maximal reductions in heart dose while maintaining target coverage, such as in the present report.

## Conclusion

In this study, we found that aggressive cardiac dose reduction is often achievable in patients being treated with adjuvant whole breast radiation therapy for early-stage left-sided breast cancer, and that this can be achieved without sacrificing target coverage in the majority of cases. Advanced treatment techniques including breath hold and prone positioning are valuable tools for achieving these goals. This highlights the utility of a CQI framework in driving progressive refinement of treatment techniques to achieve increasingly complex planning goals and ultimately maximize quality of patient care.

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