ORIGINAL ARTICLE

Treatment Outcomes of Patients with Ductal Carcinoma In Situ Treated at the Faculty of Medicine, Vajira Hospital

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Background: Ductal carcinoma in situ (DCIS) denotes the presence of malignant cells confined within the basement membrane, commonly referred to as intraductal carcinoma. The incidence of DCIS has surged owing to advancements in breast cancer screening.

Objective: The present study aims to assess the 5 and 10-year disease-free survival (DFS), overall survival (OS), and prognostic factors among patients diagnosed with DCIS, treated at the Faculty of Medicine Vajira Hospital.

Materials and Methods: A retrospective descriptive analysis was conducted on DCIS patients who underwent treatment at the Faculty of Medicine Vajira Hospital, between 2007 and 2022. DFS and OS were evaluated using the Kaplan-Meier method. The study investigated the association between patient-tumor characteristics with DFS using the log-rank test and Cox proportional hazards models.

Results: The study comprised 72 DCIS patients. Both 5-year OS and 5-year DFS were 100%, with 10-year OS remaining at 100% and 10-year DFS at 91.2%. Only expression of Ki-67 index (HR of 5.52; 95% CI: 3.89 to 9.50) is significantly prognostic factor related to recurrence.

Conclusion: DCIS patients demonstrated excellent long-term survival outcomes. Moreover, there was no significant discrepancy in outcomes between mastectomy and BCS plus whole breast radiation. The expression of the Ki-67 index emerged as a crucial prognostic factor influencing recurrence.

Keywords: Ductal carcinoma in situ; DCIS; Surgery; Radiotherapy; Outcomes

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Ductal carcinoma in situ (DCIS), also known as intraductal carcinoma or stage 0 breast cancer, represents malignant cells within the basement membrane. DCIS is considered a precancerous or noninvasive lesion of the breast and comprises approximately 20% to 30% of newly diagnosed breast cancer cases[1,2]. The global incidence of DCIS is increasing, paralleling the increased use of mammography screening for the detection of breast cancer[3-6].

DCIS manifests as a broad spectrum of diseases with varying malignant potential, and the breast cancer–specific mortality rate is 3.3% over a 20-year period[7]. Remarkably, it is estimated that in approximately 80% of individuals diagnosed with DCIS, it will not progress to an invasive disease[7-11]. Presently, the primary objective in managing noninvasive breast cancer is to reduce recurrence rates, prevent the progression to invasive cancer, minimize treatment-related side effects, and prevent overtreatment.

Treatment modalities include surgery, such as mastectomy or breast-conserving surgery (BCS), radiation therapy (RT), and hormonal therapy (HT).

The standard treatment for DCIS commonly presents two primary options: mastectomy or breast-conserving surgery followed by adjuvant radiotherapy. Meta-analyses and prospective randomized trials have demonstrated the efficacy of adjuvant RT following BCS in reducing the risk of ipsilateral breast events, although no significant effect on overall survival (OS) has been observed[7,12-20]. Hormonal therapy emerges as a crucial adjunct for patients with hormone receptor-positive DCIS. This therapy aims to curtail the risk of recurrence by targeting hormone-sensitive pathways. Prognostic factors for DCIS include age, nuclear grade, tumor size, margins, and the use of adjuvant therapy[21-32].

The Ki-67 index measures the proportion of cells within a tumor that are actively dividing. Several studies have shown that DCIS patients with a Ki-67 index ≥14%

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are associated with a higher risk of progression to invasive breast cancer and may indicate a greater likelihood of recurrence after treatment compared to those with a lower Ki-67 index[28-32].

In the present study, we aim to evaluate the treatment outcomes and identify associated risk factors for women diagnosed with DCIS at the Faculty of Medicine, Vajira Hospital. By conducting a comprehensive analysis, our goal is to offer valuable insights into optimizing the management of this increasingly prevalent condition.

Materials and Methods

The institutional ethics committees approved the present study (CAO176/62). We conducted a retrospective evaluation of patients diagnosed with pathologically proven DCIS who were treated at the Faculty of Medicine, Vajira Hospital, between 2007 and 2022. Inclusion criteria included patients with DCIS who had completed standard treatment, whereas exclusion criteria encompassed patients with a history of other cancers, acquired Immunodeficiency Syndrome (AIDS) (affecting survival), prior thoracic irradiation, or insufficient medical information. We collected patient, tumor, and treatment details from the medical records.

Surgical options included mastectomy and BCS. Mastectomy patients typically do not require postoperative RT, except in cases with positive margins. For patients receiving BCS, adjuvant whole-breast RT (WBRT) is considered the treatment standard. HT is offered to patients with hormone receptor-positive tumors[7,12-20].

RT involved treating the entire breast to a total dose of 50 Gy over 5, 6 weeks using median and lateral tangential fields. Treatment was administered once daily, 5 days per week, with a daily fraction size of 1.8 to 2 Gy[20]. Clinical assessment determined breast tissue extent and treatment coverage, with wedges used for compensation. A boost dose of 10 to 15 Gy in three to five fractions was administered to this select group of patients.

Patients underwent regular follow-up, with physical examinations performed every 3 months during the first 2 years and every 6 months thereafter until death. Primary outcomes included 5- and 10-year disease-free survival (DFS), whereas secondary outcomes comprised 5- and 10-year OS and prognostic factors for recurrence. We diagnosed a disease recurrence in the patient upon discovering pathologically confirmed lesions at the primary site of the breast, contralateral site, or beyond the breast. We measured OS from treatment initiation to death from any cause or last follow-up, whereas we calculated DFS from treatment onset to disease progression, recurrence, or right censoring at the last follow-up.

We used SPSS statistical software (version 22.0, IBM Corp., Armonk, NY) for statistical analysis. We analyzed DFS and OS using the Kaplan–Meier method and compared them between groups using the log-rank test. A value of $p<0.05$ was considered statistically significant. We performed multivariate analysis using Cox proportional hazards regression analysis in a forward stepwise manner with a p-value of 0.05 as inclusion.

Results

The study included 72 patients diagnosed with DCIS who underwent treatment at the Faculty of Medicine, Vajira Hospital, between 2007 and 2023. The median duration of follow-up was 7.31 years (range, 1 to 16.50 years). Table 1 shows patient characteristics. Notably, the median age at diagnosis was 51 years, with a range of 34 to 83 years. Most patients (72.2%) were older than 45 years.

Treatment modalities predominantly included mastectomy (68.1%), with only one patient in this group receiving adjuvant RT. Conversely, the remaining patients (31.9%) underwent BCS, with 82.6% receiving adjuvant RT. Surgery achieved margins ≥2 mm in 90.3% of cases, whereas the remaining patients had margins of <2 mm (6.9%) or unknown (2.8%). The median tumor size was 2.1 cm (range, 0.3 to 7.4 cm), with 61.1% (n=44) of the patients' tumors being ≤2.5 cm. High-grade DCIS was predominant, accounting for 55.6% of cases (n=40), whereas low-grade DCIS comprised only 12.5% (n=9). Detailed histologic evaluation revealed positive estrogen receptor status in 80.6% of patients, positive progesterone receptor in 75%, positive human epidermal growth factor receptor-2 in 18.1%, and a proliferative index of Ki-67 ≥14% in 19.4%. Endocrine therapy was administered to 80% of all patients (Table 1).

At the time of analysis, three patients (4.17%) experienced relapse, with two and one patients exhibiting recurrent invasive tumors in the ipsilateral and contralateral breasts, respectively. Both 5-year OS and DFS were 100%, whereas 10-year OS was 100% and DFS was 91.2% (Figure 1).

Univariate analysis identified high tumor grade ($p=0.037$) and a proliferative index of Ki-67 ≥14% ($p=0.028$) as factors affecting DFS. However, multivariate analysis revealed only a proliferative index of Ki-67 ≥14% (hazard ratio [HR] 5.52; 95% confidence interval [CI]: 3.89 to 9.50) as significantly influencing DFS (Table 2).

Discussion

The present study provides a comprehensive analysis of outcomes and patient tumor characteristics among patients with DCIS undergoing various treatment modalities, including surgery and/or radiotherapy with or without HT, within a single institution. Our findings revealed

Table 1. Patient, tumor and treatment characteristics

Characteristics	n (%)
Age (years)	51 (34 to 83)
Age group	
≤45	20 (27.8)
>45	52 (72.2)
Margin status	
<2 mm	5 (6.9)
≥2 mm	65 (90.3)
Unknow	2 (2.8)
Tumor size	
≤2.5 cm	5 (7.1)
>2.5 cm	65 (92.9)
Histologic type	
Ductal	147 (93)
Lobular	6 (3.8)
Others	5 (3.2)
Tumor grade	
Low grade	9 (12.5)
Intermediated grade	23 (31.9)
High grade	40 (55.6)
ER status	
Negative	14 (19.4)
Positive	58 (80.6)
PR status	
Negative	18 (25.0)
Positive	54 (75)
Her-2 status	
Negative	56 (77.7)
Positive	13 (18.1)
Unknow	3 (4.2)
Triple negative	
No	63 (87.5)
Yes	6 (3.8)
Unknow	3 (4.2)
Ki67 Index	
<14% proliferation index	41 (56.9)
≥14% proliferation index	14 (19.4)
Unknow	17 (23.6)
Surgery type	
BCS	23 (31.9)
Mastectomy	49 (68.1)
RT	
No	52 (72.2)
Yes	20 (27.8)
Hormonal treatment	
No	14(19.4)
Yes	58 (80.6)

promising 5- and 10-year DFS rates of 100% and 91.2%, respectively, along with 100% OS rates at both intervals. These results align closely with the findings of historical

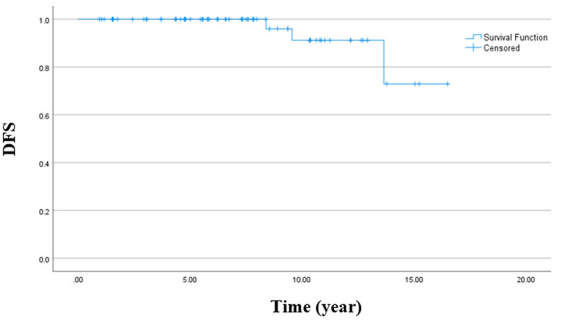

Figure 1. Disease-free survival.

randomized controlled trials, emphasizing the favorable long-term outcome for patients with DCIS. The low risk of locoregional recurrence observed in our study (4.2%) is similar to previous research, which reported cumulative breast cancer death rates of 0 to 2.8% at 10 years and recurrence rates of 1% to 4%[22-24,31,32].

Surgical intervention for treating DCIS involves two primary options: mastectomy or BCS. Mastectomy is typically reserved for patients with extensive disease involvement. Unless positive margins are detected, adjuvant RT is typically unnecessary for these patients. Conversely, for patients opting for BCS, WBRT is regarded as the standard of care. Numerous trials and meta-analyses have consistently demonstrated the efficacy of WBRT in reducing in-breast recurrence rates by 50% to 70% while not affecting OS[7,12-20].

The NSABP B-17 trial[19] demonstrated that after 15 years, RT led to a significant 52% reduction in ipsilateral invasive recurrence compared with excision alone (HR 0.48; 95% CI: 0.33 to 0.69, p<0.001). Furthermore, the study found no notable disparities in OS or cumulative all-cause mortality rates between the RT and excision-only groups in the same 15-year period (HR 1.08; 95% CI: 0.79 to 1.48). A meta-analysis of four large, multicenter randomized trials confirmed the results of the individual trials, demonstrating that the addition of WBRT after BCS for DCIS statistically and clinically significant reduces ipsilateral breast events (HR 0.49; 95% CI: 0.41 to 0.58, p<0.00001), and did not show OS benefit[20]. Similar outcomes were reported by the SEER database, which included 108,196 patients with DCIS. In a subgroup analysis at 10 years of 60,000 patients treated with BCS, with or without WBRT, the addition of WBRT was associated with a 50% reduction in the risk of ipsilateral recurrence (HR 0.47; 95% CI: 0.42 to 0.53, p<0.001). However, in the present study, breast cancer–specific mortality was found to be similar (HR 0.86; 95% CI: 0.67 to 1.10, p=0.22)[7]. The authors found comparable treatment outcomes for mastectomy and BCS.

Another important aspect of treating patients with DCIS

Table 2. Factors affected DFS: univariate and multivariate analysis

Characteristics	Univariate analysis			Multivariate analysis		
	p-value	HR	95% CI	p-value	HR	95% CI
Age (≤45 years (n=20) vs. >45 years (n=52)	0.107	0.17	(0.02 to 1.92)			
Tumor size (≤2.5 cm (n=6) vs. >2.5 cm (n=66)	0.399	2.7	(0.24 to 29.96)			
Margin status (<2 mm (n=5) vs. ≥2 mm (n=65)	0.753	21.63	(0.00 to 8.79)			
Histologic grade (Low & Intermediate (n=32) vs. High (n=40)	0.037	4.863	(3.49 to 6.55)	0.48	0.07	(-0.32 to 0.71)
ER status (Negative (n=14) vs. Positive (n=58))	0.451	0.36	(0.02 to 5.77)			
PR status (Negative (n=18) vs. Positive (n=54))	0.608	0.49	(0.03 to 7.90)			
Her-2 status (Negative (n=56) vs. Positive (n=13))	0.612	1.85	(0.17 to 20.43)			
Ki 67 index (<14% (n=41) vs. ≥14% (n=14))	0.028	5.32	(3.91 to 9.72)	0.008	5, 52	(3.89 to 9.50)
Triple negative (No (n=63) vs. Yes (n=6))	0.178	5.45	(0.34 to 87.25)			
Surgery type (BCS (n=23) vs. Mastectomy (n=49))	0.96	0.98	(0.43 to 2.21)			
RT (No (n=52) vs. Yes (n=20))	0.867	1.23	(0.11 to 13.94)			
Hormonal Rx (No (n=14) vs. Yes (n=18))	0.451	0.36	(0.22 to 5.77)			

involves identifying patient, pathologic, and treatment-related factors that may increase the risk of recurrence after treatment. Various studies have identified young age as a potential independent predictor for recurrence[21-23], whereas others have not found this association[24,25]. In our study, however, we did not observe a significant association between younger age and disease recurrence.

Margin status represents another important variable shown to influence the risk of local recurrence[27]. In a meta-analysis involving 4,660 patients with DCIS treated with BCS and RT, margins <2 mm were associated with higher rates of recurrence compared with margins of ≥2 mm[26].

Another study retrospectively reviewed a database of 2,996 patients with DCIS who underwent BCS to investigate the association between margin width and recurrence, controlling for all other characteristics. Wider margins were significantly associated with a lower rate of recurrence only in patients who did not receive RT ($p<0.0001$) but not in those treated with radiation ($p=0.95$)[21].

In a retrospective analysis of a database comprising 2,996 patients with DCIS who underwent BCS, researchers investigated the association between margin width and recurrence while controlling for all other relevant characteristics. Interestingly, they found wider margins to be significantly associated with a lower rate of recurrence, but they observed this association only among patients who did not receive RT ($p<0.0001$). Conversely, in patients treated with radiation, the width of the margins did not significantly affect the recurrence rate ($p=0.95$)[27]. In our current study, we did not find a correlation between margin width and recurrence. Notably, most patients with margins <2 mm received RT, which might explain why margin width did not emerge as a significant factor in our analysis, unlike in other studies.

Our findings corroborate the results of a study by Kerlikowske et al.[28] and Rakovitch et al.[29] that demonstrated that expression of the Ki-67 index is independently associated with increased recurrence rates following treatment for DCIS. In addition, a systematic review and meta-analysis highlighted that the expression of Ki-67 predicts the risk of both invasive (HR=1.53; 95% CI, 1.14 to 2.06) and noninvasive (HR=1.59; 95% CI, 1.19 to 2.13) recurrence[32].

Although several reports have indicated that certain histologic features such as high tumor grade, large tumor size, poor histochemistry status, and adjuvant treatment may contribute to increased recurrence rates[21-32], we did not observe associations between these factors and higher recurrence rates in our study.

The limitations of this research are due to the infrequence of the disease, resulting in a small number of patients, and it being a retrospective study, which may affect the interpretation of results.

Conclusion

The findings of our study reveal remarkable long-term overall survival and disease-free survival outcomes among patients diagnosed with DCIS. The choice between mastectomy and BCS plus WBRT yielded comparable treatment outcomes. The only significant factor predicting recurrence was expression of Ki-67. Consequently, continuous surveillance for local recurrence of DCIS is paramount throughout the patient's lifetime. In selected optimally treated patients with DCIS of the breast, BCS plus RT and mastectomy had no significant difference in OS and DFS.

What is already known on this topic?

The incidence of DCIS has increased due to increases breast cancer screening. DCIS patients had an excellence

long-term survival outcome.

What this study adds?

Treatment with mastectomy or BCS plus WBRT no significant difference in outcome. The important prognostic factor affecting disease-free survival was expression of Ki-67 index.

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Conflicts of interest

The authors declare no conflict of interest.

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