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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Invasive ductal carcinoma with coexisting ductal carcinoma in situ (IDC/DCIS) versus pure invasive ductal carcinoma (IDC): a comparison of clinicopathological characteristics, molecular subtypes, and clinical outcomes

Chih Wan Goh[1] · Jiayi Wu[1] · Shuning Ding[1] · Caijin Lin[1] · Xiaosong Chen[1] · Ou Huang[1] · Weiguo Chen[1] · Yafen Li[1] · Kunwei Shen[1] · Li Zhu[1]

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Abstract

Purpose Ductal carcinoma in situ (DCIS) is widely recognized as the precursor of invasive ductal carcinoma (IDC). We aimed to analyze the clinicopathological characteristics and clinical outcomes of coexisting DCIS component in IDC and its clinical significance according to molecular subtypes.

Methods Data from 3001 patients with IDC (79.4%) and IDC/DCIS (20.6%) who underwent surgery from January 2009 to June 2016 were retrospectively assessed. The clinical outcomes of IDC with coexistent DCIS in different molecular subtypes were evaluated.

Results IDC/DCIS patients were more likely to be younger ($P<0.001$), had low tumor grade ($P=0.001$), had less lymph node involvement ($P=0.038$) and received more mastectomy ($P=0.002$) than IDC patients. In the comparison of molecular subtype prevalence, IDC/DCIS patients were more frequently presented with luminal B/HER2 positive (12.5% vs 11.0%, $P<0.001$) and HER2 positive subtypes (20.9% vs 9.8%, $P<0.001$). The 5-year disease-free survival (DFS, 90.9% vs 87.5%, $P=0.021$) and 5-year overall survival (OS 96.1% vs 94.0%, $P=0.018$) were significantly improved in IDC/DCIS patients compared to IDC patients. In multivariate analysis, the presence of coexisting DCIS ($P=0.048$), tumor size ($P<0.001$), lymph node status ($P<0.001$), lymphovascular invasion ($P=0.007$) and molecular subtypes ($P<0.001$) were independent prognostic factors for DFS. Furthermore, coexistence of DCIS component in IDC significantly improved DFS in HER2 positive (94.8% vs 78.5%, $P=0.003$), but had no association in luminal and triple negative subtypes.

Conclusions IDC with coexisting DCIS was associated with improved prognosis. Patients with IDC/DCIS presented with more HER2 positive expression and might improve DFS in HER2 positive breast cancer.

Keywords Ductal carcinoma in situ · Mammary ductal carcinoma · Breast cancer · Molecular subtypes · Prognosis

Chih Wan Goh and Jiayi Wu contributed equally to this work and should be considered co-first authors.

✉ Li Zhu
zhuli8@yeah.net

Chih Wan Goh
gohchihwan@hotmail.com

Jiayi Wu
pinkscorpio@163.com

Shuning Ding
nannanyard@163.com

Caijin Lin
529323577@qq.com

Xiaosong Chen
chenxiaosong0156@hotmail.com

Ou Huang
ou_huang@126.com

Weiguo Chen
cwg-dr@hotmail.com

Yafen Li
lyf10313@rjh.com.cn

Kunwei Shen
kwshen@medmail.com.cn

[1] Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China

Introduction

Mammary ductal carcinoma, as the most prevalent type of invasive breast carcinoma, is largely divided into invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS). DCIS refers to a malignant growth of breast ductal cells that confine at the inner layer basal membrane while IDC invades the ducts and exists in stroma (Sgroi 2010; Tavassoli 1998). Studies reported that around 20–50% of DCIS might develop into invasive carcinoma if untreated. (Collins et al. 2005; Kuerer et al. 2009; Page et al. 1982; Sanders et al. 2005; Virnig et al. 2009).

The exact drivers, biomarkers and subtypes of DCIS which tend to progress to IDC remain to be elucidated. By investigating the intratumor heterogeneity involves in invasive transition, two main evolutionary models have been proposed: independent lineage and direct lineage. Independent lineage suggests that the DCIS and IDC tumors in the normal breast tissue of the same individual are proliferated separately from two different progenitor cells. Meanwhile, the direct lineage model assumes that DCIS and IDC tumors are proliferated from a single normal cell origin (Casasent et al. 2017; Sgroi 2010). In clinical observation, coexistent DCIS component and adjacent IDC component have a high similarity in receptor expression (Doebar et al. 2016). While in genomic level, recent studies showed that coexisting DCIS with adjacent IDC have remarkably similar gene expression and copy number profile, indicating progression comes from a common origin (Berman et al. 2005; Burkhardt et al. 2010; Cowell et al. 2013; Lesurf et al. 2016). Basic characteristics and neoplastic clone established at the in situ stage are found to be carried through the invasive stage in breast carcinoma and may eventually affect the prognosis of patients (Gupta et al. 1997). Collectively, these findings suggested the direct lineage may be the more common model in the invasion of DCIS, which also has important clinical implications for investigating the biological behavior of coexistent DCIS in IDC.

It is now widely accepted that different breast cancer molecular subtypes exhibit distinct pathological entities and clinical outcomes. Gene expression analysis classified invasive breast cancer into five major molecular subtypes, luminal A, luminal B/HER2 negative, luminal B/HER2 positive, HER2 positive and triple negative, which were correlated with immunohistochemical (IHC) markers of estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki-67 index (Goldhirsch et al. 2013; Parker et al. 2009). There are substantial gene expression differences between intrinsic subtypes. Each subtype is postulated to undergo a distinct pattern of disease progression in microenvironment from DCIS to IDC (Lesurf et al. 2016), thus suggesting that IDC with coexisting DCIS may have different prognostic significance in different molecular subtypes. Other than one study reported coexisting DCIS in breast cancer with IDC improved local recurrence-free survival in luminal patients (Dieterich et al. 2014), relatively little is known regarding the significance of coexisting DCIS in survival outcome according to molecular subtypes.

This analysis, therefore, aims to compare the clinicopathological characteristics and prognosis between IDC and IDC/DCIS and to evaluate the clinical outcomes of IDC and IDC/DCIS in different molecular subtypes.

Methods

Patients who underwent radical surgery at Comprehensive Breast Health Center, Shanghai Ruijin Hospital between January 2009 and June 2016 were retrospectively reviewed. Clinicopathological data of patients were analyzed from a prospectively maintained institutional database. Follow-up information regarding recurrence and survival status were completed up to 31st May 2018.

The inclusion criteria were as follows: patients undergoing breast cancer conserving surgery and mastectomy without neoadjuvant therapy, histological types as pure IDC or IDC/DCIS (IDC of no special type, NST), tumor stage T1a–T4, nodal stage N1–N3 and unilateral breast cancer. Post-mastectomy breast reconstruction in invasive breast cancer patients such as skin-sparing mastectomy or nipple sparing mastectomy was included in the mastectomy cohort.

The exclusion criteria were as follows: patients with neoadjuvant chemotherapy, breast cancer histology other than pure IDC and IDC/DCIS such as lobular, mucinous or papillary type, bilateral breast cancer, diagnosed with stage IV breast cancer, had prior malignancies, incomplete immunohistochemical and adjuvant treatment information, incomplete follow-up information. All cases of pure IDC and IDC/DCIS patients who met all the inclusion and not meet any of the exclusion criteria were collected.

Tumor histopathology and lymph node involvement were analyzed by routine hematoxylin–eosin (H&E) staining. IDC/DCIS in our study is defined as the presence of DCIS component accounted for at least 5% for entire area of IDC, excluding IDC with microinvasion, lobular carcinoma in situ (LCIS) and invasive lobular carcinoma (ILC). AJCC TNM staging system was applied for tumor stage classification (Edge and Compton 2010). The status of ER, PR, HER2 and Ki-67 were determined by IHC staining on 4-μm slices of paraffin embedded specimens. The median Ki-67 value for hormone receptor-positive and HER2 negative subtype of our database was 15.0%, therefore the threshold of 15% Ki-67 was used in distinguishing between luminal A and luminal B/HER2 negative subtypes (Coates et al. 2015).

HER2 expression either with IHC 3 + or FISH amplified (ratio of HER2 to CEP17 of ≥ 2.0 or with a mean HER2 copy number ≥ 6) was considered positive. Evaluation of histological grade was based on Elston and Ellis scoring system (Elston and Ellis 1991), we further divided grade I and grade II as non-high grade and grade III as high grade tumor. All tumor histopathology and IHC data were performed through a standard operating procedure in the Department of Pathology. The surrogate definitions of breast cancer molecular subtypes were identified by immunohistochemical (IHC) analysis, low PR expression was defined as ≤ 20% (Prat et al. 2013).

- Luminal A: ER positive and/or PR high, HER2 negative, and Ki-67 < 15%.
- Luminal B/HER2 negative: ER positive, HER2 negative, and at least one of the following: Ki-67 ≥ 15% and/or PR low/negative.
- Luminal B/HER2 positive: ER positive, HER2 positive, any PR, any Ki-67.
- HER2 positive: HER2 positive, ER, and PR negative.
- Triple negative: ER and PR negative, HER2 negative.

Statistical data analysis was carried out using IBM SPSS Statistics 22.0. We used Pearson's Chi-square test to compare the distribution of clinical and pathological features between groups. The Kaplan–Meier method and log-rank test were used to compare disease-free survival (DFS) and overall survival (OS). DFS was defined as the length of time from surgery to recurrence of DCIS, invasive breast cancer (local, regional or distant), invasive contralateral breast cancer or second primary malignancy, or death without breast cancer recurrence or second primary malignancy. OS was defined as the length of time from surgery to death from any cause (Hudis et al. 2007). Multivariate Cox regression was performed to identify hazard ratio (HR), 95% confidence interval (CI) and clinicopathological factors related to survival outcomes. The final set of variables was defined by backward selection. An analysis with p less than 0.05 was considered to be statistically significant.

Results

From January 2009 through June 2016, 3001 patients were eligible for evaluation in this analysis. 2384 (79.4%) patients had pure IDC and 617 (20.6%) patients had IDC/DCIS.

Patients' clinicopathological features and distribution according to molecular subtype

Table 1 presents an overview of clinicopathologic characteristics between patients with IDC and IDC/DCIS. The median age of our patient population was 54 years (range 23–95). IDC/DCIS patients were younger ($P < 0.001$) and more premenopausal ($P < 0.001$). They were also presented with low tumor grade ($P = 0.001$) and had less lymph node involvement ($P = 0.038$) compared to pure IDC patients. In addition, IDC/DCIS patients were observed to have a higher rate of multifocality ($P < 0.001$), which may also be related with a higher rate of mastectomy among this patient cohort ($P = 0.002$).

Strong correlations were observed between IHC-based molecular subtype and the presence of DCIS component in IDC. Compare with IDC, patients with IDC/DCIS were more often to have HER2 positive expression, with 12.5% vs 11.0% in luminal B/HER2 positive subtype and 20.9% vs 9.8% in HER2 positive subtype. In contrast, there was a lower proportion of triple negative in patients with IDC/DCIS compared to patients with IDC, with 11.8% vs 16.7% in each group (all $P < 0.001$).

Survival outcomes of IDC and IDC/DCIS patients

Table 2 shows the recurrences and survival outcomes between patients with IDC and IDC/DCIS. During the follow-up period, seven patients with local, regional or contralateral breast cancer recurrences developed distant metastasis, while two patients with second primary malignancy developed metastasis. Furthermore, eight patients had recurrences, eight patients had secondary malignancy and 75 patients had metastasis before death.

The Kaplan–Meier curves for 5-year DFS and 5-year OS between patients with IDC and IDC/DCIS are shown in Fig. 1. The median follow-up period was 49 months (range 1–111). Survival outcomes were significantly improved in patients with IDC/DCIS compared to patients with IDC alone. The 5-year DFS was 90.9% in IDC/DCIS patients and 87.5% in IDC patients ($P = 0.021$) and 5-year OS was 96.1% in IDC/DCIS patients and 94.0% in IDC patients ($P = 0.018$).

Subgroup analysis according to molecular subtype

The Kaplan–Meier curves for 5-year DFS in IDC and IDC/DCIS after stratification by molecular subtypes are shown in Fig. 2. Notably, in HER2 positive subtype, the DFS of IDC/DCIS was significantly improved than that of IDC, with 94.8% vs 78.5% ($P = 0.003$). We failed to find a statistically significant difference in DFS between IDC/DCIS and IDC in luminal A (94.7% vs 92.6%, $P = 0.127$), luminal B/HER2 negative (91.2% vs 88.0%, $P = 0.394$), luminal B/HER2 positive (86.5% vs 91.6%, $P = 0.631$) and triple negative subtypes (81.6% vs 81.4%, $P = 0.830$).

Table 1 Clinicopathologic characteristics between patients with IDC and IDC/DCIS

	IDC ($n=2384$) (%)	IDC/DCIS ($n=617$) (%)	P value
Age at diagnosis (year), median	54	54	< 0.001
< 55	1149 (48.2)	368 (59.6)	
≥ 55	1235 (51.8)	249 (40.4)	
Menopausal status			< 0.001
Pre	933 (39.1)	318 (51.5)	
Post	1451 (60.9)	299 (48.5)	
Tumor stage			0.268
T1	1346 (56.5)	370 (60.0)	
T2	990 (41.5)	234 (37.9)	
T3–4	48 (2.0)	13 (2.1)	
Lymph node status			0.038
Negative	1488 (62.4)	413 (66.9)	
Positive	896 (37.6)	204 (33.1)	
Lymphovascular invasion			0.056
No	2251 (94.4)	570 (92.4)	
Yes	133 (5.6)	47 (7.6)	
Histological grade			0.001
G1	100 (4.2)	39 (6.3)	
G2	1165 (48.9)	315 (51.1)	
G3	1078 (45.2)	231 (37.4)	
Unknown	41 (1.7)	32 (5.2)	
Tumor focality			< 0.001
Unifocal	2284 (95.8)	563 (91.2)	
Multifocal	100 (4.2)	54 (8.8)	
Molecular subtype			< 0.001
Luminal A	422 (17.7)	111 (18.0)	
Luminal B/HER2 negative	1069 (44.8)	227 (36.8)	
Luminal B/HER2 positive	262 (11.0)	77 (12.5)	
HER2 positive	233 (9.8)	129 (20.9)	
Triple negative	398 (16.7)	73 (11.8)	
Type of surgery			0.002
Mastectomy	1617 (67.8)	459 (74.4)	
BCS	767 (32.2)	158 (25.6)	
Hormonal therapy			0.005
No	737 (30.9)	227 (36.8)	
Yes	1647 (69.1)	390 (63.2)	
Chemotherapy			0.007
No	581 (24.4)	183 (29.7)	
Yes	1803 (75.6)	434 (70.3)	
Radiotherapy			0.126
No	1185 (49.7)	328 (53.2)	
Yes	1199 (50.3)	289 (46.8)	
Her2-targeted therapy			< 0.001
No	2044 (85.7)	458 (74.2)	
Yes	340 (14.3)	159 (25.8)	

IDC invasive ductal carcinoma, *IDC/DCIS* invasive ductal carcinoma with coexisting ductal carcinoma in situ, *BCS* breast conserving surgery, *HER2* human epidermal growth factor receptor 2

Table 2 Recurrence and survival outcomes between patients with IDC and IDC/DCIS

	IDC (%)	IDC/DCIS (%)	*P* value
Local/regional/contralateral recurrence	77 (3.2)	12 (1.9)	0.093
Metastasis	133 (5.6)	18 (2.9)	0.007
Second primary malignancy	24 (1.0)	4 (0.6)	0.409
Death	139 (5.8)	12 (1.9)	< 0.001

IDC invasive ductal carcinoma, *IDC/DCIS* invasive ductal carcinoma with coexisting ductal carcinoma in situ

Univariate and multivariate analysis

Table 3 shows the results of univariate analysis. In univariate analysis, the presence of DCIS ($P = 0.022$ in DFS, $P = 0.021$ in OS), tumor size ($P < 0.001$), lymph node status ($P < 0.001$), lymphovascular invasion ($P < 0.001$), tumor grade ($P < 0.001$) and molecular subtypes ($P < 0.001$) were factors associated with both DFS and OS.

Table 4 shows the results of the multivariate analysis. In multivariate analysis, the presence of coexisting DCIS ($P = 0.048$), tumor size ($P < 0.001$), lymph node status ($P < 0.001$), lymphovascular invasion ($P = 0.007$), and molecular subtypes ($P < 0.001$) were independent prognostic factors associated with DFS. However, the presence of DCIS component in IDC was no longer an independent risk factor for overall survival ($P = 0.090$). This may due to limited case events and require longer follow-up period. Compared with luminal A subtype, HER2 positive subtype had worse survival in DFS (HR 1.724, CI 95% 1.096–2.713, $P = 0.019$) but no statistically significant differences were seen in OS (HR 1.900, CI 95% 0.910–3.966, $P = 0.087$). Patients with triple negative subtype had the poorest prognosis among all molecular subtypes with statistically significant in both DFS (HR 1.857, CI 95% 1.212–2.845, $P = 0.004$) and OS (HR 2.505, CI 95% 1.264–4.965, $P = 0.009$).

Discussion

Breast cancer is a heterogeneous disease with a high degree of genetic diversity between tumors and the outcomes may be influenced by their biological features (Kornelia 2011; Prat et al. 2012). Currently, the existence of DCIS component in IDC has no implication in determining prognosis and adjuvant treatment strategies.

The prognostic effect of coexisting DCIS component in IDC remains uncertain. Wong et al. reported that IDC with coexistent DCIS patients have a lower biological aggressiveness in lymph node positive luminal breast cancers (Wong et al. 2012). Chagpar et al. reported that IDC with coexisting DCIS has more favorable characteristics, but it is not an independent factor in improving survival outcomes (Chagpar et al. 2009). Meanwhile, Kim et al. found that the coexistent DCIS does not determine the biological behavior of breast cancer, but the grade of DCIS in IDC (Kim et al. 2013). Our data show that both 5-year DFS and 5-year OS were significantly improved in the IDC/DCIS patients than IDC patients (DFS: 90.9% vs 87.5%, $P = 0.021$; OS: 96.1% vs 94.0%, $P = 0.018$). The rate of IDC/DCIS was 20.6% in our overall population. Less lymph node involvement and lower tumor grade were favorable characteristics associated with IDC/DCIS patients. The clinicopathological features of these patients were similar to the findings of other authors as well (Dieterich et al. 2014; Wong et al. 2010). The presence of coexisting DCIS remained to have a strong correlation of improving prognosis in DFS after adjustment of these factors.

There are some possible reasons that may explain the prognostic effects of coexisting DCIS component in IDC. Firstly, in the progression of DCIS to IDC, the direct lineage model has important implications for measuring intratumor heterogeneity. Favorable biological features of DCIS component are proposed to be preserved within a clonal population of tumor cells, providing a less

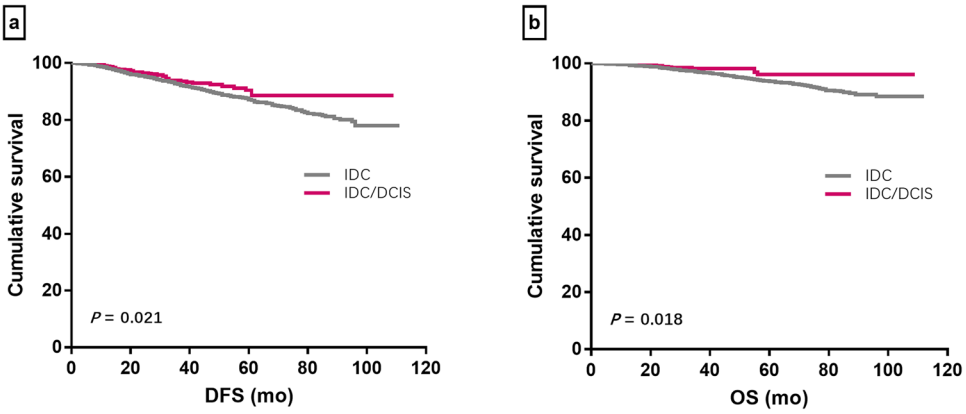

Fig. 1 Kaplan-Meier survival curves for patients with IDC vs IDC/DCIS. **a** Disease-free survival. **b** Overall survival (Graphic program: GraphPad Prism 7)

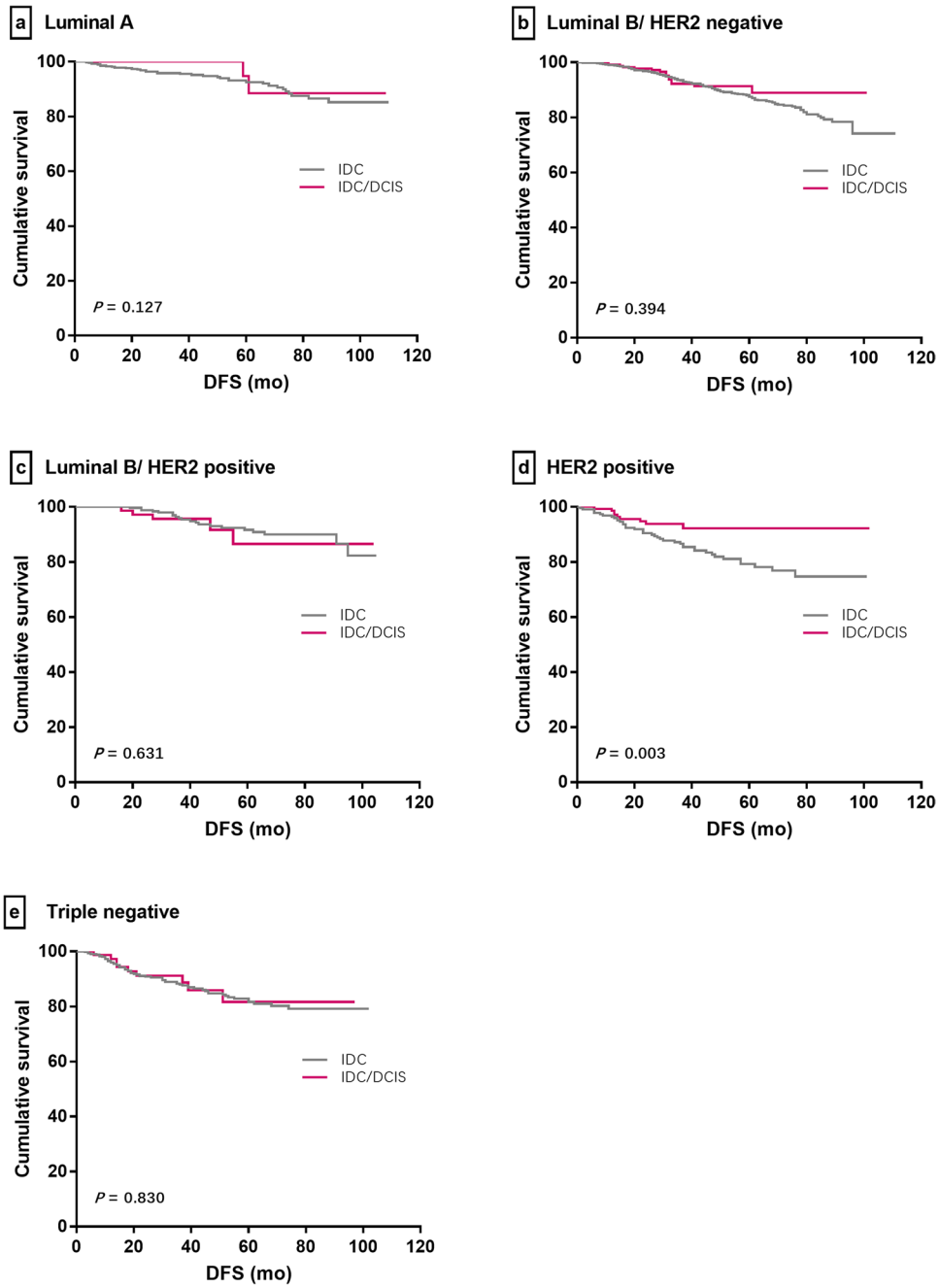

Fig. 2 Kaplan-Meier disease-free survival curves for patients with IDC vs IDC/DCIS stratified according to molecular subtypes **a** luminal A **b** luminal B/HER2 negative **c** luminal B/HER2 positive **d** HER2 positive **e** triple negative (Graphic program: GraphPad Prism 7)

aggressive phenotype to the associated invasive carcinoma (Gupta et al. 1997). Nevertheless, the intermediate DCIS precursor may remain dependent for upstream mitogens replication in the carcinogenesis of IDC/DCIS. Therefore, IDC/DCIS tumors tend to evolve from an incremental accumulation of milder tumor suppressor gene mutations, while pure IDC tumors arise from a more drastic tumor suppressor gene defect (Wong et al. 2010). Furthermore, studies suggested cell-mediated immune changes may be distinct between IDC/DCIS and IDC and have prognostic significance (Black et al. 1996). Higher expression of MMPs, a predictor of worse prognosis factor in breast cancer, is shown to be higher in IDC than IDC/DCIS tumors, suggesting IDC patients have a more aggressive biological behavior compared to IDC/DCIS patients (Gonzalez et al. 2010).

We further evaluated the prognostic significance of coexisting DCIS in different molecular subtypes defined by the IHC classification. In this study, we observed that the prevalence of DCIS/IDC patients were distinct from IDC patients according to the molecular subtypes of breast cancer. IDC/DCIS patients were more frequently presented with luminal

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

	DFS			OS		
	HR	*P* value	95% CI	HR	*P* value	95% CI
Age						
≥55	1.0	1.0	0.861–1.329	1.0	1.0	1.076–2.061
<55	1.070	0.541		1.489	0.016	
Menopausal status						
Post	1.0	1.0		1.0	1.0	
Pre	0.137	0.844	0.675–1.056	0.481	<0.001	0.334–0.693
DCIS status						
IDC	1.0	1.0		1.0	1.0	
IDC/DCIS	0.669	0.022	0.474–0.943	0.497	0.021	0.275–0.899
Tumor stage		<0.001			<0.001	
T1	1.0	1.0		1.0	1.0	
T2	2.227	<0.001	1.777–2.792	2.379	<0.001	1.692–3.347
T3–4	3.753	<0.001	2.197–6.410	7.100	<0.001	3.797–13.278
Lymph node status						
Negative	1.0	1.0		1.0	1.0	
Positive	2.095	<0.001	1.686–2.604	2.649	<0.001	1.914–3.668
Lymphovascular invasion						
No	1.0	1.0		1.0	1.0	
Yes	2.535	<0.001	1.757–3.658	3.243	<0.001	1.977–5.320
Histological grade						
Non-high grade	1.0	1.0		1.0	1.0	
High grade	1.869	<0.001	1.502–2.326	2.722	<0.001	1.949–3.801
Tumor focality						
Unifocal	1.0	1.0		1.0	1.0	
Multifocal	0.857	0.584	0.492–1.492	0.432	0.150	0.138–1.355
Molecular subtype		<0.001			<0.001	
Luminal A	1.0	1.0		1.0	1.0	1.0
Luminal B/HER2 negative	1.712	0.004	1.188–2.468	2.337	0.007	1.263–4.325
Luminal B/HER2 positive	1.103	0.706	0.662–1.838	1.599	0.250	0.718–3.559
Her2 positive	2.482	<0.001	1.616–3.813	3.318	0.001	1.641–6.711
Triple negative	2.561	<0.001	1.716–3.822	4.098	<0.001	2.145–7.829
Type of surgery						
Mastectomy	1.0	1.0		1.0	1.0	
BCS	1.250	0.086	0.969–1.614	1.991	0.002	1.285–3.084

IDC invasive ductal carcinoma, *IDC/DCIS* invasive ductal carcinoma coexisting ductal carcinoma in situ, *BCS* breast conserving surgery, *HER2* human epidermal growth factor receptor 2

B/HER2 positive (12.5% vs 11.0%, $P<0.001$) and HER2 positive (20.9% vs 9.8%, $P<0.001$), but with a lower proportion of triple negative (11.8% vs 16.7%, $P<0.001$), these findings were also consistent with previous studies (Doebar et al. 2016; Lee et al. 2016). Kurbel suggested that during the diagnosis of breast cancer tumor, more aggressive subtypes are associated with fewer DCIS lesions compared to the less aggressive subtypes. A mathematical model was proposed by the author to predict the progression speed of DCIS in different molecular subtypes (Kurbel 2013). The fastest DCIS progression is triple negative, which correlates with the findings of infrequent occurrence of DCIS lesions in basal-like immunophenotype. On the other hand, HER2 positive tumors have a slower progression and are proposed to stay longer in the state of DCIS before invasive transition (Doebar et al. 2017; Gorringe and Fox 2017; Kurbel 2013).

In subgroup analysis, we observed that HER2 positive IDC/DCIS patients have a significantly improved prognosis than HER2 positive IDC patients at 5-year DFS (94.8% vs 78.5%, $P=0.003$). Coexisting DCIS (HR 0.360, CI 95% 0.151–0.859, $P=0.021$) and lymph node status (HR 3.331, CI 95% 1.763–6.292, $P<0.001$) were independent prognostic factors for DFS (data not shown). These findings are comparable with a recent result from SEER database. They

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

	DFS			OS		
	HR	*P* value	95% CI	HR	*P* value	95% CI
Age						
≥55	1.0	1.0	0.797–1.235	1.0	1.0	0.511–0.986
<55	0.992	0.943		0.710	0.041	
DCIS status						
IDC	1.0	1.0		1.0	1.0	
IDC/DCIS	0.701	0.048	0.492–0.997	0.596	0.090	0.327–1.085
Tumor stage		<0.001			<0.001	
T1	1.0	1.0		1.0	1.0	
T2	1.778	<0.001	1.408–2.246	1.713	0.003	1.207–2.433
T3–4	2.885	<0.001	1.682–4.949	5.102	<0.001	2.708–9.613
Lymph node status						
Negative	1.0	1.0		1.0	1.0	
Positive	1.744	<0.001	1.384–2.198	2.169	<0.001	1.533–3.067
Lymphovascular invasion						
No	1.0	1.0		1.0	1.0	
Yes	1.687	0.007	1.152–2.470	1.798	0.026	1.071–3.019
Histological grade						
Non-high grade	1.0	1.0		1.0	1.0	
High grade	1.413	0.004	1.113–1.794	1.938	<0.001	1.354–2.773
Molecular subtype		<0.001			<0.001	
Luminal A	1.0	1.0		1.0	1.0	
Luminal B/HER2 negative	1.331	0.133	0.916–1.934	1.603	0.140	0.856–3.003
Luminal B/HER2 positive	0.793	0.385	0.470–1.338	1.016	0.969	0.448–2.307
Her2 positive	1.724	0.019	1.096–2.713	1.900	0.087	0.910–3.966
Triple negative	1.857	0.004	1.212–2.845	2.505	0.009	1.264–4.965

IDC invasive ductal carcinoma; invasive ductal carcinoma with coexisting ductal carcinoma in situ, *HER2* human epidermal growth factor receptor 2

found that extensive DCIS component in IDC tended to have lower tumor grade, HER2 positive subtype and better survival outcome before propensity-matched (Wu et al. 2018).

In addition, immunological parameters have a major effect on the efficacy of chemotherapy and affect survival outcomes. The presence of tumor-infiltrating lymphocytes (TILs) concentration is associated with improved survival outcomes in HER2 positive and triple negative patients (Denkert et al. 2018; Kashiwagi et al. 2017). Lee et al. found that the degree of TILs is significantly associated with the degree of adjacent tertiary lymphoid structure (TLS), while the presence of TLS strongly correlates with DCIS percentage in HER2 positive breast cancer (Toss et al. 2018). Hence, given that HER2 positive IDC/DCIS tumors are distinct from pure IDC tumor in immune response and microenvironment; these factors might be associated with an improved disease outcome for patients with coexisting DCIS.

To our knowledge, the present work has the largest single institution patients scale focusing on clinicopathological characteristics and clinical outcomes of IDC/DCIS and IDC. Advantages of analyzing our own database included complete IHC record for molecular subtypes classification and detailed follow-up information for clinical assessment. However, this study has several limitations. First, our study is a retrospective analysis, treatment decisions were affected by physician recommendations and patient preferences rather than randomization. Second, longer follow-up periods should be conducted to expect major differences in DFS and OS. More clinical observations and gene expression research need to be done to provide more definitive evidence.

Conclusion

In summary, our study suggested that IDC/DCIS patients had more favorable clinicopathological features and improved survival outcome compared to IDC patients. Moreover, coexisting DCIS tumors were associated with more HER2 positive subtype and significantly improved prognosis in this cohort of patients. However, greater efforts in gene expression profiling studies and clinical research

are essential to explain the biological behavior of IDC with coexisting DCIS.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Ethical Committees of Shanghai Ruijin Hospital. Written informed consent was obtained according to the institutional guidelines. Our study was a retrospective work without treatment modification; patient information has been fully anonymized before data analysis.

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