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FULL PAPER

Diagnostic value of halo sign in young women (aged 45 to 49 years) in a breast screening programme with synthesized 2D mammography

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Objective: To assess the clinical performance of the halo sign in tomosynthesis and synthesized 2D mammography, and to identify age groups where its diagnostic value may be greater.

Methods: 183 patients with nodules were recalled from the breast screening programme (with tomosynthesis and 2D synthesized mammograms). The patients were separated into two groups, 45–49 years and 50–69 years, and depending on the presence or not of halo sign. We calculated the predictive values for the different age groups.

Results: In 45–49 years group, 86 nodular lesions were recalled, 66 (76.7%) with positive halo sign and 20 (23.3%) with negative halo sign. In positive halo sign group, biopsy was considered in 23 (34.8%), with histological features of benignity. In 50–69 years group, 98

nodular lesions from 97 patients were recalled, 51 (52%) with positive halo sign and 47 (48%) with negative halo sign. In positive halo sign group, biopsy was considered in 13 (25.5%); four (30.8%) were malignant and nine (69.2%) were benign.

Conclusion: Halo sign could be considered as a marker of benign lesion in females < 50 years. In females ≥ 50 years, other breast imaging techniques should be considered, with or without histological studies, to rule out malignancy.

Advances in knowledge: The trend of a positive halo sign to act as a marker of benign lesion could be improve the recall rate and positive predictive values in the breast screening programme with tomosynthesis and synthesized 2D mammography, especially in young females.

INTRODUCTION

In 2011, the United States Food and Drug Administration (FDA) approved digital breast tomosynthesis used in combination with digital mammography for breast cancer screening; the effectiveness of this technology has been since then documented in multiple large-scale studies.^{1,2} In 2013, the FDA approved a version of 2D synthesized mammography software, which together with tomosynthesis for breast cancer detection, was not inferior to digital mammography alone, suggesting that it could be more effective for breast cancer screening with the additional benefit of limiting exposure to radiation.³

The results in some studies show that breast cancer screening with 2D synthesized mammograms and tomosynthesis improve the recall rate and positive predictive values without affecting cancer detection rates, in comparison to tomosynthesis and digital mammography or digital mammography alone.⁴ Most improvements in the detection results with 2D mammograms and tomosynthesis are associated to a better distinction between overlapping glandular tissue and the margins of the nodules, particularly in dense breasts.⁵ This would imply a decrease of recall or false positive in females aged 45 to 49 years. A well-circumscribed nodule is usually indicative of benign lesion. Sickles⁶ reported low probability of malignancy in circumscribed, non-palpable, non-calcified nodules, from which 1.4% were malignant.

Halo signs are frequently present in tomosynthesis images; thus, the margins of the circumscribed nodules appear lighter when this technique is used. On the other hand, it is unclear if 2D mammograms and tomosynthesis can help differentiate between benign and malignant circumscribed nodules.⁷ There is an emerging problem associated to the management of circumscribed nodules detected through this type of mammographic technique in the screened population.

We aim to assess the accuracy of the presence of a halo sign as a prognostic marker in recalled females from breast cancer screening programme. Furthermore, we intend to evaluate the possibility of differentiation by age group and to evaluate if we can identify specific age groups where its diagnostic value may be greater.

PATIENTS AND METHODS

The breast cancer early detection program in the province of Toledo (Spain) covers a health area of around 74,350 females between 45 and 69 years of age. We conducted a retrospective, descriptive study between October 2015 and May 2016. During this period, 18,511 females attended the screening program, from which 334 were recalled (1.8%). We detected 184 nodules with or without other associated disorders (such as microcalcifications and skin retraction) in 183 females recalled after the screening. Written informed consent was obtained from all subjects in this study.

Mammographic technique

For the study, we used 2D synthesized mammograms and tomosynthesis using the Selenia Dimensions mammography system (Hologic, Bedford, MA). Two views per breast were performed (craniocaudal and mediolateral oblique) that were interpreted by two breast imaging experts during the screening (2 to 20 years of professional experience), including the support of a computer-aided detection system.

Once nodules detected, additional examinations for recalled patients were performed with a 12 MHz Ultrasound Linear Probe (Aplio MX, Toshiba Medical Systems, Tokyo, Japan). Depending on the findings, ultrasound-guided 14G core-needle biopsy was also performed. Breast MRI (1.5 T Avanto, Siemens, Erlangen, Germany; using T_1 - and T_2 weighted imaging sequences, diffusion, and dynamic study post-gadolinium administration) was used in cancer staging. Nodule follow-up was done for 23 to 30 months, until April 2018.

The analysis of data was conducted in a comprehensive manner; the patients were separated into two age groups, 45–49 years and 50–69 years (pre- and postmenopausal females) and depending on the presence or not of a halo sign. The halo sign was defined as a thin hyperlucent ring that surrounds >50% of the contour of the nodule, detected in at least one mammographic view,⁷ as shown in the example of the [Figure 1](#) and [Supplementary Video 1](#), where positive halo sign is better visualized in 3D images of tomosynthesis followed by synthesized 2D mammogram and conventional 2D mammogram.

Figure 1. (a) Medium lateral oblique views of conventional 2D mammogram and (b) synthesized 2D mammogram, in woman from screening with a fibroadenoma in heterogeneously dense breast, whose edge with positive halo sign (thin radiolucent-line) is defined in more 75% in synthesized 2D mammogram compared to conventional 2D mammogram. Go to [Supplementary Video 1](#) to see the complete delimitation of halo sign in 3D image soft tomosynthesis.

Breast density was analyzed in each study subgroup (per age and presence of a halo sign) using the BI-RADS lexicon (predominantly fat -a-, scattered fibroglandular density -b-, heterogeneously dense -c-, and extremely dense -d-).⁸ In this work, the number of patients in the predominantly fat and extremely dense categories was small. Because of this, we grouped the four breast density categories in two: predominantly fatty or disperse (low-density group) and heterogeneously or extremely dense (high-density group).

The following findings were also analyzed: type of lesion (nodule, nodule with microcalcifications, or nodule with skin retraction), existence or not of previous mammography, density of the nodule compared to the density of the surrounding breast tissue (same or higher), evolution of nodule size, initial BI-RADS classification, presence or not of interventionism, and histological results.

Statistical analysis

Categorical variables were expressed as counts (percentages). We calculated the predictive values (sensitivity, specificity, positive and negative predictive value) for the general population and for the different age groups, aiming to evaluate the halo sign as predictor of benign breast disease.

Table 1. Main features of mammographic breast density, radiological findings, and histological results of nodular lesions in patients aged 45–49 and 50–69 years^a

	45–49 years		50–69 years	
	Halo (+) (n = 66)	Halo (-) (n = 20)	Halo (+) (n = 51)	Halo (-) (n = 47)
Breast density				
Low density	31 (47%)	8 (40%)	35 (68.6%)	35 (74.5%)
High density	35 (53%)	12 (60%)	16 (31.4%)	12 (25.5%)
Radiological findings				
Nodule	66 (100%)	17 (85%)	49 (96.1%)	43 (91.5%)
Nodule with microcalcifications	–	2 (10%)	2 (3.9%)	4 (8.5%)
Nodule with skin retraction	–	1 (5%)	–	–
Histological results ^a				
No biopsy	43 (65.2%)	5 (25%)	38 (74.7%)	9 (19.1%)
Benign	23/23 (100%)	6/15 (40%)	9/13 (69.2%)	2/38 (5.3%)
Risk lesion	–	–	–	1/38 (2.6%)
Malignant	–	9/15 (60%)	4/13 (30.8%)	35/38 (92.1%)

^aIn each age group there is a statistically significant difference ($p < 0.001$) between the groups with or without halo sign in relation to the histological results of benignity and malignancy (including risk lesions as malignant).

RESULTS

183 (54.8%) patients out of 334 were recalled because of nodular lesions with or without other associated disorders; 174 (52.1%) were nodules, 8 (2.4%) nodules with microcalcifications, and one (0.3%) nodule with skin retraction. One patient over 50 years old was recalled because of two nodules, one in each breast, with ultrasound diagnosis of simple cysts. There were 130 (70.7%) previous mammography in the total population, where the evolution of the size of the nodule was 12 (9.2%) equal, 52 (40%) greater and 66 (50.8%) new. Regarding density of the nodule compared to the density of the surrounding breast tissue, there were 83 (45.1%) with same density and 101 (54.9%) with higher density in the total population. In terms of initial BI-RADS classification, there were 143 (77.7%) BI-RADS 0 and 41 (22.3%) BI-RADS 4/5. In all this, no significant differences were found between the two age groups. Nodule follow-up was performed between 23 and 30 months, until April 2018, without changes in diagnostic behaviour.

The main features of mammographic breast density, radiological findings, and histological results of nodular lesions in study patients are described in Table 1. 86 patients between 45 and 49 years with 86 nodular lesions were recalled, 66 (76.7%) with positive halo sign and 20 (23.3%) with negative halo sign. The 66 (100%) patients with positive halo sign had nodules without other associated findings. Biopsy was considered in 23 nodules (34.8%), for which histological analyses revealed to be benign. Within the group of patients with negative halo sign (20 patients), 17 (85%) nodules, two (10%) nodules with microcalcifications, and one (5%) nodule with skin retraction were analyzed. Biopsy was considered in 15 cases (75%), from which nine (60%) showed histological features of malignancy and six (40%) were benign. From the nine nodules with malignant histology, eight (88.9%) were invasive ductal carcinoma and one (11.1%) carcinoma *in*

situ. The two nodules with microcalcifications, as well as the nodule with skin retraction were invasive ductal carcinomas as per the histological results.

98 nodular lesions from 97 patients older than 50 years were recalled, 51 of which (52%) had positive halo sign and 47 (48%) negative halo sign. Regarding the type of lesions with positive halo sign, 49 (96.1%) nodules and two (3.9%) nodules with microcalcifications were found. One of the two nodules with microcalcifications was stable with respect to tests performed in another center and provided by the patient; a biopsy was performed in the other nodule with a benign result. Biopsy was considered in 13 nodules (25.5%), for which the histology showed malignancy in four (30.8%) cases and nine (69.2%) appeared to be benign. The radiological evaluation of the four nodules with positive halo sign and malignant on histology, revealed lobulated/microlobulated contours. The anatomopathological characterization is shown in Table 2. Cases 1 and 2 (Figures 2 and 3, and Supplementary Videos 2 and 3), under 2 cm, underwent immediate surgery. The anatomopathological analysis of all borders for these two lesions showed a fibrous band with haemorrhagic foci. Case 3, being larger than 2 cm, underwent neoadjuvant chemotherapy; pathological complete remission was achieved following surgery. Case 4 was a diffuse large B-cell lymphoma; percutaneous biopsy and chemotherapy was performed. Within the groups of patients with negative halo sign (47 patients), 43 (91.5%) nodules and four (8.5%) nodules with microcalcifications were analyzed. The four nodules with microcalcifications were invasive ductal carcinomas. Biopsy was considered in 38 (80.9%) cases; in 35 (92.1%), the histology was malignant, one (2.6%) was determined to be a risk lesion (papilloma and radial scar), and two (5.3%) histologically benign. From the 35 histologically malignant nodules, 25 (71.4%) were determined to be invasive ductal

Table 2. Anatomopathological features of the four nodules with positive halo sign with malignant histology

	Case 1	Case 2	Case 3	Case 4
Type	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Lymphoma
Subtype	Medullary signs	Medullary signs	Medullary signs	–
Tumour grade	3	3	3	–
Hormone receptors	Negative	Negative	Negative	–
HER2	Negative	Negative	Negative	–
Ki-67	60%	90%	45%	80%
p53	Positive	Positive	Negative	Negative

carcinomas, seven (20%) invasive lobular carcinomas, and three (8.6%) were classified as other (invasive tubular-lobular, colloid, and tubular).

In the total population, including risk lesions as malignant, there was negative halo sign in 8 (15.1%) benign lesions and 45 (84.9%) malignant lesions, and positive halo sign in 32 (88.9%) benign lesions and 4 (11.1%) malignant lesions, with statistical significance ($p < 0.001$) between the two groups with or without halo sign, in relation to the distribution of the lesions.

In both age groups, there were statistically significant differences ($p < 0.001$) between the groups with or without halo sign in the distribution of benign and malignant histological results. We found four malignant lesions with positive halo sign in only within the 50–69 years group.

Table 3 describes the sensitivity, specificity and predictive values for the general population and the various age groups, establishing the halo sign as a predictor of benign lesion.

DISCUSSION

Nodular lesions are frequently found in recalled patients that participate in a screening program (54.8% in our series). The evaluation of the contours of these nodular lesions is possible with the aid of slices obtained by tomosynthesis and 2D mammograms that minimize tissue overlapping. This is of great relevance within the setting of breast cancer screening, as it helps to determine if a patient needs to be recalled, allowing an increase of specificity.

A feature to keep in mind when analysing the contour of nodular lesions is the halo sign, defined as a thin hyperlucent ring that surrounds >50% of the margin of the nodule and is detected

Figure 2. (a) Craniocaudal view of synthesized 2D mammogram and (b) ultrasound, in patient from screening with newly merging nodular lesion presenting microlobular margin and incomplete halo sign. See [Supplementary Video 2](#).

Figure 3. (a) Medium lateral oblique view of synthesized 2D mammogram and (b) ultrasound, in patient from screening with newly emerging nodular lesion presenting microlobular margins and in complete halo sign. See [Supplementary Video 3](#).

in at least one mammographic view.⁷ On the other hand, the mechanism and significance of the halo sign have changed in line with the development of mammography systems. Wolfe⁹ suggested that the halo sign results from the compression of fat by the circumscribing lesions. Moskowitz¹⁰ and Gordenne et al¹¹ challenged this theory, suggesting that the halo was a perceptual illusion (Mach band), associated with the principle of lateral inhibition: the eye is disturbed by adjacent structures with markedly different optical densities and seen not only around localized tumours in a fatty environment, but frequently also around fibroglandular tissue. Cupples et al¹² went a step further. They used an optical magnification method (magnifying glass or binocular microscope) and suggested that a halo is not always a perceptual illusion seen around benign and malignant lesions. Nakashima et al⁷ suspected that halo signs in digital mammography are magnified due to the contour highlight effect of image processing. Furthermore, in tomosynthesis, this contour highlight effect overlaps due to the reconstruction of a limited number of data samples with a narrow angular range of X-ray emissions.¹³ Although the cause of the halo sign has not yet been established, the presence of this sign is useful as an indicator of a smooth margin of the lesion at a macroscopic level and contributes to increase the contrast between a circumscribing mass and the surrounding breast tissue.⁷

In a study developed in Japan,⁷ the halo sign was recognized in three benign lesions in 2D mammograms; however, when tomosynthesis was used it was shown in 41 lesions, 30 benign and 11 malignant ($p = 0.988$). The authors concluded that, although tomosynthesis was superior in detecting circumscribed lesions, it was not possible to assure if they were benign. The limitation of this study is that the age of the subjects was not considered.

In our series of cases, we did take into account the age of the females recalled in the screening; two age groups were considered, 45 to 49 and 50 to 69 years. In our autonomous community screening is initiated at 45 years, unlike in the others (starting at 50). In females under 50 years, we detected halo signs in 79.3% benign lesions and their presence is a reliable marker (positive predictive value 100%) of benign lesions. In females ≥ 50 years, the halo sign identifies 81.8% of benign lesions and its presence implies slightly over half (69.2%) of the probability of a benign lesion. Regardless of the age, the presence of a halo sign identifies 80% of benign lesions and if a halo sign is seen, there is an 88.9% of probability that the patient has a benign lesion. In both age groups, and in the general population, the halo sign is a significant marker of benign lesion (in all cases with $p < 0.001$).

In our study, only four lesions with positive halo sign were malignant, found in the 50 to 69 age group, which could be influenced by the higher incidence of breast cancer in females aged ≥ 50 .^{14,15} Three of the lesions were medullary carcinomas hormone receptor- and HER2-negative, and with a Ki-67 higher than 45%. Histologically, this tumour shows well-defined borders, a lymphoplasmacytic infiltrate, and high-grade cells with sheet-like growth, without glandular or fibrosis formation.¹⁶ The histological features of this type of tumour do not explain its favourable prognosis.¹⁷ In 1989, Meyer et al¹⁸ described the mammography findings and ultrasonography of medullary carcinomas. The lesion commonly mimics a benign tumour, round or oval shaped with a well-defined lobulated contour. In ultrasound, the most common presentation is a hypoechoic lesion, generally with no attenuation of the sound and occasional cystic areas, similar to what we found in our series.

Concerning this aspect, the radiological description of the border of the malignant neoplasm could direct us to the histological type, as also reflected in one of our series,¹⁹ in which we characterize hidden breast cancers in tomosynthesis. These

Table 3. Accuracy of positive halo sign (and 95% confidence interval) as predictor of benign lesion on the general population and various age groups

	S	E	PPV	NPV
General population (including risk lesions as malignant)	80% (72%–88%)	91.8% (86%–97%)	88.9% (83%–95%)	85% (78%–92%)
Females aged 45 to 49 years	79.3% (71%–87%)	100% (95%–100%)	100% (95%–100%)	60% (50%–69%)
Females aged 50 to 69 years (including risk lesions as malignant)	81.8% (74%–89%)	90% (84%–96%)	69.2% (60%–78%)	94.7% (90%–99%)

E, specificity; NPV, negative predictive values; PPV, positive predictive values; S, sensitivity; PPV, positive predictive values.

neoplasms were invasive ductal carcinomas, poorly or moderately differentiated, most luminal B, with a worse prognostic outcome. Histologically, a mixture of non-neoplastic ducts and lobules characterizes these neoplasms.

There are several limitations in this study. First, the study was done with one center that uses only one tomosynthesis system. There is no assurance that the same results will apply to other tomosynthesis systems. Second, larger series are needed to confirm these findings and establish a larger number of subgroups with better diagnostic use.

From our findings, we conclude that the trend of a halo sign is to act as a marker of benign lesion in females < 50 years. In females ≥ 50 years, other breast imaging techniques should

be considered, with or without histological studies, to rule out malignancy.

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ETHICS APPROVAL

Institutional Review Board approval was not required because no new technology was used. Methodology: retrospective, case-control study, performed at one institution.

INFORMED CONSENT

Written informed consent was obtained from all subjects (patients) in this study.

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