ORIGINAL ARTICLE
https://doi.org/10.29289/259453942023006

Clinicopathological characteristics and recurrence risk in patients with ductal carcinoma in situ of the breast

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ABSTRACT

Introduction: With the widespread adoption of mammographic screening for breast cancer, ductal carcinoma in situ (DCIS) has been detected more frequently. In developing countries, the prevalence of ductal carcinoma in situ is low due to the opportunistic nature of breast cancer screening. The aim of this study was to evaluate the clinicopathological characteristics and recurrence rate in a cohort of patients with ductal carcinoma in situ in Brazil. **Methods:** This study was an retrospective analysis of all 1,736 patients with non-metastatic breast cancer treated at a reference public hospital between 1999 and 2013. All data were collected from medical records and the descriptive statistics were performed to characterize the clinical and pathological features. **Results:** In the present cohort, we identified 102 (5.2%) patients with non-invasive breast neoplasms. Mean age at diagnosis was 54±12.7 years and most patients were treated with breast conserving surgery. There is a strong association between nuclear grade and the expression of estrogen and progesterone receptors in ductal carcinoma in situ. Ipsilateral and contralateral recurrence rates in 10 years were 7.2% and 2%, respectively. **Conclusion:** The pathological features of ductal carcinoma in situ diagnosed in Brazil are similar to those observed in patients diagnosed in countries following a systematic screening program, and the treatment in our patients achieves similar success compared with published data in high-income countries.

KEYWORDS: ductal carcinoma in situ; DCIS; local neoplasm recurrence; breast; prognoses.

INTRODUCTION

Ductal carcinoma in situ (DCIS) was rarely diagnosed before widespread adoption of breast cancer screening, but it currently accounts for 20%–25% of breast cancer detected in developed countries that have introduced an adequate population screening program[1].

DCIS is a proliferation of neoplastic luminal cells that are confined to the duct system of the breast[2]. The risk of developing metastasis or death in a patient with pure DCIS is rare[3]. However, DCIS can progress to invasive carcinoma and is currently considered a direct precursor to invasive breast malignancy. The key point of treatment is local excision of the lesion. Simple mastectomy and conservative surgery followed by radiation therapy are the standard options for local disease control[4]. Patients with positive hormone receptor tumors benefit from receiving endocrine therapy to reduce the risk of future invasive breast cancer[5].

The 10-year local recurrence rate is about 1%–2% in women undergoing mastectomy[6], while patients who undergo conservative surgery with adjuvant radiotherapy have a 10-year local recurrence rate of 13%, but no difference in breast cancer mortality was detected[7]. An invasive carcinoma is diagnosed in half of patients who experience a local recurrence[8]. Among all the risk factors, only the size of the margin is potentially modifiable by re-excision[9]. Although the involvement of margins is associated with a higher risk of recurrence after conservative surgery, there is still no consensus on the ideal size of the resection margin[10].

In Brazil, there is a lack of evidence-based data on recurrence rates of DCIS in the Brazilian population. Recent studies

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Conflicts of interests: nothing to declare. Funding: none.
Received on: 03/19/2022. **Accepted on:** 06/02/2022.

have demonstrated that DCIS detection rate is low due to the opportunistic nature of the breast cancer screening program[11]. This may interfere with the clinical and pathological presentation, the type of treatment, and the risk of recurrence. The aim of this study was to evaluate the clinicopathological characteristics and recurrence rate in a cohort of patients with DCIS treated in a public hospital in Brazil.

METHODS

This study is a retrospective cohort dataset including all 1,736 patients with non-metastatic breast cancer treated at the Breast Disease Division of the Hospital das Clínicas of Ribeirão Preto Medical School. The cohort was previously approved by the Research Ethics Committee (approval number 2.638.453/05/07/2018). The following attributes were used for data analysis: age, menopause status, histological grade, immunohistochemistry (IHC) for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), type of surgery, lesion size, adjuvant radiotherapy, adjuvant endocrine therapy, follow-up time, and presence of local recurrence.

The overexpression of HER2 and the expression of hormonal receptors (HR) were determined by IHC in accordance with specific guidelines[12,13]. HER2 positivity was established in accordance with the pathology report in the clinical chart. The subtype was considered luminal if ER or PR was positive and HER2 was negative; HER2/HR+ if ER and/or PR was positive and HER2 was positive; HER2 if ER and PR were negative and HER2 was positive; and triple negative (TNBC) when ER, PR, and HER2 were negative.

Statistical analysis

Descriptive statistics was performed to characterize the group of patients diagnosed with DCIS. Multiple hypothesis tests were applied to compare the clinical and pathological characteristics between the groups of patients with DCIS and invasive ductal carcinoma (IDC). The sample size was determined by convenience. Variables were classified as qualitative or quantitative. Quantitative variables were tested for normality using the Shapiro-Wilk test. Chi-square test was used to compare qualitative variables and the t-test or Wilcoxon test (depending on the normality test) was used to compare continuous variables. The local recurrence event was treated as a function of time using the Kaplan-Meier method. The recurrence time was the difference between the surgery date and the event. Cases were censored at the time of the last available clinical assessment. Univariate analysis for each potential risk factor was applied. All analyses were performed with the R software version 4.1.2 (R Core Team, Austria) and significance was determined for $P<0.05$.

RESULTS

Prevalence of non-invasive breast neoplasm and clinical characteristics of patients with ductal carcinoma in situ

We found 102 non-invasive breast neoplasms (5.2%). Most non-invasive neoplasms were pure DCIS (n=95) and two DCIS were associated with Paget disease. There were three pure Paget diseases and two papillary intracystic carcinomas that were not included in the subsequent analyses. We observed that the mean age of patients with DCIS and IDC was similar (54±12.7 and 55.9±13.8 years, p=0.1), and the DCIS/IDC prevalence ratio did not significantly change according to different age groups (p=0.2). The prevalence of DCIS diagnosis was 6.5%, 5.7%, and 3.5% in (18,50), (50,70), and (70,100) age groups, respectively. The types of local treatment between patients with DCIS and patients with IDC subjected to primary surgery were compared. The breast conserving surgery (BCS) ratio was 61.9% in DCIS patients and 67% in IDC patients (p=0.3). Adjuvant radiation therapy was delivered to 88.3% of DCIS patients and 95.6% of IDC patients subjected to breast conserving surgery (p=0.2).

Ductal carcinoma in situ pathological features

The pathological size was recorded in 58 DCIS lesions. The median size was 12 mm (interquartile range, IQR 18.9), and most DCIS are of high nuclear grade (55.2%) with the presence of comedonecrosis (55.7%). In terms of immunohistochemical analysis, 82.2% of DCIS lesions were ER positive, 75.5% were PR positive, and 29.9% were HER2 positive. According to molecular subtyping, luminal subtype was the most frequent (63.2%). Although the subtype distribution among DCIS lesions was similar to IDC (p=0.1), comparing the distribution of TNBC and non-TNBC, there is a high percentage of TNBC in IDC compared to DCIS (15.6% versus 6.9%, respectively, with p=0.04). Table 1 explains the clinical and pathological features of DCIS and IDC patients. There is a significant association between DCIS grade and the expression of ER, PR, and HER2 proteins. High-grade DCIS lesions are associated with the negative expression of ER (p=0.002) and PR (p=0.008) and there is a trend to have positive expression of HER2 (p=0.06). Table 2 shows the association of DCIS nuclear grade with ER, PR, and HER2 expression and the molecular subtypes. All HER2 positive and TNBC subtypes were of high-grade DCIS.

Ipsilateral and contralateral recurrence (Ipsilateral and contralateral recurrence, respectively)

We observed seven ILR (7.2%) and two invasive CLR (2%). Figure 1 shows the cumulative plot for ILR in DCIS patients. We analyzed the association of clinical and pathological features and the locoregional recurrence (LRR). Although we did not observe any significant predictive factor for LRR, all ILR occurred in patients

Table 1. Clinical and pathological features of patients with ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC)

	DCIS (97)	IDC (1639)	p-value
Age (years; SD)	54±12.7	55.9±13.8	0.1
Age groups (n; %)			
(18, 50)	41 (6.5)	592 (93.5)	
(50, 70)	46 (5.7)	768 (94.3)	
(70, 100)	10 (3.5)	277 (96.5)	0.2
Surgery (n; %)			
Mastectomy	37 (38.1)	293 (33)	
BCS	60 (61.9)	596 (67)	0.3
Radiation therapy (%)	88.3%	95.6%	0.2
ER positive (n; %)	74 (82.2)	1180 (72.8)	0.06
PR positive	68 (75.5)	976 (60.1)	0.005
HER2 positive	26 (29.9)	419 (25.9)	0.5
Subtype (n; %)			
Luminal	55 (63.2)	941 (58.4)	
HER2	8 (9.2)	168 (10.4)	
HER2/HR positive	18 (20.7)	251(15.6)	
TNBC	6 (6.9)	252 (15.6)	0.1

DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; SD: standard deviation; BCS: Breast-conserving surgery; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; HR: hormonal receptors; TNBC: triple negative breast cancer.

Table 2. Association of invasive ductal carcinoma (IDC) histological grade and ductal carcinoma in situ (DCIS) nuclear grade and immunohistochemical (IHC) features

	High Grade (%)	Non-high Grade (%)	p-value
DCIS – IHC			
ER positive	69.4	97.5	0.002
PR positive	63.3	90	0.008
HER2 positive	39.6	18.4	0.06
DCIS – subtypes			
Luminal	47.9	81.6	
HER2	16,6	0	
HER2/HR positive	22.9	18.4	
TNBC	12.5	0	0.0007*

IHC: immunohistochemistry; DCIS: ductal carcinoma in situ; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; TNBC: triple negative breast cancer. *Fisher's exact test.

with high-grade DCIS. ILR was observed in 15.4% of HER2 positive and 4.9% of HER2 negative (p=0.2). We observed only one disease-specific death during the follow-up after an invasive contralateral recurrence.

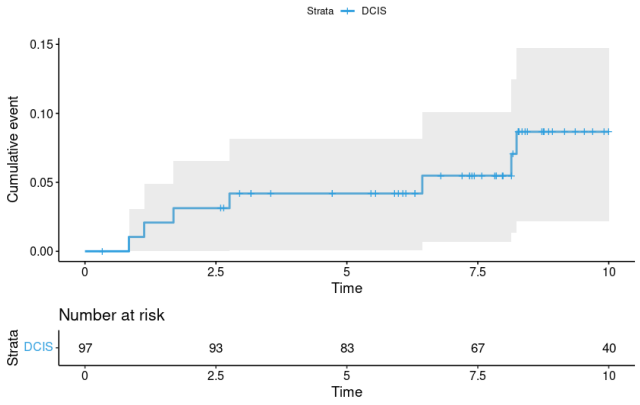

Figure 1. The 10 years cumulative plot for ipsilateral recurrence in 97 patients with ductal carcinoma in situ (DCIS).

DISCUSSION

DCIS is mainly diagnosed in asymptomatic women from breast cancer screening programs. Despite being highly curable, the major concern about the disease is the recurrence associated with invasive carcinoma and the increased risk of a new breast cancer throughout life. In Brazil, the reported DCIS detection rate is low due to the opportunistic nature of the breast cancer screening program[11,14]. In our study, we observed that about 5% of breast cancer patients were diagnosed with DCIS. The clinical and immunohistochemical features in DCIS are quite similar to the features in IDC. We observed only 7.2% of patients experienced ILR in a mean follow-up of 10 years, demonstrating the high effectiveness of the local treatment for DCIS.

The diagnosis of DCIS is a condition mainly associated with breast cancer screening nowadays. Thus, the rate of women diagnosed with DCIS in low- and middle-income countries, in general, is very low, ranging from 1% to 7%[15], compared to the rate in developed countries which is above 20%[16]. This discrepancy is due to the widespread adoption of a mammographic screening program and the efficient and rapid diagnosis and treatment onset in high-income countries. In Brazil, where 70% of women rely on the public health system (Sistema Único de Saúde, SUS), the 5% of DCIS found in our study exemplifies this scenario[17].

Although the number of women diagnosed with DCIS has increased substantially over the past decades in developed countries, the breast cancer-specific mortality in early-stage breast cancer did not significantly decrease, suggesting that the treatment of most patients with DCIS may be considered overtreatment[18,19]. Despite the fact that DCIS overtreatment is associated with emotional and physical damages and unnecessary cost, some studies have investigated the safety of low-risk DCIS active surveillance[20-22]. Low-risk DCIS may be characterized by the histological morphology, grade, size, margin width, and the expression of ER/PR and HER2 proteins[23,24].

In low-income countries, the current DCIS detection rate remains similar to the detection rate in European countries before the implementation of the breast cancer screening program[25]. A few studies characterizing the clinicopathological characteristics of DCIS in Brazil have been published, and none has investigated the efficacy of the treatment in a long-term follow-up[26-28]. Investigating the clinical and pathological features of women diagnosed with DCIS in developing countries is crucial to the management decision in the current and the near future scenario for DCIS treatment.

The incidence of DCIS is strongly related to older age and extremely uncommon before the age of 40 years, a subgroup of women not included in screening programs. The mean age of DCIS in our study was 54±12.7 years with no significant difference from women diagnosed with IDC, corroborating the mean age presented by Virnig et al., which reveals that the incidence of DCIS rises steadily to a peak of 96.7 per 100,000 at the ages of 65–69 years and then declines until the age of 79 years and abruptly after 79 years[29]. We observed the same trend with only 3.5% of cases diagnosed as DCIS in women after the age of 70 years.

Mastectomy is a reasonable option for DCIS treatment for women who do not meet the criteria for BCS. In Brazil, the opportunistic nature of the breast cancer screening program is associated with a low prevalence of DCIS[11,30]. To make inference how this may affect the local treatment decision in DCIS, we investigated the mastectomy ratio and compared it to the women diagnosed with IDC in our study population. The mastectomy ratio was 38.1% in DCIS patients compared to 33% in IDC patients subjected to primary surgery. Although our data demonstrated that the mastectomy ratio is similar when comparing patients with DCIS and early-stage IDC, the BCS ratio in our DCIS population is in accordance with other reports[31].

We analyzed the expression of ER, PR, and HER2 proteins and the breast cancer subtypes in DCIS and IDC. We observed that the distributions in luminal and HER positive subtypes are similar. The prevalence of TNBC lesions is significantly low in DCIS and the prevalence of ER and especially PR positive lesions are higher in DCIS. The IHC and subtypes distributions are highly associated with the nuclear grade in DCIS. High-grade DCIS are more likely to be ER negative compared with non-high-grade DCIS. All HER2 positive and TNBC subtypes are high-grade lesions in our cohort. This observation is in accordance with previous reports[28].

According to local recurrence, the unique randomized clinical trial specifically restricted to DCIS, published by McCormick et al., showed that unicentric disease, tumor size ≤2.5 cm, grade 1 or 2 and negative margins greater than 3 mm are factors of low risk of recurrence in patients treated with breast conserving surgery[32]. The current consensus guidelines for margins in DCIS recommend 2 mm to decrease local recurrence rates[33], and some studies include comedonecrosis as a pathological feature of high risk of recurrence[34]. In our study, none of the characteristics (mean size of 12 mm [IQR 18.9]), 55% of high-grade tumors, 55.7% of comedo DCIS, and 63.2% of luminal tumors) were correlated to local failure. Other studies demonstrated similar results[8,35]. The ipsilateral and contralateral local recurrence observed in our cohort (7.2% and 2%, respectively) was similar to an American study which included 2,759 DCIS patients, and the competing risk analysis demonstrated 7.8% and 2.9% rates for 5-year ILR and CLR, respectively[36].

The limitations of this study include those associated with observational and retrospective studies. This is a single-centered study cohort based on a convenience sampling. The tumor size measurements were missing in 40% cases. However, it is a common problem in DCIS studies. The frequent multifocal nature of DCIS makes it hard to accurately measure the lesion. Also, we could not explore the exact margin width because of unavailable data. After all, since we lack data of Brazilian DCIS patients, more studies are warranted to identify the clinicopathological features of DCIS and the risk factors for recurrence in our population.

CONCLUSION

Although the rate of patients diagnosed with DCIS is low and most of the patients with DCIS come from an opportunistic screening program in Brazil, our data suggest that the clinical and pathological features are similar to those observed in patients diagnosed in countries following a systematic screening program. Moreover, the DCIS treatment in our patients achieves similar success compared with published data in high-income countries.

AUTHORS' CONTRIBUTIONS

MHCNB: Conceptualization, Writing – original draft, Writing – review & editing. VHS: Conceptualization, Writing – original draft, Writing – review & editing. LFO: Writing – original draft, Writing – review & editing. HHAC: Conceptualization, Writing – review & editing. FJCR: Conceptualization, Writing – review & editing. JMA: Conceptualization, Writing – review & editing. PLB: Conceptualization, Writing – review & editing. DGT: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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