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Relationship of breast arterial calcification and radiotherapy

Gökhan Karataş[1], Osman Kula[2], Nermin Tunçbilek[2]

[1]Department of Radiology, VM Medical Park Bursa Hospital, Bursa, Turkey; [2]Department of Radiology, Trakya University, Faculty of Medicine, Edirne, Turkey

ABSTRACT

Objectives: The purpose of this research is to compare the pre and post-radiotherapy mammograms of patients who had breast-conserving surgery (BCS) and radiotherapy to see how radiotherapy affects breast arterial calcifications (BAC).

Methods: The study retrospectively compared the mammography examinations at least 24 months after radiotherapy and pre-radiotherapy mammography examinations of 123 female patients diagnosed with breast cancer and treated with BCS and radiotherapy between December 2001 and July 2011.

Results: Breast arterial calcifications (BAC) increased statistically significantly in 25 patients who underwent radiotherapy after BCS.

Conclusion: Our results indicate that BAC increases significantly after RT, especially in breasts treated with radiotherapy, with age being also a risk factor for BAC development.

Keywords: Breast arterial calcification, radiotherapy, mammography

Breast cancer is the most frequent cancer in women worldwide, except from non-melanoma skin cancer [1]. Breast cancer accounts for approximately 30% of all malignancies diagnosed among the adult women [2].

Breast-conserving surgery (BCS) followed by radiation therapy (RT) is the preferred treatment for early-stage breast cancer [3-6]. Administration of RT following BCS can be greatly reduce the recurrences and the breast cancer deaths [3-6]. Yet, there is worry that radiation therapy may have an effect on the cardiovascular architecture and other comorbidities [7, 8].

Breast arterial calcifications (BAC) are medial calcifications that are a manifestation of arteriosclerosis [9, 10]. Calcification in the medial layer occurs independently of atherosclerosis or inflammation, happens in both small and big arteries, and is considered harmful as it lowers arterial compliance [11]. BAC has also been linked to hypertension, diabetes, and cardiovascular diseases in some studies [12-14]. However, only one study was found in the literature examining the relationship between BAC and RT [15].

In this study, we examined the relationship between RT and BAC with the hypothesis that RT would increase BAC by predicting that BAC is a form medial arteriosclerosis.

METHODS

This study retrospectively evaluated 123 female patients who had BCS due to breast cancer and then re-

Corresponding author: Gökhan Karataş, MD.,
Phone: +90 224 270 60 00, E-mail: gokhankaratas1984@gmail.com

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ceived RT between December 2001 and July 2011 at Trakya University Medical Faculty Hospital. This study was approved Trakya University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee under protocol number TÜTF-GOKAEK 2012/179 dated 22/02/2012.

All patients underwent BCS and RT, and regular control mammography was done at Trakya University Faculty of Medicine's Department of Radiology and evaluated by consensus of a resident radiologist and a 10 year experienced Radiologist in Breast Radiology. The research included only individuals with routine control mammography who underwent BCS and RT. In the inclusion criteria, a period of at least 2 years after RT was looked for in cases where RT was performed following BCS.

Cases with a length of less than two years and cases with inaccessible personal background material were excluded from the research. A personal history form asking chronic illnesses such as age, smoking, diabetes, hypertension, cardiac diseases, malignancy, and stroke was regularly filled out in all cases during the pre-surgical time.

The mammography images of the cases who applied between December 2001 and July 2011 are returned to the workstation from MIMS (Mammography Image Management Solutions), the digital archive of the full-field digital mammography 'Selenia Digital Mammography System' (2008 Lorad, Hologic, USA) device in the Radiology Department. It was evaluated by calling or examining old conventional mammography films.

In all cases evaluated with full-field digital mammography, images were obtained from both breasts in standard CC and MLO positions. Additional radiographs for diagnostic purposes (spot compression, magnification, axillary, mediolateral, rounded inner and outer quadrant images) were taken in cases deemed necessary. In the digital mammography archive system, mammography images are compressed by 1/3 and archived and images can be recalled without loss of information. Digital mammography images were evaluated on a Barco MGD 521 M, 2x2.5 K medical monitor. This monitor is a 5 Megapixel medical monitor designed to display digital mammography images.

Fig. 1. Grade 1 breast arterial calcification(arrow).

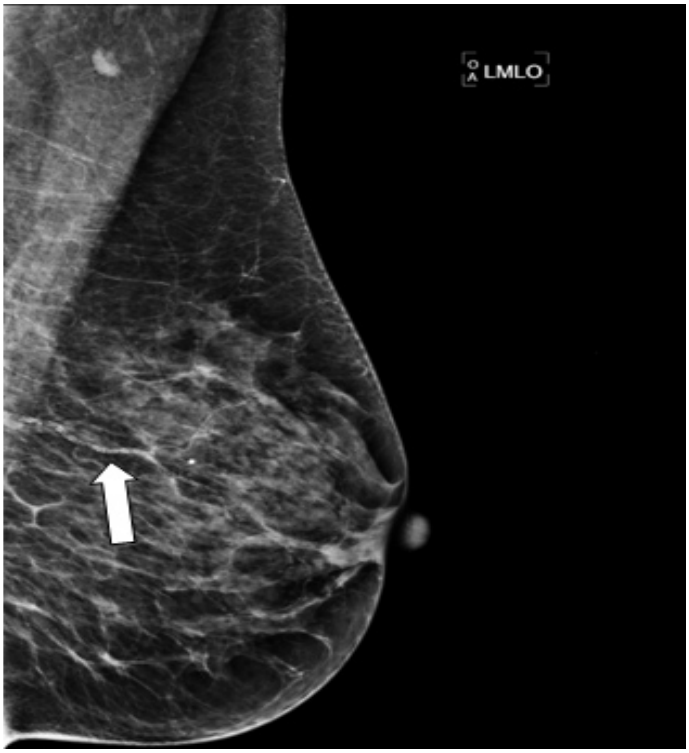

Fig. 2. Grade 2 breast arterial calcification (arrow).

Fig. 3. Breast arterial calcification (arrow).

In the study, BACs detected by mammography were graded from zero to three by consensus according to the literature [16].

Grade 0 (none): No surrounded calcium.

Grade 1 (mild): Artery or arteries are slightly surrounded by calcium (Fig. 1).

Grade 2 (moderate): Artery or arteries are markedly surrounded by calcium (Fig. 2).

Grade 3 (severe): Artery or arteries are surrounded by a prominent and thick column of calcium (Fig. 3). With this grading system, pre and post-RT mammograms of all cases were evaluated and recorded in terms of BAC by consensus of a resident radiologist and a 10 year experienced Radiologist in Breast Radiology.

Statistical Analysis

The analyses were carried out using the IBM Statistics V19 application. Descriptive Statistical Metrics for qualitative variables include frequency and percentage, whereas quantitative variables include mean, standard deviation, minimum, maximum, and median. Chi-square analysis was used to investigate the relationships between qualitative variables. Pearson Chi-square in cross tables when the predicted incidence of variable does not exceed 20%, and Final Test results in cross tables where it exceeds 20%.

RESULTS

The mean age of the patients participating in the study ranged from 30 to 76, with a mean age of 48 (Table 1). All 123 patients in the research were diagnosed with primary breast cancer and got BCS+RT treatment.

When the accompanying systemic diseases were investigated, there was hypertension (HT) in 14 cases (11.4%), multiple chronic diseases in 11 (8.9%) cases, chronic liver disease in 1 (0.8%) case, and chronic kidney disease in 1 (0.8%) case. One (0.8%) patient (0.8%) had hypothyroidism and 1 (0.8%) patient had hyperthyroidism. No systemic pathology was observed in the remaining 94 (76.4%) cases (Table 1). Twenty (16.3%) patients were smokers.

Prior to RT, BAC was detected in 9 (7.3%) out of 123 cases, while 114 (92.7%) cases showed no evi-

Table 1. Characteristics of the subjects included in the study

Characteristics	Data
Age (years)	48±8.872 (30-76)
Time elapsed after radiotherapy (years)	7±2.4 (3-12)
Comorbitidities, n (%)	
None	94 (76.4)
Hypertension	14 (11.4)
Multiple chronic diseases	11 (8.9)
Chronic liver disease	1 (0.8)
Chronic kidney disease	1 (0.8)
Hyperthyroidism	1 (0.8)
Hypothyroidism	1 (0.8)

Data are shown as mean±standard deviation or minimum-maximum or n (%)

Table 2. Number of people with mammographic breast arterial calcification before radiotherapy

n=123	Pre-RT BAC (+)
Breasts Underwent RT, n (%)	9 (7.3)
Contralateral Breasts, n (%)	9 (7.)

RT=Radiotherapy, BAC=Breast Arterial Calcification

dence of BAC (Table 3). Similarly, in the contralateral breast, BAC was found in 9 (7.3% cases) and not detected in 114 (92.7%) cases prior to RT (Table 2).

The cases who underwent RT were compared in terms of pre- and post-RT BAC. There was an increase in BAC in 25 (20.3%) patients, and an increase in BAC was found in both breasts in 7 (5.7%) of these patients. The increase in BAC on the side that underwent RT was found to be statistically significant (P<0.001) (Table 3).

Pre- and post-RT BAC increase in both breasts was detected in 7 (5.6%) cases, with a mean age of 55 years. It was statistically significant that the increase in BAC in the cases was compatible with age (P<0.001) (Table 4).

There was no cigarette smoking in the cases with increased BAC after post-RT. In our study, when pre-RT BAC and post-RT BAC were compared, no statistically significant relationship was found between smoking and increased BAC.

The duration of the RT treatments to the post-RT mammograms we have evaluated of the cases ranged from a minimum of 3 years to a maximum of 13 years. There was no statistically significant relationship between the time elapsed after RT and BAC (P>0.05).

Case 1: In the control MG of a 50-year-old patient who underwent RT after BCS, did not have a history of comorbid disease, and was a non-smoker, shows increase in BAC was found on the side with BC and underwent RT (Fig. 4).

Case 2: No increase in BAC was detected in the control MG after 3 years of a 64-year-old patient who underwent RT after BCS, had a history of known HT for 5 years, and was a non-smoker (Fig. 5).

DISCUSSION

In this study, we evaluated the relationship between RT and Breast Arterial Calcification (BAC) by using mammography. The results showed that BAC increased significantly after RT only in the breasts underwent RT.

There is only one research [15] studied the impact of RT on BAC that we could find in the English liter-

Table 3. Increased mammary arterial calcification in pre- and post-radiotherapy mammograms of both breasts

	Pre-RT BAC case number	Post-RT BAC case number	Increase in BAC case number	(%)
Breasts Underwent RT	9	26	25	20.3
Contralateral Breasts	9	16	10	8.1

RT=Radiotherapy, BAC=Breast Arterial Calcification

Table 4. The relationship of increased arterial calcification of the breast between breasts receiving and not receiving radiotherapy

	No increase in BAC case number	Increase in BAC case number	Mean age of the Increase in BAC
Breasts Underwent RT	98	25	47
Contralateral Breasts	113	10	50
Bilateral	116	7	55

RT=Radiotherapy, BAC=Breast Arterial Calcification

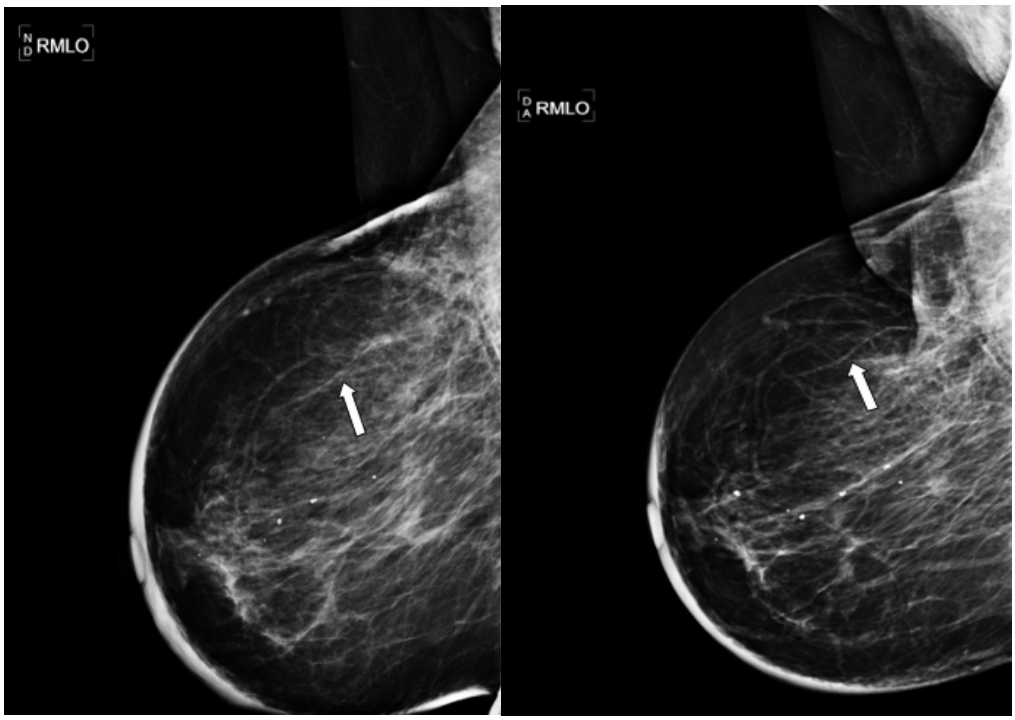

Fig. 4. **Arterial calcification of the breast at 1 and 4 years after radiotherapy (arrows).**

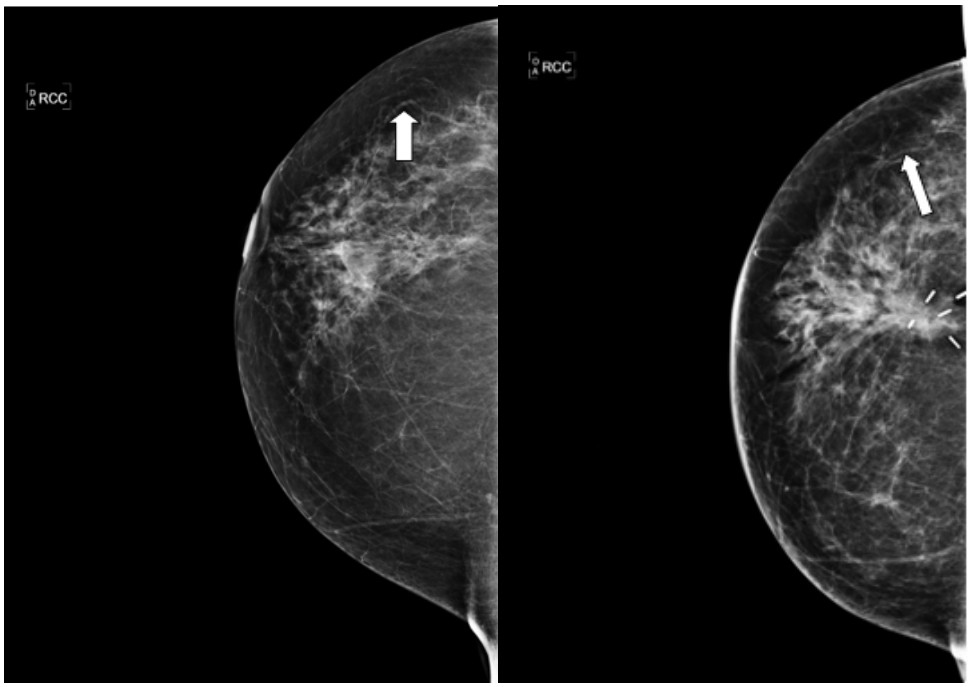

Fig. 5. **No change was detected in breast arterial calcification after radiotherapy (arrows).**

ature. Yet, they discovered differences in their research. They reported no statistically significant relationship between BAC observed on baseline mammography and BAC found on follow-up (post-RT) mammography and later cardiac events. They found that subdividing individuals with a left-sided tumor based on BAC did not predict cardiac events either [15].

We attribute the existence of different results to the diversity of study populations and the complexity of the relationship between the diseases that we think may affect cardiovascular events, let alone the fact that radiotherapy in a patient with breast cancer causes an intense pathophysiological change. Therefore, it is crucial to conduct further research to better understand the relationship between RT and BAC [17].

Radiation damage to artery walls, followed by accelerated arteriosclerosis development in the irradiated arteries, is a well-documented phenomena in both experimental animals [18-20] and humans [9, 16, 21, 22].

A meta-analysis [16] found that while radiation therapy reduced local recurrence in individuals with early breast cancer, there was a statistically significant rise in blood vessel-related mortality 10 years later [16]. This study found that RT leads to long-term vascular illness [16]. Another study reported that women with a history of cardiac illness who had radiation therapy for left-sided breast cancer had higher incidence of Percutenous Cardiac Interventions (PCI) and a worse chance of survival if treated with PCI [9].
In patients getting RT for breast cancer, Roos *et al*. [21] discovered a direct link between the calcium value of the coronary artery prior to treatment with acute coronary events.

However, we should also mention that there are studies reporting different results in the literature on this subject. A study conducted in 2018 showed no variation in the incidence of cardiac side effects observed in standard and hypofraction RT systems [22].

Another meta-analysis suggested BAC as an expression of arteriosclerosis and reported that it appears to be related with an elevated risk of cardiovascular disease events while only being associated with part of the recognized cardiovascular risk factors [9]. Osman *et al*. [23] found a statistically significant association between BAC and Coronary Artery Disease (CAD). They suggest that BAC is a potential noninvasive imaging marker that may improve CAD risk prediction in women. A different meta-analysis showed that BAC is highly associated with both CAD and stroke [24].

Our study also found a statistically significant difference in the mean age of the cases with increased BAC in both breasts compared to the cases without BAC increase or only on the side that underwent RT. This result suggests that age may be a risk factor for the development of BAC after RT. Topal *et al*. investigated the relationship between BAC detected in mammography and Cardiovascular diseases (CVD); they found a relationship between BAC and age and duration of menopause [16]. Hendriks *et al*. [9] showed a clear and constant link between increasing age and the prevalence of BAC.

Smoking was also evaluated in our study, and no statistically significant result was found between smoking and BAC increase. Shah *et al*. [25] reported reduced prevalence of BAC among women who smoke. Hendriks *et al*. [9] are also in line with the results in their meta-analysi.

Limitations

While our findings provide insight on the relation between RT and BAC, it is necessary to appreciate the limitations of our study. The following might have impacted the validity of our findings. Firstly, because the study is retrospective in nature, it may have limitations in terms of data accuracy and completeness. Secondly, the study's sample size is relatively small, which can reduce the statistical power and precision of the results. Finally, the interobserver variability of the grading method used to evaluate BAC was not assessed in the study, which may have affected the reliability of the results.

CONCLUSION

As a conclusion, our research provides insight on the long-term effects of radiation on BAC. Our results indicate that BAC increases considerably after RT, especially in RT-affected breasts, with age being also a risk factor for BAC development.

Keypoints

(1) Administration of Radiotherapy (RT) following Breast Conserving Surgery (BCS) can be greatly

reduce the recurrences and the breast cancer deaths [3-6]. Yet, there is worry that radiation therapy may have an effect on the cardiovascular architecture and other comorbidities [7, 8].

(2) Breast arterial calcifications (BAC) are medial calcifications that are a manifestation of arteriosclerosis [9, 10].

(3) In our study the results showed that BAC increased significantly after RT only in the breasts underwent RT.

Authors' Contribution

Study Conception: NT, GK; Study Design: NT, GK; Supervision: NT; Funding: GK; Materials: GK; Data Collection and/or Processing: GK; Statistical Analysis and/or Data Interpretation: OK, NT; Literature Review: OK, GK; Manuscript Preparation: GK and Critical Review: GK, OK, NT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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