Original Article
Middle East Journal of Cancer; July 2022; 13(3): 472-482

Does Existence of Ductal Carcinoma In Situ Accompanying Invasive Ductal Carcinoma Lead to Different Clinicopathological Features and Clinical Outcome? Report of a Breast Cancer Registry

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Please cite this article as: Tahmasebi S, Shahin B, Ghoddusi Johari M, Akrami M, Zanguri V, Talei A, et al. Does existence of ductal carcinoma in situ accompanying invasive ductal carcinoma lead to different clinicopathological features and clinical outcome? Report of a breast cancer registry. Middle East J Cancer. 2022;13(3):472-82. doi: 10.30476/mejc.2022.86985.1384.

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Abstract

Background: Ductal carcinoma in situ (DCIS) is widely recognized as the precursor of invasive ductal carcinoma (IDC). We aimed to compare clinicopathological characteristics and prognosis between IDC with and without coexisting DCIS stratified by biological subtypes to evaluate the clinical outcome of these two groups.

Method: Data from 5814 patients with IDC (32.4) and IDC/DCIS (67.6%), who underwent surgery from December 1993 through December 2019, were retrospectively assessed. We evaluated the prognosis of IDC with coexisting DCIS in different molecular subtypes.

Results: IDC/DCIS patients were younger ($P < 0.001$). They also presented with a low tumor grade and had less lymph node involvement compared with the pure IDC patients. Compared with the patients with IDC, luminal B subtype was more frequent in those with IDC/DCIS, with 19.4% versus 13.2 %; human epidermal growth factor receptor-2 enriched subtype was also more frequently observed, with 12.2 vs. 8.7%. The 5-year disease-free survival (DFS) was higher in the IDC/DCIS patients ($P = 0.036$). The survival outcomes significantly improved in the cases with a higher amount of DCIS. The presence of coexisting DCIS ($P =0.038$), tumor size ($P < 0.001$), lymph node status ($P = 0.005$), lymph vascular invasion ($P = 0.02$), and molecular subtypes ($P < 0.001$) were found to be DFS-associated independent prognostic factors.

Conclusion: DCIS along with IDC were associated with improved prognosis. The presence of DCIS may be a marker of lower aggressiveness, and could be noticed as a prognostic factor in future treatment algorithms.

Keywords: Ductal carcinoma in situ, Carcinoma, Breast, Prognosis, Survival

Received: June 16, 2020; Accepted: March 15, 2022

Introduction

Breast cancer is known as the leading cause of cancer-related deaths in women worldwide.[1] It is the most prevalent cancer among women both in developed and developing countries. The most common type of breast cancer, mammary ductal carcinoma, is divided into invasive (invasive ductal carcinoma (IDC)) and non-invasive (mainly ductal carcinoma in situ (DCIS)) tumors.[2] Recent screening programs and the development of new technologies have resulted in early detection of breast cancer, thereby increasing the detection rate of DCIS.[3]

DCIS is generally recognized as the precursor of IDC.[4, 5] Several studies have reported that approximately 20%-50% of DCIS might progress into invasive carcinoma if untreated.[6] The currently available evidence supports a clonal relationship between the DCIS and IDC components of IDC-DCIS, based on concordant expression of immunohistochemical[7-10] and genomic markers.[11-13] Nonetheless, the clinical significance associated with the coexistence of DCIS in invasive disease has not been conclusively defined. Research has previously shown that IDC-DCIS is characterized by lower proliferation rate and metastatic propensity in comparison with size-matched pure IDC, especially if the ratio of DCIS to IDC size is high; IDC-DCIS is also more often estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, and/or human epidermal growth factor receptor 2 (HER2)-positive compared with pure IDC.[14] One study similarly reported more frequent ER and PR positivity in IDC-DCIS,[15] which was not confirmed by other smaller patient cohorts.[16, 17] Despite minor inconsistencies across studies, it can generally be recognized that IDC-DCIS represents a clinical and biological entity distinct from pure IDC. In fact, IDC-DCIS has been associated with better disease-free survival (DFS)[15] and a trend for better overall survival (OS), which did not reach statistical significance in certain studies.

However, the association between these two entities has not been studied in detail. Although a number of studies concluded that the presence of DCIS was associated with a trend towards better DFS and OS,[14, 18, 19] Jacquemier J et al. described a high number of recurrence when DCIS was accompanied with IDC.[3]

The available results are highly controversial in this context and it remains unclear whether the survival outcomes are similar for IDC when it is present alone or is accompanied by co-existing DCIS. Thus, the current study aimed to compare

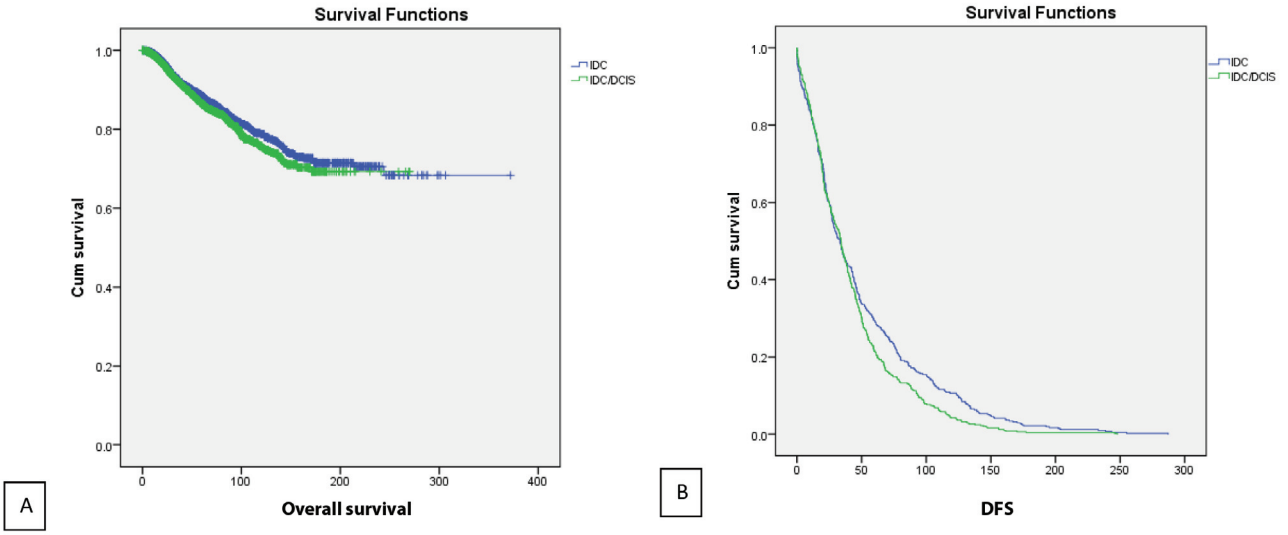

Figure 1. This figure shows the patients' OS and DFS according to the groups: A) OS, B) DFS.
OS: Overall survival; DFS: Disease-free survival; IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; Cum: Cumulative

Table 1. Baseline and clinical characteristics of the groups

Variables		Disease status		*P* value
		IDC (n=1885) N (%)	IDC/DCIS (n=3929) N (%)	
Age (Years)	Mean	48.87 ± 0.33	47.89 ± 0.25	<0.001
Age	<55	1261(66.9)	2849(72.5)	<0.001
	>55	625(33.1)	1080(27.5)	
Sex	Male	17(0.9)	19(0.5)	0.054
	Female	1781(99.1)	3760(99.5)	
Breast side	Left	983(52.1)	2006(51.1)	0.477
	Right	903(47.9)	1923(48.9)	
Type of surgery	Mastectomy	841(44.6)	1720(43.8)	0.666
	BCS	1045(55.4)	2208(56.2)	
LN management	SLNB	566(36)	1191(37.9)	<0.001
	ALND	812(51.6)	1445(46)	
	SLNB# ALND	195(12.4)	503(16)	
Tumor Size	<2	956(50.7)	1863(47.4)	0.046
	2-5	870(46.1)	1915(48.7)	
	>5	60(3.2)	151(3.8)	
Tumor grade	One	309(17.8)	752(20.3)	0.002
	Two	1053(60.6)	2290(61.8)	
	Three	376(21.6)	664(17.9)	
Invasion	None	702(32.9)	1365(35.2)	0.038
	Lymphatic Vascular	583(32.5)	1269(35.4)	
	Perineural1	53(8.5)	322(8.5)	
	Both	355(19.8)	842(22.2)	
Molecular subtype	Luminal A	872(62.0)	1754(59.4)	<0.001
	Luminal B	186(13.2)	572(19.4)	
	Triple Negative	226(16.1)269(9.1)		
	HER2 Enriched	123(8.7)	360(12.2)	
Chemotherapy	No	1217(79.3)	2685(87.3)	<0.001
	Yes	318(20.7)	389(12.7)	
Radiotherapy	No	328(19.8)	661(19.5)	0.874
	Yes	1330(80.2)	2730(80.5)	
Hormonal therapy	No	323(19.7)	583(17)	0.018
	Yes	1313(80.3)	2842(83.0)	
Tumor necrosis	No	1104(66.5)	1179(33.4)	<0.001
	Yes	557(33.5)	2349(66.6)	

IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; BCS: Breast conserving surgery; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection

clinicopathological characteristics and prognosis between IDC with and without coexisting DCIS stratified by biological subtypes in order to evaluate the clinical outcome of these two groups.

Materials and Methods

Study settings

We conducted this survey in Shiraz Breast Clinic, Shiraz, Iran, which is the main referral center for breast cancers in South of Iran. The registry is affiliated with Shiraz University of Medical Sciences and contains data on an excess of 8000 breast cancer patients. Shiraz Breast Cancer Registry (SBCR) includes information on financial status, clinical history and examination, histopathological characteristics, imaging, follow-up date, and prognosis data of all patients with breast cancer.[20] The Ethics Committee of Shiraz University of Medical Sciences approved the study (Ethics code: IR.SUMS.REC.1398.1044).

Study protocol

In this retrospective study, the medical records of 8000 patients were assessed at Breast Diseases Research Center (Shiraz, Iran), from December 1993 to December 2019. A complete history and physical examination, bilateral breast mammography, chest X-Ray radiology, and routine blood and biochemical tests were required for all the patients prior to the surgery. The inclusion criteria were as follows: the patients undergoing breast cancer conserving surgery or

mastectomy without neoadjuvant therapy, histological types as pure IDC or IDC/DCIS. The exclusion criteria were breast cancer histology other than pure IDC and IDC/DCIS, such as lobular, mucinous, or papillary type, neoadjuvant chemotherapy, having a prior malignancy, occult breast cancer presented with axillary lymph nodal involvement, and incomplete follow-up information.

IDC and DCIS are defined as mentioned previously by the WHO criteria classification. We retrospectively reviewed the clinicopathological features, including the side of breast involvement, size of tumor, tumor grade (which was related to invasive component), operation types (lumpectomy versus mastectomy), sentinel lymph node biopsy (SLNB) and axillary node dissection (AND) for axillary management, histopathology characteristics (including histological grade, sub-type, and invasion status), immunohistochemical findings (such as ER, PR, and HER2 status), adjuvant systemic therapy (hormone therapy, radiotherapy, and chemotherapy), recurrence rate, as well as DFS and OS. Unfortunately, we did not have any data according to which we could evaluate the impact of comedonecrosis on the behavior of IDC/DCIS tumors.

It should be noted that the cut-off for ER/PR was positivity 1%. Regarding HER2 expression, scoring was done according to the manufacturer's guidelines in immunohistochemistry as follows: 0 as without any staining or staining of less than 10% of cells, 1+ as weak staining in 10% of cells (staining in any part of the membrane), 2+ as weak to moderate staining in all of the membranes in 10% of cells, and finally 3+ as strong staining of whole membrane in 10% of cells. Those with 0 and 1+ results were considered negative for HER2 expression. Those with 3+ results were considered positive. Those showing 2+ (or equivocal) results, using the CB11 antibody (Novocastra Laboratories, Newcastleon-Tyne, UK), had fluorescence in situ hybridization (FISH) (PathVision; Vysis, Downers Grove, IL) for evaluation of HER2 gene amplification. The individuals with a positive FISH and a 2+ HER2 expression were considered to be HER2 positive.[21]

Luminal A: ER positive and PR positive, HER2 negative

Luminal B: ER positive, PR positive and HER2 positive

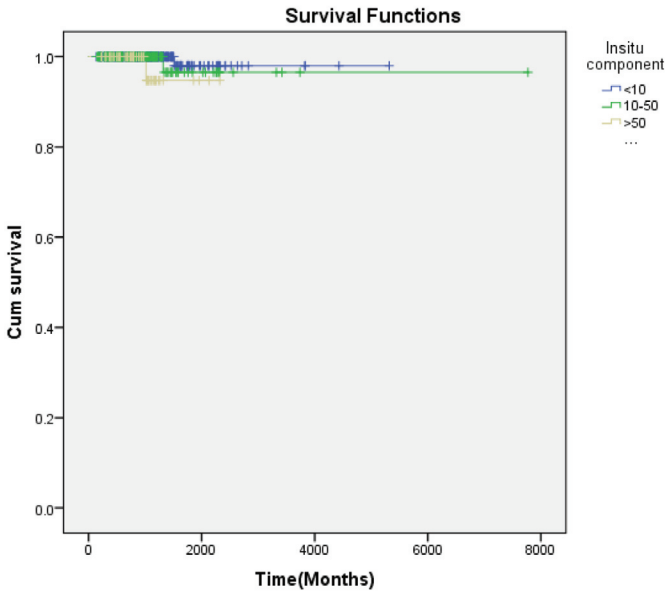

Figure 2. This figure shows the overall survival for the patients with IDC/DCIS. According to the percentage of DCIS component.
IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; Cum: Cumulative

HER2 enriched: ER negative, PR negative and HER2 positive

Triple negative: ER and PR negative, HER2 negative

Pathological slides of all the available cases were retrieved and reviewed by a breast cancer expert pathologist. The patients who died from other causes than breast cancer were excluded from the final analysis.

Statistical analysis

We used chi-square test for making a comparison among qualitative data. One-way ANOVA and Kruskall-Wallis tests were employed for the quantitative data with normal distribution and without normal distribution, respectively. We utilized Kaplan-Meier analysis for OS and DFS data. DFS was defined as the duration from the surgery to the recurrence of DCIS, invasive breast cancer (local, regional, or distant). OS was defined as the time from the surgery to death from any reason. The significance of the differences concerning the survival rates was determined using the log-rank test. Through the use of Kaplan-Meier, we also estimated the survival experience

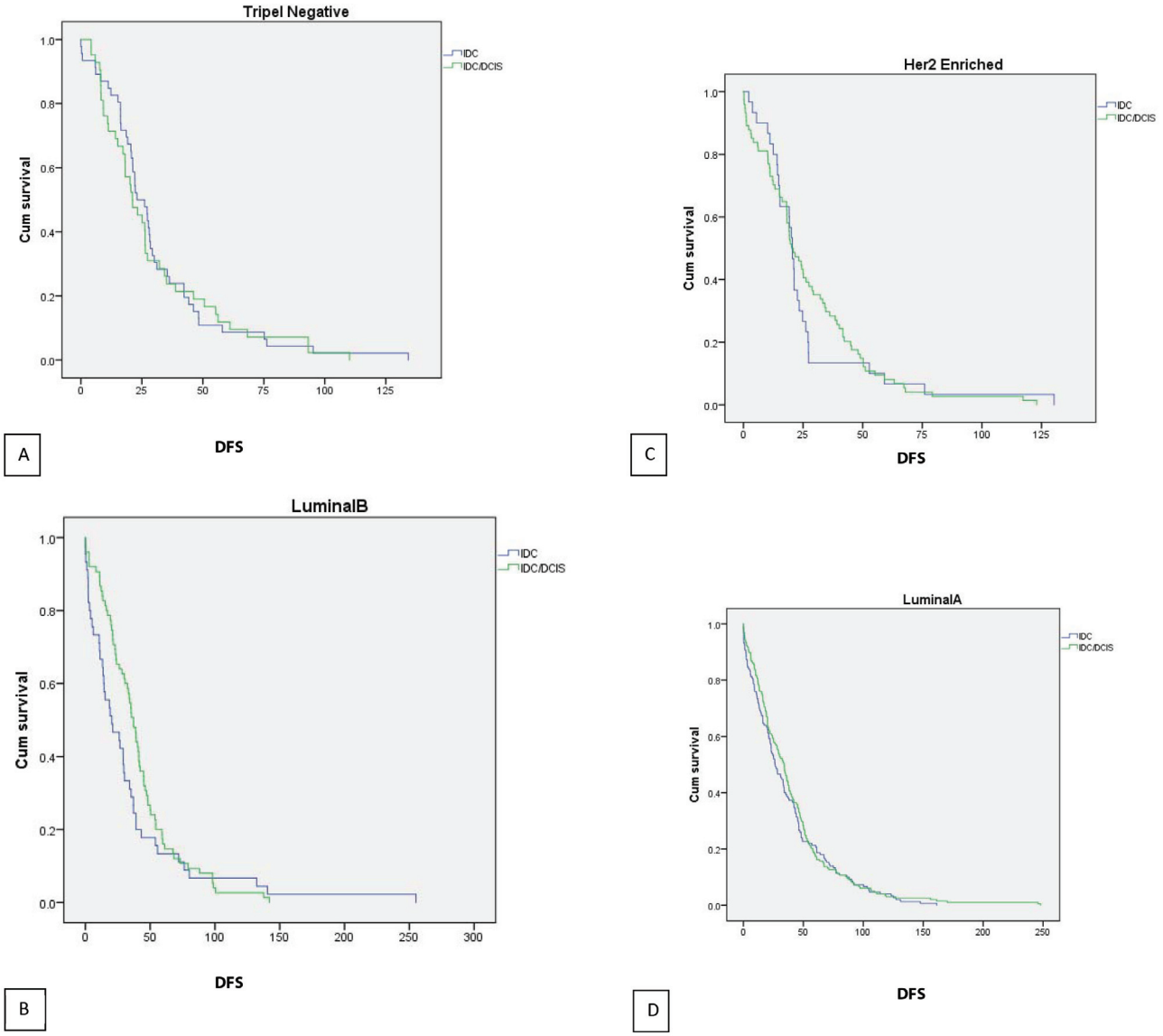

Figure 3. This figure shows the patients' OS and DFS according to the molecular subtypes: A) Triple negative, B) luminal A, C) HER2 enreached, and D) luminal B.

OS: Overall survival; DFS: Disease-free survival; IDC: Invasive ductal carcinoma, DCIS: Ductal carcinoma in situ; Cum: Cumulative

Table 2. Recurrence and survival outcomes in the patient with IDC and those with IDC/DCIS

	IDC (Recurrence)						IDC/DCIS (Recurrence)						*P* value
	1	2	3	4	5	Total	1	2	3	4	5.	Total	
Local/regional	37	5	7	3	2.	54(2.8)	117	21	24	8	3	173(1.8)	0.053
Metastasis	146	18	19	4	2	189(10)	357	34	33	10	2	436(11)	<0.001
Death		186(10.3)						452(12.3)					0.007

IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ

of different groups of prognostic factors. Multivariate Cox regression was performed to identify hazard ratio (HR). HR with 95% confidence interval (CI) was calculated for the clinicopathological factors related to the survival outcomes. All the analyses were performed via SPSS software® for windows®, version 21.0 and a *P* value of less or equal to 0.05 was considered to be statistically significant.

Result

From December 1993 through December 2019, 5814 patients were eligible for evaluation in this analysis. 1885 (32.4%) cases had pure IDC and 3929 had IDC/DCIS.

Patients' clinicopathological features and distribution according to†molecular subtype

Comparison of the baseline and clinical characteristics between these two groups, according to the pathological subtype, showed that the groups were significantly different regarding tumor size, tumor grade, tumor necrosis, invasion status, molecular subtype, lymph node management, chemotherapy, and hormone therapy. Table 1 presents an overview of the clinicopathological characteristics in the two groups.

The mean age of our patient population was 48 years (ranging from 21 to 97). The IDC/DCIS subjects were younger ($P < 0.001$). They also presented with a low tumor grade ($P = 0.002$) and had less lymph node involvement ($P = 0.001$) compared with the pure IDC patients. Evaluating tumor grade revealed that grade II was the most common type in both groups and the group with pure IDC had a higher rate of individuals with grade II of tumor (21.6% versus 17.9%) ($P = 0.002$).

The IDC and IDC/DCIS cases mostly presented with <2 cm (T1, 50.7%) and between 2-5 cm (T2, 48, 7%) of tumor size ($P = 0.046$), respectively. The mean tumor size was 2.56 ± 0.34.

Strong correlations were observed between IHC-based molecular subtype and the presence of DCIS component in IDC. Compared with the patients with IDC, luminal B subtype was more common in those with IDC/DCIS, with 19.4% versus 13.2 %; the same trend was observed for HER2 enriched subtype with 12.2 versus 8.7 %. In contrast, there was a lower proportion of triple negative in the patients with IDC/ DCIS compared with those with IDC, with 9.1% versus 16.1% in each group, respectively (all $P < 0.001$).

Survival outcomes of IDC and IDC/DCIS patients

Table 2 depicts the recurrences and survival outcomes of the patients with IDC and IDC/DCIS. During the follow-up period, in the IDC group, the rate of locoregional recurrence was 2.8%; whereas it was 1.8% in the DCIS/IDC group, the difference was statistically significant ($P = 0.05$). Contrariwise, the rate of distant metastasis was 10 % in the IDC group, while it was 11% in the DCIS/IDC group ($P < 0.001$).

Figure 1 represents the Kaplan-Meier curves for 5-year DFS and 5-year OS between the patients with IDC and those with IDC/DCIS. The median follow-up period was 44 months. The survival outcomes significantly improved in the patients with IDC/DCIS compared with those with IDC alone. We observed that 5-year DFS was 83% in the IDC/DCIS and 80% in the IDC patients ($P = 0.036$). Moreover, 5-year OS was 90% in the IDC/DCIS and 88% in the IDC patients, but the difference was not statistically significant.

Amongst all the IDC/DCIS, the data on the percentage of DCIS were recorded for 809 patients. Figure 2 illustrates OS curves according to the extent of DCIS component within this group. We divided the patients into four groups (1 :< 10%, 2:10-25 %, 3:25-50 %, and 4 :> 50%).

Table 3. Cox univariate regression analysis of the risk factors for DFS and OS

		OS			DFS		
		HR	*P* value	95% CI	HR	*P* value	95% CI
Age	>55	1.0	1.0	-	1.0	-	-
	<55	1.396	0.0211	1.025-1.849	1.236	0.005	1.062-1.431
DCIS status	IDC	1.0	1.0	-	1.0	-	-
	IDC/DCIS	1.002	0.37	0.779-1.001	0.842	0.007	1.001-1.003
Tumor grade	1	1.0	1.0	-	1.0	-	-
	2	1.373	<0.001	1.163-2.051	1.456	<0.001	1.209-1.754
	3	2.269	<0.001	1.849-3.925	1.809	<0.001	1.451-2.254
Tumor size	<2	1.0	1.0	-	1.0	-	-
	2-5	1.424	0.002	1.213-1.978	0.859	0.025	0.752-0.981
	>5	1.982	<0.001	1.536-3.541	0.952	0.033	0.718-1.262
Lymph node involvement	No	1.0	1.0		1.0	1.0	
	Yes	1.928	0.003	1.200-3.097	0.752	0.020	0.591-0.957
Type of surgery	Mastectomy	1.0	1.0	-	1.0	1.0	-
	BCS	0.479	0.39	0.411-1.024	1.115	0.199	0.927-1.440
Invasion	None	1.0	1.0	-	1.0	1.0	-
	Lymphatic Vascular	1.796	<0.001	1.119-2.874	1.041	0.628	0.885-1.224
	Perineural	0.931	0.571	0.652-1.344	0.978	0.890	0.713-1.342
	Both	1.767	<0.001	1.434-2.179	1.153	0.133	0.958-1.388
Molecular Subtype	Luminal A	1.0	1.0	-	1.0	1.0	-
	Luminal B	2.163	<0.001	1.437-3.567	1.682	0.006	1.217-2.651
	Triple Negative	3.982	<0.001	1.674-6.739	2.327	<0.001	1.179-3.856
	Her2 Enriched	3.521	0.003	1.982-5.486	2.116	<0.001	1.537-3.235
Tumor necrosis	No	1.0	1.0	-	1.0	1.0	-
	Yes	1.212	<0.001	0.962-1.346	1.212	0.003	0.102-1.789

OS: Overall survival; DFS: Disease-free survival; IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; BCS: Breast conserving surgery; CI: Confidence interval; HR: Hazard ratio

The survival outcomes significantly improved in the subjects with a higher amount of DCIS. In group 1, 5-year OS was 89 % ($P = 0.001$) in comparison with group 2 and 3 with a 5-year survival of 98 % ($P = 0.001$).

Figure 3 demonstrates the Kaplan-Meier curves for 5-year DFS in the IDC and IDC/ DCIS groups after stratification by molecular subtypes. Notably, in luminal B subtype, the DFS of IDC/DCIS significantly improved compared with that of IDC, with 93% versus 86% ($P < 0.001$). Unfortunately, we observed no statistically significant differences concerning DFS between the IDC/DCIS and IDC groups in luminal A (93% versus 91%, $P = 0.348$), HER2 enriched (93.0% versus 92.0%, $P = 0.527$), and triple negative subtypes (91.0% versus 93.0%, $P = 0.123$).

Univariate and multivariate analysis

Table 3 presents the result of univariate analysis. The factors associated with both OS and DFS were as follows: age ($P = 0.02$), tumor size ($P \leq 0.001$), tumor grade ($P \leq 0.001$), lymph node status ($P = 0.003$), lymph vascular invasion ($P \leq 0.001$), tumor necrosis ($P \leq 0.001$), and molecular subtypes ($P \leq 0.001$). However, the presence of DCIS was only associated with DFS ($P = 0.007$).

Table 4 exhibits the result of Cox multivariate analysis. In multivariate analysis, the presence of coexisting DCIS ($P = 0.038$), tumor size ($P < 0.001$), lymph node status ($P = 0.005$), lymph vascular invasion ($P = 0.02$), and molecular subtypes ($P < 0.001$) were independent prognostic factors associated with DFS. Nevertheless, the presence of DCIS component in IDC was not an independent risk factor for the OS ($P = 0.063$).

In both groups, compared with luminal A subtype, HER2 enriched subtype had a worse survival in DFS (HR 1.724, CI 95%, 1.749-2.396, $P = 0.006$); meanwhile, we found no statistically significant differences in OS (HR 1.900, CI 95% 0.910-3.966, $P = 0.087$). The patients with triple negative subtype had the poorest prognosis among all the molecular subtypes with a statistical significance in both DFS (HR 2.002, CI 95%, 1.831-3.354 $P < 0.001$) and OS (HR 2.112, CI 95%, 1.821-2.866, $P < 0.001$).

Table 4. Cox multivariate regression analysis of the risk factors for DFS and OS

		OS			DFS		
		HR	*P* value	95% CI	HR	*P* value	95% CI
Age	>55	1.0	1.0	-	1.0	1.0	-
	<55	0.832	0.0314	0.617-1.203	1.038	0.049	0.981-1.253
DCIS status	IDC	1.0	1.0	-	1.0	1.0	-
	IDC/DCIS	0.671	0.063	0.528-1.112	1.031	0.038	0.879-1.541
Tumor size	<2	1.0	1.0	-	1.0	1.0	-
	2-5	1.4629	0.004	1.113-2.078	1.839	0.002	1.359-2.971
	>5	3.586	<0.001	1.736-5.641	2.346	<0.001	1.718-4.202
Lymph node involvement	No	1.0	1.0	-	1.0	1.0	-
	Yes	2.028	0.008	1.380-3.467	1.452	0.005	0.991-2.357
Invasion	None	1.0	1.0	-	1.0	1.0	-
	Lymphatic Vascular	1.682	<0.001	1.019-2.624	1.412	0.021	1.105-1.946
	Perineural	0.834	0.412	0.552-1.248	0.878	0.990	0.763-1.044
	Both	1.560	<0.001	1.214-2.297	1.132	0.119	0.988-1.481
Molecular subtype	Luminal A	1.0	1.0	-	1.0	1.0	-
	Luminal B	1.485	0.089	1.227-1.649	0.794	0.561	0.997-1.719
	Triple Negative	2.112	<0.001	1.821-2.866	2.751	<0.001	1.831-3.354
	HER2 Enriched	2.002	0.006	1.749-2.396	2.271	0.023	1.794-3.868

OS: Overall survival; DFS: Disease-free survival; IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; HR: Hazard ratio; CI: Confidence interval; HER2: Human epidermal growth factor receptor-2

Discussion

In the present study, we showed that for patients with IDC, the presence of a DCIS component is associated with favorable prognostic features and results in a statistically significant improvement in DFS. Our findings also showed less lymph node involvement, lower tumor grade, and grater ER and PR positivity in patients with IDC/DCIS. However, prior studies failed to demonstrate a significant improvement in DFS for patients with IDC + DCIS versus. IDC alone, probably due to limited statistical power.

The prognostic effect of coexisting DCIS component in IDC remains unclear and research results are highly controversial in this regard. As shown in several studies, IDC with coexistent DCIS have a lower biological aggressiveness in the luminal type with more favorable characteristics;[14, 22] nevertheless, it is not an independent factor in improving survival consequences.[23] On the other hand, Kim et al. found that the coexistent DCIS does not determine the biological behavior of breast cancer, but the grade of DCIS in IDC should be mentioned.[4]

As previously reported by Wong et al., IDC was increasingly self-detected compared with IDC/DCIS, which were detected by patients screening, indicating the higher tumor aggressiveness of IDC. It should be noted that the increased Ki67 in pure IDC compared with that in IDC/DCIS in their study supported this finding.[14]

Herein, we observed that the prevalence of the DCIS/IDC patients was distinct from that of the IDC ones according to the molecular subtypes of breast cancer. The IDC/ DCIS patients more frequently presented with luminal B (19.4% versus 13.2 %, $P < 0.001$) and HER2 enriched (12.2 versus 8.7 %, $P < 0.001$). Meanwhile, a lower proportion of triple negative (9.1% versus 16.1%, $P < 0.001$) was observed in this group; these findings were also consistent with those reported in previous papers.[24]

The presence of coexisting DCIS continued to have a strong correlation with improving the prognosis in DFS after adjustment of these factors. Our data showed that 5-year DFS was more significantly improved in the IDC/DCIS patients than that in the IDC cases (DFS: 83% versus 80%, $P = 0.036$). Less lymph node involvement and lower tumor grade were favorable characteristics associated with the IDC/ DCIS patients. In this work, the presence of IDC + DCIS was associated with significantly improved DFS compared with IDC alone on univariate analysis (5-year DFS, 83% versus 0, $P = 0.03$; HR= 0.84;

95% CI, 1.001-1.003, $P < 0.007$) (Figure 2).

A total of nine variables were included in our multivariable Cox survival model: tumor histology (IDC versus IDC + DCIS), age, tumor size, tumor grade, lymph node involvement, molecular subtype, tumor necrosis, and type of the surgery. After adjustment of all variables in this model, the IDC + DCIS group still had improved DFS than IDC group. (HR 0.103, 95% CI 0.879-1.541, $P = 0.03$).

Conventionally, in the breast conserving surgery, the presence of an extensive intraductal component has been considered as a negative prognostic factor for local recurrence,[25-27] due to the load of residual DCIS in the breast. However, no differences were detected between the setting of an appropriate surgery and the local recurrence risk, with extensive in situ component similar to that of non-extensive in situ component patients.[28-30]

In our analysis of patients, we found that DFS was actually better when an intraductal component (between 10%-25% or 25%-50% DCIS) was present compared with that in the patients with a low (<10%) intraductal component (5-years DFS rate of 98% versus 86 % $P = 0.001$). Based on these observations, we could recommend that tumors with larger proportions of DCIS might be less naturally aggressive. Cedolini et al. found that invasive cancers with high DCIS component were associated with longer DFS and lower local recurrence rates. However, several studies have found that the presence of DCIS was not an independent prognostic factor in survival outcomes, including locoregional, distant recurrence, and disease-specific death.[31] Although our data suggested the hypothesis that IDC + DCIS may be biologically less aggressive, the molecular pathways which support this theory remain unclear.

Since recently the clinicians interested more to decrease the adjuvant therapies for some patients' population, so detection of the aggressiveness degree of each tumor type is of a great importance. For instance, the guidelines which were changed by the National Comprehensive Cancer Network (NCCN) to support the deletion of adjuvant RT in elderly patients with favorable disease could be mentioned.[32] Furthermore, such modern studies, such as the IDEA study (Individualized Decisions for Endocrine Therapy Alone) and TAILORx (Trial Assigning Individualized Options for Treatment) have investigated whether adjuvant RT or adjuvant chemotherapy could be omitted when tumors are presented with a favorable gene-expression molecular profile.[33] Despite the insignificant difference in the survival rate, we observed that between IDC and IDC + DCIS, DCIS component could be considered as a factor for a more accurate selection of the patients eligible for treatment.[22]

To the best of our knowledge, the present study is the first survey in our country with the largest sample size, focusing on clinicopathological characteristics and clinical outcomes of IDC/DCIS and IDC. Nevertheless, the limitation of this survey is attributed to the retrospective nature of this study; accordingly, treatment decisions were affected by physician recommendations rather than randomization, but since two groups were compared only based on the presence or absence of a DCIS component, selection bias might not be proposed.

Conclusion

We observed that breast cancer survival is improved when DCIS accompanies IDC, and IDC/DCIS patients had more favorable clinicopathological features. These findings suggested that the presence of DCIS with IDC may be a marker of lower aggressiveness and could be considered as a prognostic factor in future treatment algorithms. However, further genomic investigation is essential for illustrating the biological behavior of DCIS accompanying IDC.

Funding

This work was funded by Shiraz Breast Cancer Registry, Breast Diseases Research Center.

Conflict of Interest

None declared.

References

1. Kim SY, Jung SH, Kim MS, Baek IP, Lee SH, Kim TM, et al. Genomic differences between pure ductal carcinoma in situ and synchronous ductal carcinoma in situ with invasive breast cancer. *Oncotarget*. 2015;6(10):7597-607. doi:10.18632/oncotarget.3162.
2. Sgroi DC. Preinvasive breast cancer. *Annu Rev Pathol*. 2010;5:193-221. doi:10.1146/annurev.pathol.4.110807.092306.
3. Lopez Gordo S, Blanch Falp J, Lopez-Gordo E, Just Roig E, Encinas Mendez J, Seco Calvo J. Influence of ductal carcinoma in situ on the outcome of invasive breast cancer. A prospective cohort study. *Int J Surg*. 2019;63:98-106. doi:10.1016/j.ijsu.2019.01.016.
4. Goh CW, Wu J, Ding S, Lin C, Chen X, Huang O, et al. Invasive ductal carcinoma with coexisting ductal carcinoma in situ (IDC/DCIS) versus pure invasive ductal carcinoma (IDC): a comparison of clinico-pathological characteristics, molecular subtypes, and clinical outcomes. *J Cancer Res Clin Oncol*. 2019;145(7):1877-86. doi: 10.1007/s00432-019-02930-2.
5. Groen EJ, Elshof LE, Visser LL, Rutgers EJT, Winter-Warnars HAO, Lips EH, et al. Finding the balance between over- and under-treatment of ductal carcinoma in situ (DCIS). *Breast*. 2017;31:274-83. doi: 10.1016/j.breast.2016.09.001.
6. Collins LC, Tamimi RM, Baer HJ, Connolly JL, Colditz GA, Schnitt SJ. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. *Cancer*. 2005;103(9):1778-84. doi: 10.1002/cncr.20979.
7. Leong AS, Sormunen RT, Vinyuvat S, Hamdani RW, Suthipintawong C. Biologic markers in ductal carcinoma in situ and concurrent infiltrating carcinoma. A comparison of eight contemporary grading systems. *Am J Clin Pathol*. 2001;115(5):709-18. doi: 10.1309/wbu9-22qn-c3na-2q12.
8. Wärnberg F, Nordgren H, Bergkvist L, Holmberg L. Tumour markers in breast carcinoma correlate with grade rather than with invasiveness. *Br J Cancer*. 2001;85(6):869-74. doi: 10.1054/bjoc.2001.1995.
9. Steinman S, Wang J, Bourne P, Yang Q, Tang P. Expression of cytokeratin markers, ER-alpha, PR, HER-2/neu, and EGFR in pure ductal carcinoma in situ (DCIS) and DCIS with co-existing invasive ductal carcinoma (IDC) of the breast. *Ann Clin Lab Sci*. 2007;37(2):127-34.
10. Schorr MC, Pedrini JL, Savaris RF, Zettler CG. Are the pure in situ breast ductal carcinomas and those associated with invasive carcinoma the same? *Appl Immunohistochem Mol Morphol*. 2010;18(1):51-4. doi: 10.1097/PAI.0b013e3181acaded.
11. Iakovlev VV, Arneson NC, Wong V, Wang C, Leung S, Iakovleva G, et al. Genomic differences between pure ductal carcinoma in situ of the breast and that associated with invasive disease: a calibrated aCGH study. *Clin Cancer Res*. 2008;14(14):4446-54. doi: 10.1158/1078-0432.CCR-07-4960.
12. Castro NP, Osório CA, Torres C, Bastos EP, Mourão-Neto M, Soares FA, et al. Evidence that molecular changes in cells occur before morphological alterations during the progression of breast ductal carcinoma. *Breast Cancer Res*. 2008;10(5):R87. doi: 10.1186/bcr2157.
13. Aubele M, Mattis A, Zitzelsberger H, Walch A, Kremer M, Welzl G, et al. Extensive ductal carcinoma In situ with small foci of invasive ductal carcinoma: evidence of genetic resemblance by CGH. *Int J Cancer*. 2000;85(1):82-6. doi: 10.1002/(sici)1097-0215(20000101)85:1<82::aid-ijc15>3.0.co;2-s.
14. Wong H, Lau S, Yau T, Cheung P, Epstein RJ. Presence of an in situ component is associated with reduced biological aggressiveness of size-matched invasive breast cancer. *Br J Cancer*. 2010;102(9):1391-6. doi: 10.1038/sj.bjc.6605655.
15. Jo BH, Chun YK. Heterogeneity of invasive ductal carcinoma: proposal for a hypothetical classification. *J Korean Med Sci*. 2006;21(3):460-8. doi: 10.3346/jkms.2006.21.3.460.
16. Mylonas I, Makovitzky J, Jeschke U, Briese V, Friese K, Gerber B. Expression of Her2/neu, steroid receptors (ER and PR), Ki67 and p53 in invasive mammary ductal carcinoma associated with ductal carcinoma In Situ (DCIS) Versus invasive breast cancer alone. *Anticancer Res*. 2005;25(3A):1719-23.
17. Papantoniou V, Sotiropoulou E, Valsamaki P, Tsaroucha A, Sotiropoulou M, Ptohis N, et al. Breast density, scintimammographic (99m)Tc(V)DMSA uptake, and calcitonin gene related peptide (CGRP) expression in mixed invasive ductal associated with extensive in situ ductal carcinoma (IDC + DCIS) and pure invasive ductal carcinoma (IDC): correlation with estrogen receptor (ER) status, proliferation index Ki-67, and histological grade. *Breast Cancer*. 2011;18(4):286-91. doi: 10.1007/s12282-009-0192-y.
18. Carabias-Meseguer P, Zapardiel I, Cusidó-Gimferrer M, Godoy-Tundidor S, Tresserra-Casas F, Rodriguez-García I, et al. Influence of the in situ component in 389 infiltrating ductal breast carcinomas. *Breast Cancer*. 2013;20(3):213-7. doi: 10.1007/s12282-011-0330-1.
19. Wu SG, Zhang WW, Sun JY, He ZY. Prognostic value of ductal carcinoma in situ component in invasive ductal carcinoma of the breast: a Surveillance, Epidemiology, and End Results database analysis. *Cancer Manag Res*. 2018;10:527-34. doi: 10.2147/CMAR.S154656.
20. Talei A, Tahmasebi S, Akrami M, Zangouri V, Rezaianzadeh A, Arasteh P, et al. The Shiraz Breast Cancer Registry (SBCR): study design and primary reports. *Per Med*. 2018;15(6):471-9. doi: 10.2217/pme-2018-0047.
21. Wolff AC, Hammond ME, Hicks DG, Dowsett M,

McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997-4013. doi: 10.1200/JCO.2013.50.9984.

22. Kole AJ, Park HS, Johnson SB, Kelly JR, Moran MS, Patel AA. Overall survival is improved when DCIS accompanies invasive breast cancer. *Sci Rep*. 2019;9(1):9934. doi: 10.1038/s41598-019-46309-2.
23. Chagpar AB, McMasters KM, Sahoo S, Edwards MJ. Does ductal carcinoma in situ accompanying invasive carcinoma affect prognosis? *Surgery.* 2009;146(4):561-7; discussion 567-8. doi: 10.1016/j.surg.2009.06.039.
24. Lee JS, Oh M, Ko S, Park MH, Oh SJ, Song JY, et al. IHC-breast cancer subtypes of invasive ductal carcinoma with predominant intraductal component as an insignificant prognostic factor: A register-based study from Korea. *Cancer Treatment Communications.* 2016;7:52-7. doi: 10.1016/j.ctrc.2016.03.008.
25. Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early local recurrence in Stage I and II breast cancer treated by primary radiation therapy. *Cancer.* 1984;53(5):1049-57. doi: 10.1002/1097-0142(19840301)53:5<1049::aid-cncr2820530506>3.0.co;2-o.
26. Harris JR, Connolly JL, Schnitt SJ, Cady B, Love S, Osteen RT, et al. The use of pathologic features in selecting the extent of surgical resection necessary for breast cancer patients treated by primary radiation therapy. *Ann Surg.* 1985;201(2):164-9. doi: 10.1097/00000658-198502000-00005.
27. Osteen RT, Connolly JL, Recht A, Silver B, Schnitt SJ, Harris JR. Identification of patients at high risk for local recurrence after conservative surgery and radiation therapy for stage I or II breast cancer. *Arch Surg.* 1987;122(11):1248-52. doi: 10.1001/archsurg.1987.01400230034005.
28. Gage I, Schnitt SJ, Nixon AJ, Silver B, Recht A, Troyan SL, et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer.* 1996;78(9):1921-8. doi: 10.1002/(sici)1097-0142(19961101)78:9<1921::aid-cncr12>3.0.co;2-#.
29. Schnitt SJ, Abner A, Gelman R, Connolly JL, Recht A, Duda RB, et al. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer.* 1994;74(6):1746-51. doi: 10.1002/1097-0142(19940915)74:6<1746::aid-cncr2820740617>3.0.co;2-y.
30. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Int J Radiat Oncol Biol Phys.* 2014;88(3):553-64. doi: 10.1016/j.ijrobp.2013.11.012.
31. Cedolini C, Bertozzi S, Londero AP, Seriau L, Andretta M, Agakiza D, et al. Impact of the presence and quantity of ductal carcinoma in situ component on the outcome of invasive breast cancer. *Int J Clin Exp Pathol.* 2015;8(10):13304-13.
32. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31(19):2382-7. doi: 10.1200/JCO.2012.45.2615.
33. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379(2):111-21. doi: 10.1056/NEJMoa1804710.