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Research Article

Correlation between Margin Width and Time to Local and Systemic Recurrence of Ductal Carcinoma in Situ

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Abstract

Background: Recurrence after DCIS treatment is common and half are invasive cancers. Positive excision margin is significantly associated with recurrence, however; debate exists about close margin. We examine the pattern of treatment and recurrences at a single institute.

Objective: To investigate, in women with DCIS treated at KFMC and long follow-up, the relationship between margin width and time to local or systemic recurrence of disease, controlling the other characteristics.

Method: We retrospectively reviewed a prospectively maintained database of DCIS patients treated at single institution from 2014-2018. A multivariable Cox model was used to evaluate the association of margin width with recurrence while controlling for other variables.

Results: We identified 56 cases with a median follow-up of 51 months (range 3 - 120), of which four (7%) had a recurrence within 2 years of initial treatment. Three were invasive ductal cancer while one was high grade DCIS. After controlling the other variables, no association of margin width with recurrence was identified (p-value 0.81) in the current study, however; all recurrences were on the left side (p-value <0.001).

Conclusion: The current study did not identify any correlation between margin width and LR, however; relation between site and LR was statistically significant as more LR was identified in left breast. Low rate of LR in current study could be due to more aged population of patients in present study.

Introduction

Ductal carcinoma in situ (DCIS) now accounts for up to 21% of all breast cancers diagnosed in the United States each year. [1] There is a variety of management options for DCIS that range from a Breast-Conserving (BCS) alone, to Complete Mastectomy (CM) and BCS with adjuvant radiation therapy (RT). The overall morbidity and mortality due to DCIS are low and are unrelated to the type of local therapy (BCS versus CM with or without RT). However, in different studies, a higher rate of local recurrence up to 35% has been reported. [2-4] Interestingly approximately 45% of those recurrences were invasive disease. There are few treatment options available to target local (LR) and Systemic Recurrences (SR). One of them is RT that does reduced local recurrence by a number of 50% without any effect on overall mortality, [5] with additional associated increase risk of radiation induced malignancies and cardiovascular disease. [6,7] Second option is systemic treatment by estrogen receptor modulator Tamoxifen which can also reduce both local and systemic recurrence in women in whom DCIS is estrogen receptor positive. Likewise, RT, Tamoxifen fail to reduce mortality on cost of elevated risk of symptoms of low estrogen state, thromboembolic events and

elevated risk of uterine cancer. [3,8,9] Numerous risk factors have been identified for LR and SR of DCIS that include patient age, [4-6,10] family history of breast malignancy, [11] menopausal status, size of disease, grade of lesion, number of excisions, width of margin and necrosis within the lesion. Among these factors, the width of margin is the only modifiable factor that a surgeon can control of. Which means that the risk of local recurrence can be minimize by achieving an appropriate width of resection margin. Although there are multiple studies that have demonstrated that achieving a close or positive margin are associated with a higher risk of recurrence after BCT for DCIS. However, a few studies talk about the disease recurrence in relation to width of margin after BCS. [12] We conducted this retrospective review of the patients to evaluate the pattern of DCIS presentation, management and association of margin width and local and systemic recurrence in women who underwent surgery with and/or without RT over a 4-year time period. Currently, there is a paucity of epidemiological data on the management of DCIS in the Middle East. Current study focused to identify any associated factors for the local or systemic recurrence. As per our knowledge, the present study is the first of its kind from the Middle East that is addressing this issue.

Objective

To investigate, in a population of women with DCIS and long follow-up, the relationship between margin width and time to local and systemic recurrence of disease, controlling the other characteristics.

Methods

After obtaining approval from the Institutional Review Board, a prospectively maintained database was used to identify all patients underwent definitive BCS for DCIS from 2014- 2018 at King Fahad Medical City, Riyadh, Saudi Arabia. All patients with DCIS who underwent BCT were Included. Bilateral lesions were included once for each breast. Clinical, variables included were; age at the diagnosis, menopausal status, family history, clinical presentation, nuclear grade, number of excisions, margin width in mm, RT, endocrine therapy, and date of definitive surgery. The outcome of interest was any recurrence-defined as ipsilateral breast recurrence of DCIS or invasive cancer, ipsilateral axillary nodal recurrence, or distant recurrence in the absence of breast primary. Time to event was defined as the interval between definitive surgery and date of first recurrence. Kaplan-Meier recurrence estimates were calculated by margin width for the entire cohort as well as for the subsets with and without RT. A multivariable Cox model was created to evaluate the association of margin width with recurrence while controlling for other variables. Interaction between RT and margin width was assessed, and separate models were created for the subsets with and without RT. Statistical analysis was performed using SPSS 25.

Results

A total of 56 women age 28 -71 years (mean-50.8 years) old were treated for pure DCIS at KFMC from year 2014-2018 (Table 1). 34 patients (60%) were postmenopausal and 35 (62%) were presented as asymptomatic through breast cancer screening program. 55 (98%) patients were having unilateral while only 1 patient (2%) had bilateral disease. The location of lesion in breast was upper outer quadrant-32 patients (57%) followed by upper inner-8 patients (14%), central-7 patients (13%), Lower inner-6 patients (11%) and lower outer quadrant-3 patients (5%) respectively. 34 patients (60%) were hormone positive and 44 patients (77%) were Her-2 negative. Among 56 patients, 4 had a LR within 2 years of initial treatment; three were invasive disease (Invasive Ductal Cancer-IDC) while one was high grade DCIS. Similarly, three were ipsilateral tumors and one was a contralateral disease (IDC). All of them had a surgery in the form of BCS with > 2mm margins. Two of them were triple negatives while other two were hormone positive lesions. The triple-negatives had re-excision of margins as a second surgery (2-3 weeks after the first surgery) and adjuvant radiotherapy. The recurrences had treatment as WLE for three and complete mastectomy with sentinel node biopsy for one patient. All LR received local treatment in the form of surgical excision while one of the IDC recurrences received both local and systemic therapy. Among four recurrences, one patient developed brain metastasis at 20 months follow up from the initial treatment. After controlling the other variables, no association of margin width with recurrence was identified (p-value 0.81) in the current study (Table 1).

Local/Systematic Recurrence association with the studied factors					
Characteristic	Description	No	Yes	Total	p value
		52 (92.9)	4 (7.1)	56 (100.0)	
Age (year)	Mean ± SD	50.2 ± 8.9	58 ± 9.2	50.8 ± 9	0.096
	Median (min - max)	50.5 (28 - 71)	59.5 (46 - 67)	51 (28 - 71)	
Size mm	Mean ± SD	29.9 ± 31.6	15.5 ± 14.1	28.9 ± 30.8	0.371
	Median (min - max)	16.5 (1 - 125)	15 (2 - 30)	16.5 (1 - 125)	
Follow up (month)	Mean ± SD	55.4 ± 24.9	61.8 ± 29.8	55.9 ± 25.1	0.63
	Median (min - max)	49 (3 - 120)	68.5 (20 - 90)	51 (3 - 120)	
Menopause		31 (59.6)	3 (75.0)	34 (60.7)	0.544
Presentation	Mass	16 (30.8)	2 (50.0)	18 (32.1)	0.105
	Nipple Discharge	2 (3.8)	1 (25.0)	3 (5.4)	
	Screening	34 (65.4)	1 (25.0)	35 (62.5)	
Site	Bilateral	0 (.0)	1 (25.0)	1 (1.8)	<0.001
	Left	25 (48.1)	3 (75.0)	28 (50.0)	
	Right	27 (51.9)	0 (.0)	27 (48.2)	
Location	Central	6 (11.5)	1 (25.0)	7 (12.5)	0.691
	Lower Inner	5 (9.6)	1 (25.0)	6 (10.7)	
	Lower Outer	3 (5.8)	0 (.0)	3 (5.4)	
	Upper Inner	8 (15.4)	0 (.0)	8 (14.3)	
	Upper Outer	30 (57.7)	2 (50.0)	32 (57.1)	
Grade	I	10 (20.0)	1 (25.0)	11 (20.4)	0.948
	II	24 (48.0)	2 (50.0)	26 (48.1)	
	III	16 (32.0)	1 (25.0)	17 (31.5)	
Necrosis		28 (53.8)	1 (25.0)	29 (51.8)	0.266
Calsification		40 (76.9)	3 (75.0)	43 (76.8)	0.93
ER		32 (74.4)	2 (50.0)	34 (72.3)	0.296
PR		31 (72.1)	2 (50.0)	33 (70.2)	0.355
Her-2		4 (9.1)	0 (.0)	4 (8.3)	0.529
First Surgery	Lumpectomy	30 (57.7)	4 (100.0)	34 (60.7)	0.095
	Mastectomy	22 (42.3)	0 (.0)	22 (39.3)	

Margin Width	<1mm	7 (13.5)	0 (.0)	7 (12.5)	0.81
	1 mm	4 (7.7)	1 (25.0)	5 (8.9)	
	2 mm	5 (9.6)	1 (25.0)	6 (10.7)	
	3 mm	2 (3.8)	0 (.0)	2 (3.6)	
	4 mm	1 (1.9)	0 (.0)	1 (1.8)	
	5 mm	1 (1.9)	0 (.0)	1 (1.8)	
	> 5 mm	32 (61.5)	2 (50.0)	34 (60.7)	
Margin Width	≤1mm	11 (21.2)	1 (25.0)	12 (21.4)	0.891
	2 - 5 mm	9 (17.3)	1 (25.0)	10 (17.9)	
	> 5 mm	32 (61.5)	2 (50.0)	34 (60.7)	
|No of Surgeries	One	37 (71.2)	2 (50.0)	39 (69.6)	0.604
	Two	14 (26.9)	2 (50.0)	16 (28.6)	
	Three	1 (1.9)	0 (.0)	1 (1.8)	
Re-Excision		14 (26.9)	2 (50.0)	16 (28.6)	0.325
Second Surgery	Margin Re-Excision	6 (42.9)	2 (100.0)	8 (50.0)	0.131
	Mastectomy	8 (57.1)	0 (.0)	8 (50.0)	
Radiotherapy		21 (40.4)	2 (50.0)	23 (41.1)	0.706
Hormonal Rx		13 (25.0)	1 (25.0)	14 (25.0)	1
Site (LR)	Ipsilateral		3 (75.0)	3 (75.0)	
	Contralateral		1 (25.0)	1 (25.0)	
Local recurrence time (month)	18		4 (100.0)	4 (100.0)	
Location (LR)	Upper outer		3 (75.0)	3 (75.0)	
	Central		1 (25.0)	1 (25.0)	
Type (LR)	DCIS		1 (25.0)	1 (25.0)	
	Invasive Ductal		3 (75.0)	3 (75.0)	
Grade (LR)	I		0 (.0)	0 (.0)	
	II		1 (33.3)	1 (33.3)	
	III		2 (66.7)	2 (66.7)	
ER (LR)			1 (33.3)	1 (33.3)	
PR (LR)			1 (33.3)	1 (33.3)	
Her-2 (LR)			0 (.0)	0 (.0)	

Table 1: Local/Systematic Recurrence association with the studied factors.

Discussion

The present study spanning 4-year period, demonstrated the pattern of DCIS from its presentation to the actual treatment and longer follow-up at a single institution. Examination of the results reveals that majority were screen detected lesions and presentation with a breast mass and nipple discharge were the second and third common presentation respectively. Likewise, the most common surgery performed was a BCS in 60% of the patients and majority of patients (70%) needed only one surgery (either a BCS or CM) for a complete excision which is in concordance with the past work of other colleagues. In our study, to achieve a negative margin as a part of initial treatment; 8 patients (14%) required a second surgery in the form of re-excision of margins and another 8 patients (14%) required a CM as a second surgery (total of 30% of patients that require more than one surgery for complete excision of DCIS). The recurrence of the disease in current study was found to be 7% (four patients) all of them had a BCS as initial treatment with re-excision of margins was required in two patients to achieve a negative margins (complete excision). This is in discordance to the previous studies performed where local recurrences were as high as 35%. [2,3,4] However; P Subhedar et al in her work has demonstrated a much lower recurrence rate of 16% without adjuvant RT and 9% with RT, which is still higher than the results of current study.[13] Two of the four local recurrences did not receive adjuvant RT due to patient's preferences, however; all patients had a negative margin of > 2mm. Over all 39% of patients had a mastectomy for the treatment of DCIS in current study which is in line with the results of other researches in the past [13,14].

A Mamtani et al in her recent work described the similar findings as present study, they evaluated 3121 patients who underwent treatment for DCIS with or without micro invasion and found no relationship with margin width, however; LR was significantly associated with age. Patients younger than 40 years had a much higher LR than patients in their 50s (P-vale 0.001). [14] They concluded that young age is an independent risk factor for LR after BCS or mastectomy. Concordantly, a much lower LR rate in present study can partial be explained by the fact that majority of our patients were more than 50 years of age and were post-menopausal. Whether it is due to the vanishing effect of estrogen in post-menopausal females is still to be studied and proved. Another interesting find of the current study is that all recurrences were detected at 18 months postop follow up which could be represented by the fact that almost all patients had their follow-up breast imaging around that period of time either in the form of a breast ultrasound, mammogram and/or MRI. This is in concordance with other studies where majority of LR were within 2 years from the initial surgery. [3,4] In this study, although; all of the ipsilateral LR were in the left breast (p-value 0.001), however; there is scarce data available in literature about the site/laterality of the disease itself or the LR. Therefore, to generate a conclusion about the site of LR will be irrational for the time being and much larger studies are required to prove that. Although, the current study demonstrates impressive results regarding pattern of DCIS presentation, management and risk factors for recurrences. However, there are few flaws of this study; firstly, it is a retrospective review of patient's chart, secondly; number of patients is small because some data was not included in the study due to ethical reason.

We acknowledge the fact that the results of observational studies are not definitive due to potential confounding differences between groups could be eliminated. Although to prove the correlation between age, margin width, size of tumor and LR would require long-term Randomized Controlled Trials (RCTs), these are expensive, difficult to perform, and there are several challenges regarding the feasibility of conducting large RCT. However, an alternative to a large RCT is a pooled analysis of carefully designed observational studies with the use of a robust statistical methodology. Although the main limitation of the present study was its retrospective design, we followed a standardized protocol, and to ensure accurate data collection, all variables were harmonized and collected prospectively. The strengths of this study were the longer follow-up and consistency in terms of the management of patients as all patients were operated by a single surgeon.

Conclusion

The current study did not identify any correlation between margin width and LR, however; relation between site and LR was statistically significant as more LR was identified in left breast due to unknown reasons. Low rate of LR in current study could be due to more aged population of patients in present study.

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References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA: A Cancer Journal for Clinicians 65: 5-29.
2. Correa C, McGale P (2010) Early Breast Cancer Trialists' Collaborative Group. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010: 162-177.
3. Donker M, Litiere S, Werutsky G (2013) Breast-conserving treatment with or without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol 31: 4054-4059.
4. Warnberg F, Garmo H, Emdin S (2014) Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. J Clin Oncol 32: 3613-3618.

5. Wapnir IL, Dignam JJ, Fisher B (2011) Long-Term Outcomes of Invasive Ipsilateral Breast Tumor Recurrences After Lumpectomy in NSABP B-17 and B-24 Randomized Clinical Trials for DCIS. Journal of the National Cancer Institute 103: 478-488.

6. Darby SC, Ewertz M, McGale P (2013) Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. New England Journal of Medicine 368: 987-998.

7. Henson KE, McGale P, Taylor C (2013) Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer 108: 179-182.

8. Allred DC, Anderson SJ, Paik S (2012) Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol 30: 1268-1273.

9. Fisher B, Dignam J, Wolmark N (1999) Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353: 1993-2000.

10. Rudloff U, Jacks LM, Goldberg JI (2010) Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol 28: 3762-3769.

11. Szelei-Stevens KA, Kuske RR, Yantsos VA (2000) The influence of young age and positive family history of breast cancer on the prognosis of ductal carcinoma in situ treated by excision with or without radiation therapy or by mastectomy. Int J Radiat Oncol Biol Phys 48: 943-949.

12. Fregatti P, Gipponi M, Depaoli F, Murelli F, Guenzi M, et al. (2019) No Ink on Ductal Carcinoma In Situ: A Single Centre Experience. Anticancer Res 39: 459-466.

13. Preeti Subhedar, Cristina Olcese, Sujata Patil, Monica Morrow, Kimberly J. Van Zee (2015) Decreasing recurrence rates for ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery over 30 years. Ann Surg Oncol 22: 3273-3281.

14. Mamtani A, Nakhlis F, Downs-Canner S, Emily C. Zabor, Monica Morrow, et al. (2019) Impact of Age on Locoregional and Distant Recurrence After Mastectomy for Ductal Carcinoma In Situ With or Without Microinvasion. Ann Surg Oncol 26: 4264-4271.