

# Predictive factors of invasion in ductal carcinoma *in situ* diagnosed by core-needle biopsy

## Factores predictivos de invasión en carcinoma ductal *in situ* diagnosticado por biopsia con aguja de corte

Felipe Villegas-Carlos<sup>1</sup>, Verónica Andino-Araque<sup>2</sup>, Margarita Valverde-Quintana<sup>3</sup>, Kictzia Y. Larios-Cruz<sup>4</sup>, Yosef Pérez-González<sup>1</sup>, Juan J. Solano-Pérez<sup>1</sup>, and Eva Ruvalcaba-Limón<sup>1\*</sup>

<sup>1</sup>Department of Breast Surgical Oncology, Fundación del Cáncer de Mama A.C. (FUCAM), Mexico City, Mexico; <sup>2</sup>Department of Mastology, Centro Médico Hospital Axxis, Quito, Ecuador; <sup>3</sup>Department of Pathology, Fundación del Cáncer de Mama A.C. (FUCAM), Mexico City, Mexico; <sup>4</sup>Department of Radiology and Imaging, Fundación del Cáncer de Mama A.C. (FUCAM), Mexico City, Mexico

### Abstract

**Objective:** To identify clinical, radiological, and histopathological characteristics that could be predictive factors of microinvasive/invasive breast carcinoma in patients with diagnosis of ductal carcinoma *in situ* (DCIS) by core-needle biopsy. **Material and methods:** This is a retrospective study conducted from 2006-2017, which included women  $\geq 18$  years of age with initial DCIS, and who were treated with surgery. Final diagnosis was divided in DCIS and microinvasive/invasive carcinoma. **Results:** 334 patients were included: 193 (57.8%) with DCIS and 141 (42.2%) with microinvasive/invasive carcinoma (microinvasive 5.1%, invasive 37.1%). Lymph node metastasis occurred in 16.3%. Differences between DCIS and microinvasive/invasive groups included the presence of palpable nodule (36.7% vs. 63.2%), radiological nodule (29% vs. 51%), bigger radiological-tumor size (1.2 cm vs. 1.7 cm), and larger microcalcification extension (2.5 cm vs. 3.1 cm), all of these variables  $p \leq 0.05$ . Hormonal receptors and HER2 expression were similar. After logistic regression analysis, predictive factor of invasion was the presence of palpable nodule (OR = 4.072, 95%CI = 2.520–6.582,  $p < 0.001$ ) and radiological multicentric disease (OR = 1.677, 95%CI = 1.036–2.716,  $p = 0.035$ ). **Conclusions:** In patients with DCIS, palpable nodule, and radiological multicentric disease, upgrade to microinvasive/invasive is high, and sentinel lymph node is recommended.

**Keywords:** Ductal carcinoma *in situ*. Predictive factors. Microinvasive carcinoma

### Resumen

**Objetivo:** Identificar características clínicas, radiológicas e histopatológicas como factores predictivos de carcinoma mamario microinvasor/invasor en pacientes con Carcinoma Ductal *In Situ* (CDIS) diagnosticado mediante aguja de corte. **Material y métodos:** Estudio retrospectivo de 2006–2017, en mujeres  $\geq 18$  años con CDIS diagnosticado con aguja de corte y tratadas con cirugía. Los diagnósticos finales fueron CDIS y carcinoma microinvasor/invasor. **Resultados:** Se incluyeron 334 pacientes, 193 (57.8%) con CDIS y 141 (42.2%) con carcinoma microinvasor/invasor (microinvasor 5.1%, invasor 37.1%). Hubo 16.3% casos con afección ganglionar. Las diferencias entre el grupo de CDIS y carcinoma microinvasor/invasor fue la presencia de tumor palpable (36.7% vs. 63.2%), nódulo visto por imagen (29% vs. 51%), tumores más grandes (1.2 cm vs.

### Correspondence:

\*Eva Ruvalcaba-Limón

Av. Bordo, 100,

Col. Viejo Ejido de Santa Úrsula Coapa C.P. 04980,

Alcaldía Coyoacán, Ciudad de México, México

E-mail: evaruvalcaba@yahoo.com.mx

Date of reception: 09-02-2021

Date of acceptance: 27-02-2021

DOI: 10.24875/CIRU.21000136

Cir Cir. 2022;90(1):41-49

Contents available at PubMed

www.cirugiaycirujanos.com

0009-7411/© 2021 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1.7 cm), y mayor extensión de microcalcificaciones (2.5 cm vs. 3.1 cm), estas variables con  $p \leq 0.05$ . Los receptores hormonales y HER2 fueron similares. En el análisis de regresión logística, los factores predictivos de invasión fueron tumor palpable ( $OR = 4.072$ ,  $IC95\% = 2.520-6.582$ ,  $p < 0.001$ ) y multicentricidad radiológica ( $OR = 1.677$ ,  $IC95\% = 1.036-2.716$ ,  $p = 0.035$ ). **Conclusiones:** En CDIS, tumor palpable y enfermedad multicéntrica radiológica, el escalamiento a carcinoma microinvasor/invasor es alto y es recomendable realizar ganglio centinela.

**Palabras clave:** Carcinoma ductal in situ. Factores predictivos. Carcinoma microinvasor

## Introduction

Breast cancer is the most frequent malignant neoplasm in women worldwide, both in new cases and in mortality<sup>1</sup>. In Mexico, Globocan 2018 estimated 27,283 new cases and 6,884 deaths<sup>2</sup>. Ductal Carcinoma *In Situ* (DCIS) is a heterogeneous group of pathologies with malignant proliferation of the mammary epithelial cells that are confined inside the basal membrane of the lobular duct unit<sup>3,4</sup>. Before 1980, DCIS was considered a rare condition, fewer than 5% of all cases of breast cancer. The most common presentation of DCIS comprise microcalcifications, and the diagnosis of this pre-invasive lesion has increased during recent years due to breast-cancer screening programs with mammography, with an incidence of up to 20%<sup>5</sup>. The prevalence of DCIS at our Institution is reported as 6.8%<sup>6</sup>.

DCIS is considered a precursor to invasive carcinoma, although not all DCIS progresses. Patients with untreated DCIS could be diagnosed with invasive breast cancer in 20-53%, according to data obtained from long-term studies. Some cases with DCIS have a slow growth disease and that never exerted an impact on health<sup>7-9</sup>. Invasive carcinoma usually developed within the first decade of the DCIS diagnosis<sup>8</sup>. Breast cancer mortality 10 years after the diagnosis of DCIS is less than 2%<sup>10</sup>.

Some factors are related to the recurrence of DCIS, such as younger age, positive surgical margins, tumor size, grade, and the presence of comedonecrosis<sup>11</sup>. Sentinel Lymph Node Biopsy (SLNB) is indicated in patients with DCIS undergoing mastectomy when there is a high suspicion of invasive carcinoma in the surgical specimen, such as younger age (less than 40 years), palpable tumor<sup>12</sup>, tumors >2.5 cm, multicentricity, extensive microcalcifications, high-grade lesions, and comedonecrosis. The upgrade or coexistence of an invasive component and/or microinvasion is reported in 25-35.9% in final surgical specimens of patients with an initial biopsy of DCIS<sup>13,14</sup>. SLNB also could be carried out in patients in whom

surgery could affect lymphatic flow drainage<sup>15</sup>, with a reported procedure in 18% of SLNB in patients with DCIS who underwent conservative surgery<sup>16</sup>. The objective of the present study is to identify the clinical, radiological, and histopathological characteristics that could be predictive factors of microinvasive/invasive carcinoma in patients with an initial diagnosis of DCIS by core-needle biopsy.

## Materials and Methods

This is a retrospective, cross-sectional, and analytical study that included consecutive patients with an initial diagnosis of DCIS and who were treated with surgery from January 2006 to June 2017, at a breast pathology referral institution that cares for women from an open population of the metropolitan area of Mexico City. Inclusion criteria were women aged  $\geq 18$  years, a diagnosis of DCIS performed with guided imaging or office core-needle biopsy, and treatment with mastectomy or conservative breast surgery. Patients were excluded if they underwent a previous excisional biopsy, they had incomplete information in their clinical records, and/or if they had metaplastic carcinoma in the final histopathological study. SLNB was conducted if the patient underwent mastectomy or if conservative surgery could compromise the performance of a future SLNB. At the Institution, SLNB is carried out with a double technique employing a preoperative radiotracer and 1 ml of peri-areolar Patent Blue V (Bleu patenté V, Sodique Guerbet 2.5%; Laboratory Guerbet, 95943 Roissy CdG Cedex, France).

Analyzed variables included age, Body Mass Index (BMI), clinical aspects of the disease, breast density, imaging features and the extension of radiological lesions, tumor grade, and immunohistochemistry. DCIS grade was evaluated in the biopsy specimen and was catalogued as grade I, II, or III. Immunohistochemistry for hormonal receptor status, HER2 expression, and Ki67 was carried out on the final surgical specimen (mastectomy or conservative surgery). Positive

hormonal receptor status was considered if the Estrogen Receptor (ER) or the Progesterone Receptor (PR) was  $\geq 1\%$ . Ki67 was classified as low if it was  $<20\%$ <sup>17</sup>, this cut-off point apparently better for classifying sub-rogate subtypes<sup>18,19</sup>.

Patients were divided into two groups: those with an initial and final diagnosis of DCIS, and those with an initial diagnosis of DCIS and a final diagnosis of invasive or microinvasive carcinoma in the histopathological surgical specimen.

## Statistical analysis

Descriptive statistics with central tendency, dispersion, measurement of frequencies, and a univariate analysis were carried out to describe the included population. Fisher exact test was used for categorical variables, while Mann–Whitney *U* test was utilized for differences between quantitative variables. A non-conditional logistic regression model was performed for multivariate analysis. Covariates were selected in a forward stepwise manner to identify predictive factors for invasive or microinvasive carcinoma. The study was approved by the Institutional Ethics and Research Committee. Two-sided  $p \leq 0.05$  was considered statistically significant, and the SPSS ver. 23.0 statistical software package for Windows was used.

## Results

From 2006–2017, we included 334 patients in the study with an initial diagnosis of DCIS who underwent surgical treatment. Average age was 51.7 years (range, 24–98 years). Mean BMI was  $27.9 \pm 5.3$  kg/m<sup>2</sup>, with 67% in overweight/obesity (Table 1). A family history of breast cancer in at least one first-degree member or in two second-degree members of the family was documented in 41 (12.3%) of patients. The presence of a palpable lump was documented in 117 (35%) cases, with a median tumor size of 3 cm.

All patients had digital mammography and high-resolution ultrasound. According to the American College of Radiology (ACR) classification, the most frequent breast density was B type with 211 (63.2%) cases, (Table 1). Imaging findings were evaluated. The presence of a nodule or mass detected by imaging studies occurred in 128 (38.3%) of patients, with a clinical median tumor size of 1.5 cm; microcalcifications was present in 276 (82.6%), with a median

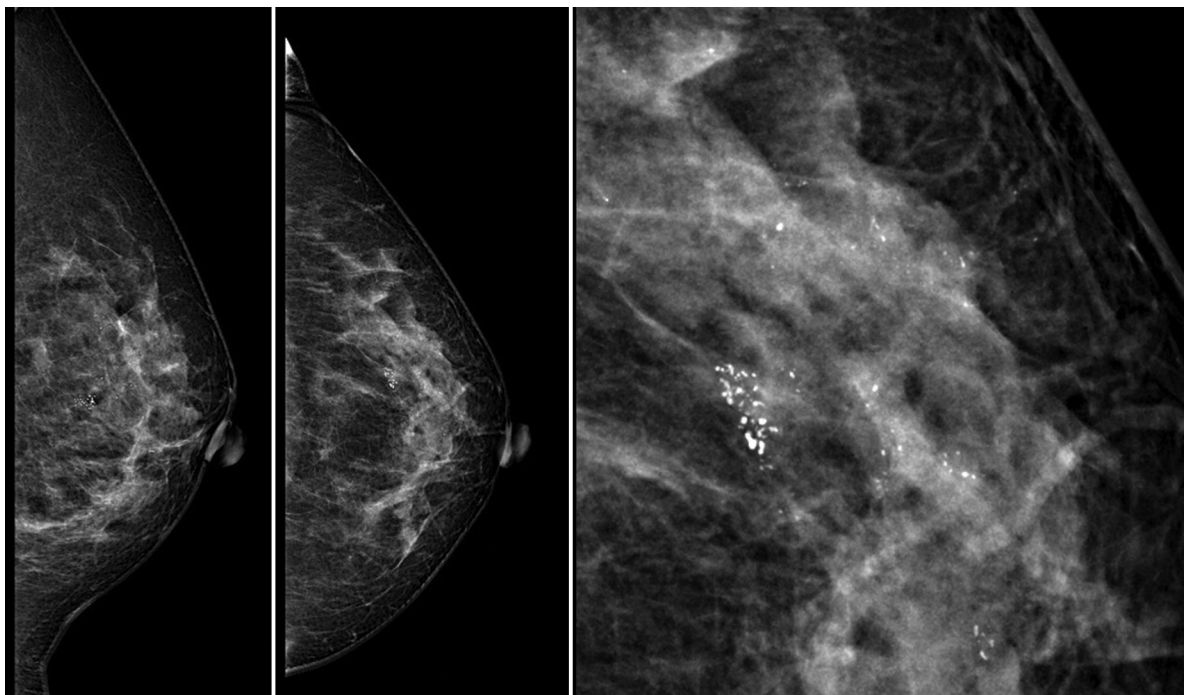
**Table 1. Sociodemographic, disease, and immunohistochemical characteristics**

Variable	Total
Patients	334
Age (years)	51.7 $\pm$ 10.9
BMI (kg/m <sup>2</sup> )	27.9 $\pm$ 5.3
Normal	110 (32.9%)
Overweight	131 (39.2%)
Obesity	93 (27.8%)
Palpable nodule	117 (35%)
Palpable nodule size (cm)	3 (0.8–7.5)
Breast density	
A	19 (5.7%)
B	211 (63.2%)
C	94 (28.1%)
D	10 (3%)
Presence of radiological nodule	128 (38.3%)
Radiological tumor size (cm)	1.5 (0.2–7.1)
Microcalcifications	276 (82.6%)
Microcalcification extension (cm)	2.7 (0.4–12)
Multicentricity	117 (35%)
Grade*	
I	39 (11.7%)
II	131 (39.2%)
III	164 (49.1%)
Surgical procedure	
Conservative surgery	91 (27.2%)
Mastectomy	237 (70.9%)
Pathological stage	
0	193 (57.8%)
I (mic)	17 (5.1%)
I	57 (17.1%)
IIA	39 (11.7%)
IIB	17 (5.1%)
IIIA	8 (2.4%)
IIIB	0
IIIC	2 (0.6%)
SLNB	275 (82.3%)
Lymph node metastasis in SLNB, <i>n</i> = 275	45 (16.3%)
Immunohistochemistry**	
Estrogen receptor	
Positive	239 (71.6%)
Negative	95 (28.4%)
Progesterone receptor	
Positive	200 (60%)
Negative	134 (40%)
HER2 ( <i>n</i> = 239)	
Positive	97 (40.6%)
Negative	142 (59.4%)
Ki 67 ( <i>n</i> = 262)	
Median expression (%)	10% (0–85)
Ki67 expression	
Low ( $\leq 20\%$ )	214 (81.7%)
High ( $> 20\%$ )	48 (18.3%)

Nominal variables are expressed as number and percentage. Scale variables are expressed as mean  $\pm$  Standard Deviation (SD) or median with minimal-maximal values.

BMI = Body Mass index; SLNB=Sentinel Lymph Node Biopsy.

\* Biopsy specimen; \*\* Final surgical specimen.



**Figure 1.** Digital mammography on left breast with cluster pleomorphic microcalcifications with a biopsy histopathological report of Ductal Carcinoma In Situ (DCIS), with the definitive histopathological study reporting two microinvasion foci within the DCIS.

extension size of 2.7 cm, and one-third of the included population had multicentric disease in radiological studies, the majority of these with a microcalcification focus (Fig. 1). In the biopsy specimen, DCIS grade III was the most frequent histopathological grade in 164 (49.1%) patients (Figs. 2-3). The most frequent surgery was mastectomy in 237 (70.9%) patients.

According to immunohistochemistry in the final surgical specimen, positive ER and PR were identified in 71.6% and 60% of patients, respectively. HER2 expression was evaluated in 239 patients. The most common HER2 status was negative expression in 142 (59.4%) patients. Determination of Ki67 has been carried out since the year 2010 at the Institution. Since that date and according to the inclusion criteria, 262 had a Ki67 evaluation. The median proliferation marker Ki67 was 10%, considered as high expression (>20%) in 48 (18.3%) patients.

After surgery, the final histopathological study of the surgical specimen identified 193 (57.8%) patients with DCIS, microinvasive carcinoma in 17 (5.1%), and invasive carcinoma in 124 (37.1%) patients. The predominant invasive pathological stages were pI and pIIA in 113 (33.8%) patients.

Sociodemographic variables did not reveal any differences between patients with final DCIS or with

invasive carcinoma (Table 2). According to disease features and immunohistochemistry, the variables associated with the presence of invasion or microinvasion were the presence of a palpable lump (36.7% vs. 63.2%), and the presence of a radiological nodule (29% vs. 51%), both features with statistically significant differences. Tumor size in imaging studies also demonstrated significant differences between groups (1.2 vs. 1.75 cm,  $p = 0.015$ ), and between the extension of microcalcifications (2.5 vs 3.1 cm,  $p < 0.001$ ). According to the core-needle biopsy device information ( $n=200$ ), the thinner the cutting needle, the greater the chance of invasive component, being 29.3%, 38%, and 58.7% with 10-gauge, 11-gauge, and 14-gauge, respectively ( $p=0.006$ ).

Median Ki67 expression was higher in patients with invasive carcinoma (5% vs. 10%,  $p = 0.005$ ), but if the comparison had employed the cut-off point of 20%, there were no differences. Other variables, such as palpable tumor size, breast density, the presence of microcalcifications, radiological multicentric disease, grade, hormonal receptor, and overexpression of HER2 had no statistically significant differences.

SLNB was carried out in 275 patients, 43 conservative surgeries, and in 232 mastectomies. Sentinel lymph node detection was 99.2%; in two patients,

**Table 2. Sociodemographic, disease, and immunohistochemistry characteristics between DCIS and microinvasive/invasive carcinoma**

Variable	DCIS	Microinvasive/invasive carcinoma	p
Patients	193	141	
Age (years)	52.5±11.4	50.5±10	0.175
BMI (kg/m <sup>2</sup> )	27.6±5.2	28.4±5.3	0.118
BMI (WHO classification)			0.130
Normal	69 (35.6%)	41 (29.3%)	
Overweight	79 (40.7%)	52 (37.1%)	
Obesity	46 (23.7%)	47 (33.6%)	
Palpable nodule, n = 117	43 (36.7%)	74 (63.2%)	<0.001
Palpable nodule size (cm)	3 (1–6.9)	3 (0.8–7.5)	0.634
Palpable nodule by range			0.343
≤2 cm	12 (27.9%)	27 (36.5%)	
>2 cm	31 (72.1%)	47 (63.5%)	
Breast density			0.691
A	9 (4.6%)	10 (7.1%)	
B	121 (62.4%)	90 (64.3%)	
C	58 (29.9%)	36 (25.7%)	
D	6 (3.1%)	4 (2.9%)	
Presence of radiological nodule	56 (29%)	72 (51%)	<0.001
Radiological nodule tumor size (cm)	1.2 (0.2 – 6)	1.7 (0.4–7.1)	0.015
Microcalcifications	159 (82.3%)	117 (82.9%)	0.137
Microcalcification size (cm)	2.5 (0.4 –12)	3.1 (0.4–12)	<0.001
Multicentricity	60 (31.1%)	57 (40.4%)	0.146
Core-needle biopsy, n = 200			0.006
10-gauge	12 (70.6%)	5 (29.4%)	
11-gauge	49 (62.0%)	30 (38.0%)	
14-gauge	43 (41.3%)	61 (58.7%)	
Grade*			0.510
I	26 (13.4%)	13 (9.3%)	
II	75 (38.7%)	56 (40.0%)	
III	93 (47.9%)	71 (50.7%)	
Grade I/II	101 (52.1%)	69 (49.3%)	
Grade III	93 (47.9%)	71 (50.7%)	0.617
Surgical procedure			
Conservative surgery	48 (24.8%)	0	
Conservative surgery + SLNB	22 (11.4%)	21 (14.9%)	
Mastectomy	4 (2%)	1 (0.7%)	
Mastectomy + SLNB	115 (59.6%)	117 (82.9%)	
Immunohistochemistry**			
Estrogen receptor			0.592
Positive	141 (72.7%)	98 (70%)	
Negative	53 (27.3%)	42 (30%)	
Progesterone receptor			0.386
Positive	120 (61.9%)	80 (57.1%)	
Negative	74 (38.1%)	60 (42.9%)	
HER2 (n = 239)	108	131	0.453
Positive	41 (38%)	56 (42.7%)	
Negative	67 (62%)	75 (57.3%)	
Ki 67 (n = 262)	150	112	
Median expression (%)	5% (0–85)	10% (1–80)	0.005
Ki67 expression			0.425
Low (≤20%)	125 (83.3%)	89 (79.5%)	
High (>20%)	25 (16.7%)	23 (20.5%)	

Nominal variables are expressed as number and percentage. Scale variables are expressed as mean±Standard Deviation (SD) or median with minimal-maximal values.

DCIS=Ductal Carcinoma In Situ; BMI=Body Mass Index; SLNB=Sentinel Lymph Node Biopsy;

\*Biopsy specimen; \*\*Final surgical specimen.



axillary lymph node dissection was performed because there was no migration of radiotracer nor of the blue dye, both cases without lymph node metastases at the final histopathological study. Lymph node metastasis was reported in 45 (16.3%) of the 275 cases who underwent SLNB.

In the multivariate analysis using the logistic regression model, including all variables except immunohistochemistry ( $n = 344$ ), the variables considered as predictive factors for invasive/microinvasive carcinoma were the presence of a palpable nodule (OR = 4.072) and radiological multicentric disease (OR = 1.677), both with statistically significant differences (Table 3). In the logistic regression model, including all variables and immunohistochemical features ( $n = 170$ ), the sole variable found associated with invasion was a palpable nodule (OR = 3.248, 95%CI = 1.642–6.421,  $p = 0.001$ ).

## Discussion

The presence of invasive and microinvasive carcinoma at the final histopathological study in patients with an initial diagnosis of DCIS reported in 21% and 14%, respectively<sup>20</sup>. In the present study, the prevalence of invasive carcinoma was much higher (38%), and that of microinvasive carcinoma was much lower (4.2%).

The variables identified predicting invasion were palpable nodule, high DCIS grade, and the presence of an opacity by mammography<sup>20</sup>. In the meta-analysis published by Brennan et al.<sup>13</sup>, which included 52 studies with 7,350 patients, the preoperative variables associated with the underestimation of invasive carcinoma were the presence of a palpable lesion, the use of a 14-gauge automated biopsy device, high-grade DCIS, the presence of a mammographic mass, and a BI-RADS category of 4 or 5. The underestimation of invasive carcinoma was 25.9% (95% CI = 22.5%–29.5%). When the lesion is observed as a mass, an ultrasound guided biopsy is conducted, upstaging is as high as 42.7%, with the identification of four predictive factors in order to upstage as follows: a palpable lesion; a lesion size of >2 cm; a high-grade lesion, and the use of the 14-gauge needle method<sup>21</sup>. In the present study, with 334 patients with an initial diagnosis of DCIS, upstaging with different biopsy techniques was 42.2%, and the only predictive factors identified in the present study were the presence of palpable tumor and multicentric disease in the imaging studies. Even the thinner the cutting needle, the greater the chance of invasive component, but it

**Table 3. Logistic regression model for predicting microinvasion/invasion in patients with an initial diagnosis of DCIS**

Variable	OR	95% CI	<i>p</i>
Palpable nodule	4.072	2.520–6.582	<0.001
Multicentric disease	1.677	1.036–2.716	0.035

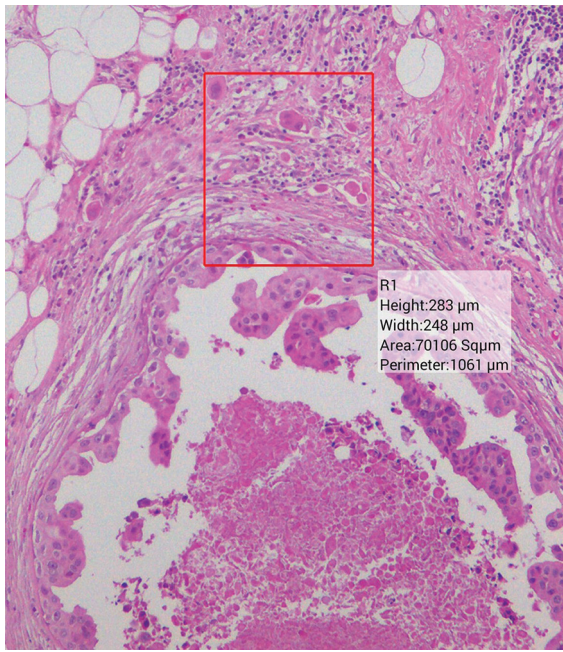
DCIS = Ductal Carcinoma In Situ.

had no statistical significance in multivariable analysis.

There is a great deal of variability in predictive factors, both in the characteristics and in the number of features to take into account on suspecting the presence of microinvasive/invasive carcinoma and for considering a patient as a candidate for SLNB, even in conservative surgery. The more frequent variables identified in patients with DCIS as diagnosed by core-needle biopsy are palpable tumor<sup>13,20,22</sup>, the presence of a nodule or mass in imaging studies (mammogram and/or ultrasound)<sup>13,20,23</sup>, High-grade DCIS<sup>13,19,20,21,24</sup>, and a tumor size of >2 cm<sup>13,21,23–25</sup>. Some authors proposed a larger tumor size, such as Maffuz et al.<sup>26</sup> with tumors >2.5 cm, and Yen et al.<sup>27</sup> with  $\geq 4$  cm as a predictive factor of invasion. In the present study, after multivariate analysis, the sole two predictive factors of microinvasion/invasion were palpable tumor and the presence of multicentric disease in the imaging studies.

Other predictive factors for microinvasion that are described in the literature with less frequency are the presence of comedo-like necrosis, hormone receptor negativity, and radiological features such as a high degree of vascularization<sup>28</sup>, peri-tumoral vascular invasion, multifocality/multicentricity that correlate with larger lesions, and a tumor grade of  $\geq 2$ <sup>29</sup>. In the present study, multicentric disease identified in imaging studies was one of the two predictive factors in the multivariate analysis.

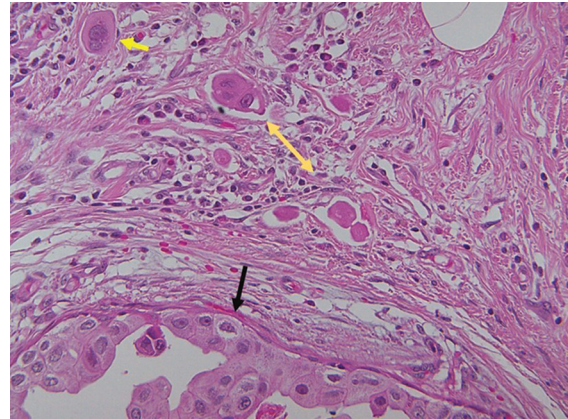
Younger age is also reported as a predictive factor of the invasive component. Trentin et al.<sup>23</sup> reported an age of <40 years, a mammographic size of >2 cm, and residual lesion on post-vacuum-assisted breast biopsy mammogram, such variables being associated with the invasive component. Yen et al.<sup>27</sup> reported 20% of invasive carcinoma at final pathology and identified four variables associated with the former: an age of  $\leq 55$  years; diagnosis by core-needle biopsy; mammographic lesion of  $\geq 4$  cm, and high-grade DCIS. In the present study, age was similar between groups.



**Figure 2.** Photomicrograph (10X) H&E section. Presence of micro-invasive foci (<1 mm) associated with high-grade Ductal Carcinoma In Situ (DCIS), with a micropapillary and comedonecrosis pattern.

For DCIS masses that underwent ultrasound-guided biopsy, predictive factors of invasion were the final BI-RADS assessment category and a high nuclear grade. With elastography, the maximal stiffness value was higher in the invasive carcinoma group<sup>30</sup>. Recently, Sun et al.<sup>31</sup> proposed a nomogram including five independent factors associated with a histological upgrade from DCIS to invasive carcinoma. The included variables comprised the presence of high-grade DCIS, positive HER2 expression, a pattern of comedonecrosis, larger lesion size, and a higher mean of shear-wave velocity value identified by elastography, with an Area Under the Curve (AUC) of 0.896. If elastography is not included, the AUC was 0.788. This tool could be helpful in deciding which patient should undergo SLNB even in breast conservative surgery, due to the high suspicion of invasive carcinoma. The limitation of this nomogram lies in that not all DCIS lesions are visible by ultrasound, and elastography could not be performed.

Considering immunohistochemistry, in a retrospective study of 219 cases, Wan et al.<sup>19</sup> identified that patients with DCIS with microinvasion have a lesser expression of hormonal receptors and a higher expression of HER2. In our study, hormonal receptor status and HER2 expression (in patients in whom the test was



**Figure 3.** Photomicrograph (40X) H&E section. Presence of invasive neoplastic cells (yellow arrows) with basal membrane rupture (black arrow) without myoepithelial cells (microinvasive carcinoma).

carried out), there were no differences between them. A high proliferation index based on Ki67 expression in a DCIS biopsy is considered as a risk factor for disease recurrence<sup>32</sup>, and a lack of evidence for considering this marker as a predictive factor of upstaging to invasive carcinoma, in addition to their being a controversy in terms of the cut-off point. In a recent study by Lui et al.<sup>33</sup>, upstaging to microinvasive carcinoma was associated with high-grade DCIS, large tumor size, comedonecrosis, the absence of hormonal receptors, HER2 overexpression, and a high Ki67 index ( $\geq 14\%$ ), while for invasive carcinoma, the associated variables were high-grade DCIS, large tumor size, a high Ki67 index ( $\geq 14\%$ ), and lymph node metastasis.

In the present study, Ki67 was not processed in 21.8% of the included patients, because this tumor marker has been employed at the Institution since 2010 and is usually carried out in the final histopathological surgical specimen. Even if Ki67 expression were higher in patients with a microinvasive/invasive component, we would not be able to recommend this marker as a predictive factor due to the incomplete information available on these variables.

SLNB should not be performed routinely for all patients with an initial diagnosis of DCIS. Given the low probability of positive lymph node metastasis, this one is documented approximately 1%–13%. The majority of these identified such micrometastases and detected these by immunohistochemistry<sup>20,34,35</sup>. American Society of Clinical Oncology (ASCO) guidelines<sup>36</sup> recommended SLNB in patients with DCIS when mastectomy is performed. There are efforts to identify predictive

factors of lymph node metastasis in patients with an initial diagnosis of DCIS who underwent breast conservative surgery, with published SLNB published in 18% and positive sentinel lymph node metastasis in 0.9%<sup>16</sup>. In patients with a high suspicion of the invasive component, SLNB is indicated<sup>24,33</sup>. These factors usually are the same factors as those identified by the underestimation of invasive carcinoma. Yen et al.<sup>27</sup> recommended SLNB in younger patients, DCIS diagnosed by core-needle biopsy, or high-grade DCIS. The only variable identified as a predictive factor of positive sentinel lymph node was the presence of a palpable lesion. There is no consensus for decision-making. In a previous report deriving from our Institution of patients with as initial diagnosis of DCIS, SLNB were performed in patients undergoing mastectomy, in those with a palpable tumor, a radiological lesion of  $\geq 5$  cm, with an inadequate breast/tumor relationship, and/or in patients in whom surgery could affect lymphatic flow drainage. Patients with positive sentinel lymph nodes were younger (44.5 vs. 51 years), with more palpable tumors, larger clinical and radiological lesions, with a greater comedonecrosis pattern, more undifferentiated tumors, and fewer cases with hormonal receptors, all of these variables without statistically significant differences<sup>22</sup>. The predictive factors of nodal involvement identified by Trentin et al.<sup>23</sup> included a mammographic size of  $>2$  cm and residual lesion in the post vacuum-assisted breast-biopsy mammogram.

## Conclusions

In this retrospective study of 334 patients with an initial diagnosis of DCIS with core-needle biopsy, the global upgrade was 42.2% (38% invasive and 4.2% microinvasive carcinoma), higher than reports in the literature. In the presence of DCIS with palpable nodule and radiological multicentric disease, SLNB should be conducted due to the high probability of an upgrade and the chance of axillary lymph node metastasis, regardless of the type of surgery. Another aspect that needs to be explored in order to diminish underestimation of the invasive component is improvement in biopsy techniques to obtain more tissue samples with thicker needles.

## Acknowledgements

The authors thank FUCAM for supporting research.

## Conflicts of interest

The authors who took part in this study declare that they do not have anything to disclose regarding funding or conflicts of interest concerning this manuscript.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

## References

1. International Agency for Research on Cancer. World Health Organization. Cancer Today. GLOBOCAN 2018. <https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf> Consultation date: 26 November 2020.
2. International Agency for Research on Cancer. World Health Organization. Cancer Today. GLOBOCAN 2018. <https://gco.iarc.fr/today/data/factsheets/populations/484-mexico-fact-sheets.pdf> Consultation date: 26 November 2020.
3. Broders AC. Carcinoma in situ contrasted with benign penetrating epithelium. *JAMA* 1932;99(2):1670-4.
4. Wellings SR, Jensen HM. On the origin and progression of ductal carcinoma in the human breast. *J Natl Cancer Inst* 1973;50(5):1111-8.
5. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67: 439-48.
6. Maffuz-Aziz A, Labastida-Almendares S, Espejo-Fonseca A, Rodríguez-Cuevas S. Características clinicopatológicas del cáncer de mama en una población de mujeres en México Clinical and pathological features of breast cancer in a population of Mexico. *Cir Cir*. 2017 May-Jun;85(3):201-207.
7. Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. *Breast Cancer Res Treat*. 2006;97(2):135-44.
8. Sanders ME, Schuyler PA, Simpson JF, Page DL, Dupont WD. Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow-up. *Mod Pathol*. 2015;28(5):662-9.
9. Collins LC, Tamimi RM, Baer HJ, Connolly JL, Colditz GA, Schnitt SJ. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. *Cancer*. 2005;103(9):1778-84.
10. Fisher ER, Dignam J, Tan-Chiu E, Costantino J, Fisher B, Paik S, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. *Cancer*. 1999; 86(3):429-38.
11. Virnig BA, Tuttle T, Shamlan T, Kane RL. Ductal Carcinoma in situ of the breast: a Systematic review of incidence, treatment and outcomes. *JNCI*; 2010;102:170-8.
12. Schneider C, Trocha S, McKinley B, Shaw J, Bielby S, Blackhurst D, et al. The use of sentinel lymph node biopsy in ductal carcinoma in situ. *Am Surg* 2010;76(9):943-6.
13. Brennan ME, Turner RM, Ciatto S, Marinovich ML, French JR, Macaskill P, et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. *Radiology*. 2011;260:119-28.
14. Miyake T, Shimazu K, Ohashi H, Taguchi T, Ueda S, Nakayama T, et al. Indication for sentinel lymph node biopsy for breast cancer when core biopsy shows ductal carcinoma in situ. *Am J Surg*. 2011;202:59-65.
15. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer, NCCN Evidence Block. Version 1.2021.



16. James TA, Palis B, McCabe R, Pardo JA, Alapati A, Ukandu O, et al. Evaluating the role of sentinel lymph node biopsy in patients with DCIS treated with breast conserving surgery. *Am J Surg*. 2020;220(3):654-9.
17. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26(8):1533-46.
18. Escala-Cornejo RA, García-Muñoz M, Olivares-Hernández A, Sancho de Salas M, Gómez-Muñoz MA, Claros Ampuero J, et al. Identifying the best Ki67 cut-off for determining luminal breast cancer subtypes using immunohistochemical analysis and PAM 50 genomic classification. *EMJ Oncol*. 2020;8(1):47-8. Abstract Review No. AR3.
19. Wan Z-B, Gao H-Y, Wei L, Zhang A-Q, Zhang J-Y, Wang Y, et al. Expression of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and Ki-67 in ductal carcinoma in situ (DCIS) and DCIS with microinvasion. *Medicine* (2018) 97(44): e13055.
20. Guillot E, Vaysse C, Goetgheuck J, Falcou MC, Couturaud B, Fitoussi A et al. Extensive pure ductal carcinoma in situ of the breast: Identification of predictors of associated infiltrating carcinoma and Lymph node metastasis before immediate reconstructive surgery. *Breast* 2014; 23 (2): 97 – 103.
21. Kim J, Han W, Lee JW, You J-M, Shin H-C, Ahn SK, et al. Factors associated with upstaging from ductal carcinoma in situ following core needle biopsy to invasive cancer in subsequent surgical excision. *Breast* 2012; 21(5):641-5.
22. Ruvalcaba-Limon E, de Jesús Garduño-Raya M, Bautista-Piña V, Trejo-Martínez C, Maffuz-Aziz A, Rodríguez-Cuevas S. Sentinel lymph node metastasis in patients with ductal breast carcinoma in situ. *Cir Cir* 2014; 82:107-18.
23. Trentin C, Dominelli V, Maisonneuve P, Menna S, Bazolli B, Luini A, et al. Predictors of invasive breast cancer and lymph node involvement in ductal carcinoma in situ initially diagnosed by vacuum – assisted breast biopsy: experience of 733 cases. *Breast* 2012; 21(5): 635-40.
24. Chehade EH, Headon H, Wazir U, Abtar H, Kasem A, Mokbel, K. Is sentinel lymph node biopsy indicated in patients with a diagnosis of ductal carcinoma in situ? A systematic literature review and meta-analysis. *Am J Surg*. 2017;213(1):171 – 180.
25. Francis AM, Haugen CE, Grimes LM, Crow JR, Yi M, Mittendorf EA, et al. Is sentinel lymph node dissection warranted for patients with a diagnosis of ductal carcinoma in situ? *Ann Surg Oncol*; 2015; 22(13):4270-9.
26. Maffuz A, Barroso-Bravo S, Nájera I, Zarco G, Alvarado-Cabrero I, Rodríguez-Cuevas SA. Tumor size as predictor of microinvasion, invasion, and axillary metastasis in ductal carcinoma in situ. *J Exp Clin Cancer Res*. 2006;25(2):223-7.
27. Yen TWF, Hunt KK, Ross MI, Mirza NQ, Babiera GV, Meric-Bernstam F, et al. Predictors of invasive breast cancer in patients with an initial diagnosis of ductal carcinoma in situ: a guide to selective use of sentinel lymph node biopsy in management of ductal carcinoma in situ. *J Am Coll Surg* 2005; 200(4):516-26.
28. Yao JJ, ZhanWW, Chen M, Zhang XX, Zhu Y, Fei XC, et al. Sonographic features of ductal carcinoma in situ of the breast with microinvasion: correlation with clinicopathologic findings and biomarkers. *J Ultrasound Med* 2015; 34(10):1761–8.
29. Bertozzi S, Cedolini C, Londero AP, Baita B, Giacomuzzi F, Capobianco D, et al. Sentinel lymph node biopsy in patients affected by breast ductal carcinoma in situ with and without microinvasion: Retrospective observational study. *Medicine (Baltimore)*. 2019 Jan;98(1):e13831.
30. Shin YJ, Kim SM, Yun BL, Jang M, Kim B, Lee SH. Predictors of invasive breast cancer in patients with ductal carcinoma in situ in ultrasound-guided core needle biopsy. *J Ultrasound Med* 2018; 00:1–8.
31. Sun X-L, Dai Y-P, Chen Z, Zhang J. An improved nomogram including elastography to predict the histological upgrade of ductal carcinoma in situ of the breast. *Eur Rev Med Pharmacol Sci*. 2020; 24(20):10586-93.
32. Poulakaki N, Makris GM, Papanota AM, Marineli F, Marineli A, Battista MJ, et al. Ki-67 expression as a factor predicting recurrence of ductal carcinoma in situ of the breast: a systematic review and meta-analysis. *Clin Breast Cancer* 2018, 18(2):157-67.
33. Liu BT, Ding JN, Wang JL, Li ZS, Ding YL, Ma R. Differences in pathologic characteristics between ductal carcinoma in situ (DCIS), DCIS with microinvasion and DCIS with invasive ductal carcinoma. *Int J Clin Exp Pathol* 2020;13(5):1066-72.
34. Huo L, Sneige N, Hunt KK, Albarracín CT, Lopez A, Reshetkova E. Predictors of Invasion in Patients With Core-Needle Biopsy-Diagnosed Ductal Carcinoma in Situ and Recommendations for a Selective Approach to Sentinel Lymph Node Biopsy in Ductal Carcinoma in Situ. *Cancer* 2006;107(8):1760–8.
35. Han JS, Molberg KH, Sarode V. Predictors of invasion and axillary lymph node metastasis in patients with a core biopsy diagnosis of ductal carcinoma in situ: an analysis of 255 cases. *Breast J* 2011;17(3):223-9.
36. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017; 35(5):561-4.