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FULL PAPER

Does accelerated hypofractionated adjuvant whole-breast radiotherapy increase mammographic density or change mammographic features?

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Objective: To compare mammographic features before and after accelerated hypofractionated adjuvant whole-breast radiotherapy (AWB-RT) and to evaluate possible appearance of modifications.

Methods: A retrospective review of 177 females before and after an AWB-RT treatment (follow-up ranging from 5 to 9 years) was performed by four radiologists focused in breast imaging who independently evaluated diffuse mammographic density patterns and reported on possible onset of focal alterations; modifications in density and fibrosis with parenchymal distortion were deemed as indicators of AWB-RT treatment impact in breast imaging.

Results: Prevalent mammographic density (D) patterns in the 177 females evaluated were according to the American College of Radiology–Breast Imaging Reporting and Data System (ACR–BIRADS): D1, fibroadipose density (score percentage from 55.9% to 43.5%); and D2, scattered fibroglandular density (from 42.9% to 32.7%). No change in diffuse mammographic density and no significant difference in mammographic breast parenchymal structure were observed. “No change” was reported

with score percentage from 87% to 79.6%. Appearance of fibrosis with parenchymal distortion was reported by all radiologists in only two cases (1.1%, $p = 0.3$); dystrophic calcification was identified with percentage score from 2.2% to 3.3% (small type) and from 9.6% to 12.9% (coarse type).

Conclusion: No statistically significant changes in follow-up mammographies 5–9 years after AWB-RT were detected, justifying large-scale selection of AWB-RT treatment with no risk of altering radiological breast parameters of common use in tumour recurrence detection.

Advances in knowledge: The hypofractionated radiotherapy (AWB-RT treatment) is a new proven, safe and effective modality in post-operative patients with early breast cancer with excellent local control and survival. In our study, the absence of changes in mammographic density patterns and in breast imaging before and after AWB-RT treatment (up to 5–9 years after radiotherapy) justifies large-scale use of AWB-RT treatment without hindrance in tumour recurrence diagnosis.

INTRODUCTION

Adjuvant whole-breast radiotherapy (AWB-RT) after breast conservative surgery is the usual standard of care in combined modality treatment approach to early breast cancer (EBC), usually being performed in 5-week intervals with fractionated schedule (1.8–2 Gy daily) up to a total dose of 50 Gy with subsequent tumour bed boost dose of 10–16 Gy; overall treatment time is 6–7 weeks.¹ At the “Local Health

Authority Turin 4” Radiation Oncology Department, a different scheme of radiotherapy hypofractionation (called accelerated hypofractionated AWB-RT) has been in use since 2005, delivering lower nominal total dose in larger and fewer fractions representing a valid alternative for both patient and healthcare providers with reduction in hospital turn-arounds, increase in patient throughput and lower costs.² Basic course of AWB-RT consisted of 45 Gy whole-breast

dose in 20 fractions with 2.25 Gy/fraction with two opposing 6-MV tangential field (using three-dimensional confirmed radiotherapy); additional daily 0.25 Gy boost dose was concomitantly delivered to lumpectomy cavity tantamount to an additional total dose of 5 Gy, using a direct 6-MV photon field.

The cumulative nominal dose was 50 Gy in 4 weeks. The same isocentre was used for both tangents and boost field. This was also used as the normalization point. Acceptable levels of coverage for both whole-breast planning target volume (WB-PTV) and concomitant boost planning target volume (CB-PTV) were as follows: 95% of PTV was required to receive a minimum of 95% dose, and 99% of PTV was required to receive a minimum of 90% dose.³

For set-up, patients were positioned on a wingboard with both arms raised above the head and radio-opaque markers along breast borders. Subsequently, the 5-mm-thick-slice axial images were acquired from the lower mandible aspect to lung bases; an isocentre was found in virtual simulation. The whole-breast clinical target volume (WB-CTV) encompassed breast palpable tissue, with a superior–inferior border within the extent of the radio-opaque catheters. A uniform limit of 5 mm separated the WB-CTV from the skin surface and the thoracic wall. The WB-PTV was generated by adding a 5-mm isotropic margin around the WB-CTV. The definition of the tumour bed was driven by radio-opaque clips placed during surgery. The CB-CTV was generated by adding a 5-mm isotropic margin around the tumour bed; the consequent planning target volume (CB-PTV) required a further margin of 5 mm around the CB-CTV. The heart and ipsilateral lung were separately contoured as organs at risk: the heart was outlined to the pulmonary trunk superiorly, including pericardium and excluding major vessels.

AWB-RT proved to be as effective as conventional whole-breast radiotherapy (WBRT).^{3,4} After 60-month median follow-up (range, 42–88 months) and with percentages of 97.6% for 5 year overall survival, 99.4% for cancer-specific survival, 96.6% for disease-free survival and 100% for local control (LC), the AWB-RT was officially introduced into clinical practice with excellent or good cosmetic results and with no major toxicity and outperformed conventional WBRT.

With continuous increase in AWB-RT application, diagnostic radiologists were faced with a diagnostic dilemma in follow-up studies fearing that evaluation of breast parenchymal structures could be somehow hindered by this procedure: a retrospective evaluation of radiological findings of common usage in mammography was thus undertaken before and after AWB-RT in order to detect whether AWB-RT could modify diffuse mammographic density or create focal parenchymal changes such as fibrotic changes with parenchymal distortions.

METHODS AND MATERIALS

Out of 247 females who underwent accelerated hypofractionated AWB-RT after conservative surgery for EBC (pathological stage pTis, pT1 or pT2, pN0–N1) at the “Local Health Authority Turin 4” Radiation Oncology Department from February 2005

to June 2009, a subgroup of 177 females with all radiological follow-up studies from 2010 to 2014 performed at the “Local Health Authority Turin 4” Radiologies (particularly at “Ivrea Community Hospital” and “Cirié Community Hospital”, in province of Turin, Italy) was finally selected. Patients who were lost to follow-up or had scheduled mammographies performed at other locations were not considered in our study.

Mammographies were independently examined by four radiologists specialized in breast images; pre-treatment analogue examinations obtained either with Siemens Mammomat® (Siemens Healthcare, Erlangen, Germany) 3000 or GE Senographe® (GE Healthcare, Waukesha, MI) 800T were compared with four yearly follow-up digital mammograms from 2010 to 2014 with GIOTTO® I.M.S (IMS, Bologna, Italy) after AWB-RT treatment completion (follow-up ranging, 5–9 years).

All images complied with current quality requirements in mammography such as high contrast, good spatial resolution, optimal radiation beam penetration, dose reduction and correct positioning and breast compression. All mammography systems were equipped with radiolucent compressors with rigid and not deformable structure characterized by chamfer edges to avoid breast trauma and straight profile on chest side. Well-known benefits of good compression are reduction in scattered radiation, better breast tissue representation, reduction in motion artefacts and reduction in absorbed dose. In particular with GIOTTO® I.M.S X-ray photons, direct conversion is possible with 85-µm pixel size flat panel selenium detector allowing for satisfactory compromise between high spatial resolution and low noise; also significant dose reduction can be achieved by means of tungsten anode tube with a silver filter.

Mammographic density patterns were separately evaluated by each radiologist. According to the American College of Radiology–Breast Imaging Reporting and Data System (ACR-BIRADS)⁵ mammographic density (D) was classified into four categories: D1, “almost entirely fat” or fibroglandular tissue (FGT) <25%; D2, scattered FGT of 25–50%; D3, “heterogeneously dense” or FGT of 50–75%; and D4, “extremely dense” or FGT >75%.

The mammographic density was evaluated with visual quantitative classification (ACR-BIRADS) criteria because of a significant increase in cancer risk in breasts of higher density reported by some studies.^{6,7}

Modifications in breast parenchymal structures in follow-up radiograms were detected independently by each radiologist reporting the onset of signs such as: fibrosis (F) without parenchymal distortion or fibrosis with parenchymal distortion (F-with distortion) or small dystrophic calcification (S-calcification), coarse dystrophic calcification (C-calcification) or other alterations such as the association of more changes (F + S-calcification or F + C-calcification); if no change in density or in breast parenchymal structures were recorded when comparing first mammography and follow-up examinations after AWB-RT treatment, “no change” (N) was reported.

As fibrosis without parenchymal distortion and dystrophic calcification (small or coarse) after RT is indistinguishable from

similar alterations in ageing females, change in density and onset of fibrosis with parenchymal distortion (F-with distortion) were selected as parameters of possible impact of AWB-RT treatment in breast imaging.

The percentages of the parameters expressed by each radiologist on modifications in density and fibrosis with parenchymal distortion were used to evaluate the statistical significance of a possible AWB-RT treatment impact in breast imaging, using χ^2 statistics, with a “*p*-value” of 0.05 as significance limit. Closeness of agreement between radiologists in density pattern and breast parenchymal structure modification analysis was evaluated using Cohen’s kappa statistics.

RESULTS

177 females were included in this analysis, age ranging from 47 to 88 years (with average value of 71 ± 10 years).

Each of the four readers independently reviewed mammography performed at first diagnosis (in analogue mode) and assigned a visual density value of breast parenchymal structure based on quantitative classification (ACR-BIRADS). Prevalent mammographic patterns were ACR-BIRADS: D1 with a varying percentage from 55.9% (99/177) for Radiologist A to 43.5% (77/177) for Radiologist D, and D2 with a varying percentage from 42.9% (76/177) for Radiologist D to 32.7% (58/177) for Radiologist A, as shown in Table 1.

Closeness of agreement between four radiologists was high in the allocation of all four density categories, with an overall score about Density Categories of 0.81 Cohen’s kappa value (as shown in Table 2); each mammogram was compared with four follow-up mammograms performed from 2010 to 2014 after AWB-RT treatment (carried out between 2005 and 2009), alteration of density pattern was never detected.

Also, no significant differences in mammographic breast parenchymal structure were detected: “no change” (N) was reported with score percentage varying from 87% (154/177) for Radiologist A to 79.6% (141/177) for Radiologist D, as shown in Table 3. Overall closeness of agreement score between four radiologists about presence or absence of modifications was 0.89 Cohen’s kappa value (as shown in Table 4).

Appearance of fibrosis with parenchymal distortion (F-with distortion) secondary to AWB-RT was reported by all radiologists in only 2 of 177 mammograms examined (1.1%), both in young females (under 50 years of age) with high-density pattern (ACR-BIRADS: D3); fibrosis with parenchymal distortion was apparent from the first follow-up mammography and it also remained unchanged in the subsequent mammograms.

All calcifications visualized, even small ones, were of round morphology with radiolucent centre and typically benign radiological features. Dystrophic calcifications were identified with score percentage ranging from 2.2% (4/177, Radiologist A) to 3.3% (6/177, Radiologist D) in small calcification subgroup (S-calcification) and from 9.6% (17/177, Radiologist A) to 12.9% (23/177, Radiologist B) in coarse calcification subgroup (C-calcification).

Fibrosis without parenchymal distortion (F) (apparent as slight changes only in the last follow-up mammography) was reported in a few cases; four cases for Radiologist B and seven for Radiologist D (of these five cases of fibrosis were without parenchymal distortion not unlike those of ageing parenchyma; two cases of fibrosis were without parenchymal distortion associated with coarse calcifications). None of the 177 females presented tumour recurrence.

DISCUSSION

Mammographic density is an important parameter in breast imaging, with higher density linked to a decrease in sensitivity and specificity owing to the so-called “masking effect”^{8,9} jeopardizing the effectiveness of breast screening. In the ideal setting, radiotherapy performed after surgery should not lead to radiologically detectable changes of parenchymal structures, especially in females with high risk of tumour recurrence. Radiotherapy, widely used in current treatment of numerous malignancies, may be associated with unwanted effects in normal tissues surrounding the target tumour. While early effects (desquamation, erythema and hair loss) typically resolve, chronic ones persist as unpredictable and often troublesome sequelae of cancer treatment, long after oncological treatment has been completed.¹⁰ After breast-conserving surgery and radiation therapy, several breast alterations occur and evolve over time; mammographic findings such as breast oedema, skin thickening, fluid collections, architectural distortion and calcifications have nearly

Table 1. Distribution of the density categories (ACR-BIRADS density, “D”) assigned by the radiologists in the classification of the mammography performed at diagnosis

Radiologists	ACR-BIRADS density			
	D1, <i>n</i> (%)	D2, <i>n</i> (%)	D3, <i>n</i> (%)	D4, <i>n</i> (%)
A	99 (55.9)	58 (32.7)	10 (5.6)	10 (5.6)
B	78 (44)	75 (42.3)	15 (8.4)	9 (5)
C	97 (54.8)	60 (33.8)	9 (5)	11 (6.2)
D	77 (43.5)	76 (42.9)	15 (8.4)	9 (5)

ACR-BIRADS, American College of Radiology–Breast Imaging Reporting and Data System mammographic density (“D”) categories: D1—“almost entirely fat” or fibroglandular tissue (FGT) <25%; D2—scattered FGT of 25–50%; D3—“heterogeneously dense” or FGT of 50–75%; and D4—“extremely dense” or FGT >75%.

Table 2. Density categories: closeness of agreement between the four readers

Density score				
Radiologists	A	B	C	D
A	–	0.84	0.96	0.82
B	0.84	–	0.84	0.97
C	0.96	0.84	–	0.82
D	0.82	0.97	0.82	–

Cohen's kappa values about density: 0.81.

always a standardized pattern of evolution towards final stability whose awareness in conservative breast therapy minimizes unnecessary recalls from screening also permitting early detection of possible recurrences;¹¹ in one study, approximately half of the patients with breast cancer had fluid collections at the surgical site 4 weeks after surgery and about 25% after 6 months;¹² fluid collections generally subside and resolve completely 12–18 months after surgery, but a small number may persist after this interval.¹² Breast oedema and skin thickening are best appreciated when compared with contralateral breast or with pre-treatment mammograms. At mammography, maximal breast oedema and skin thickening are usually seen up to 6 months after completion of radiation therapy,¹³ then subsiding and attaining stability in the majority of females within 2–3 years.¹²

Architectural distortion in treated breast develops secondary to post-surgical scar formation and fat necrosis. Parenchymal scarring and fat necrosis can cause spiculated or irregular poorly marginated soft-tissue density with skin retraction mimicking recurrent malignancy; mammographic features more likely to suggest that benign architectural distortion rather than tumour recurrence may be ascertained such as central lucencies, varying appearance in different projections¹² and thick, curvilinear spiculations.¹¹ Architectural distortion usually diminishes in conspicuity and stabilizes in a 2-year period. In evaluating suspicious lesions, compression and magnification views are helpful in showing features of scarring excluding recurrent tumour.

Benign calcifications may develop at the post-operative site with a reported incidence of 28% 6–12 months after radiation therapy;¹² dystrophic calcifications generally develop in areas of fat necrosis, usually with round and coarse morphology or as smooth and large alterations often with lucent centres. Most calcifications with clear benign features in conservatively treated breast appear as thin arc-like rims surrounding radio-lucent oil cysts.¹¹ Suture material may also calcify with distinctive shapes, knot-like, rod-like and curvilinear and are most commonly observed in irradiated breast and only rarely after benign breast biopsy.

Hypofractionated radiotherapy (AWB-RT treatment) is a proven, safe and effective modality in post-operative patients with early breast cancer¹⁴ with excellent LC and survival, consistent cosmetic results and mild toxicity.³ Furthermore, AWB-RT treatment, delivering a lower nominal total dose in larger and fewer fractions (50 Gy in 4 weeks), allows both for fewer hospital visits and increase

Table 3. Modifications observed in radiograms performed in the years from 2010 to 2014 after 5–9 years of adjuvant whole-breast radiotherapy treatment

Radiologists	No change (N), n (%)	Fibrosis with parenchymal distortion (F-with distortion), n (%)	Fibrosis without parenchymal distortion (F), n (%)	Small dystrophic calcification (S-calcification), n (%)	Coarse dystrophic calcification (C-calcification), n (%)	Association of alterations (F+S-calcification), n (%)	Association of alterations (F+C-calcification), n (%)
A	154 (87)	2 (1.1)	–	4 (2.2)	17 (9.6)	–	–
B	143 (80.7)	2 (1.1)	4 (2.2)	5 (2.8)	23 (12.9)	–	–
C	153 (86.4)	2 (1.1)	–	5 (2.8)	17 (9.6)	–	–
D	141 (79.6)	2 (1.1)	5 (2.8)	6 (3.3)	21 (11.8)	–	2 (1.1)

Table 4. Modifications: closeness of agreement between the four readers

Modifications score				
Radiologists	A	B	C	D
A	–	0.93	0.99	0.90
B	0.93	–		0.93
C	0.99	0.95	–	0.91
D	0.90	0.93	0.91	–

Cohen's kappa values about modifications: 0.89

in patients turnover with better female compliance and satisfaction together with cost reduction.^{2,3}

In our study, modifications in mammographic density patterns and possible onset of parenchymal distortion associated to fibrotic changes in follow-up mammograms (up to 5–9 years after radiotherapy) were assessed in order to determine whether large-scale use of AWB-RT treatment was feasible with no hindrance in tumour recurrence diagnosis; mammographic density before and after AWB-RT treatment was evaluated according to ACR-BIRADS classification in four categories by comparing first mammography with the last four follow-up examinations.

No significant change in mammographic density was observed 5–9 years after AWB-RT treatment, and relevant changes in breast parenchymal structures were not recorded (with high agreement among four readers, particularly about modifications with a Cohen's kappa values of 0.89).

The high concordance degree among readers (Cohen's kappa values >0.80, equivalent to excellent agreement) also confirmed quantitative classification ACR-BIRADS as a valid diagnostic tool in mammographic density pattern evaluation, simple and handy although based on visual assessment.¹⁵

Result analyses regarding possible onset of fibrotic changes with parenchymal distortion in follow-up mammograms confirms that AWB-RT has no effect ($p = 0.3$) in breast imaging; the two reported cases (1.1%) occurred in high-density mammographic pattern (ACR-BIRADS: D3) with breast parenchymal structure alterations already evident at the first follow-up mammography with no further changes.

As described in other studies,^{16,17} annual mammography after breast conserving surgery with associated radiotherapy showed substantial results in recurrent cancer detection; as the majority of recurrent tumours are mammographically similar to primary tumours, pre-operative mammogram review is fundamental in follow-up of patients. In our study, no tumour recurrences were detected.

Our study has some limitations, mainly the relatively small sample size and over-representation of fibroadipose type (ACR-BIRADS: D1) mammographic density pattern, more prone to cell necrosis phenomena with dystrophic calcifications appearance and with limited parenchymal component.

Cell necrosis phenomena in fat tissue also explains the high percentage of benign calcifications in our series (from 2.2% to 3.3% regarding small calcification and from 9.6% to 12.9% regarding coarse calcification). All calcifications (even small ones) visualized in mammograms had round morphology often with radiolucent centre, thus were easily radiographically distinguishable from a possible tumour, and biopsy was never deemed of value.

In conclusion, neither significant changes in mammographic density nor significant onset of parenchymal distortion associated with fibrosis were detected in mammographies performed 5–9 years after AWB-RT treatment, thus supporting large-scale use of AWB-RT treatment without any risk of alteration of radiological parameters of common use in tumour recurrence diagnosis.

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