Original paper

Comparison of radiation dose to the left anterior descending artery by whole and partial breast irradiation in breast cancer patients

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Abstract

Purpose: Breast conserving surgery (BCS) followed by whole breast irradiation (WBI) is the standard of care for breast cancer patients. However, there is a risk of coronary events with WBI therapy. In this study, we compared the radiation dose in the left anterior descending artery (LAD) in patients receiving partial breast irradiation (PBI) with WBI.

Material and methods: We evaluated consecutive patients who underwent adjuvant radiotherapy after BCS between October 2008 and July 2014. Whole breast irradiation patients received 50 Gy in fractions of 2 Gy to the entire breast. Partial breast irradiation was performed using multicatheter brachytherapy at a dose of 32 Gy in eight fractions. The mean and maximal cumulative doses to LAD were calculated. The radiotherapeutic biologically effective dose of PBI was adjusted to WBI, and radiation techniques were compared.

Results: Of 379 consecutive patients with 383 lesions receiving radiotherapy (151 WBI and 232 PBI lesions), 82 WBI and 100 PBI patients were analyzed. In WBI patients, the mean and maximal cumulative doses for left-sided breast cancer (2.13 ± 0.11 and 8.19 ± 1.21 Gy, respectively) were significantly higher than those for right-sided (0.37 ± 0.02 and 0.56 ± 0.03 Gy, respectively; $p < 0.0001$). In PBI patients with left-sided breast cancer, the doses for tumors in inner quadrants or central location (2.54 ± 0.21 and 4.43 ± 0.38 Gy, respectively) were significantly elevated compared to outer quadrants (1.02 ± 0.17 and 2.10 ± 0.29 Gy, respectively; $p < 0.0001$). After the adjustment, the doses in PBI patients were significantly reduced in patients with tumors only in outer quadrants (1.12 ± 0.20 and 2.43 ± 0.37 Gy, respectively; $p = 0.0001$).

Conclusions: Tumor control and dose to LAD should be considered during treatment since PBI may reduce the risk of coronary artery disease especially in patients with lateral tumors in the left breast.

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Key words: brachytherapy, breast cancer, coronary artery, partial breast irradiation, radiation dosage.

Purpose

Breast cancer is one of the most common cancers in women worldwide. The incidence is lower in Asia than in North America and Western Europe, but it is rising and expected to continue to increase for the next 10 years [1]. The rate of detection of early disease is also increasing because of breast cancer awareness and widespread mammography screening, and breast-conserving therapy has been gradually accepted as a standard procedure in Asian countries [2-4]. Breast conserving therapy consists of breast conserving surgery (BCS), followed by adjuvant breast irradiation, and whole breast irradiation (WBI) is generally recommended as radiation therapy [5,6]. However, the 'Early Breast Cancer Trialists Collaborative Group' reported excessive mortality from heart disease in patients receiving radiation therapy [7]. In fact, cardiac mortality is reported to be higher in left-sided breast cancer patients than in right-sided breast cancer patients because WBI can deliver higher cardiac radiation doses in patients with left-sided breast cancer [8-10]. Therefore, further investigation is required that focuses on the reduction of radiation dose to the heart during left-sided breast radiotherapy.

Partial breast irradiation (PBI) as an alternative to WBI was evaluated in several phase III trials [11-15] – it allows dose delivery to the tumor bed and a margin of 1-2 cm and may reduce the dose to the heart. The highest radiation dose is likely to be delivered to the anterior heart, including the left anterior descending coronary artery (LAD), which is one of the typical sites for ischemic heart disease [16]. In this study, we retrospectively reviewed

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patients receiving PBI and WBI after BCS and evaluated radiation doses to the whole LAD to compare the two different radiation techniques.

Material and methods

Patients

We evaluated consecutive patients who underwent adjuvant radiotherapy after BCS from October 2008 (when the prospective observational study on PBI using multicatheter brachytherapy was initiated) to July 2014. Among them, we retrospectively evaluated radiation exposure to LAD. The radiation doses to LAD were evaluated in right- and left-sided breast cancer patients receiving WBI. Multicatheter PBI was considered to be an alternative to WBI in patients meeting the eligibility criteria of age ≥ 40 years, histologically documented breast cancer, unifocal disease, maximum tumor diameter ≤ 3.0 cm on pre-operative imaging, sentinel nodes negative for metastases, and no prior treatment, including chemotherapy and hormonal therapy [17]. In patients receiving PBI, only the left-sided breast cancer patients were selected for analysis because the radiation dose to LAD is virtually zero for the right-sided breast cancer patients.

Radiation techniques

In WBI, patients received an external beam radiation therapy (EBRT) with a total dose of 50 Gy in fractions of 2 Gy to the entire breast. All treatment plans were created using a three-dimensional treatment planning system (Philips' Pinnacle 3 treatment planning system, Fitchburg, WI, USA). The surgical cavity and the residual breast parenchyma were included in the clinical target volume (CTV). The planning target volume (PTV) included an 8 mm anterior and a 6 mm posterior CTV borders. Patients with risk factors, such as positive margins and young age (< 40 years old), generally received a subsequent 10 Gy boost using electrons to the tumor bed that included a 1 cm margin of normal tissue. Regional nodal irradiation was added in patients with ≥ 4 positive nodes. However, patients receiving a boost or regional nodal irradiation were excluded from this analysis.

In PBI, various approaches have been reported using different brachytherapy techniques [18]. Interstitial multicatheter brachytherapy was initiated, which had been used with cosmetic success and long-term disease control [18,19]. The details of our multicatheter brachytherapy with CT and template guidance [20,21] have been introduced elsewhere [17]. In brief, applicators for the introduction of iridium wires were inserted following the simulation in preoperative planning by enhanced computed tomography (CT). The PTV included the surgical cavity delineated by ligating clips plus a 10-20 mm margin. The maximum dose to the skin and chest wall was kept to less than 75% of the prescription dose. Dose-volume histograms (DVH) were provided by postoperative CT. Partial breast irradiation was performed in an accelerated fashion with a dose of 32 Gy in eight fractions over 5-6 days.

Contouring method and evaluation of the dose

The whole LAD in patients receiving WBI or PBI were retrospectively contoured using plain CT images by radiation specialists, which were taken for the radiation planning. In principle, LAD was outlined from its origin to each utmost visible end through the scrutiny of each planning CT image. In uncertain cases, to determine LAD itself, each LAD was identified with reference to the preoperative enhanced CT images in PBI patients.

The mean and maximal cumulative doses delivered to the whole LAD in patients treated by two different radiation techniques were calculated. To compare the clinically relevant doses between the two distinct treatment schedules, the absolute doses were adjusted with the total prescribed dose and fraction size. Biological effective dose (BED) calculations for each coronary artery (unadjusted for treatment time as a presumed late-responding normal tissue with no acute proliferative response) were performed with an $\alpha/\beta = 3.4$ for each patient receiving PBI [22].

Statistics

The χ^2 test was used to analyze associations among categorical variables between treatment groups. Comparisons in the LAD doses were made between the WBI patients and PBI patients with lateral tumors, and between the WBI patients and PBI patients with central or medial tumors. Statistical analysis of continuous variables was performed by using Student's *t*-test. A $p < 0.05$ was considered statistically significant. Statview 5.0 (SAS Institute Inc. Cary, NC, USA) was used to perform statistical analyses. All patients provided written informed consent for inclusion in the study, and the institutional review board approved the observational study of PBI patients.

Results

A total of 379 patients with 383 lesions received adjuvant radiotherapy (151 lesions in WBI and 232 lesions in PBI patients). Among them, we retrospectively reviewed 182 patients to evaluate radiation exposure to the whole LAD. Eighty two patients who underwent WBI were randomly selected during the above mentioned period of time. Forty two patients had right-sided breast cancer and forty patients had left-sided cancer. On the other hand, 100 consecutive patients whom were administered PBI for left-sided breast cancer between September 2009 and December 2013 were selected for the analysis. Fifty five patients had lateral tumors and forty five had medial or central tumors. Table 1 lists selected patient characteristics. The mean age of WBI patients (53.0 years) was lower than that of PBI patients, but not significantly (55.5 years, $p = 0.16$). In the selected PBI patients, the mean number of catheters and implant planes was 6.1 (3-12) and 1.6 (1-3), respectively. Table 2 shows, according to tabular DVH, the treatment related variables and dosimetric parameters, including breast and cavity volumes, organs at risk, PTV, volume of tissue encompassed by the 100% (V_{100}) and 150% (V_{150}) isodose line, and dose non-uniformity ratio (DNR) – (V_{150}/V_{100}).

The mean and maximal cumulative doses to the whole LAD with WBI for left-sided breast cancer (2.13 ± 0.11 and 8.19 ± 1.21 Gy) were significantly higher than those for right-sided cancer (0.37 ± 0.02 and 0.56 ± 0.03 Gy; $p < 0.0001$; Table 3). In the PBI patients with left-sided breast cancer, the mean and maximal cumulative doses to the whole LAD were 1.71 ± 0.15 and 3.15 ± 0.26 Gy, respectively. However, these doses were influenced by the tumor location because of minimizing radiation exposure to the surrounding normal tissues. The mean and maximal cumulative doses for tumors in inner quadrants or central locations (2.54 ± 0.21 and 4.43 ± 0.38 Gy) were significantly higher than those in outer quadrants (1.02 ± 0.17 and 2.1 ± 0.29 Gy; $p < 0.0001$; Table 4).

After adjustment of the cumulative LAD dose of PBI to WBI using the BED equations, the mean and maximal doses in PBI patients were significantly reduced in patients with tumors in outer quadrants (1.12 ± 0.20 and 2.43 ± 0.37 Gy; $p = 0.0001$; Figures 1 and 2). When compared with the dose to WBI, the radiation dose to LAD was reduced by one third to one half using PBI in patients with tumors in the outer quadrants. However, although a reduction in the cumulative dose to LAD in PBI patients with inner quadrant or central tumors was observed only at the maximal dose (5.39 ± 0.56 Gy, $p < 0.05$), there were slightly but significant increases in the mean LAD dose compared to WBI patients (2.85 ± 0.27 Gy, $p < 0.05$).

Table 1. Selected patient characteristics in two radiation treatment groups

	PBI (*n* = 100)	WBI (*n* = 82)	*p* value
Age, years (mean)	55.5 (35-92)	53.0 (28-81)	0.16
< 50	39 (39.0%)	37 (45.1%)	
50-59	25 (25.0%)	21 (25.6%)	
≥ 60	36 (36.0%)	24 (29.3%)	
Pathological T-stage			0.053
pTis	7 (7.0%)	15 (18.3%)	
pT1	85 (85.0%)	59 (71.9%)	
pT2	8 (8.0%)	8 (9.8%)	
Pathological N-stage			< 0.05
pN0	87 (87.0%)	65 (79.3%)	
pN1	13 (13.0%)	16 (19.5%)	
NR	0 (0%)	1 (1.2%)	
Tumor location			
Right	0 (0%)	42 (51.2%)	
Left	Lateral tumors: 55 (55.0%) Medial or central tumors: 45 (45.0%)	40 (48.8%)	

PBI – partial breast irradiation, WBI – whole breast irradiation, LAD – left anterior descending artery

Discussion

The number of breast cancer survivors is increasing, and the long-term survivors may display adverse events related to cardiovascular disease. Moreover, the direct effects of cardiotoxic cancer therapies such as aromatase inhibitor, trastuzumab, and anthracyclines may elevate the risk of the heart disease [23]. Recently, radiation induced heart diseases, including pericarditis, coronary artery disease, valvular heart disease, rhythm abnormalities, etc. have been focused, and monitoring of the heart for early identification of these diseases is recommended [24]. Among them, radiation induced coronary artery disease (RICAD) has especially been investigated, and is speculated to be related to microangiopathy of the small vessels as well as macroangiopathy of the coronary arter-

Table 2. Treatment-related variables and dosimetric parameters for the PBI patients

Treat-related variables	Breast (volume)	Cavity (volume)	Skin (max. dose)	Lung (max. dose)
Mean (range)	288.3 cm^3 (19.6-953.3)	23.9 cm^3 (2.4-279.0)	1.9 Gy (0.4-6.1)	2.2 Gy (0.6-9.1)
Dosimetric parameters	PTV	V_{100}	V_{150}	DNR
Mean (range)	35.8 cm^3 (6.8-135.8)	29.8 cm^3 (7.0-106.5)	9.7 cm^3 (2.5-59.3)	0.3 (0.2-0.6)

PBI – partial breast irradiation, PTV – planning target volume, V_{100} – volume of tissue encompassed by the 100% and 150% (V_{150}) isodose line, DNR – dose non-uniformity ratio (V_{150}/V_{100})

Table 3. The mean and maximal cumulative dose to the whole LAD with WBI

	Right breast cancer (*n* = 42)	Left breast cancer (*n* = 40)	*p* value
Mean dose to LAD (Gy)	0.37 ± 0.02	2.13 ± 0.11	< 0.0001
Range	0.20-0.58	1.13-4.87	
Maximal dose to LAD (Gy)	0.56 ± 0.03	8.19 ± 1.21	< 0.0001
Range	0.23-0.93	2.31-36.85	

WBI – whole breast irradiation, LAD – left anterior descending artery

Table 4. The mean and maximal cumulative doses to the whole LAD with PBI in left-sided breast cancer patients according to tumor locations

	Inner or central location (n = 45)	Outer quadrants (n = 55)	p value
Mean dose to LAD (Gy)	2.54 ± 0.21	1.02 ± 0.17	< 0.0001
Range	0.40-8.00	0.00-6.56	
Maximal dose to LAD (Gy)	4.43 ± 0.38	2.10 ± 0.29	< 0.0001
Range	1.04-13.20	0.00-10.80	

PBI – partial breast irradiation, LAD – left anterior descending artery

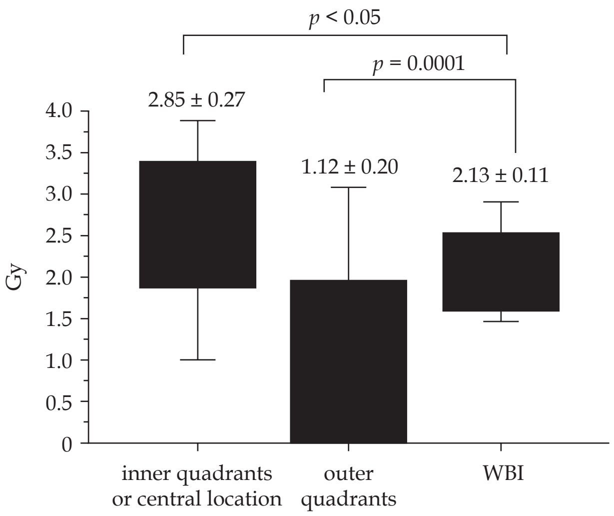

Fig. 1. Comparison of the mean cumulative doses to LAD between PBI and WBI for left-sided breast cancer. The mean doses in PBI patients were significantly reduced in patients with tumors in outer quadrants (1.12 ± 0.20 Gy, $p = 0.0001$), but increased in inner quadrants or central location (2.85 ± 0.27 Gy, $p < 0.05$)

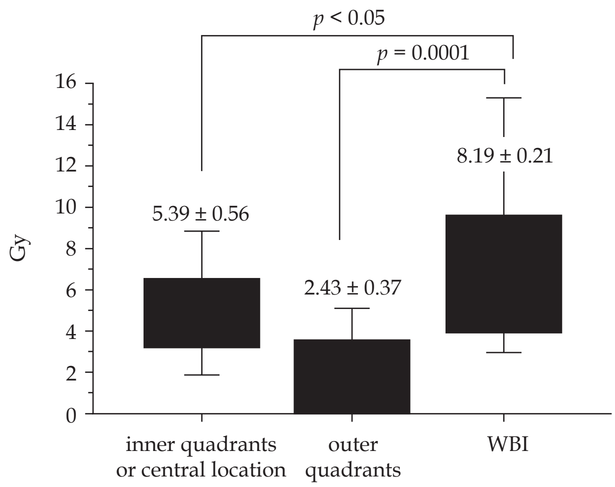

Fig. 2. Comparison of the maximal cumulative doses to LAD between PBI and WBI for left-sided breast cancer. The maximal doses in PBI patients were significantly reduced in patients with tumors both in outer quadrants and inner quadrants or central location (2.43 ± 0.37; $p = 0.0001$ and 5.39 ± 0.56 Gy; $p < 0.05$)

ies caused by radiation exposure [25]. The relative risk of a major coronary event increases linearly with the radiation dose to the heart (the threshold below, which no risk was found), and risk started to rise within the first 5 years after exposure and continued for at least 20 years [26]. However, radiotherapy reduces the rates of ipsilateral tumor recurrence, the protective effect of BCS may last as long as 5 years [27]. Therefore, specific attention should be paid to radiation exposure to the heart.

In terms of the radiation exposure to the heart, the whole heart is often selected for the evaluation of cardiac dose, but some of the newer studies reported the dose to the coronary arteries, irradiated left ventricular volume, and highest dose to the small cardiac volume, especially to the anterior portion of the heart. Although the most appropriate site to evaluate in order detect RICAD has not been determined, there is a report that arteries are particularly sensitive to radiation and LAD is one of the typical sites of origin for the disease [16,28,29]. Moreover, the extent of radiation exposure by PBI is too small to cover the whole heart, and the radiation dose to the whole LAD was selected as a parameter in this study. The mean dose or maximal dose was not established as a parameter to evaluate the risk of RICAD. The dose distribution in the heart is not homogeneous enough for evaluation because of the continuous movement of the heart; therefore, the mean radiation dose might have more meaning rather than the maximum dose.

Reduction in radiation doses to the whole LAD could be successfully achieved by administration of PBI in left-sided breast cancer patients with lateral tumors, leading to a potential decrease in RICAD risk. However, the radiation dose in some patients with central or medial tumors was slightly higher than that in patients receiving WBI. Even though the extent of the radiation field in PBI was very small, it probably reached LAD in the patients whose hearts were close to the chest wall.

Improvements in breast imaging for widening the application of breast-conserving therapy and the advantage of systemic treatments such as chemotherapy, biological therapy, and hormonal therapy have collectively reduced local recurrence rate [30]; however WBI even for older patients is not without some risk [31]. Excess cardiac mortality is derived from outdated radiation techniques, and the magnitude of the cardiac risk after modern radiation techniques such as CT-based three-dimensional conformal treatments remains unknown. Another comparative study of WBI and PBI has been reported [32]. Although the LAD doses in our WBI patients were slightly lower than those in the other report, dose reductions to the LAD could be achieved in PBI patients with lateral tumors. Therefore, a strength of this study is that the dose to the coronary arteries could be calculated precisely because all patients received CT-based radiation planning. Moreover, since no patients were irradiated by inverse planning intensity modulated radiation therapy (IMRT) or forward IMRT, the genuine accumulated doses were verified based on ordinary radiotherapy utilizing conventional, widely used radiation techniques with two opposite tangential fields.

Conversely, the widely varying radiation dose could be related not only to the position of the heart relative to the anterior chest wall, but also to the relative curvature of the anterior chest wall, size of the breast, position of the breast on the chest wall, size of the heart, ptotic breast, etc. [33,34]. Significant uncertainty associated with contouring of the LAD remained, and the motion of the LAD also could have affected calculation of the LAD doses. Moreover, the radiation dose to the whole LAD using both techniques could be markedly increased in left-sided breast cancer patients with any of the above-mentioned unfavorable cardiac anatomies. Therefore, a limitation to the study is that the cardiac anatomy of patients was not taken into consideration; future studies should examine cardiac anatomy to compare radiation doses to LAD between WBI and PBI.

Conclusions

Partial breast irradiation is not yet proven equivalent to WBI in terms of radiation techniques for disease control after BCS, however, a putative advantage ascribed to the use of PBI relates to the reduction in dose to the whole LAD especially in patients with unfavorable cardiac anatomy or preexisting cardiac risks. In our study, we compared two different radiation treatments in terms of radiation exposure to the whole LAD. Our findings suggest that the risk of tumor recurrence and the relatively high dose to LAD in patients with the left-sided breast cancer should be examined before treatment. Moreover, the use of PBI should be considered when comparing risk benefit profiles on a patient-to-patient basis in order to choose the appropriate radiation therapy for breast-conserving treatment. PBI may reduce burden from long-term radiation therapy and the risk of heart disease as a radiation related complication.

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Disclosure

Authors report no conflict of interest.

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