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Original article

Ductal carcinoma in situ diagnosed by breast needle biopsy: Predictors of invasion in the excision specimen

S.C. Doebar [a, *], C. de Monyé [b], H. Stoop [a], J. Rothbarth [c], S.P. Willemsen [d], C.H.M. van Deurzen [a]

[a] Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[b] Department of Radiology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[c] Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[d] Department of Biostatistics, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

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ABSTRACT

Background: A substantial proportion of women with a pre-operative diagnosis of pure ductal carcinoma in situ (DCIS) has a final diagnosis of invasive breast cancer (IBC) after surgical excision and, consequently, a potential indication for lymph node staging. The aim of our study was to identify novel predictors of invasion in patients with a needle-biopsy diagnosis of DCIS that would help us to select patients that may benefit from a sentinel node biopsy (SNB).
Patients and Methods: We included 153 patients with a needle-biopsy diagnosis of DCIS between 2000 and 2014, which was followed by surgical excision. Several pre-operative clinical, radiological and pathological features were assessed and correlated with the presence of invasion in the excision specimen. Features that were significantly associated with upstaging in the univariable analysis were combined to calculate upstaging risks.
Results: Overall, 22% (34/155) of the patients were upstaged to IBC. The following risk factors were significantly associated with upstaging: palpability, age $\leq$40 years, mammographic mass lesion, moderate to severe periductal inflammation and periductal loss of decorin expression. The upstaging-risk correlated with the number of risk factors present: e.g. 9% for patients without risk factors, 29% for patients with 1 risk factor, 37% for patients with 2 risk factors and 54% for patients with $\geq$3 risk factors.
Conclusion: The identified risk factors may be helpful to predict the upstaging-risk for patients with a needle-biopsy diagnosis of pure DCIS, which facilitates the performance of a selective SNB for high-risk patients and avoid this procedure in low-risk patients.

Introduction

Ductal carcinoma in situ (DCIS) is regarded as a non-obligate precursor of invasive breast cancer (IBC) [1]. The detection rate of DCIS has dramatically increased over the last decades as a result of breast screening and improved resolution of mammography [2]. Currently, DCIS accounts for approximately 20% of all breast carcinomas detected in the well-screened population [3,4]. Pure DCIS has no metastatic potential and therefore lymph node staging is not indicated. However, a substantial proportion (13–48%) of patients with an initial needle-biopsy diagnosis of pure DCIS is upstaged to IBC after final breast surgery [5–8]. These patients with a final diagnosis of IBC may benefit from lymph node staging. So, if we could pre-operatively identify patients with a high risk of upstaging after surgery, we would be able to select patients that may benefit from a sentinel node biopsy (SNB) in the same session as the breast surgery.

So far, several risk factors have been reported to be associated with IBC in the final surgical specimen. These predictive factors included clinical features (age, size of lesion and palpable mass), radiological features (number and type of biopsies, density on mammography, signal intensity curves and large size on MRI) and histopathological features (high grade DCIS, Her2 positive DCIS, comedonecrosis, and solid growth pattern) [9–21]. However, as the interpretation of these predictive features in daily

* Corresponding author. Erasmus MC Cancer Institute, P. O. Box 2040, 3000 AC Rotterdam, The Netherlands. Tel.: +31 010 7035816.
E-mail address: s.doebar@erasmusmc.nl (S.C. Doebar).

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practice is equivocal, it results in inadequate prediction of invasion, and consequently, a suboptimal use of nodal staging in patients with a biopsy-diagnosis of pure DCIS. This obviously results in increased costs and complications without a clinical benefit [22,23].

Several studies reported that the microenvironment of DCIS might play an important role in the progression of DCIS to IBC [24–32]. The role of inflammation in DCIS progression has not been elucidated yet. Angiogenesis increases with the malignant transformation of benign ducts to DCIS and IBC [29,30]. Therefore, microvessel density in needle biopsies with DCIS could be a predictive factor for upstaging. Decorin is a protein of the extracellular matrix and is a potent inhibitor of tumor cell proliferation [31]. A reduced expression of periductal decorin expression in the excision specimen of patients with DCIS has been reported to be associated with an increased risk for ipsilateral locoregional recurrence, either in situ or invasive [32]. However, data is limited regarding the significance of stromal changes in needle biopsies with pure DCIS. We hypothesize that analysis of the microenvironment in needle biopsies with pure DCIS could identify better predictors of upstaging after final excision. Therefore, the aim of our study is to combine several known pre-operative clinical and radiological features with novel pathological features in order to build a prediction model for upstaging, which may facilitate the selective use of a SNB for high-risk patients only.

Patient and methods

Patients

In this retrospective study, patients with a breast needle-biopsy diagnosis of pure DCIS were consecutively selected from the histopathology files of the Erasmus MC Cancer Institute. These patients were diagnosed and treated between 2000 and 2014. Only cases with a subsequent surgical excision within 3 months after diagnosis were included. The following exclusion criteria were applied: history of ipsilateral BC or suspicion of invasion on needle biopsy. Patient characteristics included age, palpability of the lesion and history of mantle field radiation for non-Hodgkin disease.

Radiology

In all patients a mammography was performed before breast needle biopsy, with or without ultrasound and/or MRI. The following imaging features were documented: type of image guidance (stereotactic, ultrasound or MRI), number of biopsies, type of biopsy (vacuum-assisted biopsy (VAB) or automated core biopsy (ACB)) and needle size. The number and size of biopsies were categorized in 2 groups: low number ($\leq$10) vs. high (>10) and small size (14- and 18-gauge) vs. large size (10-gauge) respectively.

The pre-operative mammogram and/or ultrasound and/or MRI were reviewed by a dedicated breast radiologist (CM) regarding the presence, type and size of a lesion. Lesions were categorized according to the BIRADS classification [33]. Imaging features for mammography included breast composition as defined by the ACR reporting system [33]. Type of mammographic lesion was categorized as microcalcifications only or mass (±microcalcifications). The enhanced MRI features included type of enhancement (mass vs. non-mass) and late enhancement–time curves. Late enhancement–time curves were recorded as type 1 (slow and persisting curve), type 2 (curve with plateau), and type 3 (curve with washout).

Pathology

Needle biopsy samples were reviewed by two pathologists (CvD and CD), blinded for outcome. Several histologic features of DCIS were reported, including the predominant growth pattern, grade [34], presence or absence of comedonecrosis, microcalcifications and lobular cancerization. Stromal changes included the intensity of peri-tumoral inflammation (minimal to mild or moderate to severe) and stromal architecture (sclerotic or myxoid). Inflammation intensity was scored according to the method previously described for IBC, as illustrated in Fig. 1 of the study published by Lee et al. [35] Examples of a case with minimal inflammation and a case with moderate to severe inflammation are provided in Fig. 1 (A and B). Myxoid stroma was defined as “loose”, pale-to-lightly basophilic peritumoral stroma [36]. In case of mixed patterns, the predominant pattern was recorded.

Oestrogenreceptor and Progesteronreceptor were considered positive when at least 10% of the tumor cell nuclei were positive, according to Dutch guidelines for scoring of IBC [37]. Her2 expression was scored according to international guidelines [38]. The proliferation index of DCIS was estimated by the percentage of Ki-67-positive tumor cells. The cut-off value for high proliferative index was a percentage of 20%, according to the St. Gallen criteria for IBC [39]. The number of CD31 positive microvessels were counted with a 40-time magnification in 5 HPF of periductal lesional stroma [40]. Microvessel density was arbitrarily categorized in 2 groups: low density ($\leq$75 vessels per 5 HPF) and high density (>75 vessels per 5 HPF). The intensity of periductal stromal decorin expression was scored semiquantitatively, using normal stroma outside the DCIS area as an internal reference, as either normal expression (comparable to normal stroma), slightly decreased expression (weak loss of intensity as compared to normal stroma) or highly decreased expression (strong loss of intensity as compared to normal stroma). Fig. 1 (C and D) shows an example of normal and highly decreased decorin expression.

Surgical excision

Several features of the final surgical excision were recorded including type of surgery (BCS or mastectomy, presence/absence of lymph nodes), number of sampled tissue blocks and final diagnosis (pure DCIS or IBC). The extent of DCIS and, if present, the invasive component was recorded. Nodal status was recorded for those patients that underwent nodal staging.

Statistics

Statistical analysis was performed using SPSS version 21.0. Two groups of patients were created: patients with invasion and patients without invasion in the subsequent excision. Chi-square tests were used to analyze the correlation between categorical variables and presence of invasion in the surgical excision. All variables that were associated with upstaging in the univariable analysis were tested as potential predictors in a multivariable logistic regression analysis. P-values <0.05 were considered to be statistically significant.

Results

A total number of 155 biopsies, derived from 153 patients (two patients had bilateral lesions) with a pre-operative diagnose of DCIS were included. DCIS was confirmed in 121 (78%) women after surgery. The remaining 34 cases (22%) were upstaged to IBC.