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Original Research

Influence of ductal carcinoma in situ on the outcome of invasive breast cancer. A prospective cohort study

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ABSTRACT

Background: Ductal carcinoma *in situ* (DCIS)-associated invasive ductal carcinoma (IDC) is present in a large number of patients with breast cancer. However, the association between these two entities has not been studied in detail. The aim of this study is to compare the clinical and histopathological factors associated to recurrence of IDC with those of DCIS-associated IDC (IDC + DCIS).

Materials and methods: A prospective observational longitudinal study of 464 patients was performed between 2010 and 2015. Patients with IDC and DCIS + IDC were included and analyzed.

Results: IDC + DCIS was present in 243 patients (52.4%). No difference on histopathological characteristics were found, only Grade I and II of invasive component were more frequent in patients with IDC + DCIS than those with IDC ($p = 0.038$). No differences on recurrence were found between the main groups ($p = 0.256$). For patients who received neoadjuvant chemotherapy, those with IDC + DCIS had lower response than those with IDC alone ($p = 0.014$). No differences between the main groups were found on recurrence ($p = 0.256$). For patients who received neoadjuvant chemotherapy, recurrence was present in 19 patients (30.6%) in the IDC group in contrast to 5 (12.2%) in the IDC + DCIS group ($p = 0.030$). Mortality was present in 15 patients (24.2%) in the IDC group in contrast to 3 (7.3%) in the IDC + DCIS group ($p = 0.027$). At 7 years, 80.8% patients were alive: 71.9% from the IDC group and 92.7% from the IDC + DCIS group.

Conclusions: The presence of DCIS seems to be indicative of a benign behavior in patients who receive neoadjuvant chemotherapy. Longer DFS and higher overall survival were found in the IDC + DCIS group despite presenting with a lower response to chemotherapy. These findings help us identify patients with better prognosis in breast cancer.

1. Introduction

Current screening programs and the emergence of new technologies have allowed early detection of breast cancer and have increased the detection rate of ductal carcinoma *in situ* (DCIS).

Some invasive breast cancer presents with associated DCIS. The extent of associated DCIS has been considered as a prognostic factor and a factor of local recurrence for patients treated with both breast-conserving surgery and radiation therapy.

Invasive breast cancer with extensive intraductal component (EIC) was defined by Schnitt SJ *et al.* as the presence of more than 25% of DCIS in the tumor mass or DCIS outside the main tumor mass [1]. Importantly, EIC has been associated with a higher rate of positive margins, re-excision, and local recurrence, which results in surgeons commonly performing more aggressive surgery when EIC is present [2,3]. Also, several non-randomized studies analyzing DCIS in the absence of invasive disease have suggested that high-grade DCIS is associated with a higher risk of recurrence [4].

Some authors use Schnitt SJ's *et al.* classification to determine the impact on recurrence and survival when EIC is present [5,6]. However, the absence of studies that analyze in depth the correlation between the percentage of DCIS inside the tumor mass and recurrence has not

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allowed the establishment of a more precise classification. Thus, the current classification to determine the prognosis and local recurrence of invasive breast cancer with associated DCIS has not proved to be advantageous to date.

DCIS-associated invasive ductal carcinoma (IDC) is present in a high number of patients (25–80% according to the different series). However, the association between these two entities has not been studied in detail. Despite a few studies analyzing the association of invasive breast cancer with the presence of DCIS as a prognostic factor, these studies have shown to be highly controversial. Some authors have found no differences in recurrence and survival [7–9]. Caravias MP et al. and other authors showed that the presence of DCIS associated to IDC seems to increase disease-free survival (DFS) and may be an independent and favorable prognosis factor for breast cancer [10,11]. On the contrary, Jacquemier J et al. described a high number of recurrence when DCIS was associated with IDC [6]. Interestingly, a study carried by Conny Vrieling *et al.* involving 5569 patients with a follow up of 18.2 years showed that the boost after conserving breast surgery reduced local recurrence in high-risk patients (≤50 years and associated DCIS) and, importantly, the effect of DCIS adjacent to the invasive tumor remained stable [12]. The aim of our study is to compare the clinical and histopathological factors between patients with IDC or DCIS-associated IDC (IDC + DCIS) and to find the prognostic factors associated to recurrence and mortality in each group.

2. Patients and methods

2.1. Patients

A prospective observational longitudinal study was performed on patients who had undergone curative surgery for primary invasive breast cancer between 2010 and 2015. The study was performed in a single breast pathology unit. Only patients with a definitive histopathology-based diagnostic of ductal carcinoma were included. Patients diagnosed with metastasis were excluded. Patients with bilateral breast cancer were included as two independent study cases.

Data collected included clinical characteristics (age, laterality and clinical symptoms at the time of diagnosis), histopathological information (tumor size, tumor grade, hormone receptors, nodal status, *HER*-2 mutation, percentage of Ki67, presence and percentage of DCIS, grade of DCIS, and surrogate subtype) and surgical procedure performed.

Sentinel lymph node biopsy (SLNB) was performed in all the patients with a preoperative diagnosis of infiltrative ductal carcinoma. In patients who underwent surgery with the diagnosis of ductal carcinoma *in situ* for whom the definitive anatomopathological diagnosis showed an infiltrative ductal carcinoma (these patients were included in the IDC + DCIS group), a second surgery was required to perform SLNB. Lymphadenectomy was performed in patients with macrometastasis.

Luminal A was defined as: estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, HER-2-negative and Ki67% < 20. Luminal B HER-2-negative was defined as: ER-positive, PR-positive, Ki67% > 20, and HER-2-negative. Luminal B HER-2-positive was defined as: ER-positive, PR-positive, Ki67% > 20 and HER-2-positive. HER-2-positive (non-luminal) was defined as: RE-negative, RP-negative, HER-2-positive. Basal-like [Triple negative breast cancer (TNBC)] was defined as: RE-negative, RP-negative and HER-2-negative.

Tumor histopathology and the number of lymph nodes involved were evaluated by routine hematoxylin-eosin (H&E) staining. The histological response to chemotherapy was assessed according to Miller-Payne criteria of grading (MPG) and Residual Disease in Breast and Nodes (RDBN).

The percentage of DCIS and its grade (classified as low, intermediate or high) were measured by two independent pathologists.

In order to analyze the data, the cases were divided into two groups: invasive ductal carcinoma (IDC) and ductal carcinoma with associated DCIS (IDC + DCIS).

The application of an adjuvant treatment and follow up was decided according to standard guidelines.

2.2. Statistical analysis

Quantitative data are shown as median or mean of values and their variability is expressed as range or standard deviation (SD), as specified for each analysis. Qualitative data are shown as absolute values or percentages. The incidence was used as a measure of frequency and the relative risk as a measure of association between independent groups.

The study of normality of quantitative variables was done applying the Kolmogorov-Smirnov or the Shapiro-Wilk tests, as indicated for each analysis. For significance assessment of quantitative data, the unpaired Student's T-test or the two-tailed Mann-Whitney *U* test was applied, as specified for each analysis. For significance assessment of qualitative data, the Fisher's exact test or the Chi-squared test was applied. For analysis of more than two groups, the one-way ANOVA and the Tukey's range test for *post hoc* pairwise comparison of groups, or the Kruskal-Wallis were used. Survival was analyzed with the Kaplan-Meier estimate and survival distributions compared with the Log-Rank test. The multivariate Cox proportional hazards regression model was used to simultaneously evaluate the effect of several factors on survival and mortality.

Statistical analysis was performed using the software SPSS® version 21.

The work has been reported in line with the STROCSS criteria [13].

3. Results

3.1. Patients characteristics, definitive tumor characteristics and treatment

Between January 2010 and December 2015, 464 patients were included in the study. IDC was present in 221 patients (47.6%) and IDC + DCIS was present in 243 patients (52.4%). The clinicopathological characteristics of the entire population and the analysis between groups are shown in Table 1.

As shown in Table 1, the most frequents tumors were classified as T1, T2 or N0 for both groups.

Stage I and II were the most frequent stages present in patients, followed by stage III (around 10% of the patients). Stage IV was excluded.

Nodules were present in 62.3% of patients and was the most frequent lesion observed on mammography. The presence of microcalcifications on mammography analysis was more frequent in the IDC + DCIS group (29 patients) compared to the IDC group (7 patients), with a $p < 0.001$ (Supplementary Table 1).

Patients in the IDC group received more neoadjuvant treatment such as chemotherapy or hormonotherapy as a primary treatment compared to the IDC + DCIS group, which received more surgical treatment ($p = 0.001$) (Table 1).

The surgical treatment, which was always performed by general surgeons who were part of the hospital mammary pathology unit, was lumpectomy in 258 patients, resection of the areola complex in 3 patients, quadrantectomy in 59 patients and mastectomy in 144 patients (31% of the total) without any differences between the groups ($p = 0.956$). There were no differences between groups regarding the number of mastectomies: 81 patients (36.65%) in the IDC group and 63 patients (25.9%) in the IDC + DCIS group ($p = 0.262$). A second surgery was done in 33 patients due to affected margins: 11 in the IDC group and 22 in the IDC + DCIS group, with a $p = 0.742$ (Supplementary Table 1).

In the definitive anatomopathological analysis only the grade of invasive component was different between the groups, with grade I and II being more frequent in patients from the IDC + DCIS group and grade III more frequent in the IDC group (Table 1).

Low-grade was present in 152 patients (62.6%), high-grade in 91 patients (37.4%), and no patients presented with intermediate grade of

Table 1
Clinicopathologic features of the entire study population and the IDC and IDC + DCIS study groups. Features were assessed at the end of the study and expressed as the mean of absolute values in percentages ± standard deviation for each group. Fisher's exact test or two-tailed Mann-Whitney *U* test was applied for statistical analysis. A p value (p) < 0.05 was considered statistically significant.

Variable	Entire population (n = 464)	IDC (n = 221)	IDC + DCIS (n = 243)	*p*
Age mean of years (SD)	61.57 (13.8)	62.58 (13.9)	60.65 (13.6)	0.134
Size median in mm (SD)	19.53 (16.87)	18.92 (19.1)	20.08 (22.4)	0 .110
Clinical tumor stage[a] n (%)				0.085
T1	245 (53)	110 (49.8)	135 (55.6)	
T2	159 (34)	82 (37.1)	77 (31.7)	
T3	32 (7)	17 (7.7)	15 (6.2)	
T4	22 (4.7)	12 (5.4)	10 (4.1)	
Tis[b]	6 (1.3)	0 (0)	6 (2.5)	
Clinical lymph node status[c] n (%)				0.300
N0	368 (79.3)	169 (76.5)	198 (81.5)	
N1	79 (17.1)	41 (18.6)	38 (15.6)	
N2	16 (3.4)	10 (4.5)	6 (2.5)	
N3	1 (0.2)	1 (0.5)	0 (0)	
Initial treatment n (%)				0.001*
Surgery	341 (73.5)	145 (65.6)	196 (80.7)	
Hormonotherapy	20 (4.3)	14 (6.4)	6 (2.5)	
Chemotherapy	103 (22.2)	62 (28)	41 (16.9)	
Invasive carcinoma nuclear grade n (%)				0.038*
I	127 (29.5)	53 (26.5)	74 (32)	
II	189 (43.9)	82 (41)	107 (46.3)	
III	115 (26.7)	65 (32.5)	50 (21.6)	
Quantity of DCIS % median (SD)	18.14 (22.38)	13.2 5 (21.23)	18.15 (22.43)	0.376
Estrogen receptor n (%)				0.482
Positive	388 (83.6)	182 (82.4)	206 (84.8)	
Negative	76 (16.4)	39 (17.6)	37 (15.2)	
Progesterone receptor n (%)				0.810
Positive	307 (66.17)	145 (65.6)	162 (66.7)	
Negative	157 (33.83)	76 (34.4)	81 (33.3)	
Ki67% median (SD)	22.01 (21.87)	23.23 (22.07)	20.91 (21.72)	0.121
HER-2 n (%)				0.896
Positive	78 (17.4)	37 (17.1)	41 (17.6)	
Negative	371 (82.6)	179 (82.9)	192 (82.4)	
Lymphadenectomy n (%)				0.727
Yes	183 (39.4)	89 (40.3)	94 (38.7)	
No	281 (60.6)	132 (59.7)	149 (61.3)	
Molecular subrogate subtype n (%)				0.248
Luminal A	207 (44.6)	91 (41.2)	116 (47.7)	
Luminal B HER-2 positive	42 (9.1)	22 (10)	20 (8,2)	
Luminal B HER-2 negative	139 (6.7)	72 (32.6)	67 (27.6)	
HER-2	31 (6.7)	11 (5)	20 (8,2)	
Basal-like	45 (9.7)	25 (11.3)	20 (8.2)	
Radiotherapy n (%)	377 (81.3)	180 (47.7)	197 (52.3)	0.917
External radiotherapy	365 (78.6)	173 (96.1)	192 (97.5)	0.456
Partial beast radiation	12 (2.58%)	7 (3.9)	5 (2.5)	
Hormone therapy n (%)				0.487
Yes	392 (84.5)	184 (83.3)	208 (85.6)	
No	72 (15.5)	37 (16.7)	35 (14.4)	
Adjuvant chemotherapy n (%)				0.181
Yes	142 (30.6)	61 (27.6)	81 (33.3)	
No	322 (69.4)	160 (72.4)	162 (66.7)	

[a] *TNM classification*: *T1: size* ≤ 2 cm, *T2: size 2* ≥ 5 cm, *T3: size* > 5 cm, *T4: extension to chest wall, skin or inflammatory breast cancer*, Tis (DCIS): ductal carcinoma *in situ*.
[b] Tis patients were included in the IDC + DCIS group after the definitive anatomopathological diagnosis, and used for analysis.
[c] *N0: No lymph nodes affected, N1: 1–3 ipsilateral movable axillary lymph nodes, N2: 4–9 ipsilateral fixed axillary lymph nodes, N3: infraclavicular or internal mammary lymph nodes affected. SD:* standard deviation, *n: number, *p: p* value < 0.05.

DCIS (Table 2). From analysis of the IDC + DCIS group we could observe that low-grade DCIS presented with a lower percentage of DCIS and lower Ki67%, showed higher frequency of grade I and II of invasive component, was more frequently positive for hormone receptors and was negative for HER-2 (Table 2).

Regarding the subrogate molecular type, basal-like tumors showed a higher percentage of high-grade DCIS, and luminal A subtype had a higher percentage of low-grade DCIS (Table 2).

3.2. Overall and disease-free survival

Factors associated to recurrence are described in Table 3.

With a mean follow up of 51.43 months (standard deviation (SD) of 21.10), recurrence was present in 41 patients (23 in ICD and 18 in IDC + DCIS), of which 34.1% (14 patients) were local recurrences. There were no differences between the main groups (p = 0.256). Deceased patients (3.7%) were excluded from the analysis. The mean of overall recurrence was 1.78 years (SD 1.21), with a mean of recurrence in the IDC group of 1.65 years in contrast to 1.94 in the IDC + DCIS group. There were no differences between groups (p = 0.640) (Supplementary Table 1).

Distant recurrence was present in 18 patients (8.1%) in the IDC group in contrast to 9 (3.7%) in the IDC + DCIS group (p = 0.058) (Supplementary Table 1).

The global cumulative incidence of recurrence was 8.84% [95% confidence interval (CI) of 6.58–11.77], with recurrence in the IDC

Table 2
IDC + DCIS group. The variables within the IDC + DCIS group (subdivided in low or high-grade) were quantified at the end of the study and expressed as the mean of absolute values in percentages ± standard deviation for each group. For statistical analysis, Fisher's exact test or two-tailed Mann-Whitney *U* test was applied. A p value (p) < 0.05 was considered statistically significant.

Variable	Low-grade (n = 152)	High-grade (n = 91)	*p*
Age mean of years (SD)	60.61 (13.68)	60.73 (13.72)	0.930
Invasive carcinoma nuclear grade n (%)			0.000*
I	59 (41.8)	15 (16.7)	
II	63 (44.7)	44 (48.9)	
III	19 (13.5)	31 (34.4)	
Molecular subrogate subtype n (%)			0.015*
Luminal A	85 (55.9)	31 (34.1)	
Luminal B HER-2-negative	38 (25)	29 (31.9)	
Luminal B HER-2-positive	10 (6.6)	10 (11)	
HER-2	10 (6.6)	10 (11)	
Basal-like	9 (5.9)	11 (12.1)	
			0.009*
Worst prognostic (WP)	29 (19)	31 (34)	
Better prognostic (BP)	123 (81)	60 (66)	
Estrogen receptor n (%)			0.000*
Positive	136 (89.5)	70 (76.9)	
Negative	16 (10.5)	21 (23.1)	
Progesterone receptor n (%)			0.000*
Positive	114 (75)	48 (52.7)	
Negative	38 (25)	43 (47.3)	
Ki67% mean (SD)	17.34 (19.73)	26.86 (23.64)	0.000*
HER-2 n (%)			0.038*
Positive	20 (13.2)	21 (23.1)	
Negative	127 (83.6)	65 (71.4)	
Not assessed	5 (3.3)	5 (5.5)	
Quantity DCIS % mean (SD)	16.09 (21.23)	21.59 (24.03)	0.008*
Extratumoral DCIS n (%)	2 (11.8)	15 (88.2)	0.023*

WP: basal like + HER-2 + luminal B HER-2-positive, BP: luminal A + luminal B HER-2-negative, SD: standard deviation, *n: number, *p: p* value < 0.05.

group of 10.41% [95% CI of 7.04–15.13] and in the IDC + DCIS group of 7.41% [95% CI of 4.74–11.40]. The global incidence rate was 2.29 recurrence cases per every 100 people and the 1 year-follow up showed a rate of 2.83 in the IDC group and 1.8 in the IDC + DCIS group.The relative risk of recurrence of the IDC group to the IDC + DCIS group was 1.40 [95% CI of 0.78–2.53] (Supplementary Table 2).

Extratumoral DCIS was present in 17 patients, all of them belonging to the IDC + DCIS group, and none of them had recurrence. In the majority of these patients, the type of DCIS was low-grade (Table 2).

In all the patients, lower recurrence was associated with surgery as the initial treatment, smaller definitive tumor size, grade I of invasive component and a better prognosis of the molecular subrogate subtype. Higher recurrence was associated with undergoing mastectomy, undergoing lymphadenectomy, being negative for hormone receptors, young patients, and higher Ki67%. In the chemotherapy subgroup, patients who had a lower response to neoadjuvant treatment also had higher recurrence (Table 3).

Based on the Cox proportional hazards regression model, recurrence was only associated to undergoing surgery as an initial treatment (hazard ratio (HR), 0.23; 95% CI of 0.11–0.49; $p = 0.000$), undergoing lymphadenectomy because of axillary affection (HR, 2.40; 95% CI of 1.05–5.46; $p = 0.037$), grade I of invasive component (HR, 0.2; 95% CI of 0.06–0.81; $p = 0.023$), being negative for progesterone hormone receptor (HR, 2.01; 95% CI of 1.01–4; $p = 0.046$) and large size of definitive tumor (HR, 1.02; 95% CI of 1.01–1.03; $p = 0.000$) (Table 3).

Based on the Kaplan-Meier analysis of recurrence, the average time of recurrence was 6.48 years (95% CI of 6.33–6.63), with 6.39 years in the IDC group (95% CI of 6.16–6.63) and 6.57 years in the IDC + DCIS group (95% CI of 6.38–6.76). The average time of recurrence was 0.235 years according to the Log-Rank test (Supplementary Table 3). At 7 years, DFS was 89.7%: 88.4% in the IDC group and 91.1% in the IDC + DCIS group (Supplementary Table 3).

Al the end of the study 47 patients had deceased. A total of 29 patients deceased as a consequence of breast cancer progression and the remaining 18 patients due to unrelated causes.

Mortality was lower in patients who received surgery as an initial treatment, and in patients with T0 and T1 tumors, grade I and better prognosis of the molecular subrogate subtype. Mortality was higher in patients undergoing mastectomy, undergoing lymphadenectomy, negative for hormone receptors and with higher Ki67%. In the chemotherapy subgroup, patients who had lower response to neoadjuvant treatment had higher mortality. Based on the Cox proportional hazards regression model, mortality was only associated to undergoing surgery as an initial treatment (HR, 0.17; 95% CI of 0.7–0.46; $p = 0.005$), grade I (HR, 0.08; 95% CI of 0.01–0.65; $p = 0.018$), being negative for progesterone hormone receptors (HR, 3.4; 95% CI of 1.35–8.61; $p = 0.009$) and larger size of definitive tumor (HR, 1.03; 95% CI of 1.02–1.04; $p = 0.000$) (Table 4).

The global cumulative incidence of mortality was 6.25% (95% CI of 4.33–8.88): 8.14% in the IDC group (95% CI of 5.21–12.51) and 4.53% in the IDC + DCIS group (95% CI of 2.55–7.92). The global incidence rate of mortality was 1.62 cases per every 100 people and the 1-year follow-up showed 2.22 cases in the IDC group and 1.12 in the IDC + DCIS group. The relative risk of mortality of the IDC group to the IDC + DCIS group was 1.65 (95% CI of 0.80–3.42) (Supplementary Table 2).

On Kaplan-Meier analysis of survival, the average survival time was 6.63 years (95% CI of 6.49–6.76), with 6.52 years in the IDC group (95% CI of 6.31–6.73) and 6.72 years in the IDC + DCIS group (95% CI of 6.56–6.88) (Supplementary Table 3). The average survival time was 0.104 years according to the Log-Rank test (Supplementary Table 3). At 7 years, 92.8% patients were alive: 90.8% in the IDC group and 94.7% in the IDC + DCIS group (Supplementary Table 3).

3.3. Neoadjuvant chemotherapy and hormonotherapy

The response in patients who received either neoadjuvant treatment or neoadjuvant chemotherapy is described in Table 5. The response to neoadjuvant treatment was lower in the IDC + DCIS group compared to the IDC group.

Recurrence and mortality related to neoadjuvant treatment are summarized in Table 6. For the patients who received neoadjuvant treatment (123 patients), the ones that did not respond to neoadjuvant treatment had higher recurrence with no difference on mortality. However, for patients who received chemotherapy as neoadjuvant treatment (103 patients), the ones that did not respond to treatment had higher recurrence and higher mortality. For patients who received neoadjuvant chemotherapy, the IDC group had higher recurrence and mortality than the IDC + DCIS group (Table 6).

The average time of recurrence was 5.69 years (95% CI of 5.24–6.15): 5.25 years in the IDC group (95% CI of 4.60–5.91) and 6.32 years in the IDC + DCIS group (95% CI of 5.76–6.38) (Supplementary Table 3). The mean overall time before recurrence was 0.028 years according to the Log-Rank test. At 7 years, 74.9% of patients were disease-free: 65.8% in the IDC group and 87.3% in the IDC + DCIS group (Supplementary Table 3 and Fig. 1).

At the end of the study, 15 patients in the IDC group and 3 in the IDC + DCIS group had deceased. The average survival time was 5.99 years (95% CI of 5.57–6.41): 5.58 years in the IDC group (95% CI of 4.96–6.20) and 6.56 years in the IDC + DCIS group (95% CI of 6.08–7.03) (Supplementary Table 3). The average time of recurrence was 0.023 years according to the Log-Rank test. At 7 years, 80.8% patients were alive: 71.9% in the IDC group and 92.7% in the IDC + DCIS group (Supplementary Table 3 and Fig. 2).

4. Discussion

IDC-associated DCIS is a very frequent entity. Thus, we have

Table 3
Recurrence. Information related to recurrence of the entire population was quantified at the end of the study and expressed as absolute values and/or percentages. For statistical analysis, Fisher's exact test or two-tailed Mann-Whitney *U* test was applied. Cox regression was also calculated. A p value (p) < 0.05 was considered statistically significant.

Qualitative variables	N	Recurrence (bivariate analysis)			Cox regression		
		n	%	*p*	HR	95%CI	*p*
Initial treatment				0.000*			
Surgery	341	12	3.5		0.23	0.11–0.49	0.000*
Hormonotherapy	20	5	26.3				0.893
Chemotherapy	103	24	23.3				0.893
Mastectomy				0.000*			0.475
Yes	144	24	16.7				
No	320	17	5.3				
Lymphadenectomy				0.000*			
Yes	183	32	17.5		2.40	1.05–5.46	0.037*
No	281	9	3.2				
Size							
T0, T1	292	20	6.8	0.062			
T2, T3, T4	172	21	12.2				
Grade				0.004*			
I	127	3	2.4		0.23	0.06–081	0.023*
II	189	18	9.5				
III	115	15	13				
Estrogen receptor				0.001*			
Negative	76	15	19.7				0.671
Positive	388	26	6.7				
Progesterone receptor				0.001*			
Negative	157	24	15.3	[1]	2.01	1.01–4	0.046*
Positive	307	17	5.5				
HER-2				0.654			
Negative	371	30	8.1				
Positive	78	8	10.3				
Molecular subrogate subtype				0.002*			
BP	346	22	6.4				0.589
WP	118	19	16.1				
Groups				0.326			
IDC	221	23	10.4				
IDC + DCIS	243	18	7.4				
Type of intraductal component				0.314			
High-grade	92	9	9.8				
Low-grade	153	9	5.9				
Lymph node response				0.506			
Partial or total	14	8	51.7				
No response	19	13	68.4				
Response to chemotherapy				0.000*			
No response	17	8	47.1				
< 30%	12	1	8.3				
≥30%	74	15	20.3				

Quantitative variables	**N**	**Recurrence (bivariate analysis)**			**Cox regression**		
		MEAN	**SD**	***p***	**HR**	**95%CI**	***p***
Age years**Response to**				0.030*			
Yes	41	57	17.08				0.383
No	423	62	13.39				
Size mm**Response to**				0.033*			
Yes	41	33.95	39.90		1.02	1.01–1.03	0.000*
No	423	18.3	11.80				
Ki67% n (%)**Response to**				0.000*			
Yes	41	33.95	25.29				0.582
No	423	20.85	21.19				

WP: basal like + HER-2 + luminal B HER-2-positive, BP: luminal A + luminal B HER-2-negative, SD: standard deviation, HR: hazard Ratio, CI: confidence interval, n: number, N: total number, **p*: p value < 0.05.

assessed the implications of this association as a prognostic factor in breast cancer.

Nowadays, it is considered that IDC and IDC + DCIS are two different entities with distinct genetic alterations [8]. There are studies in which patients with associated-DCIS are younger, have higher histologic grade and smaller tumor size [7]. Some histological characteristics such as c-erbB-2, bcl-2, p53 or Ki67% have been described as prognostics factors, indicating in some studies a higher tumor aggressiveness [14] and in others a lower aggressiveness [15,16]. However, in our group of patients, the clinical and histopathological characteristics of the patients were not significantly different between the groups, and only grade III showed a higher frequency in the IDC group. Also, there were no differences found in the quantity or type of the DCIS component between the groups associated to the molecular subrogate type, which is in disagreement to previous studies [17].

We observed that low-grade DCIS is associated to better prognostic factors such as lower quantity of DCIS, lower Ki67%, lower grade of invasive carcinoma, being positive for hormone receptors, being

Table 4
Mortality. Data related to mortality of the entire population was quantified at the end of the study and expressed as absolute values and/or percentages. For statistical analysis, Fisher's exact test or two-tailed Mann-Whitney *U* test was applied. Cox regression was also calculated. A p value (p) < 0.05 was considered statistically significant.

Qualitative variables	N	Mortality (bivariate analysis)			Cox regression		
		n	%	*p*	HR	95%CI	*p*
Initial treatment				0.000*			
Surgery	341	7	2		0.17	0.7–0.46	0.005*
Hormonotherapy	20	4	21.1				0.978
Chemotherapy	103	18	17.5				0.978
Lymphadenectomy				0.000*			
Yes	183	24	13.1		2.47	0.84–7.28	0.098
No	281	2	1.8				
Size				0.017*			
T0, T1	292	12	4.1				
T2, T3, T4	172	17	9.9				
Grade				0.000*			
I	127	1	0.8		0.08	0.01–0.65	0.018*
II	189	10	5.3				
III	115	14	12.2				
Estrogen receptor				0.000*			0.651
Negative	76	13	17.1				
Positive	388	16	4.1				
Progesterone receptor				0.000*			
Negative	157	21	13.4		3.4	1.35–8.61	0.009*
Positive	307	8	2.6				
HER-2				0.790			
Negative	371	21	5.7				
Positive	78	5	6.4				
Molecular subrogate subtype				0.002*			0.403
BP	346	14	4				
WP	118	15	12.7				
Groups				0.126			
IDC	221	18	8.1				
IDC + DCIS	243	11	4.5				
Type of intraductal component				0.107			
High-grade	92	7	7.6				
Low-grade	153	4	2.6				
Lymph node response				0.728			
Partial or total	14	6	42.9				
No response	19	10	52.6				
Response to chemotherapy				0.036*			
No response	17	6	35.3				
< 30%	12	0	0				
≥30%	74	12	16.2				

Quantitative variables	**N**	**Mortality (bivariate analysis)**			**Cox regression**		
		MEAN	**SD**	***p***	**HR**	**95%CI**	***p***
Age years				0.394			
Yes	29	60.3	18.33				
No	435	61.8	13.46				
Size mm				0.061			
Yes	29	36.79	43.98		1.03	1.02–1.04	0.000*
No	435	18.38	12.56				
Ki67% n (%)				0.007*			
Yes	29	34.07	26.90				0.427
No	435	21.20	21.32				

WP: basal-like + HER-2 + luminal B HER-2-positive, BP: luminal A + luminal B HER-2-negative, SD: standard deviation, HR: hazard Ratio, CI: confidence interval, n: number, N: total number, **p:* p value < 0.05.

negative for HER-2, and presence of luminal-like tumors. These findings lead us to favor the molecular theory of progression from DCIS to IDC [18,19], in which the characteristics of the infiltrating component are similar to those found in ductal carcinoma *in situ* [20].

No significant differences in recurrence were found between the two main groups despite a tendency to a lower recurrence in the IDC + DCIS group. These results may be due to the overall low number of recurrences and deaths found in our series. The Kaplan-Meier survival analysis show that the IDC + DCIS group has less patients with recurrence and higher survival rates despite lacking statistical significance.

In the majority of studies analyzing recurrence, assessment of recurrence is done according to the main groups of the study. Interestingly, Ju-Yeon Kim *et al.* [21] analyzed recurrence according to the type of DCIS and showed a 2.5-fold higher risk of recurrence when a high-grade DCIS was present. These data suggest that the factor that determines recurrence is not the existence of DCIS but, instead, its grade. Importantly, these data are in contrast to what we found in our series, where the grade of DCIS seems to be unrelated to recurrence nor to mortality. These discrepancies might be due the low number of high-grade DCIS cases analyzed in our study (91 patients, 37.4%) as compared to a total of 1047 patients (75.6%) analyzed in the Ju-Yeon Kim *et al.* study.

Table 5
Response to neoadjuvant treatment. The number of patients receiving neoadjuvant treatment is expressed as absolute values and/or percentages. Fisher's exact test was used for statistical analysis. A p value (p) < 0.05 was considered statistically significant.

Variable	Response to neoadjuvant treatment		
	IDC (%)	IDC + DCIS (%)	p
Response to neoadjuvant treatment	**(n = 75)**	**(n = 48)**	0.007*
No response	11 (14.7)	16 (33.3)	
< 30%	6 (8)	8 (16.7)	
≥30%	58 (77.3)	24 (50)	
Response to neoadjuvant chemotherapy	**(n = 62)**	**(n = 41)**	0.014*
No response	6 (9.7)	11 (26.8)	
< 30%	5 (8.1)	7 (17.1)	
≥30%	51 (82.2)	23 (56.1)	

*n: number, *p:* p value < 0.05.

Table 6
Recurrence and mortality in patients who received neoadjuvant treatment. Recurrence and mortality are expressed as absolute values and/or percentages. Fisher's exact test was used for statistical analysis. A p value (p) < 0.05 was considered statistically significant.

Variable	N	Recurrence			Mortality		
		n	%	p	n	%	p
Response to neoadjuvant treatment	123			0.021*			0.065
No response	27	12	44.4		9	33.3	
< 30%	14	2	14.3		1	7.1	
≥30%	82	16	19.5		13	15.9	
Response to neoadjuvant chemotherapy	103			0.027*			0.045*
No response	17	8	47.1		6	35.3	
< 30%	12	1	8.39		0		
≥30%	74	15	20.3		12	16.2	
Patients receiving neoadjuvant chemotherapy by main groups	103			0.030*			0.027*
IDC	62	19	30.6		15	24.2	
IDC + DCIS	41	5	12.2		3	7.3	

*n: number, *p:* p value < 0.05, N: number in groups and subgroups.

After performing the Cox proportional hazards regression model only five variables [undergoing surgery as an initial treatment, undergoing lymphadenectomy (axillar affection), grade I, being negative in progesterone hormone receptor and larger tumor size] were associated to recurrence. These results are as expected since advanced stages of tumors are associated to higher recurrence, as previously shown in the literature [22].

The use of neoadjuvant treatment has increased in recent years. Due to its relevance, our study included 22.2% of patients that received chemotherapy as an initial treatment. The infiltrative component in patients with DCIS had a lower response to chemotherapy than that in patients with IDC. This is not an unexpected finding since DCIS does not respond to chemotherapy and, as previously mentioned, DCIS and IDC have been classified as different entities due to differences in the way they behave, which may be explained by the intrinsic differences in their molecular signature. Thus, we suggest the presence of DCIS to be considered as indicative of lower tumoral aggressiveness and as a protective factor of recurrence and mortality in the short-term.

Patients in the DCIS group that presented with a higher response to neoadjuvant treatment also had lower recurrences. However, the rate of mortality was only affected in the group undergoing neoadjuvant chemotherapy. Interestingly, patients in the IDC + DCIS group that received neoadjuvant chemotherapy had lower recurrence and higher overall survival than those in the IDC group. Further studies assessing the reasons behind this observation would provide valuable data on the implications of chemotherapy for recurrence and survival where DCIS is present.

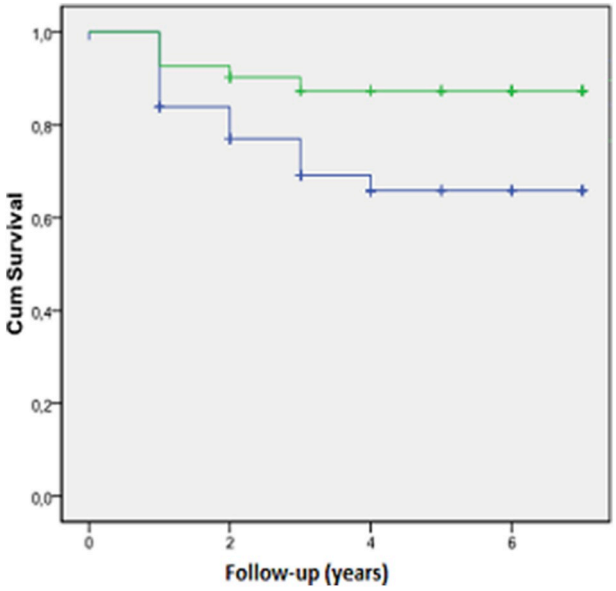

Fig. 1. Kaplan-Meier curve of disease-free survival (DFS) for the IDC + DCIS (upper line) and IDC (lower line) groups in patients receiving neoadjuvant chemotherapy. A survival Kaplan-Meier curve on DFS was calculated in patients receiving neoadjuvant chemotherapy both for the ICD and IDC + DCIS groups.

In our study, the presence of extensive intraductal component and the percentage of DCIS were not associated with higher recurrence or mortality, in contrast to previous studies [6]. In contrast, the presence of DCIS was associated with lower recurrence, which is in agreement with previous studies [10].

5. Conclusions

In our study, the presence of DCIS seemed to be indicative of tumors with a better prognosis, especially in the group of patients who received

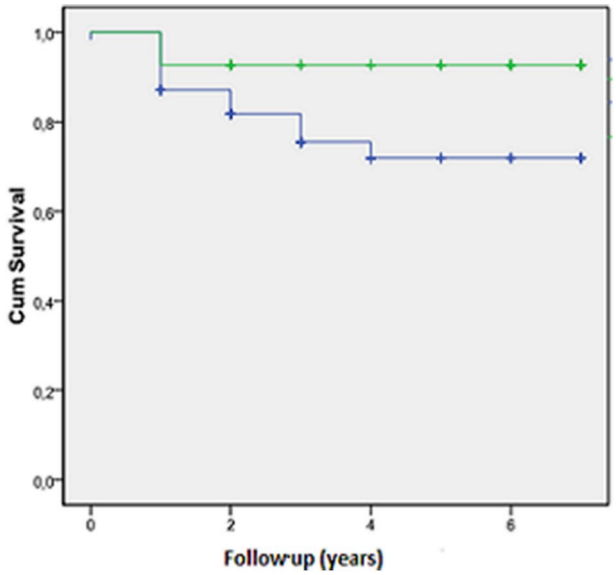

Fig. 2. Kaplan-Meier curve of the overall survival (OS) for the IDC + DCIS (upper line) and IDC (lower line) groups in patients receiving neoadjuvant chemotherapy. A survival Kaplan-Meier curve on OS was calculated in patients receiving neoadjuvant chemotherapy both for the ICD and IDC + DCIS groups.

neoadjuvant chemotherapy, since they presented with lower recurrence and mortality despite having a lower response to neoadjuvant treatment.

Study limitations

A higher number of patients within the study would help in increasing the experimental power in the study of recurrence, providing a more accurate assessment of statistically significant differences between the groups.

A median follow up of 51 months is a limited time for assessment of prognostic effect in breast cancer patients. A longer follow up would provide valuable data for the study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Other information

Because our work is an observational study, the following information has not been analyzed: post-intervention considerations, peri-intervention considerations, changes in the interventions, intervention adherence/compliance and tolerability and participants recruited with a flow diagram.

Sample size calculation was 191 patients (calculated with 12% of recurrence and 10% of loss patients). The aim of the study was not to register complications and adverse or unanticipated events.

Data statement

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Author contribution

Study design: Sandra Lopez Gordo, Dr Javier Encinas Mendez and Dr Jesus Seco Calvo.

Data collection: Sandra Lopez Gordo, Dr Javier Encinas Mendez and Dr Ernest Just Roig.

Data analysis: Jesus Blanch Falp, Sandra Lopez Gordo and Dr Estrella Lopez-Gordo.

Writing: Sandra Lopez Gordo, Dr Estrella Lopez-Gordo and Dr Javier Encinas Mendez.

Contribution: Dr Marco Molina and Dr Julian Ibañez.

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Guarantor

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.01.016.

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