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Clinical-pathological features and treatment modalities associated with recurrence in DCIS and micro-invasive carcinoma: Who to treat more and who to treat less

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ABSTRACT

The primary aim in the management of DCIS is the prevention of recurrence and contralateral tumor. Risk factors for DCIS recurrence and appropriate treatments are still widely debated. Adjuvant therapies after surgical resection reduce recurrences and contralateral disease, but these treatments have significant financial costs, side effects and there is a group of low-risk patients who would not gain additional benefit. The aim of our analysis was to identify clinical-pathological features and treatment modalities associated with recurrence in DCIS and microinvasive carcinoma. In the Thomas Jefferson University Cancer Registry of Philadelphia, we identified 865 patients with DCIS or micro-invasive carcinoma treated between 2003 and 2013. Associations between recurrence and demographic factors (age at diagnosis, ethnicity), biological features (ER, PR and HER2) and treatment modalities (surgery, radiotherapy and endocrine treatment) were assessed. Our single institution register-based study showed that distribution of age at diagnosis and biological features did not significantly differ among ethnic groups. Younger women and micro-invasive carcinoma patients were more likely to undergo mastectomy, while African Americans were more likely to take endocrine therapy and undergo radiotherapy. In our sample only ER/PR negative DCIS were associated with significantly higher recurrence rate. Moreover, we reported a high rate of HER2 positive recurrences, suggesting that expression of this oncogene may represent a potential biomarker for DCIS at high risk of recurrence. To better define the molecular profile of the subgroup at worse prognosis might help to identify biomarkers predictive of recurrence or second tumors, identifying patients candidates for more appropriate treatments.

Introduction

With the introduction of mammographic screening, the incidence of DCIS has increased exponentially over the last two decades. Currently, more than 62,000 DCIS are diagnosed in the United States each year, accounting for about 25% of all newly diagnosed breast cancer cases [1,2]. Mastectomy or breast-conserving surgery with radiotherapy is now considered the standard treatments [3], and only 1.0%–2.6% of women die of invasive breast cancer within 8–10 years of DCIS diagnosis [1]. The crucial aim in treating DCIS is represented by the prevention of ipsilateral recurrence, reported to be greater than 25% over 10 years [4]. Nevertheless, since women diagnosed with DCIS are at increased risk for contralateral new tumors (reported to be about 3–6% from 5 to 10 years after DCIS diagnosis [5]), the treatment decision-making after the first diagnosis should take into consideration also the prevention of second contralateral tumors.

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Adjuvant endocrine treatments significantly reduce recurrence rates and contralateral disease, but they do not confer any survival advantage [6–10]. Moreover, adjuvant therapies (radiation and tamoxifen) lead to significant financial costs and side effects with a subgroup of low-risk patients who would not gain additional benefit from them. Interestingly, Sanders et al. reported that the natural history of low-grade DCIS differs markedly from that of high-grade DCIS, since it can extend greater than 4 decades. On the other hand, the majority of women with low-grade DCIS treated by biopsy only eventually develop invasive breast cancer at the same site as the previous DCIS, showing worse outcome of patients with any DCIS excised to negative margins [11]. For all these reasons, current management guidelines suggest to include tamoxifen for at least 5 years in patients treated with breast-conserving surgery (especially for those with ER-positive DCIS) instead, for patients considered at low risk, include the option for surgical excision alone (without radiation) as acceptable [12,13]. Consequently, there are wide regional differences in the adoption of those prevention strategies.

Previous research has been directed to highlight histopathological characteristics of DCIS that could predict recurrence or contralateral tumors, in order to select patients that could truly take advantage of preventive treatments. To date, several risk factors for ipsilateral recurrence have been recognized, including multifocal disease, large tumor size, high nuclear grade and presence of comedo necrosis (Fig. 1 A and B), positive excision margin status, negative hormone receptor status, HER-2 amplification, young age and symptomatic detection [14–18]. Microinvasion is associated with larger DCIS, higher grade, comedo or solid histology, necrosis, and micro-calcifications but, currently, it does not seem to be correlated with significantly increase in the risk of recurrence or worse overall survival [17–20]. Less information is available regarding risk factors for contralateral tumors, which include the presence of micropapillary tumor type and large tumor size [21].

The racial differences in histopathological features, treatments and outcome of patient with DCIS are active topics of research. Previous studies showed that the distribution of molecular subtypes of DCIS and treatment modalities did not significantly differ among diverse ethnic groups [22–24]. However, despite these observations, African Americans seem to experience a higher risk of recurrence, second tumors and show worse overall survival [25–28].

The aims of our study was to analyze a single Institution experience with regards to the demographic factors, clinical-pathological features and treatment modalities associated with recurrence and contralateral tumors in DCIS and micro-invasive carcinomas (MIC).

Materials and methods

Thomas Jefferson University Hospital maintains a Cancer Registry to track all newly diagnosed cancer patient information. The data compiled on each patient includes demographics, medical history, types of treatment administered, stage of disease and lifetime follow-up. We retrospectively identified 807 patients with DCIS and 58 with MIC in the Thomas Jefferson University Cancer Registry. These are all the patients treated for DCIS or MIC at the Thomas Jefferson University Hospital between 2003 and 2013, for whom the pathological diagnosis was available. Micro-invasion is defined as invasive carcinoma measuring 1 mm or less [29]. The Department of Pathology in our institution has systematically evaluated ER, PR and HER2 status in every new diagnosis of *in situ* and micro-invasive breast carcinomas (Fig. 1 C and D). When these patients have been treated, guidelines for the evaluation of ER/PR/HER2 staining in DCIS were not clear, thus we tended to use equivalent cutoff numbers to invasive tumors according to the ASCO/CAP guidelines [30]. At that time, we considered ER/PR staining positive if 10% or above and HER2 if more than 30% with IHC or amplified with FISH test, while values of 1–9% for ER/PR and

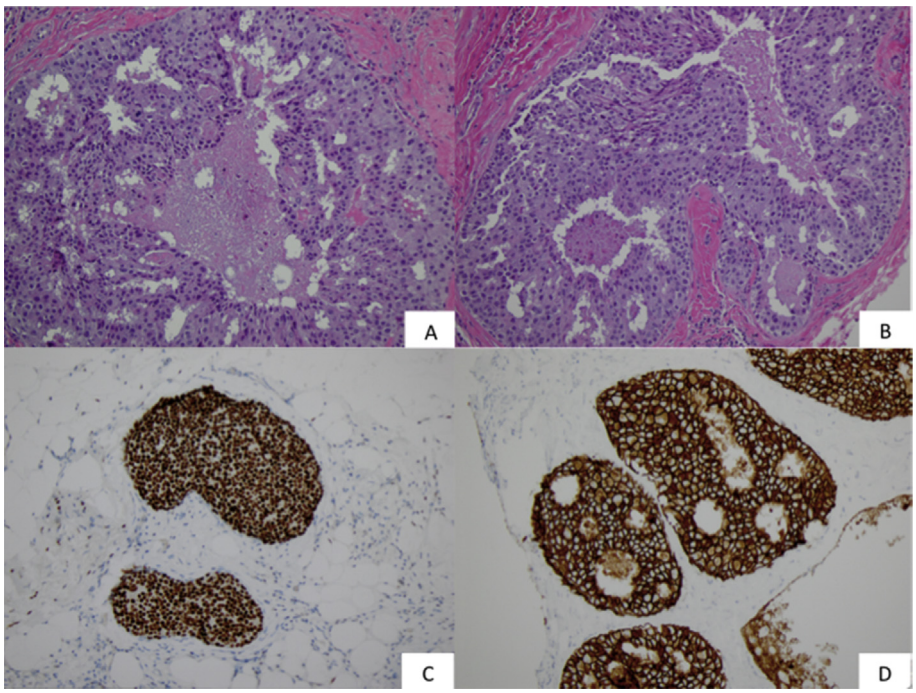

Fig. 1. **A** and **B** – Histopathologic images from high grade ductal carcinoma in situ with necrosis. Hematoxylin and eosin (H&E)-stain. **C** – Strong positive staining for ER in a ductal carcinoma in situ. **D** – Strong positive staining for HER2 in a ductal carcinoma in situ.

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10–29% for HER2 (with FISH not amplified) have been considered as borderline.

Demographic factors (age at diagnosis, ethnicity), biological features (ER, PR and HER2) and treatment modalities (type of surgery, radiotherapy and endocrine treatment) were collected through the Cancer Registry and their associations with ipsilateral recurrence or contralateral tumors were assessed.

Summary statistics were calculated for all patients on age, ethnicity, ER/PR/HER2 status, and treatment. Means and standard deviations were used for continuous variables and frequencies and percents for categorical variables. Association between age at diagnosis and ethnicity were assessed using Analysis of Variance (ANOVA). Associations between age and ER/PR/HER2 status was assessed using Student's t-test. Relationship between ethnicity and ER/PR/HER2 status was assessed using simple logistic regression in order to calculate a global effect of ethnicity along with testing for differences between African American, Asian, and Caucasian patients. Since patient ER/PR and HER2 status are not mutually exclusive, comparisons were not between ER, PR, and HER2 positive groups but rather between ER positive vs. ER negative; PR positive vs. PR negative, and HER2 positive vs. HER2 negative. A similar analysis was used to assess age and ethnicity associations with treatment. Unknown and borderline data were excluded from all analyses.

Finally, associations with recurrence were examined with regard to age, ethnicity, ER/PR/HER2 status and treatment. Two sub-analysis were performed with regard to recurrence, one on endocrine therapy limited to ER and/or PR positive women and one on radiation therapy limited to women who had conservative surgery. Student's t-test was used to determine the association with age; Fisher's Exact test was used for all other variables.

Results

Patient and tumor characteristics

Patient and tumor characteristics are listed in Table 1. Overall, ethnicity was known for 817 patients (94.5%), ER status for 656 patients (75.8%), PR status for 652 patients (75.3%), HER2 status for 221 patients (25.5%), chemotherapy use was known for 808 patients (93.4%), radiotherapy use for 817 patients (94.5%), and type of surgery for 860 patients (99.4%). The median age for DCIS was fifty-eight years (std 11.60) and for micro-invasive carcinoma was fifty-nine years (std 12.69) with prevalence of Caucasian women in both groups. There was no significant difference in age at diagnosis by ethnicity. Moreover, the associations of age and ethnicity with hormone status and HER2 status were not statistically significant for both DCIS (Table 2a) and MIC (Table 2b). We also analyzed separately DCIS and MIC characteristics and did not find any significant difference in terms of age, ethnicity, ER and HER2 status. Notably, DCIS were more likely to be PR positive than MIC ($p = 0.045$).

Treatment modalities

Regarding treatment modalities (Table 1), mastectomy was performed in 25.1% of DCIS patients and 41.4% of microinvasive carcinoma patients. Tables 3a and 3b present the associations of age and ethnicity with treatment in DCIS and MIC. There was no significant difference in age by chemotherapy or radiation treatment, while women who received conservative surgery were significantly older than those who had mastectomy for both DCIS and MIC. On the contrary, women diagnosed with DCIS who received endocrine therapy were significantly younger than those who did not receive any endocrine treatment (57.5 years vs. 59.5, $p = 0.0324$). Regarding ethnicity and treatment modalities, DCIS women who underwent radiation and/or received endocrine therapy were more likely to be African Americans (respectively, $p = 0.0021$ and $p < 0.0001$). Similarly, African Americans with DCIS were more likely to receive chemotherapy ($p = 0.0018$), while there were no significant racial differences with respect to type of surgery. Finally, among women diagnosed with MIC no significant difference in treatment modality with respect to ethnicity has been found. Nevertheless, MIC patients were more likely to undergo mastectomy and chemotherapy than DCIS patients (respectively $p = 0.005$ and $p < 0.0001$).

Recurrence and contralateral tumor characteristics

Up to December 2013, 71 (8.2%) patients developed ipsilateral recurrence (56 patients), contralateral tumors (2 patients) or both (5 patients). For 8 patients this data was unknown. None of these patients had MIC in the primary lesion and 18 (25.3%) developed invasive recurrence. Second tumors characteristics are listed in Table 4. The ER status of primary DCIS and second tumors was concordant in 88.3% of cases (data unknown in 39.4% of patients). The PR status was concordant in 82.2% of cases (data unknown in 46.4% of patients). Finally, the HER2 status was concordant in 53.8% of cases (data unknown in the 63.3% of patients). Interestingly, among recurrence with known HER2 status, 44.7% of recurrences were HER2 3+ or HER2 with FISH positive and 15.7% were HER2 2+ with FISH unknown.

No significant difference in age or ethnicity between who recurred and who did not was observed. Notably, ER and PR negative women were more likely to develop recurrence than ER positive ($p = 0.0138$) and PR positive ($p = 0.042$).

Sub-analyses

In a sub-analysis limited only to ER and/or PR positive women with information about endocrine treatment (514 patients), the 38.13% that received preventive endocrine therapy was significantly less likely to develop recurrence than the 61.87% that did not (3.06% vs. 10.97%, $p = 0.013$). In a second sub-analysis limited to the women who underwent conservative surgery, which had information about radiation therapy (594 patients), the 44.1% that received RT were significantly less likely to develop recurrence than the 55.9% that did not (3.81% vs. 14.15%, $p < 0.0001$). However, there was no significant difference in recurrence between mastectomy and conservative surgery followed by RT (3.52% vs. 3.81%, $p = 0.864$).

Discussion

Adjuvant endocrine treatments for DCIS significantly reduce recurrence rates and contralateral disease. Particularly, available data suggest that tamoxifen after surgery plus/minus radiotherapy provides risk reduction in the ipsilateral breast and in the contralateral breast, in patients with ER-positive primary tumors [6–10]. On the other hand, several randomized clinical trials demonstrated that radiation treatment after surgical excision is able to halve the risk of local recurrence, and even in DCIS patients with favorable clinical and pathologic features, the omission of RT significantly increases the risks of *in situ* and invasive recurrences through 12 years of follow-up [31]. Nevertheless, the lack of survival benefit from adding adjuvant treatments (radiation and tamoxifen) and the potential risk of side effects are reasons commonly given to omit adjuvant treatments after surgery [6–10].

Currently the treatment strategies significantly vary in different institutions and countries. For instance in Italy the approach to

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Table 1
Patient and tumor characteristics.

	DCIS	Micro-invasive carcinoma
	n (%)	n (%)
Age, n; mean (std)	807; 58.89 (11.60)	58; 59.12 (12.69)
Ethnicity		
Asian	45 (5.58)	3 (5.17)
African Americans	158 (19.58)	11 (18.97)
Caucasian	557 (69.02)	43 (74.14)
Unknown	47 (5.82)	1 (1.72)
ER		
Borderline	5 (0.62)	0 (0.00)
Negative	86 (10.66)	11 (18.97)
Positive	519 (64.31)	35 (60.34)
Unknown	197 (24.41)	12 (20.69)
PR		
Borderline	8 (0.99)	0 (0.00)
Negative	142 (17.60)	17 (29.31)
Positive	456 (56.51)	29 (50.00)
Unknown	201 (24.91)	12 (20.69)
HER2		
Borderline	57 (7.06)	5 (8.62)
Negative	63 (7.81)	9 (15.52)
Positive	77 (9.54)	10 (17.24)
Unknown	610 (75.59)	34 (58.62)
Chemotherapy		
Chemotherapy	14 (1.73)	8 (13.79)
None	737 (91.33)	49 (84.48)
Unknown	56 (6.94)	1 (1.72)
Radiation		
Beam radiation or radioactive implants/radioisotopes	241 (29.86)	25 (43.10)
None	519 (64.31)	32 (55.17)
Unknown if radiation received	47 (5.82)	1 (1.72)
Surgery		
Conservative Surgery	600 (74.35)	33 (56.90)
Mastectomy	203 (25.15)	24 (41.38)
None	4 (0.50)	1 (1.72)

dosage is considered the standard approach for the prevention of DCIS recurrence.

To our knowledge, this study of 865 DCIS and microinvasive carcinomas represents one of the largest, single-institution, long-term studies of patients including different racial groups, clinico-pathologic features and immunohistochemical analysis. In this study, the majority of patients were Caucasian (73.4%) with ER or PR positive tumors (84.4% and 74.3% respectively). The distribution of age at diagnosis and ER/PR/HER2 status do not significantly differ among diverse ethnic groups as already reported in literature [22] and, contrary to previous publications [23–27], in our study African Americans did not appear to have a higher recurrence rate than other ethnicities. These results may be explained by the fact that African Americans are more likely to have been prescribed endocrine therapy and treated with radiation irrespective of the type of surgery compare to other ethnicities, as also already reported in the literature [28]. We could hypothesize that clinicians decided to offer more aggressive treatments, on the basis of data in literature that shows a higher risk of recurrence, second tumors and worse overall survival for African American women [23–27]. Interestingly, contrary to current guidelines, 22 women in our sample received adjuvant chemotherapy after the loco-regional treatment (surgery with or without RT), not gaining any advantage in terms of reduction of recurrence rate.

The majority of patients underwent conservative surgery irrespective of ethnicity, even if the rate of mastectomy was higher in the microinvasive carcinoma group (25.1% vs. 41.4%). Notably, women who received conservative surgery were significantly older than those who had mastectomy. This finding may be explained by the fact that young patients are thought to need more aggressive surgery, in order to reduce their risk of second tumors. Nevertheless, we did not find any significant difference in recurrence between mastectomy and conservative surgery followed by RT. On the other hand, it is noteworthy that women who exclusively under-

Table 2a
Associations of age and ethnicity with ER/PR and HER2 status in DCIS patients.

	ER			PR			HER2		
	Positive	Negative	p-value	Positive	Negative	p-value	Positive	Negative	p-value
Age, *n; mean* (*std*)	519; 59.35 (11.62)	86; 57.64 (11.20)	0.1935	456; 59.11 (11.61)	142; 59.62 (11.68)	0.6524	77; 59.55 (10.49)	63; 60.35 (11.09)	0.6628
Ethnicity, *n*(%)			0.2505			0.1839			0.6051
Caucasian	354 (72.24)	66 (78.57)	Ref	307 (71.56)	109 (78.99)	Ref	52 (69.33)	44 (70.97)	Ref
AA	107 (21.84)	12 (14.29)	0.1445	96 (22.38)	21 (15.22)	0.1963	16 (21.33)	15 (24.19)	0.3842
Asian	29 (5.92)	6 (7.14)	0.4539	26 (6.06)	8 (5.80)	0.816	7 (9.33)	3 (4.84)	0.3101

Table 2b
Associations of age and ethnicity with ER/PR and HER2 status in microinvasive carcinoma patients.

	ER			PR			HER2		
	Positive	Negative	p-value	Positive	Negative	p-value	Positive	Negative	p-value
Age, *n; mean* (*std*)	35; 60.57 (12.47)	11; 62.00 (11.32)	0.7259	29; 59.10 (12.03)	17; 64.00 (11.93)	0.1892	10; 57.30 (9.60)	9; 61.67 (12.70)	0.4152
Ethnicity, *n*(%)			0.2659			0.5977			0.4427
Caucasian	27 (77.14)	6 (54.55)	Ref	22 (75.86)	11 (64.71)	Ref	6 (60.00)	5 (55.56)	Ref
AA	6 (17.14)	4 (36.36)	0.4502	6 (20.69)	4 (23.53)	0.6556	2 (20.00)	4 (44.44)	Inest
Asian	2 (5.71)	1 (9.09)	0.8389	1 (3.45)	2 (11.76)	0.3318	2 (20.00)	0 (0.00)	Inest

these patients is mostly limited to loco-regional treatments (breast conserving surgery followed by RT or mastectomy without RT) and there is active research in trying to define alternatives to the standard dose of 20 mg Tamoxifen, using low-dose Tamoxifen [32] or other molecules such as metformin [33], NSAIDs, statins and vitamin D analogs [34,35]. On the other hand, in several other countries, such as the United States, endocrine treatment at full

went conservative surgery experienced a higher recurrence rate, as also shown in previous studies [36].

Increasing evidence indicate that women with DCIS that are ER and PR-negative, or HER2-positive have an increased recurrence rate of *in situ* and invasive carcinomas [16,37]. Notably, our study confirms that ER and PR negative DCIS are associated with significantly higher ipsilateral recurrence and/or contralateral tumors. On

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Table 3a
Associations of age and ethnicity with treatment modalities in DCIS patients.

	Chemotherapy			**Radiation**		
	Yes	No	p-value	Yes	No	p-value
Age, *n; mean (std)*	14; 53.00 (11.20)	737; 59.00 (11.50)	0.0681	241; 59.15 (10.09)	519; 58.85 (12.18)	0.7237
Ethnicity, *n*(%)			0.0018			0.0021
Caucasian	4 (33.33)	513 (73.60)	Ref	153 (64.56)	366 (76.41)	Ref
AA	8 (66.67)	140 (20.09)		68 (28.69)	84 (17.54)	
Asian	0 (0.00)	44 (6.31)		16 (6.75)	29 (6.05)	
	Surgery			**Endocrine therapy**		
	Conservative	Mastectomy	p-value	Yes	No	p-value
Age, *n; mean (std)*	600; 60.36 (11.31)	203; 54.52 (11.41)	<0.0001	179; 57.53 (10.02)	556; 59.47 (11.95)	0.0324
Ethnicity, *n*(%)			0.1535			<0.0001
Caucasian	420 (75.13)	136 (68.34)	Ref	93 (52.25)	408 (78.76)	Ref
AA	109 (19.50)	48 (24.12)		69 (38.76)	84 (16.22)	
Asian	30 (5.37)	15 (7.54)		16 (8.99)	26 (5.02)	

Table 3b
Associations of age and ethnicity with treatment modalities in microinvasive carcinoma patients.

	Chemotherapy			**Radiation**		
	Yes	No	p-value	Yes	No	p-value
Age, *n; mean (std)*	8; 59.37 (11.92)	49; 58.59 (12.58)	0.8677	25; 60.44 (9.17)	32; 57.34 (14.41)	0.3286
Ethnicity, *n*(%)			0.2685			0.8889
Caucasian	8 (100.0)	34 (70.83)	Ref	20 (80.00)	22 (70.97)	Ref
AA	0 (0.00)	11 (22.92)		4 (16.00)	7 (22.58)	
Asian	0 (0.00)	3 (6.25)		1 (4.00)	2 (6.45)	
	Surgery			**Endocrine therapy**		
	Conservative	Mastectomy	p-value	Yes	No	p-value
Age, *n; mean (std)*	33; 62.12 (11.71)	24; 54.21 (12.44)	0.0189	22; 58.32 (11.06)	29; 59.55 (13.06)	0.717
Ethnicity, *n*(%)			0.485			0.5962
Caucasian	26 (81.25)	16 (66.67)	Ref	17 (77.27)	21 (75.00)	Ref
AA	5 (15.63)	6 (25.00)		3 (13.64)	6 (21.43)	
Asian	1 (3.13)	2 (8.33)		2 (9.09)	1 (3.57)	

Table 4
Recurrence and contralateral tumor characteristics in DCIS patients (n = 71).

	n (% of the total)	p-value
Age, mean (std)		0.3062
Recurrence	57.52 (11.79)	
No recurrence	59.03 (11.58)	
Ethnicity		0.058
Asian	2 (4.44)	
African American	7 (4.43)	
Caucasian	55 (9.87)	
ER		0.009
Negative	15 (17.44)	
Positive	44 (8.47)	
PR		0.042
Negative	20 (14.08)	
Positive	38 (8.33)	
HER2		0.742
Negative	4 (6.34)	
Positive	6 (7.79)	
Chemotherapy		0.098
No	64 (8.68)	
Yes	3 (21.42)	
Radiation therapy		0.0025
No	56 (10.78)	
Yes	10 (4.14)	
Surgery		<0.0001
Conservative Surgery	62 (10.33)	
Mastectomy	8 (3.94)	

the other hand, Poulakaki et al. recently reported that recurrence rates are not significantly associated with ER, PR status or HER2 expression [38], thus the utility of testing ER/PR/HER2 status in DCIS patients is still controversial. Interestingly, the HER2 over-expression is commonly seen in high-grade DCIS, suggesting that HER2 might play a role in tumor initiation and progression [39]. Particularly, one of the possible mechanisms by which HER2 might mediate breast carcinogenesis is through its role in maintaining and increasing breast cancer stem cells [40]. In our study, although there is no significant difference in recurrence according to HER2 status of primary DCIS, a high rate of HER2 positive recurrences has been reported, confirming the evidence that HER2 may represent a potential biomarker for DCIS at high risk of recurrence [16,37] and therefore HER2 targeted therapeutic interventions (e.g. vaccines, trastuzumab) can contribute to prevent it. Particularly, the NSABP B-43 study will examine this question comparing trastuzumab given concurrently with radiation therapy to radiation alone in women with HER2-positive DCIS resected by lumpectomy. The study has just completed the accrual and aims to evaluate if trastuzumab given during whole breast irradiation may improve results for HER2-positive DCIS after breast-conserving surgery. Furthermore, a HER2 pulsed autologous dendritic cell (DC1) vaccine has already shown to induce tumor regression in patients with HER2-positive DCIS [41] and particularly, in patients with ER-negative HER2-positive DCIS [42]. On these bases, other three different ongoing trials are evaluating HER-2/Neu pulsed DC1 vaccine in patients diagnosed with DCIS, also in combination with trastuzumab [43].

Interestingly, data regarding the evaluation of Ki-67 in DCIS suggest that an increased Ki-67 may be a useful prognostic and predictive factor for patients at increased risk for recurrence and in which adjuvant treatment (RT, endocrine treatment) should be considered, independently of histological grade and presence of necrosis [44–47].

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To date, the current National Comprehensive Cancer Network practice guidelines include determination of ER status as the only validated biomarker for routine clinical practice in the workup of DCIS. Nevertheless, we believe that the evaluation of the ER/PR/HER2 status should be considered in the evaluation of DCIS, since these markers may help in determining the best therapy if needed for these patients. Moreover, considering that the concordance rate of ER/PR/HER2 between primary DCIS and second tumors is 88.3%, 82.2% and 53.8% respectively, these parameters might be re-evaluated on the biopsies of second tumors for planning the next treatments.

The most important limitation of our study lies in the lack of biological data. We did not find information on ER/PR in almost 25% of cases and on HER2 in almost 75%, even if our Department of Pathology evaluates ER/PR/HER2 status in every new diagnosis unless the specimen is inadequate or the patient is an outside consult with stains already performed elsewhere. The reason for this lack of data lies mostly in the fact that this is a register-based study. Register-based studies have several strengths such as large sample size, limited selection bias, valuable time of follow up, etc. Nevertheless, they also have limitations, which are important to recognize. Particularly, data are pre-collected by others than researchers, data quality could be low or unknown and missing data are difficult to handle [48]. In our case, our Cancer Registry started to register HER2 status only in 2010, thus all the information regarding this parameter between 2003 and 2010 are missing. Moreover, the results of the FISH/ISH test are usually provided in a second moment with a different report, thus our Cancer Register might not have considered it.

Finally, we did not find any recurrence among the microinvasive carcinoma patients. Our results confirm the previous findings that microinvasion is not correlated with significantly increase in the risk of recurrence [17–20].

Based on our results, the treatment decision-making in DCIS should not be based only on age, ethnicity or the presence of microinvasion. The immunohistochemical analysis of ER/PR/HER2 status could represent important parameters for the selection of systemic therapies, as previously reported in the literature [16,37]. Particularly, in patients with ER/PR positive DCIS, adjuvant endocrine treatment with tamoxifen should be considered. Anastrozole might offer an alternative option for postmenopausal women with ER positive DCIS, which may be appropriate for women with contraindications for tamoxifen [10]. However, waiting to have more results on anastrozole, low-dose tamoxifen or alternative molecules, the standard of treatment should be the full dose of 20 mg tamoxifen. On the other hand, adjuvant chemotherapy should never be taken into consideration for the treatment of *in situ* tumors.

Regarding surgical options for these patients, mastectomy or conservative surgery (lumpectomy or quadrantectomy) are both valid options for the treatment of DCIS and, according to our results, clinicians should not decide one or the other on the basis of age and ethnicity of the patient. Among women of our sample who underwent conservative surgery, women receiving RT were significantly less likely to develop recurrence. Nevertheless, in recent literature significant improvements in survival with the use of RT after breast conserving surgery has been only observed in patients with higher nuclear grade tumors, younger age, and larger tumor size [49,50], thus decisions for RT should be tailored on the basis of patient factors and tumor characteristics [51,52].

Given the limitations of morphology and immunohistochemistry in trying to make therapeutic decisions, alternative approaches have been studied. In the last few years, the development and validation of risk stratification models, in order to provide personalized treatment recommendations in DCIS patients have been developed. The Oncotype DX DCIS Score is a multigene expression assay for DCIS patients that provides individualized estimates of 10-year risk of local recurrence following conservative surgery alone [53]. The score is generated from an algorithm that includes 12 (seven cancer related and five reference genes) of the 21 genes in the Recurrence Score assay [54]. The Oncotype DX DCIS Score has been validated in the Eastern Cooperative Oncology Group (ECOG) E5194 prospective cohort study of low-risk DCIS treated by conservative surgery alone [53] and more recently, in a larger population-based study of individuals with DCIS treated with conservative surgery alone [55]. Since the validation, the DCIS Score have become one of the most impactful factors in planning treatment [56], but several limitations still exist [57]. First of all, the test does not take into consideration other relevant prognostic factors such as age, family history, previous endocrine therapy assumption, surgical margins width, size of DCIS, nuclear grade, and necrosis. Then, the test presents significant costs and, it does not result easily accessible in most of the institutions. Concluding, since a standardized and accessible model have not been developed yet to identify patients at low-risk of recurrence, individual consideration of risks and benefits remain fundamental.

An area of great interest is the study of molecular markers compared with traditional clinical and pathologic DCIS features. This approach is based on the assumption that cells in DCIS likely already harbor molecular alterations that render them prone to progress and become invasive [58]. We believe that future research should be directed to better define the subgroup with the worst prognosis, as defined by the recurrence rate, in order to provide the classic histo-pathological and molecular biomarkers predictive of recurrence and identify patients candidate to more aggressive treatments. A combination of morphology, immunohistochemistry and molecular markers may offer a better understanding of DCIS in order to better tailor therapy for each individual patient.

Conflict of interest statement

None.

Disclosure

None.

Ethical approval

We have read and complied with the policy of the journal on ethical consent, as stated in the Guide to Authors.

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