European Journal of Surgical Oncology 45 (2019) 1152–1155

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Is it possible to predict underestimation in ductal carcinoma in situ of the breast? Yes, using a simple score!

Larissa C. Marques [a], Gustavo Nader Marta [b, c, *], Juliana Z. de Andrade [a], Danúbia Andrade [a], Alfredo C.S.D. de Barros [a], Felipe E.M. Andrade [a]

[a] Department of Surgical Oncology, Hospital Sírio-Libanês, São Paulo, Brazil
[b] Department of Radiation Oncology, Hospital Sírio-Libanês, São Paulo, Brazil
[c] Department of Radiology and Oncology of University of São Paulo, Division of Radiation Oncology, Instituto do Câncer do Estado de São Paulo (ICESP/FMUSP), São Paulo, Brazil

ARTICLE INFO

Article history:
Received 7 August 2018
Received in revised form
29 December 2018
Accepted 11 January 2019
Available online 14 January 2019

Keywords:
Breast cancer
Ductal carcinoma in situ
Needle biopsy
Prediction invasion
Risk score

ABSTRACT

Background: Approximately 30% of patients with an initial diagnosis of ductal carcinoma ductal in situ (DCIS) present stromal invasion in the final surgical specimen. This study aimed to describe the prevalence of upstaging in women with an initial diagnosis of pure DCIS and identify predictive factors of invasion.

Methods: This is a cross-sectional study including patients with an initial unilateral DCIS diagnosed through needle core or vacuum-assisted biopsy. All patients were submitted to surgical excision. Clinical, radiological and histological variables were retrospectively collected from our medical records.

Results: A total of 169 biopsies diagnosed with DCIS were included in this study. 53 patients presented upstaging for invasive carcinoma (31.4%). In the univariate analysis the following variables were significantly associated with invasive breast carcinoma (IBC) at final diagnosis: age < 46 years, the presence of a palpable mass, type of biopsy, nuclear grade, and comedonecrosis. The frequency of upstaging did not vary according to the tumor size or menopausal status. In the multivariate analysis, only the type of biopsy and the presence of comedonecrosis remained as independent predictors of invasion. Our score attributed specific points according to the type of biopsy and the presence of comedonecrosis, ranging from 0 to 2.5, showing a very good predictive ability.

Conclusions: We were able to identify that the type of biopsy and comedonecrosis are predictive factors of stromal invasion among women with DCIS. The proposed score has shown a good predictive ability and its utilization in the clinical practice can improve therapeutic planning.
© 2019 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Introduction

Ductal carcinoma in situ (DCIS) is a neoplastic proliferation of epithelial cells confined to the mammary duct, with marked cytological atypia and an inherent but not required tendency to progression to invasive cancer [1]. Its incidence has been increasing and currently corresponds to 25% of the newly diagnosed cases of breast cancer. This growth is mainly due to increased and improved mammographic screening and the different modalities of imaging methods in breast diagnosis [2,3].

The most common radiological presentation of DCIS is the presence of suspected microcalcifications in mammography, which occurs in up to 80% of cases [4]. The minimally invasive methods guided by imaging have gained prominence, making possible the preoperative anatomopathological diagnosis of suspicious lesions of the breast and facilitating the appropriate therapeutic planning.

* Corresponding author. Department of Radiation Oncology, Hospital Sírio–Libanês, Rua Dona Adma Jafet 91, Zip Code 01308–050, Sao Paulo, SP, Brazil.
E-mail address: gustavo.marta@hc.fm.usp.br (G.N. Marta).

https://doi.org/10.1016/j.ejso.2019.01.015
0748-7983/© 2019 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Table 1
Variables associated with upstaging in percutaneous breast biopsies with an initial diagnosis of DCIS.

Variables		Upstaging		p value	Crude PR	CI (95%)
		Yes (%)	No (%)			
Type of biopsy	Core biopsy	26 (56.5)	20 (43.5)	<0.001	2.57	1.69–3.92
	Vaccum assisted	27 (22.0)	96 (78.0)			
Nuclear grade	1	2 (9.5)	19 (90.5)	<0.001		
	2	14 (20.9)	53 (79.1)		2.19	0.54–8.92
	3	37 (45.7)	44 (54.3)		4.79	1.25–18.3
Comedonecrosis	Absent	9 (11.0)	73 (89.0)	<0.001	4.61	2.40–8.85
	Present	44 (50.6)	43 (49.4)	<0.001		
BIRADS	4	47 (29.0)	115 (71.0)	0.004	2.95	2.00–4.35
	5	6 (85.7)	1 (14.3)			
Clinical presentation	Suspicious calcifications	31 (24.6)	95 (75.4)	0.001	2.08	1.38–3.18
	Palpable mass	22 (51.2)	21 (48.4)			
Age (year)	<46	18 (46.1)	21 (53.9)	0.023	1.71	1.10–2.67
	>46	35 (26.9)	95 (73.1)			

Given the limited tissue sample normally available from biopsy specimens, underestimation of stromal invasion may occur in 1 out of 3 diagnoses of DCIS [5].

Patients with a final diagnosis of invasive breast carcinoma (IBC) benefit from an axillary approach for identification of the sentinel lymph node. If patients with a high risk of upstaging could be identified preoperatively, surgeons would be able to identify the subgroup of patients who would benefit from an axillary approach in the same surgical procedure, reducing the economic costs and psychological disturbance of a second procedure [6].

Some clinical and morphological features of the tumors are related to an increased risk of upstaging, such as the presence of palpable lesions, extensive lesions, and the presence of comedonecrosis [5]. However, no study or test can predict objectively and safely the underestimation of stromal invasion.

This study aims to identify anatomoclinical factors associated with an increased risk of diagnostic underestimation of stromal invasion in samples of percutaneous biopsies (core biopsy or vacuum biopsy) with a DCIS diagnosis and to develop a score to calculate the preoperative risk of upstaging.

Methods

The study focused on patients over 18 years of age with an anatomopathological diagnosis of DCIS by percutaneous biopsy (core biopsy or vacuum assisted biopsy) who underwent a surgical procedure from 2006 to 2016.

Only cases with subsequent surgical excision were included. Patients with a previous history of IBC (any histological subtype) or presence of microinvasion in the biopsy were excluded.

All patients underwent percutaneous biopsy guided by imaging (mammography or ultrasonography). The following characteristics were analyzed: type of biopsy (core biopsy or vacuum assisted biopsy), nuclear grade (1, 2 or 3), comedonecrosis (absent or present), classification based on BI-RADS (Breast Imaging Reporting and Data System) [7], clinical presentation (suspicious calcifications or palpable mass), age ($\leq$46 or > 46 years) and tumor size ($\leq$20 mm or >20 mm).

The measures of central tendency and dispersion were calculated for the quantitative variables, and absolute and relative frequencies were calculated for the categorical variables. The frequency of stromal invasion and respective 95% confidence intervals were calculated.

To assess the association between categorical variables, a chi-square association test or Fisher's exact test (if at least one of the expected frequencies is less than 5) were used. Logistic regression was used for assessment of the prediction model for stromal invasion in patients with a diagnosis of ductal carcinoma in situ based on percutaneous biopsies. The multiple models included all variables that reach $p < 0.25$ in the univariate analysis. These variables were hierarchically included in the model. The crude and adjusted odds ratios and their respective 95% confidence intervals were calculated. To verify the suitability of the model, the Hosmer & Lemeshow test was employed.

For all statistical tests, an alpha error = 5% was employed. Thus, the results were considered statistically significant when $p < 0.05$.

Results

A total of 169 biopsies diagnosed with DCIS were included in this study. Of the 169 patients, 53 (31.4%) presented upstaging for IBC. In 126 (74.6%) patients, the lesion was asymptomatic and detected by mammographic screening. In 96% of patients, the lesion was characterized as BI-RADS 4.

The mean age of the patients was 54 years old (26–86 years), and 60.4% of them were postmenopausal. Women younger than 46 years of age at the time of diagnosis had a frequency of underestimation that was increased 1.7-fold compared with that of patients over 46 years old (46.1% versus 26.9%, $p = 0.023$).

The variables associated with upstaging in the univariate analysis included age less than 46 years, presence of a palpable nodule at the initial physical examination, core biopsy as a biopsy method, high nuclear grade, and the presence of comedonecrosis (Table 1). Tumor size was not associated with upstaging in percutaneous breast biopsies with an initial diagnosis of DCIS ($p = 0.058$).

In the multivariate analysis, the presence of comedonecrosis and the use of core biopsy as a sampling method (adjusted RP 2.21 [95% CI]) remained the only independent predictive factors associated with upstaging (RP adjusted 4.19 [95% CI]).

We developed a risk predictor model as a tool for use in clinical practice. Specific scores were assigned from 0 to 2.5 based on the type of biopsy and the presence of comedonecrosis (Tables 2 and 3).

The sum of the scores was calculated, and a receiver operating characteristic (ROC) curve was drawn. The area under the curve (AUC) was 0.799 (95% CI 0.729–0.869) (Fig. 1), and the model was a

Table 2
Independent predictive factors used to construct the score.

Variable	Category	B coefficient	Score
Comedonecrosis	Absent	–	0
	Present	1.434	1.5
Type of biopsy	Vaccum-assisted	–	0
	Core biopsy	0.794	1.0

Table 3
Score and prevalence of upstaging for each category.

Comedonecrosis	Type of biopsy	Score	Upstaging prevalence
Absent	Vaccum-assisted	0	9.4
	Core biopsy	1	16.7
Present	Vaccum-assisted	1.5	35.6
	Core biopsy	2.5	82.1

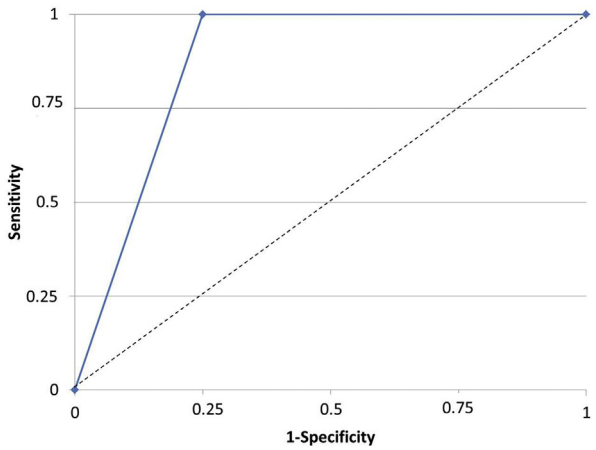

Fig. 1. Receiver operating characteristic (ROC) curve. The area under the curve (AUC) was 0.799 (95% CI 0.729–0.869).

good predictor of the risk of underestimation, ensuring good clinical applicability.

Discussion

In our study, 53 patients presented upstaging (31.4%) after complete surgical excision of the lesion. The preoperative factors most associated with an increased risk of upstaging in our series included older than 46 years old, presence of a palpable mass at the initial clinical presentation, core biopsy as the biopsy method, high nuclear grade, and presence of comedonecrosis in the biopsy.

Many studies, some with methodological flaws, reported predictive factors for upstaging after percutaneous biopsy, but the practical applicability of this information in a surgeon's routine remains poor. Thus, a large number of sentinel lymph node biopsies (SLNB) are performed in patients with a previous diagnosis of DCIS. Chinn-Lenn et al. [8] demonstrated that 72% of patients underwent unnecessary axillary evaluation (by SLNB), exposing themselves to avoidable surgical morbidity.

An ability to preoperatively identify cases of DCIS, at percutaneous biopsy, that is likely to represent understaged invasive disease would provide important information for a woman and her clinician to plan the treatment.

In a meta-analysis involving 7350 cases diagnosed with DCIS by percutaneous biopsy, Brennan et al. [5] reported an underestimation rate after the surgical procedure of 26%. In agreement that our study, nuclear grade, biopsy type, palpable mass, were associated with upstaging. For this authors, the presence of comedonecrosis was not associated with upstaging. In this meta-analysis, the number of studies reporting comedonecrosis was low (9 studies). Although this variable has been shown a toward to be associated with an invasive component at excision histologic examination, the findings have not been consistent across the studies.

For Doebar et al. [9], the upstaging rate was 22%. In multivariate analysis, only the initial clinical presentation was related to the increased risk of underestimation. In our study, patients with a palpable nodule had a 2.1-fold increased frequency of underestimation compared with asymptomatic patients.

In our study comedonecrosis had a strong association with the risk of underestimation and not all studies show similar results. This can be explained by the fact that the samples are interpreted by a specialist pathologist in mammary pathology, which can improve the histological analysis.

In the literature, many studies value the size of the lesion in imaging methods as a predictor criterion. In the study by Lee et al. [10], lesions greater than 30 mm on magnetic resonance imaging were more associated with the presence of synchronous IBC. In the study by Kondo et al. [11], the cut-off was 20 mm. In our study, the tumor size did not exhibit a significant association, which can be explained by the high rate of lesions diagnosed exclusively by screening in our sample. For our study we also used the 20-mm cut-off point, with a homogeneous distribution between the groups, but there was no significant association with the risk of stromal invasion.

In multivariate analysis, the type of biopsy and the presence of comedonecrosis were the independent factors significantly associated with an increased chance of stromal invasion in the surgical specimen. This finding can reflect the larger specimen sample that is usually obtained by using vacuum assisted biopsy. However, the most palpable mass and lesions visualized on ultrasonography, in our study, were submitted to core biopsy. These lesions have a higher underlying risk of invasive cancer, which can be a confounding factor [5]. Although central necrosis is more related to high nuclear grade, it can also occur in the low and intermediate grades and denotes lesions of more aggressive behavior [12].

A risk score was generated from these factors to aid in the therapeutic management of these patients. This risk scoring system can be a useful tool in the preoperative evaluation of these patients, and the surgeon can decide which patients will benefit from SLNB, which although reduces the incidence of complications compared to complete axillary dissection, it may cause adverse surgical effects and long-term morbidity including lymphedema, chronic pain and sensory disorders [13].

An advantage of this risk predictor model is the use of only two variables that are easily accessible and that apply to most cases given that minimally invasive methods have generally replaced excisional biopsies at present. Houssami et al. [14] created a predictor model with good accuracy (74%), but the model only applies to patients who were asymptomatic and those with microcalcifications on the mammography whose biopsy was performed under vacuum. Knowing that this method of biopsy is expensive and not accessible to most services, the score limits its clinical applicability.

Our study has limitations. First, it is a retrospective study. Second, the sample was small, and the molecular characteristics of tumors, such as hormone receptor assessment and HER-2 determination were not included. These factors are also associated with an increased risk of upstaging, as demonstrated for other authors [15].

Nevertheless, we consider that our score system can be used in a practical setting to suggest which patients diagnosed with DCIS have a high risk for invasive component in the lumpectomy. Thus, based on the high score value, the clinicians can discuss with the patients about a SLNB at the time of initial surgery or also warning the patient of the potential need of a second surgery if the invasive component was detected.

In conclusion, we were able to identify that the type of biopsy and comedonecrosis are predictive factors of stromal invasion among women with DCIS. The proposed score has shown a good

predictive ability and its utilization in the clinical practice can improve therapeutic planning. The validation in a large data set of the scoring system in other population is needed to confirm our finding.

Declaration of interest

None declared.

References

[1] Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, Van de Vijver MJ. International Agency for Research on Cancer. World Health Organization classification of tumours of the breast. fourth ed. Lyons, France: International Agency for Research on Cancer; 2012.

[2] Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 2010;102:170–8.

[3] Shah C, Wobb J, Manyam B, Kundu N, Arthur D, Wazer D, et al. Management of ductal carcinoma in situ of the breast: a review. JAMA Oncol 2016;2:1083–8.

[4] Jackman RJ, Burbank F, Parker SH, Evans 3rd WP, Lechner MC, Richardson TR, et al. Stereotactic breast biopsy of nonpalpable lesions: determinants of ductal carcinoma in situ underestimation rates. Radiology 2001;218:497–502.

[5] 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.

[6] Schulz S, Sinn P, Golatta M, et al. Prediction of underestimated invasiveness in patients with ductal carcinoma in situ of the breast on percutaneous biopsy as rationale for recommending concurrent sentinel lymph node biopsy. Breast 2013;22:537–42.

[7] American College of Radiology. Breast imaging reporting and data system. BI-RADS. fifth ed..

[8] Chin-Lenn L, Mack LA, Temple W, Cherniak W, Quinn RR, Ravani P, et al. Predictors of treatment with mastectomy, use of sentinel lymph node biopsy and upstaging to invasive cancer in patients diagnosed with breast ductal carcinoma in situ (DCIS) on core biopsy. Ann Surg Oncol 2014;21:66–73.

[9] Doebar SC, Monye C, Stoop H, Rothbarth J, Willemsen SP, Van Deurzen CH. Ductal carcinoma in situ diagnosed by breast needle biopsy: predictors of invasion in the excision specimen. Breast 2016;27:15–21.

[10] Lee CW, Wu HK, Lai HW, Wu WP, Chen ST, Chen DR, et al. Preoperative clinicopathologic factors and breast magnetic resonance imaging features can predict ductal carcinoma in situ with invasive components. Eur J Radiol 2016;85:780–9.

[11] Kondo T, Hayashi N, Ohde S, Suzuki K, Yoshida A, Yagata H, et al. A model to predict upstaging to invasive carcinoma in patients preoperatively diagnosed with ductal carcinoma in situ of the breast. J Surg Oncol 2015;112:476–80.

[12] Szynglarewicz B, Kasprzak P, Biecek P, et al. Screen-detected ductal carcinoma in situ found on stereotactic vacuum-assisted biopsy of suspicious microcalcifications without mass: radiological-histological correlation. Radiol Oncol 2016;50:145–52.

[13] Liu CQ, Guo Y, Shi JY, et al. Late morbidity associated with a tumour-negative sentinel lymph node biopsy in primary breast cancer patients: a systematic review. Eur J Cancer 2009;45:1560–8.

[14] Houssami N, Ambrogetti D, Marinovich ML, Bianchi S, Macaskill P, Vezzosi V, et al. Accuracy of a preoperative model for predicting invasive breast cancer in women with ductal carcinoma-in-situ on vacuum-assisted core needle biopsy. Ann Surg Oncol 2011;18:1364–71.

[15] Livasy CA, Perou CM, Karaca G, Cowan DW, Maia D, Jackson S, et al. Identification of a basal-like subtype of breast ductal carcinoma in situ. Hum Pathol 2007;38:197–204.