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

Kazuhiko Sato, MD, PhD1, Yoshio Mizuno, MD1, Hiromi Fuchikami, MD1, Masahi Kato, MD, PhD2, Takahiro Shimo2, Jun Kubota2, Naoko Takeda, MD3, Yuko Inoue, MD, PhD3, Hiroshi Seto, MD, PhD4, Tomohiko Okawa, MD, PhD5

1Department of Breast Oncology, Tokyo-West Tokushukai Hospital, Tokyo, 2Department of Radiation Oncology, Tokyo-West Tokushukai Hospital, Tokyo, 3Inoue Ladies Clinic, Tokyo, 4Seto Hospital, Saitama, 5Health Evaluation Center, Utsunomiya Memorial Hospital, Tochigi, Japan

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 multichannel 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.

Key words: brachytherapy, breast cancer, coronary artery, partial breast irradiation, radiation dosage.
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 α/β = 3.4 for each patient receiving PBI [22].

**Statistics**

The χ² 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% (V₁₀₀) and 150% (V₁₅₀) isodose line, and dose non-uniformity ratio (DNR) = (V₁₅₀/V₁₀₀).
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; \( p < 0.0001 \); 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, \( p < 0.05 \)).

### 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 recommend- ed [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-
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 LAD, 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 confor-

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

| Location of Tumor | Mean Dose to LAD (Gy) | Maximal Dose to LAD (Gy) | p Value |
|-------------------|-----------------------|--------------------------|---------|
| Inner or central location (n = 45) | 2.54 ± 0.21 | 4.43 ± 0.38 | < 0.0001 |
| Outer quadrants (n = 55) | 1.02 ± 0.17 | 2.10 ± 0.29 | < 0.0001 |

PBI – partial breast irradiation, LAD – left anterior descending artery.
Partial-breast irradiation reducing dose to the left anterior descending artery

Acknowledgements

This study was presented in part at the 3rd International Breast Cancer Symposium 2014 held in Jeju Island, Korea on April 25th.

The authors would like to thank Enago (www.enago.jp) for the English language review.

Disclosure

Authors report no conflict of interest.
16. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007; 67: 10-18.

17. Sato K, Mizuno Y, Kato M et al. Intraoperative open-cavity implant for accelerated partial breast irradiation using high-dose rate multicatheter brachytherapy in Japanese breast cancer patients: A single-institution registry study. *J Cancer Ther* 2012; 3: 822-830.

18. Skowronek J, Wawrzyniak-Hojczyk M, Ambrochowicz K. Brachytherapy in accelerated partial breast irradiation (APBI) - review of treatment methods. *J Contemp Brachyther* 2012; 4: 152-164.

19. Vicini FA, Baglan KL, Kestin LL et al. Accelerated treatment of breast cancer. *J Clin Oncol* 2001; 19: 1993-2001.

20. Cholewka A, Szlag M, Slosarek K et al. Comparison of 2D- and 3D-guided implantation in accelerated partial breast irradiation (APBI). *J Contemp Brachyther* 2009; 1: 207-210.

21. Koh Y, Buhari SA, Tan PW et al. Comparing a volume based template approach and ultrasound guided freehand approach in multicatheter interstitial accelerated partial breast irradiation. *J Contemp Brachyther* 2014; 6: 173-177.

22. Bentzen SM, Yarnold JR. Reports of unexpected late side effects of accelerated partial breast irradiation-radiobiological considerations. *Int J Radiat Oncol Biol Phys* 2010; 77: 969-973.

23. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res* 2008; 14: 14-24.

24. Lancellotti P, Nkomo VT, Badano LP et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2013; 26: 1013-1032.

25. Corn BW, Trock BJ, Goodman RL. Irradiation-related ischemic heart disease. *J Clin Oncol* 1990; 8: 741-750.

26. Darby SC, Ewertz M, McGale P et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987-998.

27. Wickberg A, Holmberg L, Adami HO et al. Sector resection with or without postoperative radiotherapy for stage I breast cancer: 20-year results of a randomized trial. *J Clin Oncol* 2014; 32: 791-797.

28. Correa CR, Litt HJ, Hwang WT et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol* 2007; 25: 3031-3037.

29. Nilsson G, Holmberg L, Garmo H et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012; 30: 380-386.

30. Buchholz TA, Somerfield MR, Griggs JJ et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. *J Clin Oncol* 2014; 32: 1502-1506.

31. Albert JM, Liu DD, Shen Y et al. Nomogram to predict the benefit of radiation for older patients with breast cancer treated with conservative surgery. *J Clin Oncol* 2012; 30: 2837-2843.

32. Moran JM, Ben-David MA, Marsh RB et al. Accelerated partial breast irradiation: what is dosimetric effect of advanced technology approaches? *Int J Radiat Oncol Biol Phys* 2009; 75: 294-301.

33. Hiatt JR, Evans SB, Price LL et al. Dose-modeling study to compare external beam techniques from protocol NSABP B-39/RTOG 0413 for patients with highly unfavorable cardiac anatomy. *Int J Radiat Oncol Biol Phys* 2006; 65: 1368-1374.