

Pre-Malignant Breast Lesions, Methods of Treatment and Outcome

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Abstract—This retrospective study includes 60 patients with pre-invasive breast cancer. Aim of the study: Evaluation of premalignant lesions of the breast (DCIS), different treatment methods and outcome. Patients and methods: 60 patients with DCIS were studied from the period between 2005 to 2012, for 38 patients the primary surgical method was wide local resection (WLE) (63.3%) and the other cases (22 patients, 36.7%) had mastectomy, fourteen cases from those who underwent local excision received radiotherapy, while no adjuvant radiotherapy was given for those who underwent mastectomy. In case of hormonal receptor positive DCIS lesions hormonal treatment (Tamoxifen) was given after local control. Results: No difference in overall survival between mastectomy & breast conserving therapy (wide local excision and adjuvant radiotherapy), however local recurrence rate is higher in case of breast conserving therapy, also no role of Axillary evacuation in case of DCIS. The use of hormonal therapy decreases the incidence of local recurrence by about 98%. Conclusion: The main management of DCIS is local treatment (wide local excision and radiotherapy) with hormonal treatment in case of hormone receptor positive lesions.

Keywords—Ductal carcinoma *in situ*, surgical treatment, radiotherapy, breast conserving therapy, hormonal treatment.

I. INTRODUCTION

DUCTAL carcinoma *in situ* (DCIS) of the breast is a pre-malignant condition defined by Harris et al as “a group of closely related lesions whose common histological feature is the proliferation of cancer cells within the ducts without invasion of the surrounding stromal tissue” [1].

DCIS is a precursor to invasive breast cancer, there are shared chromosomal changes between adjacent *in situ* and invasive cancers that demonstrate their clonal, evolutionary relationship [2]. It is estimated that up to 35% of individuals with DCIS may develop an invasive carcinoma over 10 years [3].

Before 1990, Most patients with DCIS were treated by simple mastectomy, a relatively radical, highly effective approach, Later the use of breast conserving surgery in combination with adjuvant radiotherapy began to gain acceptance [4]-[6].

The NSABP B-06 compared the outcome of lumpectomy, lumpectomy plus radiotherapy and modified radical

mastectomy in patients with early invasive breast cancer, a pathologic review revealed 76 women with DCIS, who were followed for a mean duration of 83 months, a local recurrence rate of 43% for lumpectomy alone compared with 7% for lumpectomy plus radiotherapy group and 0% for mastectomy was reported [7].

II. PATIENTS AND METHODS

This retrospective study was conducted on patients with the diagnosis of pre-invasive breast cancer in the National Cancer Institute (NCI), Cairo University. The study was approved by the ethical committee at NCI as the institutional review board guidelines.

Aim of the study was evaluation of premalignant lesions of the breast (DCIS) in NCI cases with emphasis on:

1. Clinical and pathological features
2. Management
3. Outcome

A. Inclusion Criteria

Patients presented to NCI during the last 8 years (2005-2012) with premalignant lesions of the breast (DCIS)

B. Exclusion Criteria

1. Patients with incomplete data
2. Patients whose specimens proved pathologically to have basement membrane invasion.

C. Data Were Collected from

1. Medical statistics' department records
2. Pathology department records
3. Outpatient clinic

D. Treatment

1. Surgical Treatment

For 38 patients the primary surgical method was wide local resection (63.3%) and the other cases had simple mastectomy.

2. Adjuvant Treatment

14 cases from those who underwent local excision received radiotherapy by a dose of 50 Gy/25 fraction/5 weeks by two tangential fields, while no adjuvant radiotherapy was given for those who underwent mastectomy. Hormonal treatment in the form of Tamoxifen (10 mg orally twice a day) was given for five years for patient who had positive hormonal receptors either after local excision or mastectomy.

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E. Statistical Methods

Data were analyzed by using SPSS win statistical package version 12. Numerical data were expressed as mean with the minimum and maximum, and qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables, and survival analysis was performed by using the Kaplan-Meier method. Finally, comparison between two survival curves was done by using Log-rank test.

III. RESULTS

This study included 60 patients with DCIS presented at NCI 2005-2012. The patients age ranged between 18 and 76 years old (median was 49.3 years).

As regards the lesion size in cases with DCIS, 18 cases (30%) were less than 1.5cm, 16 cases (26.7%) had 1.5-4cm lesions and 26 cases (43.3%) had more than 4 cm lesions as evident in Table II, Safety margin in case of DCIS was more than 1cm in 58 cases (96.7%) and less than 1cm in 2 cases (3.4%), Comedo necrosis appeared in 30 cases (50%) and micro-invasion presented in 14 cases (23.3%). Regarding multi-centricity and high grade, 3 cases (5%) were multi-centric, 3 cases (5%) were high grade.

Regarding hormonal receptors in our study we found that 28 cases (46.7%) were ER positive, 32 cases (53.3%) were ER negative, 31 cases (51.7%) were PR positive, 29 cases (48.3%) were PR negative.

Regarding L. Ns in our study, we found that 44 cases (73.3%) had level 1 Axillary clearance, only 1 case (1.7%) had positive L. Ns.

In our study, 28 cases (46.7%) have favorable Van Nuys score, 32 cases (53.3%) have intermediate score.

After a mean period of follow-up of 42,8 months and a range of 6-96 months, 54 cases (90%) were free of local recurrence or progression to carcinoma, while progression to carcinoma on the same side, DCIS on the opposite side & carcinoma on the opposite side occurred in 6 cases (10%), Patients who suffered disease progression on the same side had large initial DCIS size (≥ 3 cm).

TABLE I
THE CLINICAL FEATURES OF DCIS

Ductal carcinoma <i>in situ</i> 60 patients	
Age in years	
Mean (range)	49.3 (18-76)
Presentation	
-Mass	43(71.7%)
-Nipple discharge	8(13.3%)
-Mammography	5(8.3%)
-Paget's nipple	4(6.7%)
Mammography & ultrasound	
-Mass	15 (25%)
-Microcalcifications	10 (16.7%)
-Mass & Microcalcifications	4 (6.7%)
-no available report	31 (51.6%)

A. Survival and Prognostic Factors for DCIS

5-year disease free survival (DFS) was 85.7% and testing pathological and treatment prognostic factors against DFS

revealed no significance to all of them i.e. $P \geq 0.05$ as seen in Table IV.

TABLE II
THE PATHOLOGICAL FEATURES OF THE DCIS SPECIMENS FOR 60 PATIENTS

	Frequency (%)		Frequency (%)
Size		Grade	
<1.5cm	18(30)	Low grade	57(95)
1.5-4cm	16(26.7)	High grade	3(5)
>4cm	26(43.3)	ER receptor	
Margin		No	32(53.3)
<1mm	1(1.7)	Yes	28(46.7)
1mm-1cm	1(1.7)	PR receptor	
>1cm	58(96.7)	No	29(48.3)
Comedo necrosis		Yes	31(51.7)
No	30(50)	Axillary L.Ns	
Yes	30(50)	No Axillary clearance	16(26.7)
Micro-invasion		Axillary clearance	
No	46(76.7)	negative nodes	43(71.6)
Yes	14(23.3)	positive nodes	1(1.7)
Multi-centricity		Van Nuys score	
No	57(95)	Favorable	28(46.7)
Yes	3(5)	Intermediate	32(53.3)

TABLE III
FOLLOW UP OF DCIS CASES

Prognosis	DCIS N (60 patients)
Free	54(90%)
Progression	6(10%)
Recurrent DCIS on same side	-
Malignancy on same side	3
DCIS on opposite side	2
Malignancy on opposite side	1
Death	-

IV. DISCUSSION

In case of DCIS, the range of age was 18-76 with the mean age 49.3. Comparable to studies in western countries DCIS is also uncommon in women younger than 30 with mean age 40(8). The rate of DCIS increases with age from 0.6 per 1000 in women aged 40 to 49 years to 1.3 per 1000 in women aged 70 to 84 years.

In our study we found that the most common presentation of DCIS was a palpable mass (71.7%) and 4 patients presented with Paget's disease (6.7%). While in the Western and other high-income countries more than 90% of all cases of DCIS are detected only on imaging studies [9].

In our study we found that 34 cases (73.4%) had level 1 Axillary clearance at NCI. While 10 cases had Axillary evacuation outside NCI. only 1 case had positive L. Ns (1.7%).

Comparing our results to other studies indicates that there is no role of Axillary evacuation in case of DCIS, also Sentinel lymph node biopsy (SLNB) is not indicated in the evaluation of the patient with DCIS undergoing breast conserving therapy, because the Axillary nodes are rarely positive for metastatic disease even with extensive multi-focal high grade DCIS [10]. Axillary lymph node metastases are present in

fewer than 5% of patients with a final diagnosis of DCIS (after surgical excision) [8].

TABLE IV
DFS IN DCIS

DFS Factor		Number of cases	Number of events	5 yrs DFS (%)	P-value
All		60	6	85.7	
Size	<1.5cm	18	1	90.9	
	1.5-4cm	16	5	75.8	
	>4cm	26	0	100	0.122
Comedo necrosis	No	30	1	96.7	
	Yes	30	5	72	0.066
Van Nuys score	Favorable	28	1	96.4	
	Intermediate	32	5	72.9	0.092
Microinvasion	No	46	4	87.2	
	Yes	14	3	84.4	0.67
ER	No	32	4	79.3	
	Yes	28	2	92.7	0.443
PR	No	29	4	78.3	
	Yes	31	2	93.3	0.337
CTH	None	18	2	83.7	
	Adjuvant hormonal	31	1	96.6	
	Adjuvant chemo	11	3	64.9	0.06
RTH	None	46	4	85.2	
	Adjuvant	14	2	85.1	0.598

We found in our study that among 23 cases of DCIS who had WLE only 14 cases received adjuvant radiotherapy (60.8% of wide local excision cases). The 9 cases who did not have not adjuvant radiotherapy were > 50 year-old, low grade with negative margins.

Invasive cancer on the same side developed in 3 cases, 2 of them had no adjuvant radiotherapy (2/9, 22.2% of DCIS cases treated with wide local excision only), while it happened in only 1 case who received adjuvant radiotherapy after wide local excision (1/14, 7.1% of DCIS cases treated with wide local excision and adjuvant radiotherapy).

The radiotherapy plays important role as adjuvant treatment after wide local excision as it is observed in randomized trials which show that adjuvant radiotherapy significantly reduces the risk of local recurrence by 50% compared to excision alone. However, treating all women who undergo wide excision for DCIS with adjuvant radiotherapy may be overtreatment [11].

Radiotherapy is generally indicated for all patient to reduce local recurrence, but some patients may not benefit and may choose to omit radiotherapy (especially older women, low grade & negative margins) [12]. In addition, the reduction in the risk of a local recurrence after radiotherapy appears to be long lasting, though this is not associated with a survival advantage, this was shown in a report of the long term follow up of the National Surgical Breast and Bowel Project Trial B-17 [13]. At 15 years, compared to excision alone, RTH resulted in a significantly lower rate of ipsilateral invasive recurrence (8.9 versus 19.4%) as well as similar overall survival (83 versus 84%).

In our study, we found that 31 cases (51.7%) were hormone receptor positive and all of them received adjuvant hormonal

therapy (Tamoxifen). Our results are similar to that in other studies which show that approximately 50 to 75% of DCIS lesions express estrogen receptors (ER) and/or progesterone receptors (PR) [14], [15].

In our study, we found that 11 cases (18.3%) of DCIS received adjuvant chemotherapy. All of them had micro-invasion and had free follow up except 3 cases (27.3% of DCIS cases who received chemotherapy), 2 of them developed invasive cancer on the same side & 1 case developed invasive cancer on the opposite side.

Different studies show that the primary role of systemic treatment is to reduce the risk of invasive breast cancer in the ipsilateral or contralateral breast, and the risk of distant metastases in women with DCIS is very low. The overall prognosis is excellent, and so chemotherapy plays no role in the management of these patients [14], [15].

In our study, recurrence on the same side occurred in 3 cases after wide local excision and it did not occur after mastectomy. But there was no difference in overall survival.

Our results were the same as other studies comparing Breast conserving therapy (wide excision of the tumor with negative surgical margins followed by radiation therapy) with mastectomy for DCIS which have demonstrated equivalent long-term survival [13], [16], [17]. However, local recurrence rate is higher with BCT while disease recurrence is rare after mastectomy (1 to 2%) [18].

In our study, all local recurrence cases occurred after excision of the lesion with negative margins (>1cm). Thus, margin in our study did not affect local recurrence, while other studies showed that there is a relationship between margin width and tumor recurrence. A 2012 meta-analysis of 21 studies (n = 7564 patients) showed that negative surgical

margins on excision were significantly associated with a lower risk of recurrence compared to positive margins among those who underwent adjuvant radiotherapy and those who did not undergo radiotherapy, also showed that a wider negative margin (>10 mm) was associated with a significant reduction in the tumor recurrence risk compared to a narrower margin <2 mm [19].

In conclusion, we recommend national based screening program for breast cancer for early detection in the pre-invasive or even early invasive stages.

DCIS cases can be treated safely with high survival rate by local excision with negative margin to be followed by breast irradiation and hormonal treatment for positive hormonal receptors.

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