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Estrogen Receptor-negative Ductal Carcinoma *In Situ* (DCIS) of the Breast – an Institutional Review of Outcomes

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Abstract. *Background/Aim: Estrogen receptor (ER)-negative [ER(–)] invasive breast cancers (IBCs) are known to be more aggressive than their ER(+) counterparts. This is less well defined for ductal carcinoma in situ (DCIS). This study investigated the outcomes following the treatment of ER(–) DCIS. Patients and Methods: A total of 103 ER(–) DCIS patients diagnosed between 2004-2018 were retrospectively analyzed. Median follow-up was 63.9 months. Statistical analysis included descriptive statistics, non-parametric tests, T-test, logistic regression. The outcomes were compared to a group of 102 ER(+) DCIS patients from our institution. Results: Any breast event (BE) occurred in 10 (9.7%) patients at a median of 3.2 (1.7-7.2) years. The incidence of ipsilateral breast events (IBEs) was 5.8% (6/103). All IBE cases were ER(–) DCIS. All (n=4) contralateral breast events (CBEs) were ER(+) including 3 IBCs. Cumulative incidence of any BEs at 1, 2, and 5 years was 0%, 1.1%, and 9.1%, respectively. Among patients with ER(–) DCIS who developed BE, breast conserving surgery (BCS) had been performed for the initial DCIS in 90% of cases. In those without any BE, the BCS rate (vs. mastectomy) was 58.1% (p=0.08). Adjuvant radiotherapy after BCS was used less often among patients with vs. without subsequent BE (55.5% vs. 77.4%) (p=0.22). Predictors for BE occurrence were not identified. The incidence of any BE among patients with ER(+) DCIS was 6.9% and was not significantly different compared to ER(–) DCIS group (p=0.46). Conclusion: ER(–) DCIS outcomes were similar to our institutional ER-positive DCIS group and the previously reported ones for predominantly ER-positive DCIS cohorts.*

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Breast cancer is the most common cancer diagnosis among women in the United States. It accounts for approximately 30% of all new cancer diagnoses, and comprises 15% of all cancer deaths, making it the leading cause of cancer deaths for women aged 20 to 59 years old (1). The growing use of screening programs as well as recent advancements in treatment regimens contributed to a 40% drop in breast cancer death rates between 1989 and 2016, with the most recent survival rates reaching 90% (1). Along with these strides in increasing favorable outcomes for patients with breast cancer, the technological advancements have also contributed toward the recent rise in detection of breast cancers, including ductal carcinoma in situ (DCIS).

DCIS constitutes 20%-25% of newly diagnosed breast cancers and accounts for 17 to 34% of mammography-detected cases (2). Though detected early enough, there is some controversy regarding the extent to which these patients should be treated.

If left untreated, about 40% of DCIS will progress to invasive breast cancer (IBC) (3). Breast cancer-specific mortality rate following a diagnosis of DCIS has been reported to be low; however, the risk of dying from breast cancer increases after an invasive recurrence (4), which accounts for approximately 50% of all breast events (BEs) following the initial DCIS diagnosis (5).

The current DCIS treatment paradigm includes either breast conservation surgery (BCS) followed by radiation therapy or mastectomy alone. Data from randomized clinical

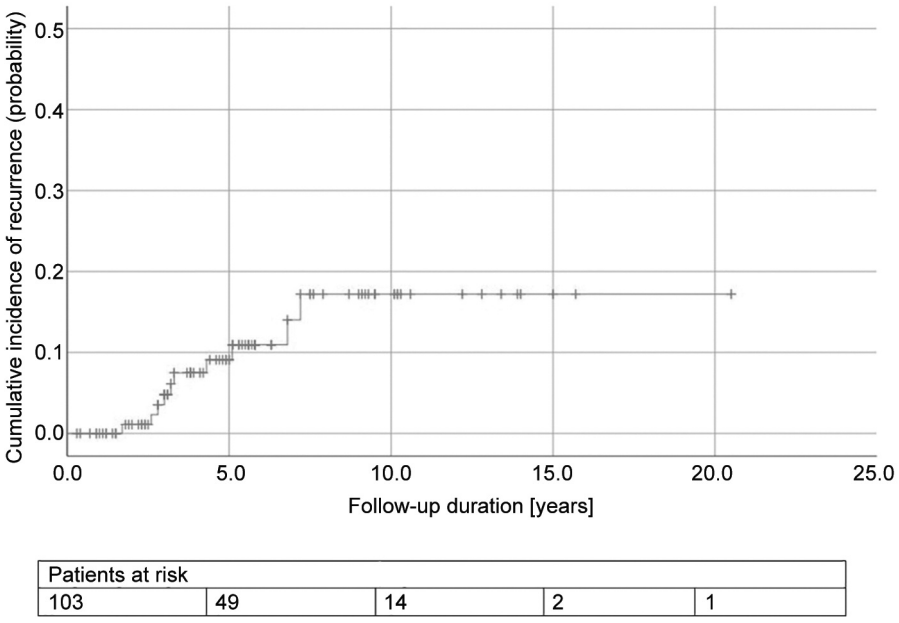

Figure 1. *Kaplan-Meier curve demonstrating cumulative incidence of recurrence. It was 0% at 1 year, 1.1% at 2 years, and 9.1% at 5 years.*

trials consistently demonstrate approximately 50% reduction in relative risk for invasive and non-invasive ipsilateral breast events (IBEs) with addition of adjuvant radiotherapy (RT) after BCS (5-7).

Estrogen receptor (ER) status is one of the most important prognostic factors in IBCs. Studies have shown that ER(–) IBCs are characterized by more aggressive biologic behavior and result in worse outcomes compared to ER(+) IBCs (8-10). In DCIS, however, the association between ER(–) receptor status and prognosis has not been well studied. While 70-75% of DCIS express estrogen receptors, ER(–) DCIS is a far less common diagnosis (11-13), making the investigation of this entity much more challenging.

The aim of this study was to investigate the outcomes among patients diagnosed with ER(–) DCIS and to compare them with the ones reported for ER(+) DCIS patients.

Patients and Methods

Following the approval from our institutional review board, we have retrospectively analyzed the charts of patients with ER(–) DCIS diagnosed at our institution between 2004 and 2018. Patients whose length of follow up was less than 3 months were excluded. In total, 103 patients were identified. A randomly selected group of 102 patients with ER(+) DCIS treated at our institution between 2008-2014 and with ≥3-month follow up served as a comparator.

Patient charts were further reviewed for the occurrence of any (ipsilateral and contralateral) BEs defined as IBC or DCIS. Characteristics of patients with and without BEs were collected, including tumor size, nuclear grade (low, intermediate, high), tumor necrosis (grade 1 – focal, grade 2 – extensive), progesterone receptors (PR) status, width of surgical margins, type of surgery (mastectomy, breast conservation therapy) as well as adjuvant RT. Descriptive statistics, Fisher's exact test, Pearson Chi^2 test, and *T* test for independent samples were used in statistical analysis. Logistic regression was used to analyze the relationship between BEs and clinical factors including tumor size, grade, necrosis, width of surgical margins, type of surgery, the use of adjuvant RT, and cumulative RT dose. Statistical analysis was performed using IBM SPSS software (Armonk, NY, USA).

Results

The median age at the time of the initial ER(–) DCIS diagnosis was 62.1 (31-90) years. Overall, 43 (41.7%) patients with ER(–) DCIS were treated with mastectomy. Of the remaining 60 patients who underwent lumpectomy, 48 (80%) received adjuvant RT. Information on the PR status was available in 93 (90.3%) cases and DCIS was PR(+) in 4 (4.3%) cases.

During a median follow up of 63.9 (4-246.1) months, 10 out of 103 patients (9.7%) developed any breast cancer event. Six patients (5.8%) were found to have IBE, all of which were ER(–) DCIS. Four patients developed CBE; One patient had ER(–) DCIS, and 3 patients developed ER(+) invasive ductal carcinoma in the contralateral breast with pathologic stage ranging from pT1bN0 to pT1cN1a according to the AJCC 7th edition staging system.

The median time to a BE was 3.2 (1.7-7.2) years. Cumulative incidence of any BE was 0% at 1 year, 1.1% at 2 years, and 9.1% at 5 years (Figure 1), indicating that most of the events occurred within the first 5 years of the initial diagnosis.

Table I. *Characteristics of patients with estrogen receptor-negative ductal carcinoma in situ (DCIS) who developed breast events following the initial treatment.*

	Initial diagnosis								Breast event			
Case no.	Age	Nuclear grade	Necrosis grade	Margin width (mm)	Tumor size (mm)	Initial surgery	Adjuvant RT	RT boost	Time to breast event (months)	Laterality	Type	ER status
1	58	3	2	1.5	3	TM	No	–	51.8	Contralateral	DCIS	NEG
2	41	2	1	12	6	PM	Yes (46 Gy/25 fx)	Yes	33.2	Contralateral	IDC	POS
3	55	3	2	1	24	PM	Yes (50 Gy/25 fx)	Yes	61.1	Contralateral	IDC	POS
4	46	3	2	1.2	16	PM	Yes (50 Gy/25 fx)	Yes	30.7	Contralateral	IDC	POS
5	62	3	2	5	50	PM	No	–	20.8	Ipsilateral	DCIS	NEG
6	66	3	2	ND	5	PM	Yes (ND)	ND	39.7	Ipsilateral	DCIS	NEG
7	36	3	2	2	20	PM	No	–	86.7	Ipsilateral	DCIS	NEG
8	63	3	2	1	8	PM	Yes (40.05 Gy/15 fx)	Yes	36.4	Ipsilateral	DCIS	NEG
9	84	2	1	5	6	PM	No	–	37.8	Ipsilateral	DCIS	NEG
10	51	3	1	ND	3	PM	No	–	81.3	Ipsilateral	DCIS	NEG

ER: Estrogen receptor; fx: fractions; M: mastectomy; ND: no data; NEG: negative; PM: partial mastectomy; POS: positive; RT: radiation therapy; IDC: invasive ductal carcinoma.

Table II. *Comparison of patients who did and did not develop breast events following the treatment for estrogen receptor (–) ductal carcinoma in situ.*

Characteristic	Patients with subsequent breast events	Patients without subsequent breast events	*p*-Value
Nuclear grade:			
2	2 (20%)	17 (18.5%)	0.907
3	8 (80%)	75 (81.5%)	
Necrosis:			
0	0	7 (7.6%)	1.0
1	3 (30%)	25 (27.2%)	
2	7 (70%)	60 (65.2%)	
Surgery type:			
Lumpectomy	9 (90%)	54 (58.1%)	0.08
Mastectomy	1 (10%)	39 (41.9%)	
Adjuvant RT (in patients who underwent lumpectomy):			
Yes	5 (55.5%)	41 (77.4%)	0.22
No	4 (45.5%)	12 (22.6%)	
Mean age at diagnosis (years)	55.6	61.5	0.99
Mean tumor size (cm)	1.4	2.3	0.35
Mean surgical margins (mm)	3.6	6	0.25
Mean cumulative RT dose (Gy)	59.5	59.4	0.59

RT: Radiation therapy.

Characteristics of ER(–) DCIS patients who experienced BEs. The characteristics of patients diagnosed with subsequent BEs following the ER(–) DCIS treatment are shown in Table I. 80% of these patients had grade 3 ER(–) DCIS at the initial diagnosis, and 70% of patients were found to have extensive (grade 2) necrosis. The median width of surgical margin was 18 (1-12) mm, whereas median size of the initial tumor in this group was 7 (3-50) mm. One patient (10%) was treated with adjuvant hormone therapy (anastrozole) after the initial DCIS diagnosis. Nine out of 10 (90%) patients who developed BEs underwent BCS such as lumpectomy at the time of the initial DCIS diagnosis, whereas only one (10%) patient was treated with mastectomy. Of the nine patients treated with BCS, five (55.5%) received adjuvant RT. The median RT dose was 48 Gy (40.05 - 50 Gy in 15-25 fractions). Four of these patients received RT boost to the lumpectomy site (the information of the lumpectomy boost was missing in 1 patient), the dose

of which ranged between 10 and 16 Gy. Median cumulative RT dose in this group was 61 Gy (50.05-66 Gy). The BEs were addressed with mastectomy in seven cases BCS in the remaining three cases.

Characteristics of ER(–) DCIS patients without subsequent BEs. Among patients who did not develop BEs following the treatment of ER(–) DCIS, 54/93 (58.1%) were treated with BCS, 41 of which (77.4%) received adjuvant RT. Median RT dose was 50 Gy in 25 fractions. Lumpectomy boost (10-16 Gy) was delivered in 84.6% cases. The median cumulative dose of RT was 61.75 Gy (34-67.54 Gy). Median tumor size in this group was 17.5 (1-100.2) mm, and median surgical margin width was 4 (0.3-38) mm. Tumor grade ranged between intermediate and high, with a high grade (grade 3) found in most of the cases (n=75; 81.5%). Grade 2 necrosis was found in 65.2% (n=60) cases. Nine (9.9%) of patients received anti-estrogen therapy after the initial DCIS diagnosis and continued it for a median of 29.2 (1.5-54) months.

There were no statistically significant differences between patients with and without BEs in terms of age at diagnosis, tumor size, margin width or median RT dose (Table II).

Tumor grade, the grade of necrosis, surgery type, and the use of adjuvant RT were also not statistically significantly different between the groups (Table II). Additionally, logistic regression did not reveal a relationship between the aforementioned variables and the occurrence of BEs.

ER(+) DCIS patients. Among the patients with ER(+) DCIS with reported PR status, PR(+) tumors were found in 84.2%. Any BE occurred in 7/102 (6.9%) patients at a median of seven (0.6-12.6) years following the treatment completion. The incidence was not statistically significantly different when compared to the ER(–) DCIS group (p=0.46). IBE occurred in four (3.9%) patients and all but one IBE was ER(+) DCIS. All seven patients were treated with lumpectomy for their initial ER(+) DCIS followed by adjuvant RT in 6 cases. Similarly to the ER(–) DCIS group, lumpectomy was the most common treatment among patients without subsequent BEs (57/95; 60%), with adjuvant RT delivered in 72% of cases.

Discussion

Several trials reported on the incidence of BEs following the treatment of DCIS. In the NSABP B-24 trial investigating adjuvant RT with or without adjuvant tamoxifen in patients with DCIS, the rate of all breast cancer events at 5 years ranged between 8.2% and 13.4% depending on the use of tamoxifen (14, 15).

In the same trial, the risk of IBE ranged between 6% and 9.5% (14), whereas in the EBCTCG meta-analysis of four randomized trials, the IBE risk at 10 years was 13% in patients undergoing BCS (5).

There were also two major studies evaluating the risk of BEs among patients with DCIS with a more favorable disease profile, *i.e.*, ≤2.5 cm, low or intermediate grade tumors. In the ECOG-ACRIN 5194 study, 5-year IBE rate among these patients treated with BCS was 6.1% (16). The IBE rates were somewhat lower in the RTOG 9804 trial, reaching 0.4% and 3.5% in patients treated with or without adjuvant RT (17).

Although these studies were conducted prior to the era of a routine ER analysis, it can be assumed that ER(+) DCIS constituted the majority of the study groups, considering a much higher prevalence of ER(+) DCIS over ER(–) disease.

A 9.7% incidence of any breast cancer event and 5.8% incidence of IBE at a median follow up of 5.3 years reported in our study does not appear to exceed those reported in the above studies. However, direct comparisons between our study and the data from large prospective studies are limited by heterogeneity of treatment modalities in our group (mastectomy, BCS, BCT). Therefore, we compared our results to the outcomes of patients with ER(+) DCIS who were treated at our institution at the same time. The incidence of any BE in this group did not differ significantly from that of patients with ER(–) DCIS, corroborating the findings from the comparison to historic controls.

Our results are also supported by the reports from some other retrospective studies investigating the outcomes in patients with DCIS depending on the ER status. In several studies evaluating the outcomes of patients treated with either mastectomy or lumpectomy with or without adjuvant RT, ER was not a predictor of BEs in either univariate or multivariate analysis (13, 18, 19). Similarly, there have been reports of no association between ER expression and the risk of subsequent breast tumors in patients with DCIS treated with lumpectomy only (20, 21).

At the same time, our results showing similar IBE rates to the ones seen in clinical trials enrolling primarily patients with ER(+) DCIS stand in contrast to some other studies investigating this risk among patients with ER(–) DCIS. Roka *et al*. reported a significantly higher risk of developing an IBE in patients with ER(–) compared to those with ER(+) DCIS undergoing breast conservation surgery (22). Kerlikowske *et al*. also found the association between ER(–) status and subsequent breast tumors among patients with DCIS treated with wide local excision (23). Interestingly, ER status was not found to be a predictor of subsequent *invasive* ipsilateral breast cancer in the same study (23). In our cohort, all IBEs were ER(–) DCIS, which appears to support the above findings of a non-invasive rather than invasive nature of breast cancer events in this population. This is in contrast to the previously reported 1:1 ratio of invasive and non-invasive type of subsequent BEs in historic DCIS cohorts (5).

Our results may also indicate that the risk of developing further breast tumors after ER(–) DCIS diagnosis is likely multifactorial and should be considered in conjunction with other tumor features, including Ki-67, pathologic grade, expression of other receptors (progesterone, HER-2), and potentially genetic aberrations, which have been reported to have a significant impact on the outcomes in these patients (22, 24). Ringberg *et al*. evaluated the influence of several factors on the risk of developing BEs in the future, including ER and PR negativity, overexpression of HER2, low Bcl-2 expression, accumulation of p53, nondiploidy, and high Ki-67 expression, and found that ER(–) status was indeed a predictor of further BEs but only when combined with other biological factors (25). Unfortunately, small study groups, retrospective design, and variability of treatment modalities (*e.g.,* mastectomy *vs*. lumpectomy, adjuvant RT *vs*. no adjuvant treatment) used in the current studies investigating ER(–) DCIS, constitute barriers to determination of biomarker expression that could unequivocally predict the risk of further breast tumors (11).

The limitations of our study are its retrospective nature as well as the small number of patients. Nevertheless, considering that ER(–) DCIS is a rare diagnosis overall, and taking into account the paucity of clinical studies investigating the nature of this entity, we believe that our study is a valuable addition to the ongoing debate on the ER(–) DCIS outcomes.

Conclusion

In conclusion, the rates of BEs following the treatment for ER(–) DCIS in our study were similar to the previously reported DCIS ones, which is in contrast to the well-described findings for ER(–) invasive carcinomas known to be associated with worse outcomes compared to ER(+) invasive breast tumors. This may suggest that ER(–) status may not be associated with worse prognosis of DCIS, or that its prognostic significance should be considered in conjunction with other pathological features. Future prospective studies are needed to further evaluate the outcomes for this patient population.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: AS; Data curation: GL, BN, KS, JO, EZ; Formal analysis: EZ, BN; Supervision: AS, SR; Writing - original draft: EZ, GL; Writing - review & editing: AS, SR.

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