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Retrospective analysis in *in situ* ductal carcinoma; 11 years of experience

Abstract

Objective: To describe our experience in the diagnosis, treatment and follow up of patients with ductal carcinoma *in situ* (DCIS).

Materials and methods: 953 breast carcinomas treated in the Mastology service of the Department of Gynecology and Obstetrics of the Hospital Aleman of Buenos Aires, between January 2004 and December 2014, are retrospectively analyzed.

206 biopsies (BRQ 25-mammotome 151-core biopsy 30) of ductal carcinomas *in situ* were identified, resulting after definitive pathological evaluation in 172 (18%) pure ductal carcinomas *in situ* of the total of 953 patients analyzed.

Results: 206 biopsies (BRQ 25-mammotome 151-core biopsy 30) of ductal carcinomas *in situ* were identified, resulting after definitive pathological evaluation in 172 (18%) pure ductal carcinomas *in situ* of the total of 953 patients analyzed. The imaging report in the total of the 206 patients showed microcalcifications in 80.1%. The diagnosis of carcinoma *in situ* was made in 181 (87%) patients by preoperative microinvasive procedures and in the remaining 25 (13%) patients by radiosurgical biopsy (BRQ). There was evidence of 18.8% underdiagnosis after microinvasive procedures. In our case series, 84.3% were GH3/GH2 while 15.7% were GH 1. When comparing the size of the surgical specimens and correlating it with the 34 cases of invasive and microinvasive carcinoma, it showed that 54.8% of invasion in those tumors greater than 30 mm, 50.4% in those that exceeded 21 mm and in no case in those less than 10 mm. 20% of multicentric lesions were associated with invasive tumor. Sentinel lymph node technique was performed in 23.8% patients in the first surgery, resulting negative in all cases. When evaluating radiation and hormonal treatment, radiotherapy was performed in 131 patients (85.6%) and hormonal treatment was performed in 75% of the patients. In the follow-up until December 2014, 11 relapses (5.23%) were recorded.

Conclusion: Our results are consistent with the international indexed literature in reference to diagnosis, treatment and recurrence rate pure of DCIS.

Keywords: ductal carcinoma, breast, mammography, ovarian cancer syndrome

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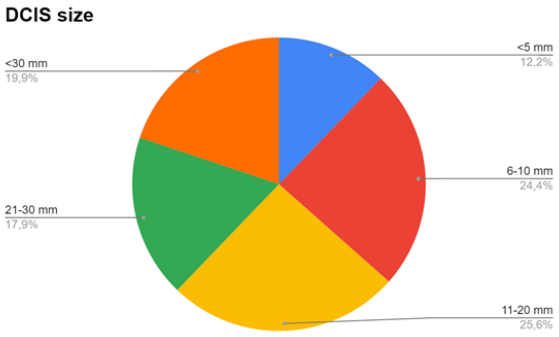
Introduction

In Situ ductal carcinoma of the breast (DCIS) represents a heterogeneous group of lesions limited to the mammary ducts that differ in their clinical, histological, and biological potential presentation, varying from low-grade lesions in which life expectancy is not modified up to high-grade lesions that can hide invasive carcinomas and potentially be precursor lesions.[1] Diagnosis has increased exponentially with the introduction of mammography in breast cancer screening. The incidence of *in situ* ductal carcinoma increased from 5.8% per 100,000 women in 1970 to 32.5 per 100,000 women in 2004 in the United States.

Approximately 25% of breast carcinomas diagnosed in the US are DCIS and some reports reach up to 40%.[1–3] This increase is mainly attributed to the systematic use of mammography (Graph 1).

DCIS is rare in women under 30 years of age and, like invasive carcinoma, its incidence increases with age. More than 90% of DCIS are detected only in imaging studies, these being mostly asymptomatic.[4–8]



Graph 1 DCIS size.

The risk factors for DCIS and invasive breast cancer are similar, and DCIS is also a component of the inherited breast and ovarian cancer syndrome due to mutations in the BRCA 1 and BRCA 2 genes; mutation rates are similar to those of invasive breast cancer.[9–11]

The 90% of women with DCIS present microcalcifications on mammography, these being the most frequent mammographic sign, but on the other hand, this manifestation underestimates the degree of DCIS and the number of tumor foci in cases of multifocal disease.[9,12,13] Underdiagnosis increases with increasing tumor size.

All patients with mammographic suspicion of DCIS should undergo percutaneous or radiosurgical breast biopsy to confirm the diagnosis and, after performing surgical treatment, treat them appropriately, since their correct diagnosis could represent a way to prevent breast cancer.

In this work we propose to describe the diagnosis, treatment and follow-up in our institution.

Materials and methods

We retrospectively analyzed 953 breast carcinomas treated in the Mastology service of the Department of Gynecology and Obstetrics of the Hospital Aleman of Buenos Aires, between January 2004 and December 2014.

206 biopsies (BRQ 25-mammotome 151- core biopsy 30) of *in situ* ductal carcinomas were identified, resulting after their definitive pathological evaluation 172 (18%) insitu pure ductal carcinomas of the total of 953 patients analyzed.

The evaluation included the age of the patients, obtaining the age range and the mean age of diagnosis; diagnostic imaging where those patients who presented microcalcifications on mammography, nodule or both were discriminated; the preoperative and postoperative histological diagnosis was compared to obtain the correlation percentage in the preoperative biopsy; Regarding surgical treatment, the percentages of conservative treatment vs mastectomy were analyzed, including the cases in which sentinel node was performed; The number of patients who received radiation treatment for locoregional control and hormonal treatment was evaluated, as well as the percentage of relapses.

The inclusion criteria for performing radiation treatment were having performed conservative surgery and patient acceptance, and the exclusion criteria were having performed a mastectomy, DCIS less than 5 mm GH1, or patient comorbidities. Regarding hormonal treatment, it was offered to any patient who had positive hormone receptors.

The 206 surgical specimens were evaluated in a delayed manner by the same team of pathologists. Within the evaluation, the cases were grouped according to histological grade, tumor size, and the relationship between them.

Results

Of the 206 patients initially evaluated, 172 (18%) were pure DCIS, with an age range between 36-85 years (average 56.5 years).

The imaging report in the total of 206 patients presented microcalcifications in 165 (80.1%), nodules in 27 (13.1%) and nodules associated with microcalcifications in 14 (6.8%).

Within the 206 patients with initial diagnosis of DCIS, the diagnosis of *in situ* carcinoma was made in 181 (87%) patients by preoperative microinvasive procedures (mammotome 151 (83.4%) and 30 (16.6%) Core biopsy), in which subsequent surgical treatment was performed, and in 25 (13%) remaining patients by radiosurgical biopsy (RBB).

90.8% (187) of the patients received conservative quadrantectomy / LBBB treatment, while 9.2% (19) underwent simple mastectomy with or without sentinel node evaluation.

Among the patients diagnosed by microinvasive procedures and after surgical treatment, the pathological anatomy result showed, 131 (72.4%) DCIS, 11 (6.07%) DCIS with microinvasion, 23 (12.7%) invasive carcinoma and 16 absences of pathology or minor pathology (Table 1). Taking these results into account, there was 18.8% underdiagnosis in microinvasive procedures. On the other hand, the 25 patients whose diagnosis was made by LBBB (13%), none showed invasion.

Table 1 Puncture diagnosis

Diagnosis operatory piece	Puncion Mammotome/ core biopsy	BRQ
DCIS	131	25
DCIS micro invasive	11	-
DCIS invasive	23	--
Absence of pathology	16	
Total	181	25

When analyzing the size of the 172 DCIS, we have that size could not be assessed in 16 (9.3%) because no pathology was found in the definitive study. Of the 156 remaining, sizes were <5 mm 19 (11.05%) cases, between 6-10 mm 38 (22.1%), between 11-20 mm 40 (23.25%), between 21-30 28 mm (16.28%) and 31 (18%) cases greater than 30 mm, reflecting that the most frequent size was between 11-20 mm (Figure 1).

Analyzed according to tumor grade, out of 172 patients evaluated, GH1 was obtained in 27 (15.7%) patients, GH2 in 74 (43%) and GH3 in 71 (41.3%). The percentage of DCIS with comedonecrosis was 15.21% (26 patients). In our casuistry, 84.3% were GH3 / GH2 while 15.7% were GH 1. While the histological grade in the 34 invasive carcinomas was GH1 in 1 (2.94%), GH2 in 8 (23, 5%) and GH3 in 25 (73.5%) patients, resulting in a directly proportional association between tumor grade and stromal invasion. In turn, the GH3 DCIS (71 patients), 22 (32%) measured more than 30 mm, 19 (26.8%) 21-30 mm, 23 (32.4%) 11-20 and 4 (5.6 %) 6-10 mm, not finding an association between size and grade between 11 and more than 30 mm, but a low probability of GH3 (5.6%) in tumors smaller than 10 mm. Table 2.

Table 2 Tumoral grade in DCIS y DCI

Grade/Tumor	DCIS (%)	C. invasive (%)
GH1	27 (15,7)	1 (2,9)
GH2	74 (43)	8 (23,5)
GH3	71 (41,3)	25 (73,5)
Total	172	34

Of the 41 patients who presented as a nodule associated or not with microcalcifications, 13 (33%) presented microinvasion or invasion in the delayed study. The grades of these were 10 (25%) GH1, 8 GH2 (19%) and 23 (56%) GH3, which shows an association between nodular lesion and a higher tumor grade.

When comparing the size of the surgical specimens and correlating them with the 34 cases of invasive and microinvasive carcinoma, it turned out that 17/48 (35.41%) tumors larger than 30 mm had invasion, 13/41 (31.7%) in tumors between 21-30 mm, 4/44 (9.09%) in tumors between 11-20 mm and we did not find invasion in DCIS smaller than 10 mm.

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The margins and the percentage of surgical correction thereof were also evaluated. In the 153 patients who had pure DCIS, the average surgical margin was 4 mm, ranging from 2.5 mm to 0 mm or compromised margin. Of these, 10 (6.53%) patients had a compromised margin and in 9 (5.9%) a recuadrantectomy was performed, finding no pathology in 6, while in the remainder it was low-grade DCIS with millimeter margin in an 80-year-old patient.

In 10 cases of 206 patients initially evaluated, radiological multicentricity was found due to microcalcifications. In all cases, a mastectomy plus sentinel node biopsy was performed, showing invasive carcinoma in 2 cases, showing that in 20% of multicentric lesions it was associated with an invasive tumor.

Regarding the axillary study, a sentinel node technique was performed in 49 (23.8%) patients in first surgery, 19 for mastectomy (10 for multicentricity and 9 for tumor volume/size ratio), 10 in LBBB without previous diagnosis associated with tumor size> 25 mm, 14 due to nodule associated with microcalcifications and 6 with a diagnosis of DCIS and tumor size> 25 mm. In the 49 cases, the sentinel node was negative in the delayed study.

At the time of evaluating radiation and hormonal treatment, in the 172 patients with DCIS, 19 patients did not undergo radiotherapy due to mastectomy as initial surgical treatment. Of the 153 remaining patients who underwent conservative treatment and excluding cases of invasive carcinoma from the analysis (34), radiotherapy was performed in 131 patients (85.6%) and the remaining 14.4% (22 patients) did not perform radiotherapy. 9 GH1s smaller than 5 mm, 4 patients who had an indication refused treatment, 2 patients older than 80 years, and 7 their cause is unknown. While hormonal treatment was carried out in 75% (129) of the patients, in the remaining 43 (25%) the reason why hormonal treatment was not carried out was in 34 due to negative hormone receptors, 3 due to small GH1 and 6 they refused hormonal treatment. Therefore, 85.6% of our patients who underwent conservative treatment received RT and 75% hormonal treatment.

In the follow-up until December 2014, 11 relapses (5.23%) were recorded, 7 (63.6%) as invasive ductal carcinoma and 4 (36.4%) as ductal carcinoma *in situ*. Of the 7 relapses as invasive carcinoma, only 2 patients did not receive radiotherapy treatment, one due to a 5 mm GH1 tumor and negative receptors with a 4 mm margin and the other due to mastectomy as initial treatment, but hormone therapy. The remaining 5 received radiotherapy plus hormone therapy. Of the 7 relapses as invasive carcinoma, 6 were ipsilateral and one contralateral after mastectomy. The 4 relapses as *in situ* ductal carcinoma, 3 did not receive further treatment after surgery, one due to a 4 mm GH1 tumor and the other two GH3 tumors of 15 and 17 mm that refused treatment, while the treated received only radiotherapy. The mean time to relapse was 3.9 years (1-7 years). Until December 2014 there were no deaths in the casuistry evaluated (Table 3).

Table 3 Recurrences

Year surgery	Year relapse	Tomural size (mm)	Age (years)	Free margin (mm)	Tumoral grade	Hormonal treatment	Radiant treatment	Type of relapse DCIS/ DCI*
2005	2012	5	70	2	GH1	No (R-)	No	DCI Homolateral
2006	2013	13	49	5	GH1	Yes	Yes	DCI Homolateral
2006	2008	30	51	3	GH3	Yes	Yes	DCI Homolateral
2007	2010	8	59	8	GH3	Yes	Yes	DCI
2007	2014	16	41	6	GH3	Yes (incomplete)	Yes	DCI
2008	2014	6	57	1	GH2	Si	Yes	DCI
2009	2014	31	63	15	GH3	Yes	No (mastectomy)	DCI
2007	2010	15	47	5	GH3	No	Yes	DCIS
2011	2013	4	53	12	GH1	No	No	DCIS
2011	2014	15	64	3	GH3	No	No	DCIS
2012	2013	17	71	4	GH3	No	No	DCIS Homolateral

Discussion

The number of DCIS increased in the last 40 years, increasing from 5.8 per 100,000 in 1970 to 32.5 per 100,000 in 2004, later showing a plateau, even this increase was manifested in all ages with a greater increase in those older than 50 years.[1–3] However, the increase in DCIS was not proportional in all histological subtypes. DCIS with comedonecrosis remains stable over the years, while the increase in non-comedocians grew between 15-22 times. This increase was also evidenced with age, with an annual incidence in people over 50 years of age that went from 5 per 100,000 in 1980 to 59-77 per 100,000 in 2004. On the other hand, the diagnosis of DCIS in those under 30 years of age is rare frequent.[4,5] The average age in our casuistry was 56.5 years, with no DCIS in children under 36 years of age.

Currently approximately 25% of breast carcinomas diagnosed and in specialized centers up to 40% are DCIS, this increase is attributed to the use of mammographic screening in breast cancer, which leads to a decrease in the diagnosis of breast carcinoma invasive and therefore to the optimization of prevention[6–8] It is noteworthy that the number of DCIS (18%) diagnosed in our institution coincides with that published in the international literature.

The adoption in recent decades of screening mammography dramatically increased the number of DCIS, especially in developed countries.[12–14] The evidence of this increase is shown in 8 studies carried out between 1963 and 1982.[15–22] Thus, more than 90% of DCIS are diagnosed or suspected by mammography, the predominant mammographic sign being microcalcifications, generally alone or associated with densities. DCIS represents 80% of all breast carcinomas that present with calcifications.[6–8,12–22] Less common findings include masses or other types of tissue changes. On the other hand, mammography underestimates the extent of DCIS and multifocal disease, a fact that increases with tumor size. High-grade lesions tend to be continuous, while low- or intermediate-grade lesions tend to be multifocal or with interfocuses of up to 1 cm.[9,10,12] In our case, 86.9% of DCIS presented with microcalcifications on mammography, while 13.1% as a nodule.

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Abnormal lesions detected by mammography must be evaluated by percutaneous punctures or radiosurgical biopsy, in order to obtain a tissue sample that allows defining between *in situ* or invasive lesions. One of the characteristics of percutaneous punctures (Core-mammotome biopsy) is the underdiagnosis between invasive lesion or *in situ*. This difference is more noticeable depending on the method used, since mammotome punctures have a lower percentage of false negatives than those performed by Core biopsy. This difference is mainly due to the diameter of the needle used. Different authors show an approximate underdiagnosis percentage between 10-20%.[23–26] Our casuistry showed an underdiagnosis percentage of 18.8%, not having analyzed the difference between the different types of puncture.[27,28]

One of the recurrence parameters taken into account was tumor size, it is even part of the Van Nuys prognostic index.[29] There are no precise methods that evaluate tumor size or extension prior to surgery. Fisher et al.[28] reported that 80% of 573 patients included in the NSABP B17 were non-palpable. The size in DCIS can be estimated by mammography by the extent of the microcalcifications, on the other hand, Coombs et al.,[30] reported an underestimation of tumor size by mammography of 23%. Several authors agree that size taking <10 mm or> 10 mm as cut-off are not reliable predictors of recurrence.[27–29] Although the average size of *in situ* carcinoma is not described, we more frequently diagnose 11 and 20 mm tumors.

One characteristic to consider is the probability of invasive carcinoma related to tumor size and tumor grade.[27,31] Lagios et al.[27] showed that the possibility of invasive carcinoma is 20% when the tumor lesion is greater than 25 mm. In our casuistry, the highest proportion of tumors measured more than 11 mm and 18% more than 30 mm, as well as the highest proportion were GH2 and GH3. And this was related to the fact that 75% of the invasive carcinomas detected in the delayed study were GH3, as well as the largest number of tumors> 30 mm. On the other hand, those patients who presented with a nodular lesion, 33% presented invasion or microinvasion, being more frequent the higher the tumor grade.

One of the most important risk factors for recurrence is compromised resection margins.[32] There is no clear consensus as to what is considered a negative margin. Numerous reports speak from 1mm to 10mm. A meta-analysis of 22 trials that included 4660 patients showed a 64% risk reduction in patients treated with conservative treatment plus radiation therapy. In this study, 2 mm or more was associated with a lower probability of recurrence.[33] In contrast, a retrospective analysis of 1100 patients suggests that a margin less than 2 mm was not necessarily associated with an increase in recurrence.[34] We report a mean resection margin of 4 mm and a percentage of surgical enlargement of 5.9%.

Multifocality is common, but multicentricity is not. Holland et al.,[31] in their series found 23% multifocality and 1.5% multicentricity. The published multicentricity data vary widely in the literature from 0% to 75% with a mean of 25%, this reflects clear differences regarding the definition of multicentricity. Multicentric tumors should not be treated with conservative treatment, while in multifocal ones, conservative treatment increases the risk of recurrence to the detriment of cosmetic results.[35–41] Of the 206 patients who were evaluated imaging, 10 (4.85%) presented multicentric microcalcifications and in all of them performed percutaneous puncture in more than one focus, showing in all DCIS and they were followed by posterior mastectomy.

Patients with DCIS can be managed conservatively or mastectomy. Although mastectomy achieves excellent results in survival with a local recurrence of 1%, in most patients it would result in aggressive treatment since they could be treated with conservative treatment followed by radiotherapy achieving the same results in terms of survival.[40,42– 46] An observational study that included 100,000 patients with SEER (Surveillance Epidemiology and End Result) DCIS comparing conservative treatment with or without radiotherapy vs mastectomy. Mastectomy resulted in similar cancer-specific mortality with a decrease in ipsilateral relapse in favor of mastectomy (1.3 vs 3.3%).[47] We report in this analysis that of the 206 patients evaluated by imaging, 90.8% of the patients underwent conservative treatment and 9.2% mastectomy.

Initially, the sentinel node should not be performed in DCIS since by definition it does not penetrate the basement membrane. The need for the sentinel node is controversial. One of the accepted indications is its practice after mastectomy since lymphatic drainage is altered after surgery and if there is an invasive carcinoma, it could not be evaluated in a subsequent surgery. While other authors suggest performing it when the mammographic lesion exceeds 25 mm or in palpable tumors. We report 23.8% of sentinel lymph node biopsies indicated by mastectomy, radiosurgical biopsy in extensive lesions without previous diagnosis, palpable nodule associated with microcalcifications and DCIS diagnosed by percutaneous biopsy in imaging lesions greater than 25 mm, not finding lymph node metastases in any case.

After conservative surgical treatment, several authors report the need for radiation treatment after it, showing a 50% reduction in ipsilateral recurrence without modifying overall survival.[42–46] Fisher et al.,[42] in 818 patients showed a recurrence at 8 years after conservative treatment with and without radiotherapy 8.2% vs 13.4% respectively. Silverstein et al.[40] in 469 patients showed similar results, but only those patients who presented margins smaller than 1 mm would benefit from radiotherapy. A meta-analysis published in 2009[46] showed a 51% reduction in conservative treatment plus radiotherapy. One of the biggest challenges is skipping radiation therapy in patients with low-grade, elderly, or small foci of DCIS. So far there is no consensus to decide which patient is not undergoing radiotherapy. In the 172 patients with a definitive diagnosis of DCIS and ruling out those who underwent a mastectomy, radiotherapy was indicated in 85.6% of the patients.

Another proposed treatment is the use of hormonal therapy (tamoxifen/aromatase inhibitors) to decrease ipsilateral and contralateral relapse. It is frequently offered to patients with positive hormone receptors, while in patients with negative receptors some authors do not recommend administering it. Between 50-75% of DCIS express positive receptors. Two studies analyze the results of Tamoxifen with or without radiotherapy, NSABP B-24[48] and the study by Houghton et al.[44] The first showed a 5% decrease in recurrence without modifying local survival, while the second showed no significant benefit. On the other hand, a trial compared tamoxifen vs anastrozole showing that the benefit was evident in those under 60 years of age and late.[49] In our work, 75% of the patients underwent hormonal treatment.

Conclusion

The percentage of 18% DCIS presented in our casuistry coincides with that published in the indexed literature. The most frequent tumor size found was between 11 and 20 mm, finding a greater association between tumor size and the probability of invasion in tumors larger than 30 mm and none in tumors smaller than 10 mm, as well as between tumor grade and invasion frequency. Our casuistry did not find sentinel node positivity in multicentric or nodular lesions regardless of tumor

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grade. Nodular lesions were associated with a higher percentage of invasion. Of the 7 relapses as invasive carcinoma, tumor grade 3 was the factor with the greatest association, while in the 4 relapses as *in situ* carcinoma, the time to relapse was shorter associated with tumor grade 3 and the non-application of subsequent treatment. During the follow-up, no deaths were recorded, but it should be taken into account that the follow-up time is short.

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Conflicts of interest

The authors have no conflicts of interest.

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