Prognostic significance of ductal carcinoma *in situ* coexisting with invasive ductal carcinoma: Biological behavior, immune response and survival outcomes

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Abstract. Biological differences exist between invasive ductal carcinoma (IDC) and IDC + ductal carcinoma *in situ* (DCIS) tumors including variations in tumor grade, hormone receptor status, human epidermal growth factor receptor 2 (HER2) expression, proliferative activity and molecular subtype. The present study evaluated the impact of the coexistence of IDC + DCIS on tumor microenvironment, tumor-infiltrating lymphocytes (TILs), clinical and pathological features, prognosis and survival. A total of 165 patients with IDC and 404 with IDC + DCIS were enrolled and treated in the outpatient clinic, Hacettepe University Department of Medical Oncology (Ankara, Turkey) between January 2014 and July 2021. Compared with IDC, patients with IDC + DCIS were more likely to be hormone receptor-positive and had a lower rate of mastectomy and Ki-67 index (both P<0.05). The co-existence of DCIS was associated with significantly improved overall survival (OS) and disease-free survival (DFS) (both P<0.05). Furthermore, patients with IDC had 2.14-fold higher odds of death and 2.44-fold higher odds of recurrence/distant metastasis/death than patients with IDC + DCIS. The present study supports the behavioral differences of IDC and IDC + DCIS and suggests these two groups of tumors may also behave differently in terms of antitumor immune response. As the DCIS component is positively associated with favorable prognostic features, the presence of the DCIS is associated with improved DFS and OS. DCIS accompaniment may have prognostic value for patients with breast cancer.

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Introduction

Breast cancer is the most prevalent cancer among female patients and also the second leading cause of cancer-associated deaths (1,2). Invasive ductal carcinoma (IDC) and is the most common type of invasive breast cancer, accounting for 70-80% of all cases (3). Ductal carcinoma *in situ* (DCIS) is a precursor to invasive breast cancer and is often found in conjunction with IDC (4,5). Studies have shown that IDCs with *in situ* components have lower histological grade and tumor size, lower Ki-67 value and less frequent local recurrence, while having a higher incidence of estrogen receptor (ER) positivity (6-8). Genomic studies have shown that IDC and DCIS accompanying IDC have a similar gene expression profile (9,10). Few studies demonstrated that IDCs with *in situ* components have better prognostic features compared with IDC (11). However, whether co-existing DCIS in IDC leads to better survival outcomes compared with IDC remains controversial. Although the positive effects of the DCIS component on prognosis have been demonstrated, this has not yet been indicated in official guidelines to plan treatment and follow-up decisions for breast cancer.

Tumor-infiltrating lymphocytes (TILs) are mononuclear inflammatory cells with both proinflammatory and immunosuppressive effects found within and outside the tumor. Studies on solid tumors suggest an association between immune system cells and clinical response (12,13). Presence of TILs in breast cancer is significantly associated with prolonged survival in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer (TNBC) (14,15). Despite these data, the use of TILs as a biomarker in clinical practice is limited and requires prospective studies.

Studies investigating the clinical, histopathological, and prognostic significance of the DCIS component accompanying IDC, conducted with a large number of patients, have been based on the previous staging system American Joint Committee on Cancer (AJCC) 7th edition (6,7).

There is a notable difference in staging and prognosis between AJCC 7th and 8th editions. The AJCC 8th edition includes two complementary staging systems for breast

cancer: Anatomical staging, based on the TNM classification, and prognostic staging, which integrates tumor biology; including grade, hormone receptor status, and HER2 expression (16). A study by Shao *et al* (17) of 184,221 primary breast cancer cases from the Surveillance, Epidemiology, and End Results database, demonstrated that the prognostic accuracy of the 8th AJCC staging system, which incorporates tumor grade, Estrogen receptor (ER), Progesteron receptor (PR) and HER2 status as biological staging factors, is superior to the 7th staging system (17).

Compared with AJCC 7, a substantial proportion of patients (53.2%) are reassigned to a different stage under AJCC 8 (17). In AJCC 7, survival rates among patients within the same stage are notably heterogeneous. Therefore, the prognostic significance of coexisting DCIS in IDC cases may not have been adequately assessed. The present study aimed to investigate the effect of the DCIS component with current staging system and data on the tumor microenvironment when present with IDC, the presence of TILs and their impact on the clinical and pathological features of the tumor, disease prognosis and patient survival.

Patients and methods

Patients. The present retrospective study was conducted on 569 patients aged between 18 and 85 years diagnosed with IDC who presented to the outpatient clinic at Hacettepe University Oncology Hospital (Ankara, Turkey) between January 2014 and July 2021. Data were collected from electronic and manual medical records retrospectively between March and September 2022. Patients with poor treatment compliance were excluded from the study. All patients had pre-treatment core biopsy, tru-cut biopsy or material obtained by surgical excision of tumorous breast tissue histopathologically examined. All specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin and stained with hematoxylin and eosin for routine evaluation. Histological grading was performed using the Nottingham modification of the Bloom-Richardson system. Immunohistochemistry was conducted for ER, PR, HER2, and Ki-67. ER and PR positivity was defined as ≥1% nuclear staining. HER2 evaluation followed ASCO/CAP guidelines, with 2+ cases confirmed by FISH. For TIL assessment, one representative formalin-fixed paraffin-embedded block containing adequate tumor stroma was selected for each case. Stromal TILs were re-evaluated independently by two pathologists and reported as percentages according to international guidelines. Based on TIL density, patients were categorized into three groups: Low (0-10%), intermediate (11-59%), and high (≥60%). In addition to the total cohort, a matched cohort (n=328) was created by pairing patients in a 1:1 ratio from the total group of included patients. Matching was based on age, stage according to AJCC 8th edition TNM staging, grade of invasive component and hormone receptor/HER2 positivity status.

The study analyzed female patients with breast cancer diagnosed with AJCC 8th edition stage I-III IDC. Age at diagnosis, menopausal status, date of first report, date of diagnosis, comorbidities such as hypertension, diabetes mellitus, Chronic obstructive pulmonary disease and coronary artery disease, treatment side effects, pathological diagnoses, molecular subtypes, Ki-67 value, proportion of stromal TILs, tumor size, number of metastatic lymph nodes, distant metastasis, type of surgery performed, date, site and pathology of recurrence, date of death, last follow-up and oncological treatment information were recorded. The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee (01.03.2022, approval no. 2022/04-15, registration no. KA-22219).

Statistical analysis. SPSS version 25.0 (IBM Corp.) was used for statistical analysis. Descriptive statistics are presented as numbers, percentages, mean ± standard deviation, median, minimum, and maximum. The Shapiro-Wilk test was used to assess the normal distribution of continuous variables. The χ^2 test was used to compare categorical variables between groups. Parametric and non-parametric tests were used based on assumptions of normality. Survival analysis was performed using the Kaplan-Meier test to determine overall and disease-free survival. The present study used univariate and multivariate Cox proportional hazards models to examine the relationship between clinicopathological factors and both overall and disease-free survival. Logistic regression analysis was applied to identify independent predictors of pathological complete response. The results were reported with 95% confidence intervals to show the strength and precision of the associations. . $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of study groups. A total of 569 patients were included, of whom 165 had IDC and 404 had IDC + DCIS. For the matched cohort a total of 328 (164 IDC, 164 IDC + DCIS) patients were recruited. IDC + DCIS group showed a significantly higher rate of ER and PR positivity (both $P<0.05$; Table I). Patients in the IDC + DCIS group were treated with hormone therapy significantly more often compared with the IDC group ($P<0.05$). The median Ki-67 for the entire cohort was 25% (range, 1-95%). In the IDC group, the median Ki-67 was 40% (range, 5-95%) and in the IDC + DCIS group, it was 25% (range, 1-90%). Compared with the IDC + DCIS group, the IDC group had a significantly higher Ki-67 percentage ($P<0.05$). All patients underwent surgery; 199 patients (35%) had breast conserving surgery (BCS), while 370 patients (65%) underwent a mastectomy. Patients in the IDC + DCIS group were significantly likely to undergo mastectomy than those in the IDC group ($P<0.05$). In the entire cohort, 415 patients (72.9%) received radiotherapy. Radiotherapy administration was significantly more frequent in the IDC + DCIS group, compared with IDC alone group ($P<0.05$).

There were no statistically significant differences regarding mean age at diagnosis, menopausal status, T and N stage, TNM classification, HER2 status, histological grade of the invasive component, comorbidities and presence of treatment side effects ($P>0.05$).

Survival analysis. The median follow-up for patients was 54 months (range, 9-100). The 5-year overall survival (OS) rate was 91.4 for the entire cohort, 84.3 for the IDC group and 93.1% for patients in the IDC + DCIS group. The 5-year

Table I. Clinical and pathological features in patients with IDC and IDC + DCIS.

Variable	IDC (n=165)	IDC + DCIS (n=404)	Matched (n=328)	Total (n=569)	P-value
Histological IDC grade (%)					
1	4 (2.4)	18 (4.5)	8 (2.4)	22 (3.9)	>0.05
2	43 (26.1)	124 (30.7)	86 (26.2)	167 (29.3)	
3	118 (71.5)	262 (64.9)	234 (71.3)	380 (66.8)	
ER status (%)					
Positive	91 (55.2)	313 (77.5)	184 (56.1)	404 (71)	<0.05
Negative	74 (44.8)	91 (22.5)	144 (48.8)	165 (29)	
PR status (%)					
Positive	81 (49.1)	283 (70)	168 (51.2)	364 (64)	<0.05
Negative	84 (50.9)	121 (30)	160 (48.8)	205 (36)	
HER2 status (%)					
Positive	55 (33.3)	123 (30.4)	110 (33.5)	178 (31.3)	>0.05
Negative	110 (66.7)	281 (69.6)	218 (66.5)	391 (68.7)	
Median Ki-67. % (range)	25 (1-95)	40 (5-95)	30 (1-95)	25 (1-90)	<0.05
Stromal TILs (%)					
Low (0-10%)	88 (53.3)	148 (36.6)		236 (58.1)	>0.05
Intermediate (11-59%)	63 (38.2)	83 (33.7)		146 (36)	
High (≥60%)	9 (5.5)	15 (3.7)		24 (5.9)	
Unknown	5 (3)	158 (39.1)		163 (28.6)	
Surgery (%)					
Breast-conserving	68 (41.2)	131 (32.4)		199 (35)	<0.05
Mastectomy	97 (58.8)	273 (67.6)		370 (65)	
Hormone therapy (%)					
Yes	94 (57)	313 (77.5)		407 (71.5)	<0.05
No	71 (43)	91 (22.5)		162 (28.5)	
Chemotherapy (%)					
No	26 (15.8)	85 (21)		111 (19.5)	<0.05
Neoadjuvant	41 (24.8)	58 (14.4)		99 (17.4)	
Adjuvant	95 (57.6)	253 (62.6)		348 (61.2)	
Unknown	3 (1.8)	8 (2)		11 (1.9)	
Radiotherapy (%)					
Yes	130 (78.8)	285 (70.5)		415 (72.9)	<0.05
No	35 (21.2)	119 (29.5)		154 (27.1)	
Diabetes (%)					
Yes	15 (9.1)	34 (8.4)	36 (11.0)	49 (8.6)	>0.05
No	150 (90.9)	370 (91.6)	292 (89.0)	520 (91.4)	
HT (%)					
Yes	19 (11.5)	68 (16.8)	53 (16.2)	87 (15.3)	>0.05
No	146 (88.5)	336 (83.2)	275 (83.8)	482 (84.7)	
COPD (%)					
Yes	5 (3.0)	6 (1.5)	9 (2.7)	11 (1.9)	>0.05
No	160 (97.0)	398 (98.5)	307 (97.3)	558 (98.1)	
CAD (%)					
Yes	5 (3.0)	5 (1.2)	8 (2.4)	10 (1.8)	>0.05
No	160 (97.0)	399 (98.8)	320 (97.6)	559 (98.2)	
Side effects (%)					
Yes	15 (9.1)	21 (5.2)	30 (9.1)	36 (6.3)	P>0.05
No	150 (90.9)	383 (94.8)	298 (90.9)	533 (93.7)	

ER, estrogen receptor, PR, progesterone receptor; HER2, human epidermal growth factor 2; IDC, ınvasive ductal carcinoma; DCIS, ductal carcinoma *ın situ* component; TIL, tumor-infiltrating lymphocyte; HT, hypertension; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease.

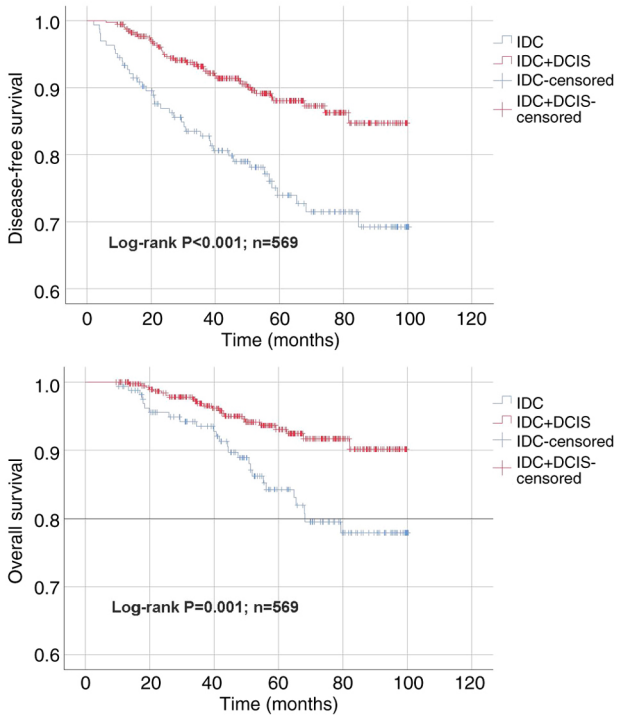

Figure 1. Kaplan-Meier curve for disease-free and overall survival analysis for the entire cohort. IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*.

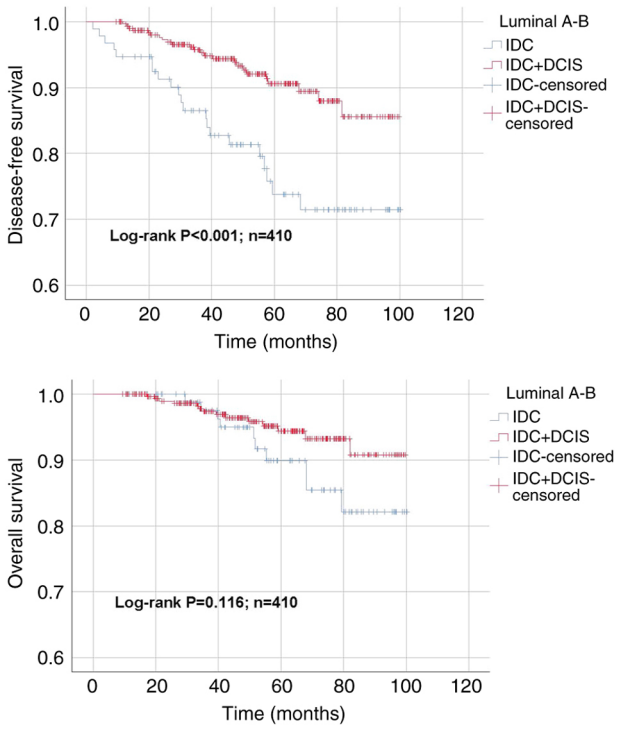

Figure 2. Kaplan-Meier curve for disease-free and overall survival analysis on luminal type breast cancer for the entire cohort. IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*.

disease-free survival (DFS) rate for the entire cohort was 83.7, compared with 73.9 for patients in the IDC group and 88.1% for patients in the IDC + DCIS group. Mean OS and DFS time were 88.3±2.1 and 80.1±2.7 in the IDC and 94.7±1 and 90.9±1.3 months in the IDC + DCIS group. OS and DFS were significantly longer in the IDC + DCIS group compared with the IDC group (both P<0.05; Fig. 1).

In the matched cohort, 5-year DFS rates for the IDC and IDC + DCIS groups were 75.8 and 90.1%, respectively (80.6±2.7 vs. 90.4±2.2 months; Fig. S1). OS rates for the IDC and IDC + DCIS groups were 84.8 and 90.7%, respectively (88.8±2.1 vs. 95.7±1.5 months). Both OS and DFS were significantly longer in the IDC + DCIS vs. the IDC group (both P<0.05).

According to the survival analyses conducted in the entire cohort for moleculer subtypes, DFS time of the IDC + DCIS group (92.6±1.3 months) was significantly longer than that of the IDC group (82.1±3.4 months; P<0.05; Fig. 2) in patients with luminal cancer. However, no significant difference was found regarding OS (IDC, 92.5±2.2; IDC + DCIS, 95.3±1 months; P>0.05). For the HER-2 positive subgroup, mean DFS time for IDC and IDC + DCIS groups were 79.0±6.0 and 86.1±4.6 months, respectively (P>0.05; Fig. 3). The OS time for IDC and IDC + DCIS groups were 85.3±4.7 and 92.1±3.4 months in HER-2 positive subgroup, respectively (P>0.05). In TNBC subgroup, DFS time for the IDC and IDC + DCIS groups was 76.2±6.4 and 81.6±5.3 months, respectively (P>0.05; Fig. 4). The OS time for IDC and IDC + DCIS groups was 79.4±5.9 and 89.4±4.2 months in TNBC subgroup, respectively (P>0.05). No statistically significant differences were found regarding DFS and OS between IDC and IDC + DCIS groups in HER2-positive and TNBC cases in the entire cohort (P>0.05).

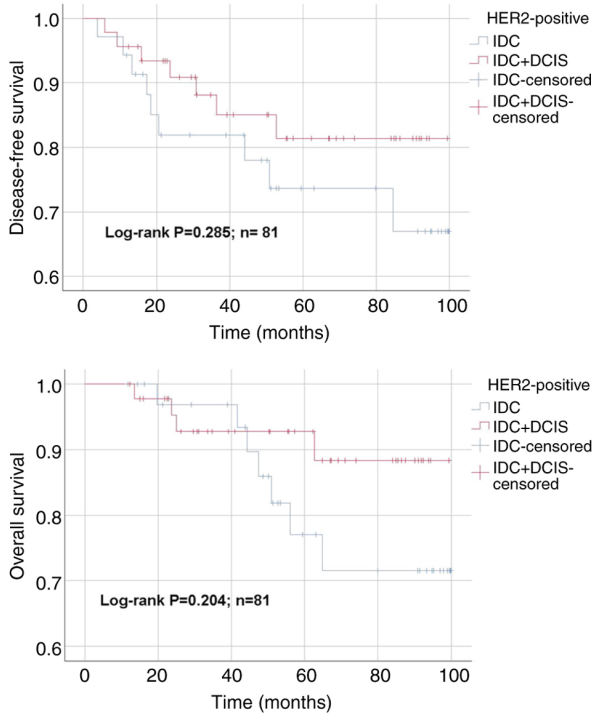

Figure 3. Kaplan-Meier curve for disease free and overall survival analysis based on HER2-positive breast cancer for the entire cohort. IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*; HER2, human epidermal growth factor receptor 2.

In the matched cohort, DFS time in the luminal type group for IDC and IDC + DCIS subgroups was 82.1±3.4 and 89.3±3.1 months, respectively (P<0.05). No significant difference

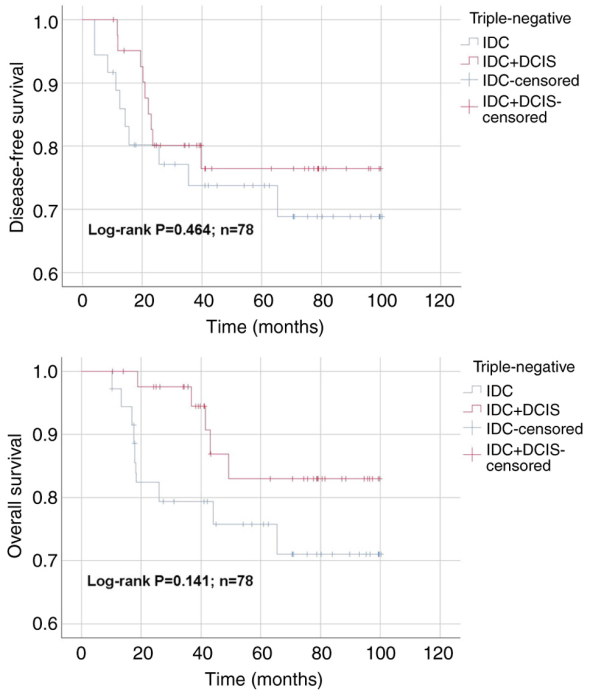

Figure 4. Kaplan-Meier curve for disease-free and overall survival analysis based on triple-negative breast cancer for the entire cohort. IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*.

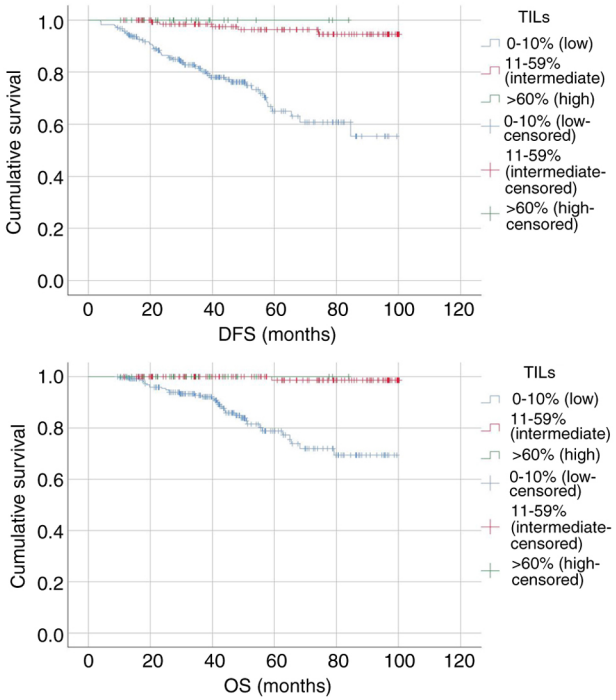

Figure 5. DFS and OS analysis based on stromal tumor infiltrating lymphocytes distribution for the entire cohort. TIL, tumor infiltrating lymphocyte; DFS, disease-free survival; OS, overall survival.

was found regarding OS between IDC and IDC + DCIS groups (92.5±2.2 and 94.3±1.8 months, respectively; P>0.05; Fig. S2). For the HER-2 positive subgroup, mean DFS time for IDC and IDC + DCIS groups was 79.1±6 and 86.4±5.3 months, respectively (P>0.05). The OS time for IDC and IDC + DCIS groups was 85.2±4.8 and 94.3±3.5 months in HER-2 positive subgroup, respectively (P>0.05; Fig. S3). For the TNBC subgroup, DFS time for the IDC and IDC + DCIS groups was 78.0±6.4 and 85.3±5.6 months, respectively (P>0.05). OS time for IDC and IDC + DCIS groups was 81.3±5.9 and 92.4±4.0 months in TNBC subgroup, respectively (P>0.05). (Fig. S4) No statistically significant differences were found regarding DFS and OS between IDC and IDC + DCIS groups in HER2-positive and TNBC cases in the matched cohort .

Patients were divided into three groups based on the percentage of stromal TILs: Low (0-10%), intermediate (11-59%) and high (≥60%). OS at 60 months for the low, intermediate and high stromal TIL subgroups was 80.3, 99.3 and 100.0% respectively (P<0.05; Fig. 5). DFS at 60 months for the low, intermediate and high stromal TIL subgroups was 76.6, 96.3 and 100.0%, respectively (P<0.05).

Multivariate analysis. Factors affecting DFS and OS, including age at diagnosis, DCIS component status, ER status (positive/negative), tumor stage (1-3), tumor size (cm), lymph node involvement stage (N), type of surgery (breast-conserving/mastectomy), chemotherapy status (none/neoadjuvant/adjuvant), patient comorbidities and treatment side effects, were investigated. Presence of DCIS component was positively associated with both PFS and OS (OS: Hazard ratio (HR), 2.144; 95% CI, 1.178-3.901; P=0.013; PFS: HR, 2.446; 95% CI, 1.550-3.860; P<0.001). The risk of death was 2.14 times higher in patients with IDC compared with those with IDC + DCIS in the entire cohort. Similarly, the risk of disease progression, including local recurrence, distant metastasis or death, was 2.44 times higher in the IDC group. OS (HR, 1.196; 95% CI, 1.048-1.363; P=0.008) and PFS were negatively associated with tumor size (HR, 1,137; 95% CI,1.022-1.264; P=0.018) and lymph node involvement (OS: HR, 4.819, 95% CI, 2.095-11.085, P=0.002; DFS: HR, 5.0567, 95% CI, 2.620-9.757 , P<0.001) in the entire cohort. ER positivity had a significant effect only on OS in the entire cohort (HR, 2.081; 95% CI, 1.151-3.765; P=0.015) (Table II).

Stromal TILs (OS: HR, 0.873, 95% CI, 0.815-0.935; P<0.001; DFS: HR, 0.899, 95% CI, 0.861-0.939, P<0,001), tumor diameter (OS: HR, 1.219, 95% CI, 1.037-1.434, P=0.017; DFS: HR, 1.147, 95% CI,1.010-1.302, P=0.035) and stage of lymph node involvement (HR: 5.314, CI, 2.364-11.949, P=0.023 and <0.001, respectively) were had a significant effect on OS and DFS in the matched cohort (Table III).

Discussion

Previous studies have shown that IDC accompanied by the DCIS component has a less aggressive course than IDC alone (7,8,11). In the present study, IDC + DCIS tumors were more positive for hormone receptors (ER, PR) and had lower Ki-67 percentages. Tumors containing a DCIS component in addition to IDC were associated with longer OS and DFS, suggesting IDC + DCIS tumors have less aggressive characteristics compared with IDC tumors.

Compared with IDC group, IDC + DCIS group had significantly higher rates of hormone-positive status and breast-conserving surgery and lower Ki-67 percentage. In

Table II. Multivariate Cox regression analysis for OS and DFS of the entire cohort.

	Univariate						Multivariate					
	OS			DFS			OS			DFS		
Variable	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
IDC vs. IDC + DCIS	2.435	1.388-4.273	0.002	2.414	1.556-3.744	<0.001	2.14	1.178-3.901	0.013	2.446	1.550-3.860	<0.001
ER-negative vs. -positive	2.627	1.497-4.612	0.001	2.149	1.383-3.340	0.001	2.081	1.151-3.765	0.015	-	-	-
Tumor diameter	1.263	1.140-1.400	<0.001	1.232	1.135-1.338	<0.001	1.196	1.048-1.363	0.008	1.137	1.022-1.264	0.018
N stage									0.002			<0.001
N1 vs. N0	0.161	0.087-0.298	<0.001	0.161	0.087-0.298	<0.001	1.531	0.673-3.486	0.31	1.36	0.725-2.552	0.338
N2 vs. N0	0.246	0.129-0.468	<0.001	0.246	0.129-0.468	<0.001	1.713	0.708-4.143	0.233	1.839	0.961-3.520	0.066
N3 vs. N0	0.422	0.223-0.797	0.008	0.422	0.223-0.797	0.008	4.819	2.095-11.085	<0.001	5.056	2.620-9.757	<0.001

OS, overall survival; DFS, disease-free survival; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ER, estrogen receptor; N, node.

Table III. Multivariate Cox regression analysis for OS and DFS of matched cohort.

	Univariate						Multivariate					
	OS			DFS			OS			DFS		
Variable	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Stromal TILs, %	0.882	0.827-0.940	<0.001	0.908	0.872-0.945	<0.001	0.873	0.815-0.935	<0.001	0.899	0.861-0.939	<0.001
Tumor diameter	1.234	1.078-1.413	0.002	1.236	1.119-1.366	<0.001	1.219	1.037-1.434	0.017	1.147	1.010-1.302	0.035
N stage									0.023			<0.001
N1 vs. N0	0.237	0.096-0.584	0.02	0.161	0.087-0.298	<0.001	1.016	0.347-2.978	0.977	1.339	0.611-2.934	0.466
N2 vs. N0	0.239	0.085-0.673	0.07	0.246	0.129-0.468	<0.001	1.119	0.383-3.265	0.383	1.457	0.665-3.190	0.347
N3 vs. N0	0.380	0.141-1.021	0.055	0.422	0.223-0.797	0.008	3.747	3.747-1.434	0.007	5.314	2.364-11.946	<0.001

OS, overall survival; DFS, disease-free survival; TIL, tumor-infiltrating lympocyte; N, node.

a study of 1,355 patients by Wong *et al* (7), patients with IDC + DCIS matched for IDC and DCIS component size had a higher prevalence of premenopausal diagnosis and HER2 positivity than patients with IDC. The same study found that diameter of the invasive component, ER positivity and the Ki-67 percentage were lower in IDC + DCIS tumors, similar to the present study (7). A study by Chen *et al* (11) of 98,097 patients with IDC and 149,477 with IDC + DCIS showed that patients with IDC + DCIS were diagnosed at a younger age than those with IDC (mean age, 58.7 vs. 60.4 years), with a higher proportion of patients diagnosed before the age of 60 years (53.4 vs. 48.3%). BCS rate was significantly lower in patients with IDC + DCIS compared with patients with pure IDC (60.2 vs. 62.4%) (11). A prospective cohort study by Gordo *et al*, observed that DCIS component is associated to better prognostic factors as being positive for HR, negative for HER2, lower Ki67%, lower grade of invasive carcinoma (18). In another study of 3,001 patients with IDC and IDC + DCIS by Goh *et al* (19), patients with IDC + DCIS were diagnosed at an earlier age than those with IDC and had a lower histological grade of the invasive component and fewer regional lymph node metastases (19). Previous studies (7,11,18), demonstrated the positive contribution of DCIS accompanying IDC to prognosis.

In the present study, no statistically significant difference was found between the two groups regarding age and BCS rates were higher in IDC + DCIS group compared with IDC. This may be due to underutilization of breast cancer screening programs in Turkey, which may delay the detection of IDC until tumors become more advanced. In contrast, the coexistence of DCIS may increase the likelihood of detection at an earlier and more operable stage.

In the present study, tumors containing a DCIS component in addition to IDC were associated with longer OS and DFS. Risk of death was 2.14 times higher in the IDC compared with the IDC + DCIS group in the entire cohort and the risk of disease (local recurrence or distant metastasis or death) was 2.44 times higher. Tumors containing a DCIS component in addition to IDC were associated with longer OS and DFS. When patients were grouped according to receptor status, IDC + DCIS affected DFS in the luminal A-B subtype. Chen *et al* (11) found that patients with IDC + DCIS have significantly higher OS compared with those with pure IDC. According to the multivariate analysis, existence of DCIS component is an independent favorable prognostic factor for OS (HR, 0.858, 95% CI, 0.839-0.8773) (11). A study by Zhou *et al* (20), conducted with 852 patients with stage II-III IDC patients who had neoadjuvant treatment followed by radical surgery showed that in the TNBC population, the DFS (88.6% vs. 75.8%, P=0.032) of patients with IDC + DCIS was significantly better than that of patients with IDC. Multivariate analysis demonstrated that IDC + DCIS (HR: 0.502; 95% CI, 0.284-0.952; P=0.048) was an independent prognostic factor for DFS. These findings were further supported by Liu *et al* (21), who reported that among 358 patients with TNBC, the IDC + DCIS group had significantly better DFS (87.9% vs. 82.6%) compared to pure IDC. Furthermore, multivariate analysis identified the coexistence of DCIS as an independent prognostic factor for DFS (HR: 0.535; 95% CI, 0.304-0.942).

The present findings suggested a significant difference in both OS and DFS between the stromal TIL groups, though further investigation is needed to confirm this. In the matched cohort, there was an association between an increase in the percentage of stromal tumor-infiltrating lymphocytes and a decrease in the risk of death and the risk of local recurrence/distant metastasis/death. In the matched cohort, each 1% increase in the percentage of stromal TILs decreased risk of death by 0.87-fold and the risk of progression by 0.89-fold. Denkert *et al* suggested that an increase of 10% in the percentage of TILs may potentially lead to a significant prolongation of DFS in patients with TNBC and HER2-positive breast cancer (HR, 0.93; 95% CI, 0.87-0.98; P=0.011 and HR, 0.94; 95% CI, 0.89-0.99; P=0.017, respectively). In TNBC, an increased percentage of TILs is associated with longer OS, whereas in luminal disease, a higher percentage of TILs is associated with shorter OS (15). In a systematic review of 14 studies and 4,105 patients by Lam and Verill (22), increased tumor infiltrating B cells were associated with a better disease course in invasive breast cancer in terms of disease-free interval and survival and recurrence-free survival and OS. A similar difference has also been noticed in studies including TNBC and/or HER2-positive cases (23,24). The association between stromal TIL percentage and survival rate is consistent with the present results.

Using the AJCC 8th edition in this study allowed us to stage patients based not only on tumor size and nodal status, but also on biological features such as hormone receptor and HER2 status. This provided a more clinically relevant risk classification. This comprehensive approach makes our findings more reflective of real world breast cancer patients and improves their relevance to clinical practice.

The data regarding grade, stromal TILs and socioeconomic status were incomplete due to the retrospective nature of the study. Also, TILs were not isolated from tumor tissue and specific surface and intracellular markers were not used to identify TIL subtypes (such as $CD4/8^{+}$T and B cells). Analysis of these TIL subpopulations would provide valuable insights into the immune microenvironment and its impact on prognosis. The patient cohort had a 90.8% 5-year OS rate, which may underestimate late recurrence or treatment-related adverse outcomes, it would be beneficial to extend the follow-up period to predict long-term outcomes, particularly in hormone receptor-positive breast cancer patients.

The present study indicated that there might be a difference in the anti-tumoral immune response between the IDC and IDC + DCIS groups, which behave differently biologically. DCIS component was associated with better prognostic and pathological features. The improved PFS and OS rates associated with DCIS may encourage consideration of more conservative surgical and systemic treatment options. These findings may lead to more individualized approaches in patient follow-up and risk stratification, allowing less aggressive monitoring in low-risk patients. Additionally, the present results may facilitate treatment de-escalation decisions by identifying DCIS accompanying IDC group which has a less aggressive behavior and led further investigations into the potential effect of DCIS accompanying IDC on prognosis. Increased levels of stromal TILs may also be associated with a favorable prognosis in invasive breast cancer. Further studies are needed to assess the potential of stromal TILs for the

identification of patients who may benefit from chemotherapy and immunotherapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NKF and NK confirm the authenticity of all the raw data. NKF, IK, GK, AU and MU collected and interpreted the data. NKF, SA and NK analyzed data. NKF, IK, GK, SA and NK wrote the manuscript. SA and NK edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study received approval from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval date, 01.03.2022; approval no. 2022/04-15; registration no. KA-22219). The requirement for informed consent was waived due to the retrospective nature of the study.

Patient consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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