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BREAST IMAGING

ORIGINAL ARTICLE

Comparison of mammography and ultrasound findings in the follow-up of patients with breast cancer treated with segmental mastectomy followed by intraoperative electron radiotherapy versus external whole breast radiotherapy

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PURPOSE

This study aims to describe imaging findings in patients treated with intraoperative electron radiotherapy and compare them with those detected in patients treated with external whole breast radiotherapy (WBRT).

METHODS

The study population consisted of 25 patients who received intraoperative radiotherapy [IORT (21 Gy)] as single-dose radiotherapy and a control group of 25 patients who received WBRT at the same institution. Mammography and ultrasound (US) findings were divided into three groups: minor, intermediate, and advanced. On mammography, mass lesions were considered advanced, and asymmetries or architectural distortions were considered intermediate. Oil cysts, linear scars, and the increase in parenchymal density were considered minor findings. On US, irregular non-mass lesions were considered advanced, and circumscribed hypoechoic lesions or planar irregular scars with shadowing were considered intermediate. Oil cysts, fluid collections, or linear scars were considered minor findings.

RESULTS

On mammography, skin thickening ($P = 0.001$), edema ($P < 0.001$), increased parenchymal density ($P < 0.001$), dystrophic calcifications ($P = 0.045$), and scar/distortion ($P = 0.005$) were significantly more common in the WBRT group. On US, irregular non-mass lesions, which made interpretation considerably difficult, were significantly more common in the IORT group ($P = 0.004$). Dominant US findings were fluid collections and postoperative linear or planar scars in the WBRT group. Minor findings were more common in low-density breasts, and major findings (intermediate and advanced) were more common in high-density breasts on both mammographies ($P = 0.011$) and US ($P = 0.027$) in the IORT group.

CONCLUSION

Ill-defined non-mass lesions detected on US in the IORT group have not been defined previously. Radiologists should be aware of these lesions because they can be confusing, especially in early follow-up studies. This study has found that minor findings are seen more frequently in low-density breasts, while major findings are more common in high-density breasts in the IORT group. This has not been reported before, and further studies with more cases are needed to verify these results.

KEYWORDS

Breast, intraoperative radiotherapy, whole breast radiotherapy, mammography, ultrasonography

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Intraoperative radiotherapy (IORT) is an adjuvant treatment option for selected cases of early-stage breast cancer. It is applied using either electron beams [intraoperative electron radiotherapy (IOeRT)] or X-ray, and it can be used alone as primary radiotherapy or as a boost followed by external whole breast radiotherapy (WBRT).[1-6] The advantages of IORT include

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the direct visualization of the tumor bed, reduced skin doses, and patient convenience.

There are only a few reports on the radiological findings in patients treated with IORT.[7-15] Some of them have reported that postoperative changes in mammography and ultrasound (US) are more pronounced in patients treated with IORT compared with those treated conventionally with WBRT.[7-9,11,13] However, radiological findings, especially sonographic results, after IORT are not well documented. During the radiological follow-up of these patients, some findings were different from those seen in patients treated with WBRT. This study's aim was to describe early and late imaging findings in patients treated with IORT as single-dose radiotherapy and compare them with those detected in a conventionally-treated WBRT group.

Methods

Intraoperative radiotherapy group

Between October 2012 and August 2021, 94 patients with breast cancer underwent IOeRT in the clinic. Forty-four of these patients received IOeRT as single-dose radiotherapy (21 Gy). Nineteen patients were excluded from this study either because they received additional WBRT after the operation, had less than six months follow-up, had previous breast surgery, or their radiological images were not available in the picture archiving and communication system. The remaining 25 patients made up the study population. IOeRT was performed using the Sordino IOeRT technologies-LIAC mobile IOeRT device. Electron energies of 12 MeV were given with 80% isodose. Applicators with different diameters (4–8 mm) were selected based on tumor size, breast volume, and flap volume.

Main points

- Mammography revealed more diffuse changes in the whole breast radiotherapy (WBRT) group as opposed to localized findings in the intraoperative radiotherapy (IORT) group in terms of skin thickening, edema, and the increase in parenchymal density.
- Ultrasound (US) demonstrated more circumscribed masses and suspicious ill-defined non-mass lesions in the IORT group, while fluid collections and linear and planar scars were more typical for WBRT.
- Minor findings were seen significantly more frequently in low-density breasts, while major findings were more common in high-density breasts on both mammography and US in the IORT group.

In the institution, the patient selection criteria for IOeRT were based on the American Society for Radiation Oncology guidelines, which were published in 2009 and updated in 2017.[16,17] Patients with histologically proven unifocal ductal invasive cancer of <2 cm or non-high grade ductal carcinoma *in situ* of <2.5 cm in size and who were at least 50 years old were chosen. For this group of patients, additional states of (–) lymphovascular invasion, (–) axillary lymph nodes, (–) grade 3 status, (+) estrogen receptor, and >2 mm clean surgical margins were required.

Whole breast radiotherapy group

The control group consisted of 25 patients with breast cancer who were treated with breast-conserving surgery (BCS) followed by WBRT in the same institution between November 2010 and July 2018. WBRT was applied using a linear accelerator (varian true beam) with a total dose of 50 Gy and a boost dose of 10–16 Gy in 5–8 fractions or with a hypofractionated schedule with a total dose of 42.5 Gy in 16 fractions with a boost dose of 10–12.5 Gy in 4–8 fractions. Patients in the WBRT group were selected in chronological order from the radiation oncology patient list using the same exclusion criteria.

Evaluation of imaging findings

Follow-up mammography and US images were retrospectively evaluated by two breast radiologists (with 10 and 25 years of experience) in consensus, and they were blinded to the treatment protocol. Digital mammography (Pristina, General Electric, Chicago, Il, United States) and US (Logic S8, General Electric, Wauwatosa, WI, United States) examinations were performed using the same equipment in all patients. At the institution, patients treated with BCS were routinely scheduled for US examination at six-month intervals and mammographic examination at 12-month intervals for follow-up during the first five years and at yearly intervals afterward. All mammography and US images that were available were evaluated sequentially. The examinations performed in the first 24 months were considered short-term follow-ups, while those taken after 24 months were considered long-term follow-ups.

On mammograms, breast density, the presence or absence of masses (Figure 1), asymmetries (Figure 2), oil cysts, postoperative scars, architectural distortion, calcifications (dystrophic or rim-like), edema (minimal, moderate, and advanced), skin thickening (localized or generalized), and the increase in parenchymal density compared with the contralateral breast (regional or diffuse) were evaluated. Breast density was assessed according to the breast parenchyma types (a–d) stated in the BI-RADS atlas 5th edition of the American College of Radiology.[18] On US images, the presence or absence of fluid collections, ill-defined, non-mass hypoechoic lesions (Figures 3, 4), circumscribed hypoechoic masses (Figure 1), oil cysts, and postoperative linear or planar scars were assessed. Planar scars were defined as irregular scars with shadowing that looked suspicious in one plane but were elongated and changed in shape in the orthogonal plane and usually continuous with skin incision (Figure 5). All focal lesions were measured, and if the patient had sequential examinations, the time of appearance of the findings was recorded.

Mammography and US findings were divided into three groups: minor, intermediate, and advanced, based on the degree to which they made interpretation difficult. On mammography, masses were considered advanced; asymmetries and architectural distortions were considered intermediate; oil cysts, linear postoperative scars, and the increase in parenchymal density were considered minor findings. On US, ill-defined, non-mass hypoechoic lesions were considered advanced; circumscribed hypoechoic lesions or planar irregular scars with shadowing were considered intermediate; oil cysts, fluid collections, or linear postoperative scars were considered minor findings.

The institutional review board granted approval for this retrospective study (ATADEK) (decision number: 2020-05/26, date: 09.04.2020), and patient consent was waived.

Statistical analysis

For statistical purposes, breast parenchyma types A and B were grouped as low density, and types C and D were grouped as high density. Moderate and advanced edema were grouped together as marked edema. Overall findings were dichotomized as minor versus major (intermediate or advanced). The software SPSS v23.0 (IBM Corp., Armonk, NY) was used for data analysis. The Shapiro–Wilk test was used to test the normality of data. Continuous data were presented using mean ± standard deviation for normally distributed data and median (interquartile range: 25%–75%) for non-normally distributed data. Categorical variables were given by n (%) and compared with Pearson's chi-square test and Fisher's exact test. The Mann–Whitney U test

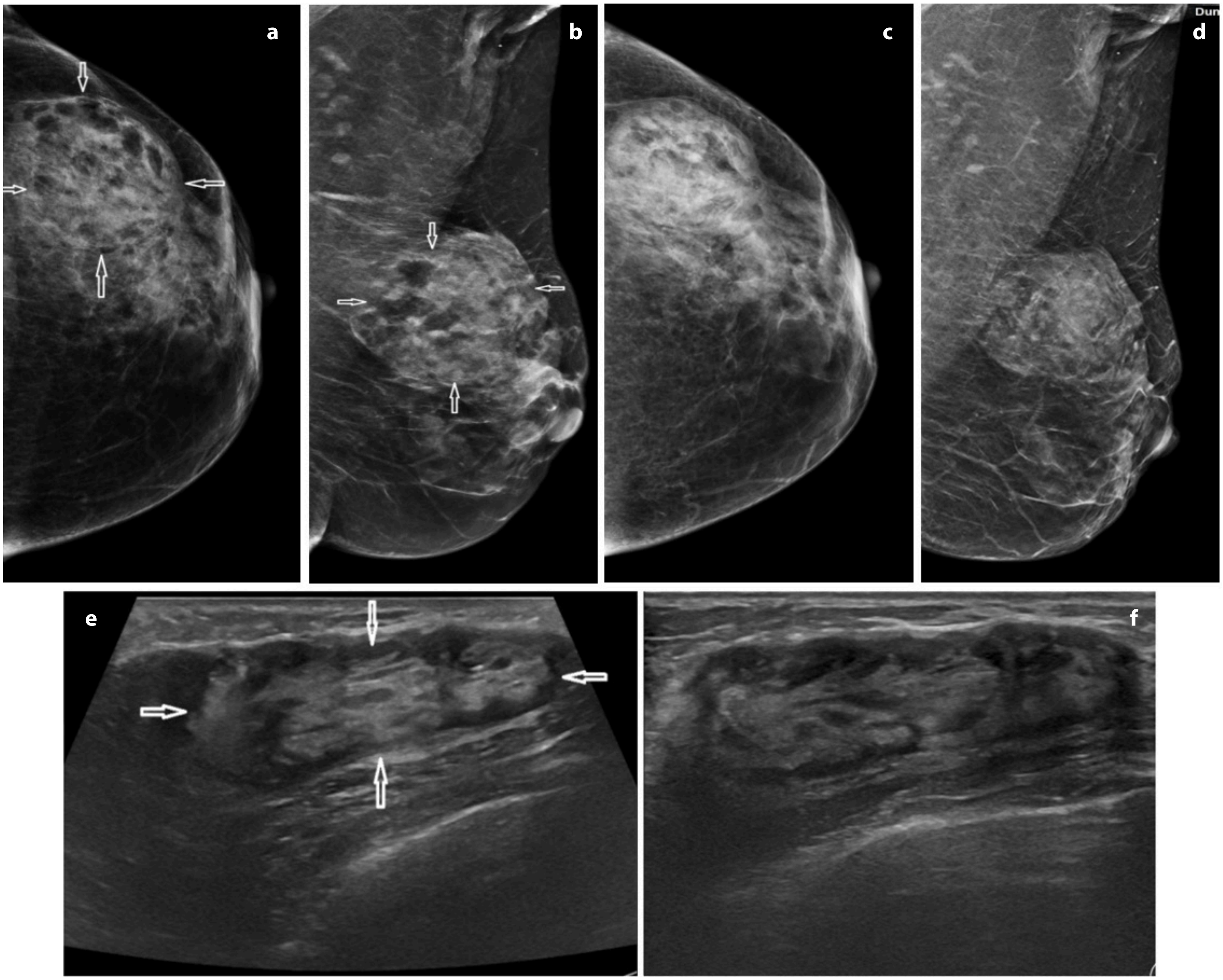

Figure 1. (a-f) Mammography and US images of a 54-year-old patient treated with IORT: initial mammograms **(a, b)** show a heterogeneous mass (arrows) in the left breast, which persists without any change on follow-up mammograms **(c, d)** taken three years after therapy. Initial US image of the same patient **(e)** shows a heterogeneous oval circumscribed mass (arrows). This lesion also persists three years after therapy **(f)**. IORT, intraoperative radiotherapy; US, ultrasound.

and the independent t-test were performed for non-parametric and parametric comparisons of continuous data between groups, respectively. A two-sided *P* value of less than 0.05 was considered statistically significant.

Results

WBRT was given in full doses to 7 patients and was hypofractionated in 18 patients. Patients in the IORT group (mean age: 59.6 ± 6.41) were significantly older than those in the WBRT group (53.36 ± 8.94) ($P = 0.007$), which was expected since only patients older than 50 years of age were eligible for IORT. The most common tumor type was infiltrating ductal carcinoma in both groups, and 24/25 cases treated with IORT and 23/25 cases treated with WBRT were invasive cancers.

Tumors were mostly located in the right breast (IORT: 20/25, WBRT: 15/25) and in the upper outer quadrant (IORT: 14/25, WBRT: 18/25) in both groups. There was no statistically significant difference in tumor size. Follow-up time was significantly shorter in the IORT group ($P = 0.012$) because all eligible and more recent cases were included in this study. Six patients in the IORT group and two patients in the WBRT group had only early follow-ups. None of the patients had any local recurrences or systemic metastases during the follow-up period. Patients' characteristics are described in Table 1.

Imaging findings

The distribution of each finding, size of the lesions, and development time can be seen in Table 1. The most dominant findings in the initial examinations can be seen in Table 2. The distribution of minor versus major findings in breasts with low density versus high density can be seen in Table 3.

Mammographic evaluation

In the initial mammograms obtained after therapy, masses, asymmetries, and oil cysts were more common in the IORT group, while increased parenchymal density, edema, architectural distortion, and postoperative scars were the most dominant findings in the WBRT group (Table 2). Calcifications and some oil cysts appeared later during follow-up.

Statistically, there was a significant difference between the two groups for the following findings: skin thickening ($P = 0.001$), ede-

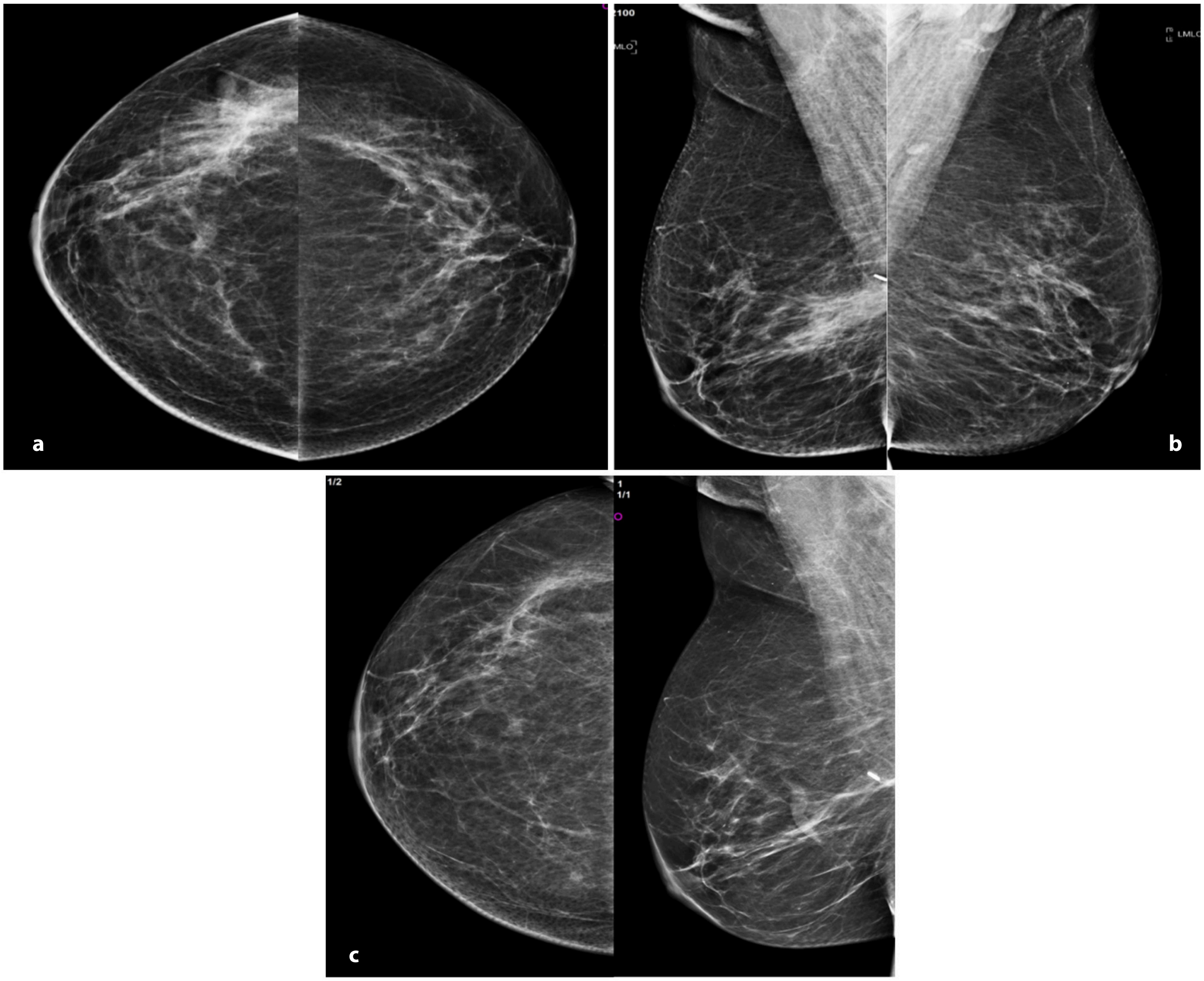

Figure 2. (a-c) Craniocaudal **(a)** and mediolateral oblique **(b)** mammograms of a 59-year-old patient treated with IORT show an asymmetry in the right breast. It resolves during follow-up and only a minor linear scar remains four years after therapy **(c)**. IORT, intraoperative radiotherapy.

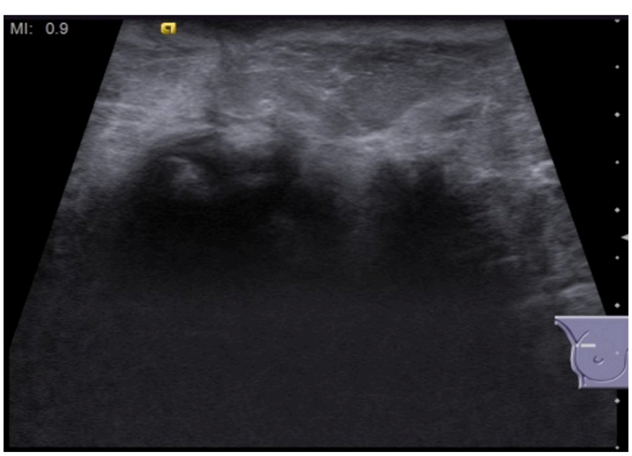

Figure 3. Early US image of a patient treated with IORT demonstrates a suspicious-looking ill-defined non-mass hypoechoic lesion at the operation site. IORT, intraoperative radiotherapy; US, ultrasound.

ma (*P* < 0.001), distrophic calcifications (*P* = 0.045), scar/distortion (*P* = 0.005), oil cysts (*P* = 0.047), and increased parenchymal density (*P* < 0.001) (Table 1).

Skin thickening was either not present or localized in most of the patients in the IORT group (8% and 68%, respectively), while generalized skin thickening was much more common (76%) in patients in the WBRT group (*P* = 0.001). Edema was either not present or minimal (84% and 12%, respectively) in patients in the IORT group, while 80% of the patients had edema in the WBRT group, and it was advanced in half of them (*P* < 0.001). The increase in parenchymal density compared with the contralateral breast was significantly more common in patients in the WBRT group (62.5% vs. 40%); it was mostly regional in the IORT group but diffuse in the WBRT group (*P* < 0.001) (Figure 6). Parenchymal distortion or scar formation was more common among patients in the WBRT group (72% vs. 32%) (*P* = 0.005). Dystrophic calcifications were significantly more common in the WBRT group (56% vs. 28%) (*P* = 0.045). Calcifications appeared earlier during follow-up in the IORT group, but the difference was not significant. Oil cysts were significantly more common in the IORT group (62%

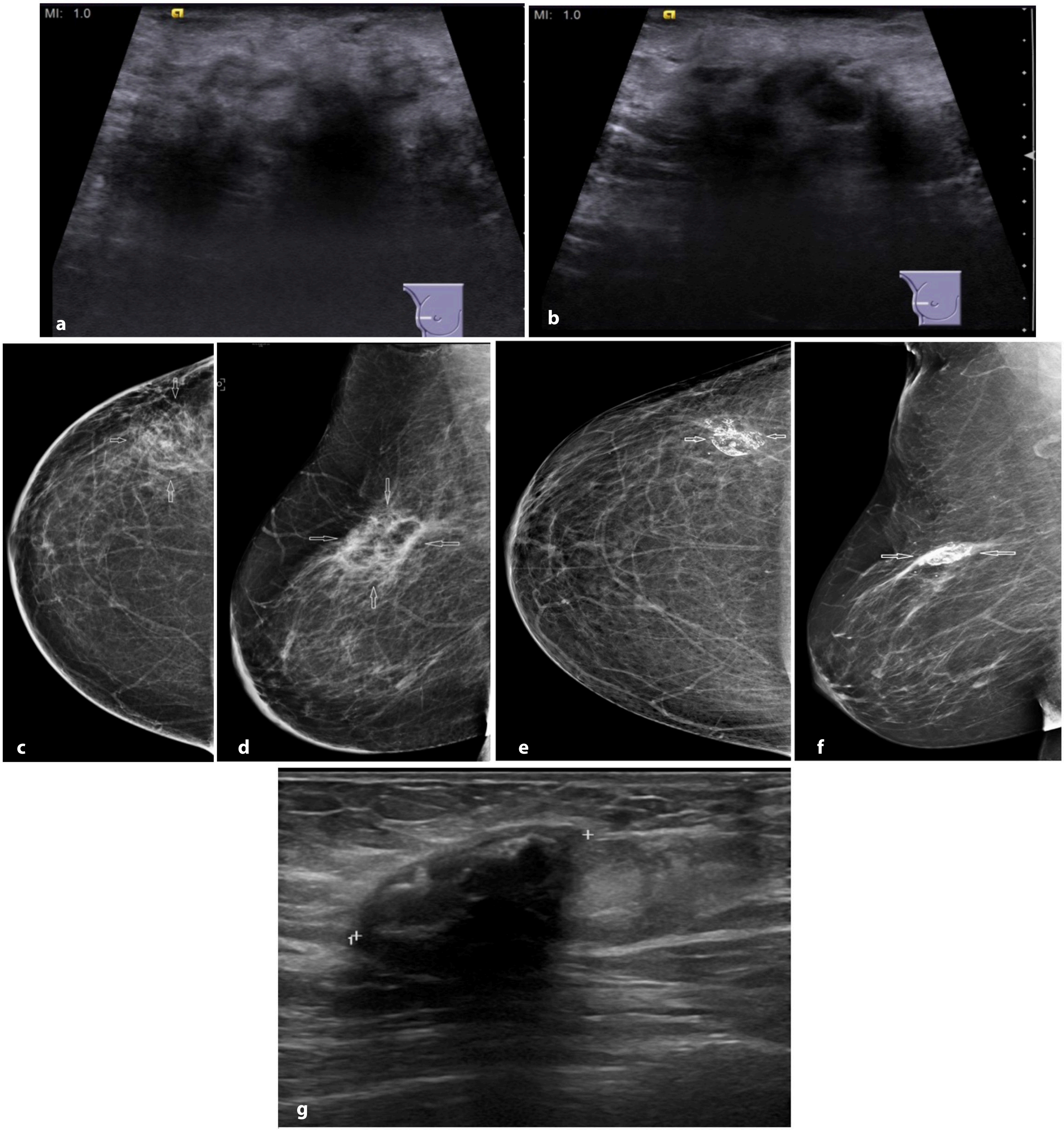

Figure 4. **(a-g)** US images of a 58-year-old patient treated with IORT, which was taken six months **(a)** and one year **(b)** after therapy show a suspicious-looking ill-defined non-mass lesion at the operation site in the right breast. However, mammograms taken at the first follow-up **(c, d)** show only minor changes compatible with fat necrosis (arrows). Mammograms **(e, f)** and US image **(g)** taken five years later show that the lesion turns into a calcified oil cyst on both examinations. IORT, intraoperative radiotherapy; US, ultrasound.

vs. 32%) (P = 0.047). Cysts were larger in the IORT group; however, differences between the median size and median time to develop were not significant.

There was no difference in the number of patients with masses or asymmetries. The sizes of both lesions were larger in patients in the IORT group, although the difference between the median sizes was significant only for asymmetries (P = 0.031). Minor findings were more common in the WBRT group, while major findings were more common in the IORT group. However, the difference was not significant.

Ultrasound evaluation

Most dominant findings in the first US examinations obtained after therapy were ill-defined, non-mass hypoechoic lesions and circumscribed hypoechoic masses in the IORT group. Dominant US findings were mostly in the form of fluid collections and

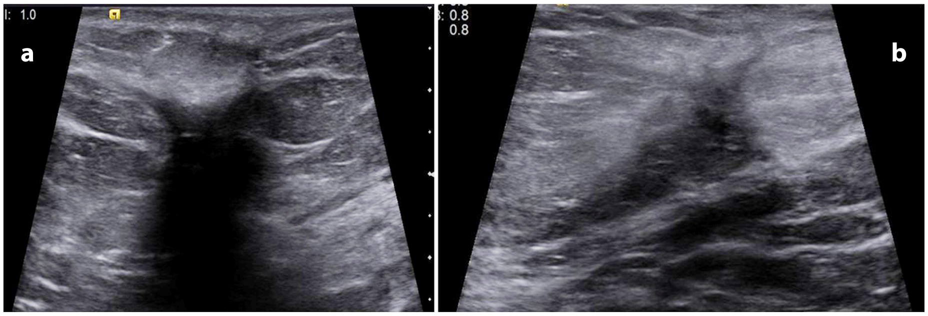

Figure 5. (a, b) US images of a 50-year-old patient treated with WBRT show a planar scar. The lesion is irregular with shadowing on one plane **(a)**, but it is elongated on the orthogonal plane **(b)** and is easily diagnosed as a scar. US, ultrasound; WBRT, whole breast radiotherapy.

Table 1. Distribution of clinical, histopathological, and radiological findings

Variables	IORT (n = 25)	WBRT (n = 25)	*P* value
Clinical findings			
Mean age (years)	59.6 ± 6.41	53.36 ± 8.94	**0.007**
Median tumor size (mm)	11.5 (8–16.5)	11 (6–15)	0.767
Follow-up			
Median follow-up time (months)	46 (29–72)	67 (56–74)	**0.012**
Median of mammograms	3 (1–6)	5 (3–6)	**0.041**
Median of US exams	4 (2–7)	7 (5–9)	**0.023**
Mammography			
Breast parenchyma			
Low density (type A + B)	16 (64)	10 (40)	0.089
High density (type C + D)	9 (36)	15 (60)	
Skin thickening			
None	2 (8)[a]	0 (0)[a]	**0.001**
Localized	17 (68)[a]	6 (24)[b]	
Generalized	6 (24)[a]	19 (76)[b]	
Median skin thickness (mm)	2.9 (2.4–3.3)	3.1 (2.6–4.6)	0.080
Edema			
None	21 (84)[a]	5 (20)[b]	**<0.001**
Minimal	3 (12)[a]	10 (40)[b]	
Advanced	1 (4)[a]	10 (40)[b]	
Calcifications			
Patients with calcifications	13 (52)	17 (68)	0.248
Dystrophic	7 (28)	14 (56)	**0.045**
Rim	10 (40)	6 (24)	0.225
Median time to develop (months)	20 (19–33)	30 (20–44)	0.300
<24 months	7 (53.8)	8 (47.1)	0.713
>24 months	6 (46.2)	9 (52.9)	
Scar/distortion	8 (32)	18 (72)	**0.005**
Masses			
Number of cases	4 (16)	1 (4)	0.349
Median size (mm)	42.5 (35.5–65.5)	25	0.400
Asymmetry			
Number of cases	9 (36)	7 (28)	0.544
Median size (mm)	50 (42–60)	30 (20–46)	**0.031**
Oil cysts			
Number of cases	15 (60)	8 (32)	**0.047**

postoperative linear or planar scars in the WBRT group. The differences were statistically significant (Table 2).

Ill-defined, non-mass hypoechoic lesions were significantly more common (44% vs. 8%) ($P = 0.004$), and the median size of these lesions was significantly larger (45 mm vs. 16.5 mm) in the IORT group ($P = 0.026$). Circumscribed mass lesions were also more common in the IORT group (28% vs. 4%) ($P = 0.049$). Patients in the IORT group had significantly fewer scars (12% vs. 80%), and planar scars were especially typical in patients in the WBRT group (0% vs. 36%) ($P < 0.001$). Fluid collections were exclusively seen in patients treated with WBRT($P = 0.049$). There was no difference in the number of cases with oil cysts, but they were significantly larger in the IORT group (26 ± 14.08 mm vs. 15.1 ± 8.9 mm) ($P = 0.043$). Minor findings were significantly more common in the WBRT group, while major findings were significantly more common in the IORT group ($P = 0.014$) (Table 1).

Overall findings

This study analyzed the relationship between parenchymal density and the rate of minor and major findings. For mammography and US, minor findings were significantly more common in low-density breasts, and major findings were more common in high-density breasts in the IORT group (mammography: $P = 0.011$, US: $P = 0.027$) (Table 3). There was no difference in the WBRT group.

Follow-up findings

Results were obtained from the follow-up data of major findings. For mammography, 9/10 patients with major findings had a late follow-up in the WBRT group, and all of them turned into minor findings. Furthermore, 11/13 patients with major findings had a late follow-up in the IORT group, and only 6 (54.55%) turned into minor findings. The difference was statistically significant ($P = 0.038$). For US, 11/12 patients in the WBRT group and 18/18 patients in the IORT group with major findings had a late follow-up. They turned into minor findings in seven patients (63.64%) in the WBRT group and in six patients (33.33%) in the IORT group at the end of follow-up. The difference was not statistically significant. Most of the circumscribed masses and ill-defined non-mass lesions persisted as circumscribed masses, which were probably compatible with fat necrosis but not in the typical form of an oil cyst.

Table 1. Continued			
Median size (mm)	39 (23–45)	20 (13.5–27.5)	0.070
Median time to develop (months)	8 (7–20)	8.5 (6.5–22.5)	0.999
<24 months	12 (85.7)	6 (75)	0.602
>24 months	2 (14.3)	2 (25)	
Increased parenchymal density			
None	15 (60)[a]	9 (37.5)[b]	**<0.001**
Regional	9 (36)[a]	2 (8.3)[b]	
Diffuse	1 (4)[a]	13 (54.2)[b]	
Ultrasonography			
Non-mass ill-defined lesion			
Number of cases	11 (44)	2(8)	**0.004**
Median size (mm)	45 (36–50)	16.5 (15–18)	**0.026**
Circumscribed mass lesion			
Number of cases	7 (28)	1 (4)	**0.049**
Median size (mm)	45 (30–55)	35	0.750
Scar/distortion			
None	22 (88)[a]	5 (20)[b]	**<0.001**
Linear scar/distortion	3 (12)[a]	11 (44)[b]	
Planar scar	0 (0)[a]	9 (36)[b]	
Fluid collection			
Number of cases	0(0)	5 (20)	**0.049**
Median size (mm)	-	22 (13–38)	-
Oil cysts			
Number of cases	14 (56)	10 (40)	0.258
Mean size (mm)	26 ± 14.08	15.1 ± 8.9	**0.043**
Median time to develop (months)	14 (7–43)	12 (7–19)	0.437
Overall findings			
Mammography			
Minor	12 (48)	15 (60)	0.430
Intermediate	9 (36)	9 (36)	
Advanced	4 (16)	1 (4)	
Ultrasonography			
Minor	7 (28)[a]	13 (52)[a]	**0.014**
Intermediate	7 (28)[a]	10 (40)[a]	
Advanced	11 (44)[a]	2 (8)[b]	

Values are expressed as means ± standard deviation, median interquartile range, or n (%). The independent t-test, Mann–Whitney U test, Pearson chi-square test, and Fisher's exact test were used. The same letters in a row (a,b) denote the lack of statistically significant differences. IORT, intraoperative radiotherapy; WBRT, whole breast radiotherapy.

Discussion

This study compared mammography and US findings of breast cancer patients who were treated with IORT with the findings of patients treated with WBRT. It was found that mammography demonstrated significantly more diffuse changes in the form of skin thickening, edema, and increased parenchymal density in patients in the WBRT group. Focal findings such as masses, asymmetries, and oil cysts were more common in patients in the IORT group. On US, irregular non-mass lesions or circumscribed masses were the dominant findings in patients in the IORT group, while postoperative scars and fluid collections were typical for patients in the WBRT group. Major findings, some of which could lead to diagnostic problems, were more common after IORT.

There are only a few articles in the literature about imaging findings in patients treated with IORT.[7-15] Most of these studies are more than 10 years old and have been performed by a few groups involved in the early clinical trials comparing IORT and WBRT. A limited number of findings have been evaluated, and conflicting results were reported. After IORT was implemented in the clinic, ill-defined non-mass hypoechoic lesions with indistinct margins were found in some cases on US examination. This was very different from the findings usually found in patients treated with WBRT. Because most of the previous reports failed to mention such a lesion, it was decided to conduct this study and describe its findings.

In this study, US revealed non-mass irregular lesions in the tumor bed of 11 patients in the IORT group (44%) but in only 2 patients in the WBRT group (8%), and the difference was statistically significant. The differential diagnosis of an irregular lesion at the surgical site included residual or recurrent tumors as well as fat necrosis. Magnetic resonance imaging and/or US-guided core needle biopsy may be needed for the final diagnosis if the lesion seems suspicious. Short-term follow-up was performed instead of biopsy as these lesions were present in the first follow-up examinations, making the timing unlikely for a malignant process. A similar finding has been mentioned only by Della Sala et al.[11] The biopsy revealed fat necrosis in their study, and lesions either persisted or turned into oil cysts over time. In this study, most of these lesions turned into circumscribed masses, probably compatible with fat necrosis. Similar cases were probably categorized as fat necrosis or unorganized scars in other studies.[11,13] Some authors have reported that mammography revealed more distinct changes after IORT and that US can be used as a problem-solving modality.[7-9,11,13] This study found the opposite: US findings were more confusing compared with mammography in many cases, as seen in Figure 4. Furthermore, mammography can help in the differential diagnosis of such cases because it can clearly demonstrate the fatty content of the lesion, enabling the diagnosis of fat necrosis.

Another interesting finding of this study was that minor findings were significantly more common in fatty breasts, and major findings were more common in dense breasts in the IORT group but not in the WBRT group. It is thought that this may be due to the localized and confined nature of fat necrosis in the dense breast tissue, which causes a suspicious appearance, especially in the early follow-up period. Moreover, more diffuse changes or more typical liquefaction may be the dominant findings in the fatty breast tissue, which do not usually lead to

Table 2. Dominant imaging findings in the early mammography and ultrasound examinations

Findings, n (%)	IORT (n = 25)	WBRT (n = 25)	*P* value
Dominant findings in early mammograms			
Increased density	1 (4)	3 (12)	0.609
Mass-like opacity	4 (16)	2 (8)	0.667
Heterogeneous non-mass opacity	9 (36)	6 (24)	0.355
Oil cysts	7 (28)	4 (16)	0.306
Scar/distortion	4 (16)	8 (32)	0.185
Spiculated scar	0 (0)	2 (8)	0.490
Dominant findings in early US examinations			
Scar/distortion	1 (4)	4 (16)	0.349
Ill-defined non-mass lesion	11 (44)	2 (8)	**0.004**
Circumscribed mass	7 (28)	1 (4)	**0.049**
Oil cyst	6 (24)	4 (16)	0.480
Planar scar	0 (0)	9 (36)	**0.002**
Fluid collection	0 (0)	4 (16)	0.110

Pearson chi-square test and Fisher's exact test were used. IORT, intraoperative radiotherapy; WBRT, whole breast radiotherapy; US, ultrasound.

Table 3. Distribution of overall imaging findings according to breast density

Findings, n (%)	Low density	High density	*P* value
All patients (n = 50)			
Mammography			
Minor	17 (65.4)	10 (41.7)	0.093
Major (intermediate/advanced)	9 (34.6)	14 (58.3)	
Ultrasound			
Minor	14 (53.8)	6 (25)	**0.038**
Major (intermediate/advanced)	12 (46.2)	18 (75)	
IORT (n = 25)			
Mammography			
Minor	11 (68.8)	1 (11.1)	**0.011**
Major (intermediate/advanced)	5 (31.3)	8 (88.9)	
Ultrasound			
Minor	7 (43.8)	0 (0)	**0.027**
Major(intermediate/advanced)	9 (56.3)	9 (100)	
WBRT (n = 25)			
Mammography			
Minor	6 (60)	9 (60)	0.999
Major (intermediate/advanced)	4 (40)	6 (40)	
Ultrasound			
Minor	7 (70)	6 (40)	0.226
Major (intermediate/advanced)	3 (30)	9 (60)	

Pearson chi-square test and Fisher's exact test were used. IORT, intraoperative radiotherapy; WBRT, whole breast radiotherapy.

diagnostic problems. Another explanation may be the difference in vascular support in fatty and dense breasts. Apparently, this difference is only valid for the local effects of IORT and not for the diffuse effects of external WBRT. The correlation between breast density and the type of imaging findings has not been reported previously.

IORT was used with varying indications (as single-dose radiotherapy, as a boost followed by WBRT, or mixed) in different studies. Patients who received IORT as a boost were excluded from this study to achieve more uniform results that are not complicated by the additional effects of WBRT applied after the operation. A study comparing the imaging findings of IORT applied as a boost prior to WBRT with those of WBRT alone reported that more pronounced findings were detected in the IORT group.[7] This shows that the focal effects of IORT in the breast tissue are apparent, even if it is followed by WBRT. In this study, skin thickening, edema, and increased parenchymal density on mammography were significantly more common and more diffuse after WBRT. These early mammographic findings are all related to each other and are as expected since external radiotherapy applied to the whole breast causes more diffuse changes. These results agree with those of Della Sala et al.[11] and Elsberger et al.[15], who have also included only patients who received single-dose IORT in their studies. Other studies where IORT was used as a boost before WBRT have not reported similar findings, probably because both groups demonstrated diffuse changes.

This study detected calcifications in more than half of the patients in both groups, and there was no significant difference in the development time for calcifications. This is similar to the results of Ruch et al.[13] and Elsberger et al.[15], and all calcifications were typically benign. Although some of them seemed non-uniform in the beginning, they developed into typical rim calcifications eventually. Similar to the findings of Ruch et al.[13], dystrophic calcifications were more common in the WBRT group, and rim calcifications were more common in the IORT group. However, other authors have reported that calcifications were significantly more common in the IORT group.[8,11,12] Jalaguier-Coudray et al.[14] have stated that non-uniform calcifications can also be associated with tungsten deposits due to the use of shielding devices composed of this material.

Oil cysts were more common after IORT on both mammography and US, but the difference was significant only for mammography. There were fewer typical oil cysts on US because some of the fat necrosis cases probably appeared as well-circumscribed hypoechoic masses or ill-defined non-mass lesions in early examinations. Circumscribed masses may also represent organized hematoma. Some of these lesions turned into oil cysts during follow-up, while the rest persisted as circumscribed masses. Mammography was superior in diagnosing oil cysts due to its ability to demonstrate inner fatty content. They were larger in the IORT group, but this was not statistically significant. Other studies have also reported more frequent oil cysts

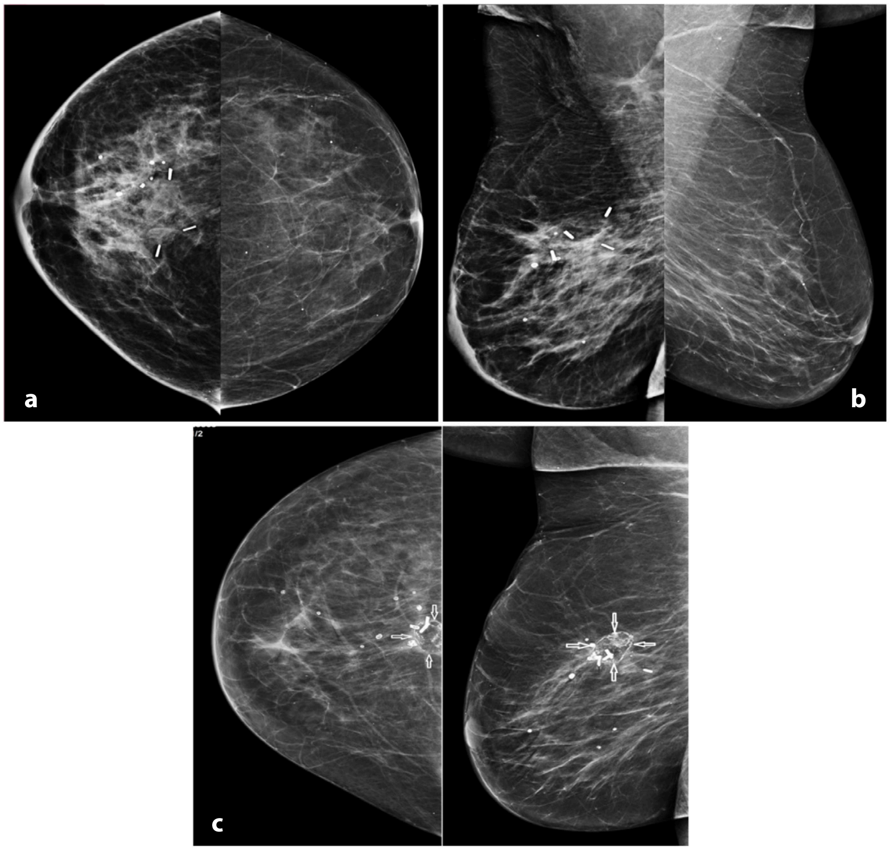

Figure 6. (a-c) Early mammograms **(a, b)** of a 46-year-old patient treated with WBRT show generalized skin thickening, diffuse increase in parenchymal density, and marked edema. These findings resolve during follow-up **(c)** and dystrophic and rim-like calcifications (arrows) appear instead. WBRT, whole breast radiotherapy.

and fat necroses as well as larger lesions in patients who received IORT.[8,11,13,15]

Scars and distortion were significantly more frequent in the mammograms of patients in the WBRT group in this study, which was contrary to other studies.[8,11,15] On US, fluid collections were more common in the WBRT group, which was in contrast to other studies.[7,11,13] This is probably because the surgeons kept surgical drains longer in patients in the IORT group because more extensive dissection was needed to place the applicator. Linear (44% vs. 12%) or planar scars (36% vs. 0%) were other dominant US findings in the WBRT group. Although planar scars seemed suspicious in one plane because of ill-defined margins and shadowing, they were elongated in the other plane along the incision line and did not cause diagnostic challenges.

This is the only study in the literature where both early and late mammography and US findings were evaluated to determine the changes that take place over time. This study has shown that major focal findings such as masses and ill-defined non-mass lesions tend to persist in the late period in patients in the IORT group, but they usually turn into minor findings in the WBRT group. Furthermore, diffuse changes such as skin thickening, increased parenchymal density, and edema regressed completely or partially in both groups over time.

Major limitations in this study include the small number of patients. In the clinic, IORT was performed in a very selective manner, and only single-dose therapy cases were included. The control group was not homogeneous and consisted of both standard and hypofractionated regimens because hypofractionation has been preferred whenever possible during recent years. Follow-up examinations were not available in every case due to the retrospective design of the study. Furthermore, the classification of radiological findings as "minor or major" was somewhat subjective as there are no standardized criteria for this classification. However, two experienced breast radiologists interpreted the findings in consensus. Although the readers were unaware of the treatment protocol, surgical markers placed at the tumor bed in some patients inevitably indicated WBRT on mammography. Finally, this study did not evaluate the rate of false positive findings leading to magnetic resonance imaging or biopsy.

In conclusion, mammography revealed more diffuse changes in the WBRT group as opposed to localized findings in the IORT group in terms of skin thickening, edema, and the increase in parenchymal density. US demonstrated significantly more ill-defined non-mass lesions and circumscribed masses in the IORT group, while fluid collections and linear and planar scars were more typical for WBRT. Radiologists should especially be aware of ill-defined non-mass lesions, which are considerably more common in patients who received IORT, because they can be confusing, especially in early follow-up studies. This study found that minor findings were seen more frequently in low-density breasts, while major findings were more common in high-density breasts on both mammography and US in the IORT group. This has not been reported before, and further studies with more cases are needed to verify these results.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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