

Contrast-enhanced mammography: imaging patterns of breast cancer molecular subtypes

Mamografía con medio de contraste: definiendo los patrones imagenológicos de los subtipos moleculares del cáncer de mama

Kelly Johana Corredor[1]
Sara Manuela Gil[2]
Melisa Naranjo Vanegas[3]
https://doi.org/10.53903/01212095.257

Key words (MeSH)
Breast Neoplasms
Mammography
Contrast media
Immunohistochemistry

Palabras clave (DeCS)
Neoplasias de la mama
Mamografía
Medios de contraste
Inmunohistoquímica

Summary

Introduction: Breast cancer (BC) is a heterogeneous disease, classified into three main intrinsic subtypes: hormone receptor positive (HR+), HER-2 oncogene overexpressing and triple negative (TN), each with representative imaging findings. Objective: Characterize and classify the findings of intrinsic subtypes of breast cancer using contrast-enhanced mammography imaging. ***Methodology:*** A descriptive analysis was conducted on a subsample of patients who were enrolled in a specialized diagnostic care program for breast pathology. From 2019 to 2022, clinical findings, histology, immunohistochemistry results and CEM (contrast-enhanced mammography) features were recorded from 71 patients with BC. ***Results:*** 49 cases of breast carcinoma that underwent CEM were hormone receptor positive, 3 had HER-2 enriched and 19 were triple-negative (TN). Spiculated tumors were associated with hormone receptor positive, calcifications occurred in hormone receptor positive and HER2 enriched, being more frequent in HER2 enriched breast cancer, and ring enhancement, was associated with the TN subtype. ***Conclusion:*** In the age of minimally invasive medicine, the use of contrast-enhanced mammography images to forecast intrinsic subtypes of breast cancer is an innovative and auspicious development. Nevertheless, gene expression analysis will continue to be the gold standard for the time being.

Resumen

Introducción: El cáncer de mama (CM) es una enfermedad heterogénea, clasificada en tres subtipos intrínsecos principales: receptores hormonales positivos (RH+), con sobreexpresión del oncogén HER2 y triples negativos (TN), cada uno de ellos con hallazgos imagenológicos representativos. ***Objetivo:*** Caracterizar y clasificar los hallazgos de los subtipos intrínsecos del CM utilizando imágenes de mamografía con medio de contraste endovenoso. ***Metodología:*** Se realizó un análisis descriptivo de una submuestra de pacientes atendidas en un programa especializado en diagnóstico de patología mamaria. Se tomaron 71 pacientes con CM, se analizaron los datos clínicos y los hallazgos en mamografía con medio de contraste (CEM, por su sigla en inglés Contrast-Enhanced Mammography), así como los resultados de la histopatología e inmunohistoquímica durante los años 2019 a 2022. ***Resultados:*** De los 71 casos de carcinoma mamario a los que se les realizó CEM, 49 fueron RH+, 3 tuvieron sobreexpresión del oncogén HER2 y 19 fueron TN. Los tumores espiculados se asociaron con los RH+, las calcificaciones se presentaron en los RH+ y HER2 sobreexpresados, más frecuentes en los HER2 sobreexpresados, y el realce en anillo se asoció con el subtipo TN. ***Conclusiones:*** La predicción de los subtipos intrínsecos del CM a partir de las imágenes de mamografía con medio de contraste resulta novedosa y prometedora en la era de la medicina mínimamente invasiva. Sin embargo, por el momento el análisis de la expresión génica seguirá siendo el estándar de oro.

[1]Radiologist, women's imaging line, Medical Imaging Group, SURA Diagnostic Aids. Medellín, Colombia.

[2]Pathologist, leader of molecular cytopathology line, Personalized Medicine group, Ayudas Diagnósticas SURA. Medellín, Colombia.

[3]Physician, MSc. in Epidemiology, MPH, Clinical Research Group, Ayudas Diagnósticas SURA. Medellín, Colombia.

Introduction

In Colombia, about 15,500 new cases of breast cancer (BC) are diagnosed each year and more than 4,000 women die from this disease (1). Therefore, it is of interest to expand the knowledge of BC beyond the traditional classification, which was based solely on histopathological characteristics.

The new characterization of BC based on immunohistochemical markers, estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2), classifies this disease into three main subtypes: HR+, HER2-overexpressing and TN. The incorporation of this new classification has made it possible to establish predictive categories of aggressiveness and to perform personalized treatments with receptor-targeted therapies.

HR+ BC accounts for 70% of all breast cancers. They are usually grade tumors with good response to hormonal therapy (2). Tumors with HER2 oncogene

amplification account for 14% of all breast cancers, they are usually intermediate to high grade tumors, with an aggressive course and a higher risk of lymph node involvement. These tumors respond to drugs directed against the oncogene, such as trastuzumab, a drug approved in 2006 by the FDA for the treatment of HER2+ cancers, which resulted in a 52% reduction in disease recurrence and a 33% reduction in mortality rate (3). TN tumors account for 16 % of all BC (4), are characterized by lack of ER, PR and HER2 expression (5), show aggressive histological features, are associated with a high incidence of interval cancer (6, 7) and have poor clinical outcome compared to the other intrinsic breast cancer subtypes (7, 8); they respond better to chemotherapy than HR+ tumors.

Methods

A retrospective descriptive study was performed on a subsample of 71 patients with BC who underwent contrast-enhanced mammography from February 2019 to January 2022. Tumor characteristics on contrast-enhanced mammography (CEM) were reviewed for lesion type, presence of microcalcifications, dominant lesion size, shape, margins, enhancement type, and breast density type. From the pathology reports we obtained the type of tumor primary, histologic grade, presence of satellite nodes and axillary lymph node metastases, as well as the status of immunohistochemical markers.

The main indications for which contrast-enhanced mammography was performed were: staging 84.5 % (60 of 71), for diagnostic doubts in conventional mammography and ultrasound 7 % (5 of 71), for suspected tumor recurrence 4 % (3 of 71), for palpable mass 1 % (1 of 71) and for multiple bilateral nodules 3 % (2 of 71).

Contrast-enhanced mammography images were acquired on Hologic Selenia equipment and the ER, PR and HER-2 status was determined by immunohistochemistry analysis from the tissue obtained from the Trucut biopsy, from which the histopathological characteristics of the tumor were also obtained.

All tumor lesions were interpreted using the morphological criteria described for contrast-enhanced mammography in the supplement to the "ACR-BI-RADS Mammography 2013" which was published in 2022 (9). The instrument used for data collection was a database designed in Excel, filled out by a radiologist physician with expertise in breast imaging; subsequently, the clinicopathological and contrast-enhanced mammography characteristics were compared among the three intrinsic tumor subtypes.

Results

Seventy-one patients with breast carcinoma were analyzed, with a mean age of 49 years (SD 11.08). Of the cases analyzed, 49 (69 %) were HR+, 19 (27 %) TN and 3 HER2 (4 %) overexpressed (Table 1). The most frequent histological type in all cases was infiltrating ductal carcinoma (83.8 %).

Table 1. Patients with breast cancer: molecular classification according to intrinsic subtype

Molecular subtype	Immunophenotype	No. of patients (%)
RH positive	ER+ and/or PR+, HER2-+	49 (69 %)
HER2 overexpressed	ER-, PR-, HER2+	3 (4 %)
Triple negatives	ER-, PR-, HER2-	19 (27 %)

The variables most commonly expressed in HR+ patients were: mass-like lesion (53 %), irregular shape (65 %), non-circumscribed/spiculated margin (30 % and 16 %), heterogeneous enhancement (57 %), calcifications (14 %), multifocality/multicentricity (49 %) (Figures 1 and 2). Nodal involvement (28.5 %). Histological grade 1 and 2 were the most frequent (38.8 % and 38.8 %, respectively).

The variables most frequently expressed in the overexposed HER-2 subtype were: non-mass type lesion (67 %), heterogeneous enhancement (100 %), calcifications (67 %), lymph node involvement (67 %), multifocality/multicentricity (33 %) and histologic grade 3 (67 %) (Figure 3).

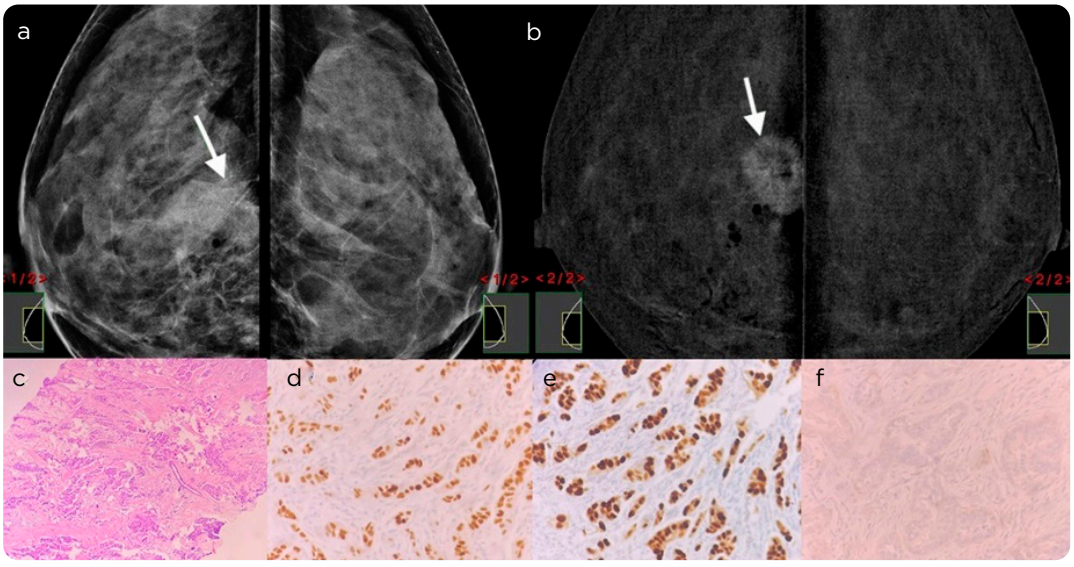


Figure 1. 53-year-old female patient with an infiltrating ductal carcinoma in the right breast histologic grade 2, Ki67: 28 % with RH+ subtype. a and b) Low energy and recombinant EMF image in craniocaudal view. Irregular mass, spiculated, with heterogeneous enhancement of the contrast medium. c) Histopathology with hematoxylin and eosin staining at 10x. d) ER strong intensity at 100 %. e) RP strong intensity at 90 %. f) HER2 negative (1+).

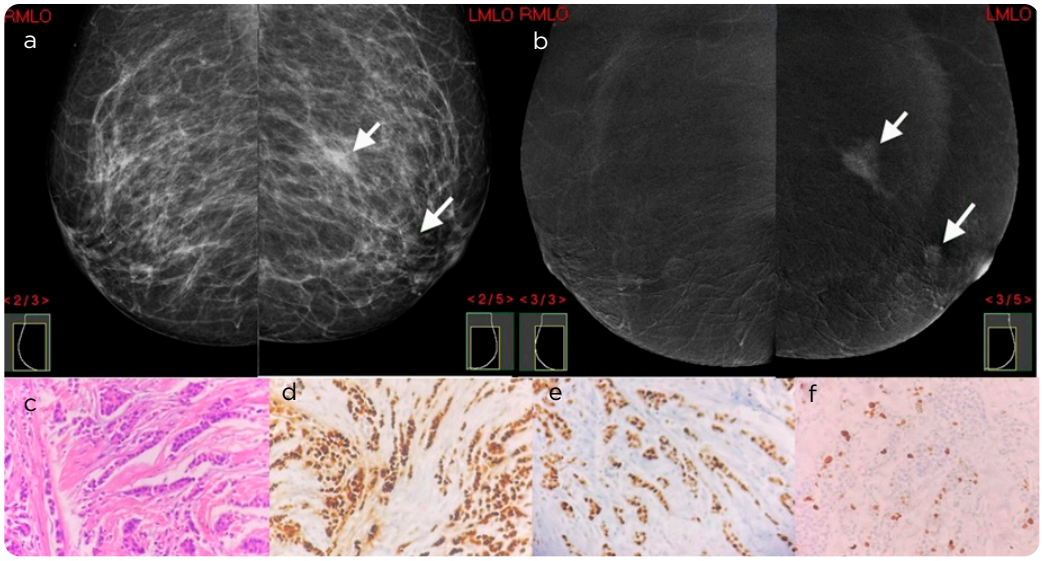


Figure 2. 43-year-old female patient with a multifocal infiltrating ductal carcinoma in left breast, histologic grade 2, Ki67: 35 % with RH+ subtype. a and b). Low-energy, recombinant EMF image in mediolateral oblique view. Two masses with irregular shape and heterogeneous enhancement of the contrast medium. c) H&E at 40x. d) ER in 100 % strong intensity. e) PR with strong intensity in 100 %. f) HER2 negative (1+).

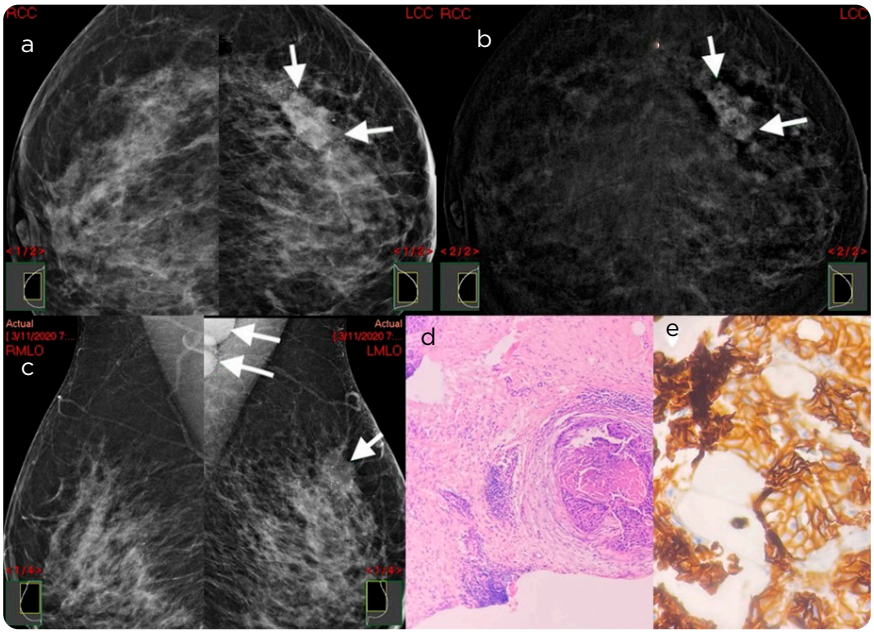


Figure 3. 46-year-old female patient with an infiltrating ductal carcinoma in the superoexternal quadrant of the right breast, histologic grade 3 Ki67: 50 % with overexpressed HER-2 subtype. a and b). Low-energy, recombinant EMF image in craniocaudal view. c) Low-energy EMF image in mediolateral oblique view. Mass with pleomorphic calcifications, irregular shape, indistinct margins and heterogeneous enhancement of the contrast medium. It is associated with metastatic involvement in the left homolateral axilla (arrows). d) H&E at 10x. e) HER2 positive (3+), strong membrane staining.

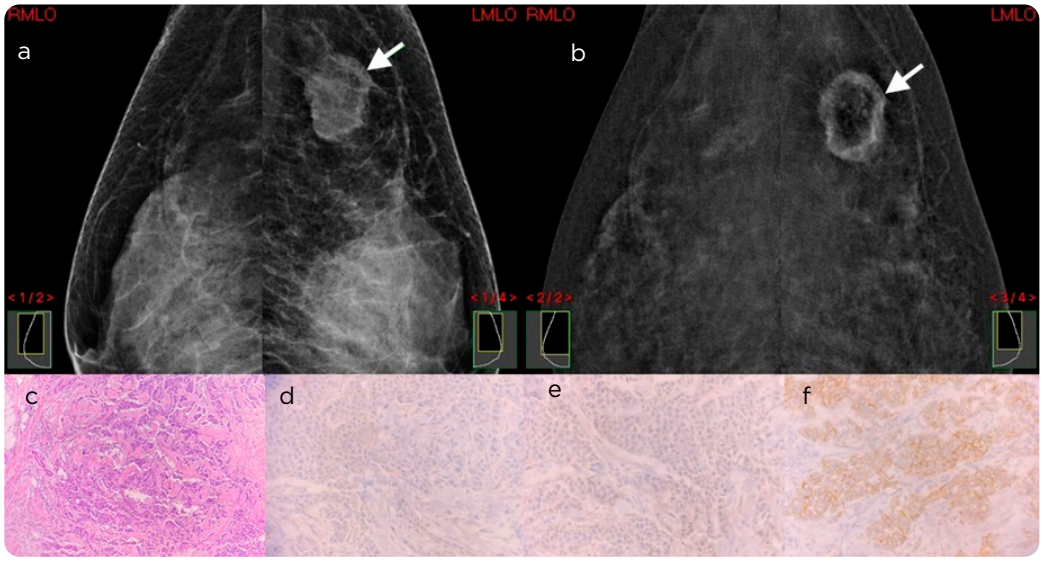


Figure 4. 42-year-old female patient with an infiltrating ductal carcinoma in the left breast, histologic grade 2, Ki67: 35 % with Triple negative subtype. a and b) Low energy and recombinant EMF image in mediolateral oblique view. Round-shaped mass, mostly circumscribed margins with real margins mostly circumscribed with ring enhancement of the contrast medium (arrow), without calcifications. c) H&E at 10x. d) ER negative. e) PR negative. f). HER2 negative 1+, weak membrane staining.

In TN tumors the most frequent lesion was mass-like enhancement (79 %), round/oval shape (68 %), non-circumscribed margin (42 %), heterogeneous internal and ring enhancement (47 % and 21 %, respectively), calcifications (15 %), multifocality/multicentricity (21 %) and lymph node involvement (26 %); most were histological grade 3 (68 %) (Figure 4); 84 % of these tumors showed a size larger than 2 cms (16/19), 66 % in HER2 overexpressing (2/3) and 67 % in HR+ (33/49).

Regarding breast parenchyma, 66 % of HER2 overexpressing subtypes are associated with dense/markedly dense glandular tissue compared to 57 % in TNs and 21 % in RH+ tumors.

The characteristics of the EMF images and histopath is shown in Table 2.

Table 2. Intrinsic breast cancer subtypes: EMF and histopathological imaging characteristics

Characteristics	RH+ (*n*=49)	HER2+ (*n*=3)	TN (*n*=19)
Pathology			
Invasive ductal carcinoma of non-special type	40 (81.6)	3 (100.0)	18 (95.0)
Poorly differentiated malignant neoplasm	0 (0.0)	0 (0.0)	1 (5.0)
Ductal carcinoma in situ	1 (2)	0 (0.0)	0 (0.0)
Infiltrating micropapillary carcinoma	4 (8.1)	0 (0.0)	0 (0.0)
Infiltrating mucinous carcinoma	1 (2.2)	0 (0.0)	0 (0.0)
Infiltrating lobular carcinoma	3 (6.1)	0 (0.0)	0 (0.0)
Axillary lymph node involvement			
Yes	14 (28.5)	2 (67.0)	5 (26.0)
No	35 (71.5)	1 (33.0)	14 (74.0)
Histological grade			
Grade I	19 (38.8)	0 (0.0)	0 (0.0)
Grade II	19 (38.8)	1 (33.0)	6 (31.5)
Grade III	11 (22.4)	2 (67.0)	13 (68.4)
Abnormal features in mammography with contrast medium			
Mass-like lesion	26 (53.0)	1 (33.0)	15 (79.0)
Non-mass type lesion	23 (47.0)	2 (67.0)	4 (21.0)
Size of dominant lesion less than 2 cms	16 (33.0)	1 (33.0)	3 (16.0)
Size of dominant lesion greater than 2 cms	33 (67.0)	2 (67.0)	16 (84.0)
Oval/round shape	17 (35.0)	1 (33.3)	13 (68.0)
Irregular shape	32 (65.0)	0 (0.0)	1 (5.0)
Circumscribed margin	4 (8.0)	0 (0.0)	6 (31.5)
Uncircumscribed margin	15 (31)	1 (33.3)	8 (42.1)
Spiculated margin	8 (16.0)	0 (0.0)	0 (0.0)
Homogeneous enhancement	10 (20.0)	0 (0.0)	3 (16.0)
Heterogeneous enhancement	28 (57.0)	3 (100)	9 (48.0)
Ring enhancement	2 (4.0)	0 (0.0)	4 (21.0)
Multinodular enhancement	9 (19.0)	0 (0.0)	2 (11.0)
Tumor-associated calcifications			
Yes	7 (14.0)	2 (67.0)	3 (15.0)
No	42 (86.0)	1 (33.0)	16 (85.0)
Multifocality/multicentricity			
Yes	24 (49.0)	1 (33.3)	4 (21.0)
No	25 (51.0)	2 (66.6)	15 (79.0)
Fatty glandular/fibroglandular tissue disperse	28 (57.0)	1 (33.3)	8 (42.0)
Fatty glandular/fibroglandular tissue dense	21 (43.0)	2 (66.6)	11 (58.0)

Discussion

The results showed that in contrast-enhanced mammography the spiculated margin was a feature that was only present in RH+ BC (16%). Li et al., in the correlation study between EMF imaging characteristics and the different molecular subtypes explained that this may be due to the fact that the cells in this tumor type infiltrated along the duct, obtaining their nutrition mainly from peripheral neovessels (10).

Other important findings in RH+ tumors were calcifications in 14 % of cases and the tendency to be multifocal/multicentric (49 %).

Regarding subtypes overexpressing the HER2+ oncogene, studies such as those by Seo (11) and Wang (12) reported an increased association of these tumors with calcifications. Similarly, the results of the study documented here showed that the presence of calcifications was higher in HER2-overexpressing tumors (67 %) than in TN tumors (15 %).

Compared to RH+ tumors and TNs, lymph node involvement was higher in the HER2-overexpressing subtype (67 % vs. 28.5 % and 26 %, respectively). In this study, non-mass-like enhancement was also more frequent in HER2+ tumors (67% vs. 47% and 21%, respectively).

Regarding TN tumors, they presented as mass-like lesions (79%), with oval/round shape (68%), without calcifications (85%) and with a tumor size larger than 2 cms (84%). These results are similar to previous publications (10, 13-15).

Our data showed that TN were often nuclear grade 3 (68 % vs. 67 % and 22 % of HER2 and RH+); similarly, 66 % of TN breast cancers described by Dent et al. were high grade (6), suggesting that they are extremely malignant with a high degree of local invasion.

One of the most striking features of TNs on EMF imaging was postcontrast EV ring enhancement (21 %). Uematsu et al. explained that this phenomenon reflects central necrosis due to the rapid growth of these tumors (16).

In comparison with conventional mammography, the advantages of contrast injection mammography are that it can overcome the superimposition effect of normal breast tissue and eliminate the fibroglandular tissue of the breasts, which allows a better characterization of the type of tumor lesion, the shape, margin, distribution and enhancement pattern of the tumors; characteristics that are decisive in predicting the tumor subtype of breast cancer. Conventional mammography, on the other hand, has the advantage of evaluating calcifications, a finding that is especially useful in differentiating HR+ and HER2-overexpressing tumors from TN.

In conclusion, the combination of morphologic detail of calcifications provided by low-energy imaging and functional information provided by intravenous contrast medium could be useful in predicting specific intrinsic subtypes of breast cancer.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869-74.
3. Romond EH, Pérez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.
4. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010;363(20):1938-48.
5. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumors. Nature. 2000;406(6797):747-52.
6. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429-34.
7. Collett K, Stefansson IM, Eide J, Braaten A, Wang H, Eide GE, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. Cancer Epidemiol Biomarkers Prev. 2005;14(5):1108-12.
8. Pal SK, Childs BH, Pegram M. Triple negative breast cancer: unmet medical needs. Breast Cancer Res Treat. 2011;125(3):627-36.
9. Lee CH, Philips J, Sung JS, Lewin JM, Newell MS. Contrast Enhanced Mammography (CEM). A supplement to ACR BI-RADS Mammography 2013. American College of Radiology. 2022.
10. Li N, Gong W, Xie Y, Sheng L. Correlation between the CEM imaging characteristics and different molecular subtypes of breast cancer. Breast. 2023;72:103595.
11. Seo BK, Pisano ED, Kuzimak CM, Koomen M, Pavic D, Lee Y, et al. Correlation of HER-2/neu overexpression with mammography and age distribution in primary breast carcinomas. Acad Radiol. 2006;13(10):1211-8.
12. Wang S, Wang Z, Li R, You C, Mao N, Jiang T, et al. Association between quantitative and qualitative image features of contrast-enhanced mammography and molecular subtypes of breast cancer. Quant Imaging Med Surg. 2022;12(2):1270-80.
13. Fallenberg EM, Dromain C, Diekmann F, Engelken F, Krohn M, Singh JM, et al. Contrast-enhanced spectral mammography versus MRI: Initial results in the detection of breast cancer and assessment of tumour size. Eur Radiol. 2014;24(1):256-64.
14. Łuczyńska E, Heinze-Paluchowska S, Hendrick E, Dyczek S, Ryś J, Herman K, et al. Comparison between breast MRI and contrast-enhanced spectral mammography. Med Sci Monit. 2015;21:1358-67.
15. Xiang W, Rao H, Zhou L. A meta-analysis of contrast-enhanced spectral mammography versus MRI in the diagnosis of breast cancer. Thorac Cancer. 2020;11(6):1423-32.
16. Uematsu T, Kasami M, Yuen S. Triple-negative breast cancer: correlation between MR imaging and pathologic findings. Radiology. 2009;250(3):638-47.

Correspondence

Kelly Johana Corredor Carrascal
SURA Diagnostic Aids
Bioentrepreneurship Unit, Biosciences Center
Carrera 48 # 26A-50, second floor Medellín, Colombia
kellycorredorca@gmail.com

Received for evaluation: March 15, 2023
Accepted for publication: April 26, 2023