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Low cardiac and left anterior descending coronary artery dose achieved with left-sided multicatheter interstitial-accelerated partial breast irradiation.

JS Witt¹, RW Gao², LJ Sudmeier³, SA Rosenberg⁴, DM Francis¹, CR Wallace¹, RK Das¹, and BM Anderson⁵

¹Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI. ²Radiation Oncology, University of Minnesota Medical School, Minneapolis, MN.

³Department of Radiation Oncology, Emory University School of Medicine, Atlanta, GA.

⁴Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL. ⁵Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI. anderson@humonc.wisc.edu.

Abstract

PURPOSE: Studies have shown that an additional mean dose of 1 gray to the heart can increase the relative risk of cardiac events. The purpose of this study was to quantify the dose delivered to the heart and left anterior descending artery (LAD) in a series of patients with left-sided breast cancer or DCIS treated with multi-catheter accelerated partial breast irradiation (MC-APBI) at a single institution.

METHODS AND MATERIALS: Patients with left-sided breast cancer or DCIS treated consecutively from 2005 to 2011 with MC-APBI were retrospectively identified. Cardiac and LAD contours were generated for each patient. Cardiac dosimetry and distance to the planning target volume (PTV) were recorded. Patient health records were reviewed and cardiac events were recorded based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

RESULTS: Twenty consecutive patients with left-sided breast cancer treated with MC-APBI were retrospectively identified. Median follow-up was 41.4 months. Mean EQD2 delivered to the heart and LAD were 1.3 (standard deviation: 0.7, range: 0.2–2.9) and 3.8 (standard deviation: 3.0, range: 0.4–11.3) Gy, respectively. There was an inverse linear relationship ($R^2=0.52$) between heart-to-lumpectomy cavity distance and mean heart EQD2. One patient (5%) experienced symptomatic cardiac toxicity.

CONCLUSIONS: MC-APBI consistently delivers average doses to the heart and LAD that are similar to those achieved in most series with deep inspiration breath-hold, and lower than free breathing radiotherapy techniques. Distance from the heart to the lumpectomy cavity and the availability of other heart-sparing technologies should be considered to minimize the risk of cardiac toxicity.

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Keywords

breast cancer; multi-catheter accelerated partial breast irradiation; cardiac dose; cardiac toxicity; left anterior descending artery dose

Introduction

Adjuvant radiation therapy (RT) is the standard of care for women receiving breast-conserving surgery for early-stage breast cancer (BC). Randomized trials demonstrate that RT following partial mastectomy reduces locoregional recurrence and BC-related death (1,2). However, long-term follow-up in these trials reveals that incidental irradiation to the heart may increase the rate of cardiac disease (1,3).

A large population-based case-control study of women undergoing RT for BC demonstrated a linear relationship between mean heart dose and subsequent risk of major coronary events (4). Each additional gray (Gy) of mean dose was found to increase the relative risk of cardiac events by 7.4%. There was no identified threshold dose, implying that there is no safe level of cardiac dose, and this effect was present in women with and without pre-existing cardiac risk factors. This increase in cardiac risk is particularly relevant in the BC patient population, as long term BC-specific survival continues to rise. The most recent SEER estimate of 5-year survival in patients with localized BC is 98.7% (5). Therefore, women should undergo adjuvant therapies that minimize their risk for long-term toxicities.

Accelerated partial breast irradiation (APBI) is an attractive alternative to whole breast irradiation (WBI) for select women, as it shortens treatment duration and can reduce radiation exposure to normal tissues. Prospective trials have shown that interstitial multi-catheter APBI (MC-APBI) achieves equivalent local control compared to WBI (6), while decreasing the risk of late skin side effects (7). Alternatively, prior studies have shown that respiratory gating and deep inspiration breath-hold (DIBH) can help minimize incidental cardiac irradiation in women receiving WBI (8–11). However, quantitative data on heart dose in patients undergoing MC-APBI are limited. In the current study, we sought to quantify dose to the heart and left anterior descending coronary artery (LAD) in patients treated with MC-APBI at a single institution.

Methods and materials

Patient selection

All patients undergoing MC-APBI from 2011 to 2015 for left-sided BC or ductal carcinoma in situ (DCIS) at our institution were retrospectively identified. Patients underwent breast-conserving surgery and sentinel lymph node evaluation. Following surgery, patients were counseled regarding their options for adjuvant radiation therapy and were offered APBI in accordance with the ASTRO 2009 consensus guidelines (12). Appropriate patients who preferred this approach were subsequently treated with MC-APBI. All treated patients had negative surgical margins, pathologically negative nodal status, and appropriate tumor size (<3 cm).

Procedure and treatment details

All patients underwent computed tomography (CT) simulation prior to the day of catheter placement for the purposes of tumor bed localization. On the day of catheter placement, patients were positioned supine with moderate sedation. A stereotactic template was placed on the breast, and a variable number of interstitial catheters were inserted such that adequate target coverage could be achieved. CT simulation was performed and images were transferred to the Oncentra planning software (Elekta AB, Stockholm, Sweden).

The lumpectomy cavity, chest wall, and an external skin contour were contoured. The lumpectomy cavity contour included all visible surgical clips within the clinical target volume (CTV). There were no constraints placed on the heart or LAD, and the heart was not contoured at the time of treatment planning. A planning target volume for treatment evaluation (PTV_{eval}) was generated by expanding the lumpectomy cavity CTV by 1.5 cm, and confining it within the bounds of the chest wall and within 5 mm of the skin surface. The chest wall was defined as the ribs and pectoral muscles underlying the breast.

Treatment planning goals were adapted from the GEC ESTRO and ASTRO guidelines (12,13). Plans were evaluated based on PTV coverage, dose heterogeneity index (V100 – V150/V100), and dose to the chest wall. The goal for PTV coverage was typically a D95 of 95% or greater, with a dose to skin <100% of prescription, and a dose to any nearby ribs <145%. Target dose heterogeneity index was >0.65. Patients were treated to a dose of 34 Gy in 10 twice daily fractions separated by at least 6 hours using a high dose rate (HDR) iridium-192 source. Representative MC-APBI plans are visible in Figure 1. This shows example cases of patients with a lumpectomy cavity and PTV_{eval} that are far (Figure 1A) and close (Figure 1B) to the heart.

Dosimetric analysis

To retrospectively determine dose to the heart and LAD, treatment-planning CTs were evaluated in the Oncentra planning software (Elekta, Stockholm, Sweden). The LAD and pericardium were contoured as per the methodology previously described by Feng et al (14). Prior studies have postulated that the LAD may be a possible area of radiation specific coronary stenosis in women treated with left sided whole breast radiation (15), and this was therefore chosen as a second organ at risk. Heart to PTV_{eval} and LAD to PTV_{eval} distances were defined on the basis of the closest distance between contours using the linear measuring tool within Oncentra. Dose volume histograms were generated for each of these structures, from which the mean and maximum dose was calculated. These were then normalized by calculating the equivalent dose in 2-Gy fractions (EQD2) using the formula $nd[(d+\alpha/\beta)\div(2+\alpha/\beta)]$, where n was the number of fractions, d was the dose to the heart per fraction (in Gy), and α/β was 3.

Evaluation of cardiac toxicity

The electronic health record was retrospectively reviewed until the date of last follow-up for each individual patient. Baseline cardiac risk factors including diagnoses of coronary artery disease, diabetes mellitus, hyperlipidemia, hypertension, and smoking status were identified at the time of original consultation. Cardiac toxicity was evaluated and graded based on

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All cardiac events occurring after MC-APBI were recorded for as long as follow-up was available.

Results

Patient, tumor, and treatment characteristics

Twenty patients were treated with MC-APBI for left-sided BC from 2011 to 2015. Median age at treatment was 61.7 years. Median follow-up was 41.4 months (range, 12.6–74.9). Twelve patients received adjuvant hormonal therapy, 1 of whom switched from anastrozole to letrozole due to arthropathy. The remaining 7 patients with hormone receptor-positive disease declined endocrine therapy. One patient was HER2-amplified but declined adjuvant trastuzumab. No other systemic agents were given in the adjuvant setting. Most patients (75%) had at least one baseline cardiac risk factor, the most common of which was hypertension (35%). Only 1 (5%) patient carried a diagnosis of coronary artery disease at the time of consultation. A total of 5 (25%) patients were either former or current smokers, 5 (25%) had hyperlipidemia, and 3 (15%) were diabetics. Additional patient, tumor, and systemic therapy characteristics are shown in Table 1.

Cardiac dose

Dose and EQD2 to the heart and LAD are shown in Table 2. Plots of mean EQD2 to the heart and LAD are displayed in Figure 2. Mean cardiac EQD2 decreased in an approximately linear distribution, with increased distance from the heart to the lumpectomy cavity ($R^2=0.52$) (Figure 3). Mean minimum linear distance from the heart to the lumpectomy cavity was 4.9 cm (standard deviation: 3.0, range: 0.9–13.0). Mean minimum distance from the heart to the PTV_{eval} was 3.3 cm (standard deviation: 2.5, range: 0.8–11.0). Median PTV_{eval} volume was 106 cm³ (range, 18.3–203.4). There was no association identified between PTV_{eval} volume and either heart or LAD dose. The smallest PTV_{eval} was within the context of subpectoral breast augmentation. A median of 15 (range, 6–22) interstitial catheters were implanted per patient.

Cardiac toxicity

Throughout the follow-up period, two patients experienced post-treatment cardiac toxicity. The first had asymptomatic grade 1 restrictive cardiomyopathy diagnosed incidentally on echocardiogram that was performed as part of survivorship surveillance. This occurred 40 months from MC-APBI. Of note, this patient had a history of diffuse large B-cell lymphoma of the anterior mediastinum treated with mini-mantle field radiation to a total dose of 45 Gy approximately 16 years prior to MC-APBI. This was her first surveillance echocardiogram, and therefore baseline cardiac function following her mantle radiation was unknown. Mean heart and max LAD EQD2 in this patient were 0.9 and 2.7 Gy, respectively. Her heart-to-lumpectomy cavity distance was 2.8 cm. Another patient had grade 2 acute coronary syndrome diagnosed 32 months following RT. Subsequent stress test demonstrated regional wall motion abnormalities in the mid-inferolateral, mid-anterolateral, and apical lateral walls. Review of her dosimetry showed a mean heart and max LAD EQD2 of 2.9 and 17 Gy, respectively. Minimum heart-to-lumpectomy cavity distance in this patient was 1.9 cm. She

also had baseline hyperlipidemia and a 5 year history of hormone replacement therapy after onset of menopause.

Discussion

Exposure of the heart to ionizing radiation increases the risk for subsequent cardiac disease. The large population-based study performed by Darby *et al.* determined that relative risk of major coronary events increases linearly at a rate of 7.4% per mean Gy to the heart (4). Minimizing cardiac dose is thus an important consideration for women undergoing adjuvant radiation therapy for left-sided BC. Here, we report the dose delivered to the heart and LAD in a series of twenty patients treated at our institution with MC-APBI following partial mastectomy for left-sided BC. Our findings demonstrate that MC-APBI treatment plans have low mean doses to the heart and LAD, comparable to other modern techniques. Some patients treated with whole breast radiation utilizing DIBH or prone position can achieve similar cardiac doses to those reported here. This largely depends on patient anatomy, and therefore not all patients can achieve low cardiac dose with these techniques. This clinical reality is reflected in contemporary trials. For example, in RTOG 1005, a phase III trial examining accelerated WBI with concomitant boost versus standard WBI with a sequential boost, acceptable mean heart dose can be as high as 5 Gy in the standard arm (18). In our series, the mean heart dose was <3 Gy for all patients, including those whose lumpectomy cavities were in very close proximity to the heart, without contouring the heart or otherwise adapting the dose distribution during the treatment planning process. This highlights the ability of brachytherapy to consistently deliver a low dose to the heart.

We performed a cross-study comparison of cardiac doses in our group to those of previously published series (Table 3), which assesses a variety of APBI and WBI techniques. Relative to other approaches, MC-APBI appears to have a relatively similar level of cardiac exposure. Several large series have shown a significant reduction in cardiac dose with the use of DIBH versus FB in the setting of WBI (8,20,21). In our study, mean heart EQD2 with MC-APBI was similar to that previously observed with DIBH-WBI (8,20). However, Holliday *et al.* performed a single institution direct comparison of DIBH-WBI to MC-APBI and found that DIBH-WBI resulted in a statistically significant reduction in biologically effective dose to the heart and coronary vessels. The clinical significance of this difference is unknown, given the low heart doses for both patient cohorts, and the cardiac doses reported with the DIBH-WBI plans are lower than other published series. Moran *et al.* investigated the benefit of DIBH using both WBI and APBI and found that DIBH spares the heart in both scenarios (19), with plans using DIBH in combination with external beam radiation therapy achieving the lowest cardiac exposure. Institutional differences in contouring technique and willingness to accept decreased breast tissue coverage at the margin likely contribute to the observed variation between the reported series. Alternatively, APBI target volume definitions are more rigid and less prone to institutional variation, leading to more consistent mean cardiac dose between reported cohorts. Further investigation is warranted to compare the relative cardiac risk of MC-APBI and DIBH-WBI, and to identify patient and tumor characteristics that optimize cardiac dose for both approaches.

Identification of patients who benefit the most from DIBH remains a challenge. Previous investigators have attempted to identify an anatomic metric to guide patient selection. In their 35-patient cohort, Rochet *et al.* examined a possible relationship between cardiac contact distance and DIBH-associated benefit (21), but did not find a correlation. In the present study, we confirmed the intuitive notion that cardiac dose is inversely proportional to heart-to-lumpectomy cavity distance. Therefore, while heart doses were consistently low, women whose lumpectomy cavities are remote from the heart may be found to benefit most from treatment with brachytherapy.

There are several limitations to this study. Primarily, the small number of patients precludes any significant evaluation of cardiac toxicity. As noted in the Darby *et al.* study, the increase in major cardiac events was not seen until beyond a 5-year period following exposure, which is longer than the median follow-up reported here. However, 9 patients were beyond the 5 year follow-up period with no cardiac toxicity reported. Even with longer follow up, the low cardiac dose achieved here with MC-APBI is unlikely to generate a significant increase in cardiac-related events.

Conclusion

In conclusion, results from this single institution dosimetric analysis of women treated with MC-APBI for left-sided BC demonstrate that MC-APBI delivers a low dose to both the heart and LAD. Especially in women with favorable anatomic and pathologic features, MC-APBI is a safe, convenient, and effective mode of radiation delivery. Contouring cardiac structures at the time of APBI planning should be performed to minimize cardiac dose in this patient population. Study of patient anatomic factors, such as distance from the heart to the lumpectomy bed, may help inform individualized patient selection of techniques that result in lowest possible cardiac dose.

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Figure 1. Representative multi-catheter accelerated partial breast irradiation plan for a patient with a lumpectomy cavity (light blue) and PTV_{eval} (red) that are (A) far from the heart and (B) near the heart. Figure A shows a representative linear distance measurement.

Figure 2.

Dose to the heart and left anterior descending artery. Each point represents the measurement from a single patient's plan. The bars represent mean and standard error of the mean.

Figure 3. Mean cardiac equivalent dose in 2 Gy fractions (EQD2) versus minimum linear distance from heart to lumpectomy cavity. Each point represents cardiac EQD2 for a single patient.

Table 1

Patient, tumor, and systemic therapy characteristics

Age at treatment (years)	
Median (range)	61.7 (46.7-78.0)
Histology, n	
Invasive ductal	14
Invasive lobular	1
DCIS	5
T stage, n	
Tis	5
T1a	1
T1b	2
T1c	11
T2	1
LVI, n	3
Nottingham grade, n	
1	9
2	9
3	2
Molecular subtype	
Luminal A	17
Luminal B	2
Triple negative	1
Tumor location, n	
UOQ	7
UIQ	5
LOQ	5
LIQ	2
Central	1
Adjuvant endocrine therapy, n	
Tamoxifen	3
Anastrozole	5
Letrozole	3
Anastrozole and letrozole	1

Abbreviations: DCIS = ductal carcinoma in situ; LVI = lymphovascular invasion, UOQ = upper outer quadrant; UIQ = upper inner quadrant; LOQ = lower outer quadrant; LIQ = lower inner quadrant

Table 2

Dose and EQD2 to the heart and left anterior descending artery in patients undergoing multi-catheter accelerated partial breast irradiation

Heart mean dose (Gy)	
Mean $\pm$ SD	2.0 $\pm$ 1.1
Median (range)	2.2 (0.3-4.3)
Heart mean EQD2 (Gy)	
Mean $\pm$ SD	1.3 $\pm$ 0.7
Median (range)	1.4 (0.2-2.9)
LAD mean dose (Gy)	
Mean $\pm$ SD	5.1 $\pm$ 3.5
Median (range)	5.0 (0.7-13.1)
LAD mean EQD2 (Gy)	
Mean $\pm$ SD	3.8 $\pm$ 3.0
Median (range)	3.5 (0.4-11.3)
LAD max dose (Gy)	
Mean $\pm$ SD	7.6 $\pm$ 5.6
Median (range)	6.8 (0.7-19.4)
LAD max EQD2 (Gy)	
Mean $\pm$ SD	6.3 $\pm$ 5.6
Median (range)	5.0 (1.2-19.4)

Abbreviations: Gy = gray; SD = standard deviation; EQD2 = equivalent dose in 2 Gray fractions; LAD = left anterior descending artery

Comparison of cardiac dose in patients receiving adjuvant irradiation using various delivery techniques following breast-conserving surgery for left-sided breast cancer

Table 3

Patients	Current study	Holliday <i>et al.</i>	Holliday <i>et al.</i>	Moran <i>et al.</i>	Nissen <i>et al.</i>	Swanson <i>et al.</i>	Nissen <i>et al.</i>	Swanson <i>et al.</i>
Technique	20	50	50	10	144	87	83	87
Total dose/fractions	MC-APBI	SC-APBI	DIBH-WBI+TB	DIBH-EB-APBI	DIBH-WBI	DIBH-WBI	FB-WBI	FB-WBI
Heart mean dose (Gy)	34/10	34/10	50/25+10/5	38.5/10	50/25	50/25	50/25	50/25
Mean $\pm$ SD	2.0 $\pm$ 1.1	2.2 $\pm$ 0.9	0.9 $\pm$ 0.4	0.4 $\pm$ NR	2.7 $\pm$ NR	2.5 $\pm$ NR	5.2 $\pm$ NR	4.2 $\pm$ NR
Heart mean EQD2 (Gy)								
Mean $\pm$ SD	1.3 $\pm$ 0.7	1.4 $\pm$ 0.6	0.6 $\pm$ 0.2	0.2 $\pm$ NR	1.8 $\pm$ NR	1.6 $\pm$ 0.2	3.7 $\pm$ NR	2.9 $\pm$ NR
LAD mean dose (Gy)								
Mean $\pm$ SD	5.1 $\pm$ 3.5	5.1 $\pm$ 2.6	3.8 $\pm$ 2.0	0.7 $\pm$ NR	NR	NR	NR	NR
LAD mean EQD2 (Gy)								
Mean $\pm$ SD	3.8 $\pm$ 3.0	3.6 $\pm$ 1.7	2.5 $\pm$ 1.3	0.4 $\pm$ NR	NR	NR	NR	NR
LAD max EQD2 (Gy)								
Mean $\pm$ SD	7.6 $\pm$ 5.6	NR	NR	2.2 $\pm$ NR	NR	NR	NR	NR
LAD max EQD2 (Gy)								
Mean $\pm$ SD	6.3 $\pm$ 5.6	NR	NR	1.4 $\pm$ NR	NR	NR	NR	NR

Note: In the Swanson *et al* analysis, only patients with DIBH plans that resulted in lower cardiac dose compared to FB were included. Abbreviations: MC = multi-catheter; APBI = accelerated partial breast irradiation; SC = single catheter; DIBH = deep inspiration breath-hold; WBI = whole breast irradiation; TB = tumor bed boost; EB = external beam; FB = free breathing; SD = standard deviation; EQD2 = equivalent dose in 2 Gray fractions; LAD = left anterior descending artery; NR = not reported