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Molecular Markers as Prognostic Factors in DCIS and Small Invasive Breast Cancers

Molekulare Marker als Prognosefaktoren für DCIS und invasive T1a Mammakarzinome

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Key words
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- DCIS
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Abstract

Ductal carcinoma in situ (DCIS) accounts for up to half of screen-detected breast cancers and thus constitutes a major public health problem. Despite effective current treatment many patients with DCIS are either over- or undertreated because of the paucity of precise models to predict recurrence or progression. The combination of clinical and molecular factors as already applied for invasive disease may help to build such models also for DCIS. We compared 53 DCIS (36.6%) and 92 (63.4%) invasive breast cancer cases and found no significant differences in age, receptor status of ER, PR, and HER2, and the use of radiotherapy. Interestingly, the proportion of disseminated tumor cells (DTC) did also not significantly differ between DCIS and invasive cases ($p = 0.57$). A negative PR status was associated with the detection of DTCs ($p = 0.026$). We then compared relationships of clinical parameters and biomarkers with patients' prognosis in 43 DCIS and 40 small invasive tumors ≤ 5 mm (T1a). ER negativity was associated with shorter relapse free survival in the complete cohort ($p = 0.004$) and showed a trend in both subgroups ($p = 0.053$ for DCIS and $p = 0.046$ for T1a, respectively). In conclusion, we found markedly similar properties of both DCIS and small invasive breast cancers with respect to the distribution of several parameters as well as to the prognostic value of biomarkers. DCIS with a luminal phenotype seem to be characterized by a favourable prognosis.

Zusammenfassung

Das duktale Carcinoma in situ (DCIS) ist aufgrund seiner durch das Mammografie-Screening stark angestiegenen Häufigkeit in den letzten Dekaden deutlicher ins Blickfeld von Forschung und Praxis gerückt. Trotz effektiver Behandlung stellt sich für viele Patientinnen die Frage einer Über- oder Untertherapie, da sich der Verlauf der Erkrankung individuell nicht vorhersagen lässt. Eine Kombination von klinischen und molekularen Parametern, wie sie bereits vielfach für das invasive Mammakarzinom angewandt wird, könnte hier möglicherweise helfen, entsprechende Prädiktoren zu entwickeln. Bei einem Vergleich von 53 DCIS (36,6%) und 92 (63,4%) invasiven Mammakarzinomen bezüglich klinischer und molekularer Parameter fanden wir keine signifikanten Unterschiede bez. Alter, Hormonrezepor- und HER2-Status sowie dem Einsatz adjuvanter Bestrahlung. Interessanterweise unterschied sich auch die Häufigkeit der Detektion disseminierter Tumorzellen (DTZ) nicht signifikant zwischen DCIS und invasiven Fällen ($p = 0,57$). Ein negativer Progesteronrezeptor-Status war mit dem DTZ-Nachweis assoziiert ($p = 0,026$). Untersucht wurde ebenfalls der Zusammenhang von klinischen Parametern und Biomarkern mit der Prognose bei 43 DCIS und 40 invasiven T1a-Karzinomen. Negativität für den Östrogenrezeptor zeigte hierbei einen signifikanten Zusammenhang zu einem kürzeren krankheitsfreien Intervall in der Gesamtkohorte ($p = 0,004$) und einen Trend in beiden Subgruppen ($p = 0,053$ bei DCIS bzw. $p = 0,046$ bei T1a). Zusammenfassend fanden wir sehr ähnliche Charakteristika bez. der Verteilung verschiedener Parameter und des prognostischen Werts von Biomarkern sowohl bei DCIS als auch invasiven Karzinomen. DCIS mit einem luminalen Phänotyp scheint durch eine günstigere Prognose gekennzeichnet zu sein.

Introduction

Before the advent of screening, DCIS represented only 2–5% of symptomatic breast cancers; at present it accounts for approximately 20–25% of all and up to half of screen-detected breast cancers [1,2]. DCIS is defined as local disease involving proliferation of abnormal epithelial cells limited by the basement membrane without stromal invasion and represents a non-obligate precursor of invasive breast cancer (IBC). Not all DCIS progress to invasive disease if untreated but the estimated range is 25–50% [1,3,4]. Thus, once DCIS has been detected, treatment is obligatory although the majority of women with DCIS are not destined to recur let alone die of their disease [3]. Moreover, present technologies do not allow accurate risk stratification such that intensity of treatment can be tailored to risk of recurrence and progression to invasive disease [1]. Therefore many women are either over- or undertreated and there is pressing need for novel diagnostic approaches to improve risk stratification [3,5]. Conventional risk factors for recurrence in DCIS patients include margin status, young age, nuclear grade, as well as family history. However, traditional prognostic factors alone or in combination (e.g the Van Nuys Prognostic Index or nomograms) have yet failed to provide the necessary precision needed for therapeutic decision making. Several attempts have been started to include molecular factors in diagnosis similar to the approaches applied for invasive disease. Although there have been efforts to develop clinical or molecular tests [6] to predict which patients are likely to relapse with invasive disease, currently no validated test is available with demonstrated clinical utility to identify this population [3,4]. Invasive breast cancer encompasses at least four major molecular subtypes which differ by their expression of estrogen (ER) and progesterone (PR) receptors, HER2, and the proliferative status of the tumor [7–9]. This gene expression based subtype classification is also supported by whole genome sequencing studies [10,11]. Similar approaches were already applied to adopt these molecular subtypes also for DCIS [12,13] but the numbers of samples analyzed are still very small.

In the present study we performed a comparison of DCIS with invasive breast cancer in two ways. First, we analyzed differences in clinical and molecular parameters between cohorts of DCIS and invasive cancers. Second, we compared the prognostic value of different parameters and biomarkers in cohorts of DCIS and small invasive cancer (T1a). Our results support molecular subtyping of DCIS as profitable step towards prognostic and predictive models for DCIS recurrence.

Table 1 Clinical characteristics of the full cohort.

Parameter		Total	Percent
Age	Age > 50	101	71.1
	Age ≤ 50	41	28.9
	n. a.	3	
	Median age	57	
T status	DCIS	53	36.6
	T1	67	46.2
	T2	15	10.3
	T3	7	4.8
	T4	3	2.1
Lymph node status	LNN	104	83.9
	N+	20	16.1
	n. a.	21	
Primary metastasis	M0	138	95.2
	M1	7	4.8
Grade*	Low (G1)	13	9.7
	Intermediate (G2)	59	44.0
	High (G3)	61	45.5
	n. a.	12	
ER status	Positive	92	64.8
	Negative	50	35.2
	n. a.	3	
PR status	Positive	72	51.1
	Negative	69	48.9
	n. a.	4	
HER2 status	Positive	45	36.3
	Negative	79	63.7
	n. a.	21	
Molecular Subtype	TNBC	18	14.6
	HER2	24	19.5
	Luminal	61	49.6
	Luminal-HER2	20	16.3
	n. a.	22	
DTC detection	Positive	17	21.2
	Negative	63	78.8
	n. a.	65	
Adjuvant radiotherapy	Yes	45	39.8
	No	68	60.2
	n. a.	32	
Adjuvant chemotherapy	Yes	20	17.7
	No	93	82.3
	n. a.	32	
Adjuvant endocrine therapy	Yes	51	45.1
	No	62	54.9
	n. a.	32	
Adjuvant trastuzumab treatment	Yes	10	8.8
	No	103	91.2
	n. a.	32	

* Nottingham histological grade for invasive cancer or nuclear grade for DCIS according to CAP guidelines

Materials and Methods

Patients and samples

The study cohort included 145 patients undergoing surgical resection for either DCIS or invasive breast cancer between January 2004 and November 2011 at the Breast Unit of the Goethe University Hospital in Frankfurt. 90 patients participated in a study on the detection of disseminated tumor cells (61 cases of invasive breast cancer and 29 cases of DCIS). The number of samples with DCIS and T1a tumors was further increased by including a second set of 55 consecutive patients (24 with DCIS and 31 with T1a tumors, respectively) for which no data on tumor cell dissemination was available. Formalin-fixed, paraffin-embedded (FFPE) tissue samples were obtained from the Senckenberg's Institute of Pathology, University Frankfurt/Main, Germany. Clinical and pathological factors were evaluated by reviewing medical charts and pathology records. The Local Research Ethics Committees approved studies of human tissue and samples were processed anonymously.

Histopathological evaluation and immunohistochemistry

Routine histopathology sections stained with haematoxylin-eosin (HE) were used for primary diagnosis and second reviewing (KE). Diagnosis and grading was performed according to current

Table 2 Comparison of clinical parameters and biomarkers between DCIS and invasive breast cancers.

Parameter		Total		DCIS		T1a		T1b–T4		T1–T4		p-value DCIS vs. T1a	p-value 3-groups	p-value DCIS vs. T1–T4
Age	Age ≤ 50	41	28.9%	12	23.1%	13	30.2%	16	34.0%	29	32.2%			
	Age > 50	101	71.1%	40	76.9%	30	69.8%	31	66.0%	61	67.8%	0.49	0.47	0.34
Grade*	Low (G1)	13	9.8%	4	8.3%	5	13.9%	4	8.2%	9	10.6%			
	Inter-mediate (G2)	59	44.4%	11	22.9%	24	66.7%	24	49.0%	48	56.5%			
	High (G3)	61	45.9%	33	68.8%	7	19.4%	21	42.9%	28	32.9%	[< 0.001] *	[< 0.001] *	[< 0.001] *
HER2 status	Negative	79	63.7%	20	60.6%	22	52.4%	37	75.5%	59	64.8%			
	Positive	45	36.3%	13	39.4%	20	47.6%	12	24.5%	32	35.2%	0.49	0.067	0.68
ER status	Negative	50	35.2%	18	36.0%	20	46.5%	12	24.5%	32	34.8%			
	Positive	92	64.8%	32	64.0%	23	53.5%	37	75.5%	60	65.2%	0.40	0.087	1.0
PR status	Negative	69	48.9%	20	40.8%	25	58.1%	24	49.0%	49	53.3%			
	Positive	72	51.1%	24	59.2%	18	41.9%	25	51.0%	43	46.7%	0.14	0.25	0.22
Molecu-lar sub-type	TNBC	18	14.6%	6	18.8%	4	9.5%	8	16.3%	12	13.2%			
	HER2	24	19.5%	4	12.5%	16	38.1%	4	8.2%	20	22.0%			
	Luminal	61	49.6%	14	43.8%	18	42.9%	29	59.2%	47	51.6%			
	Luminal-HER2	20	16.3%	8	25.0%	4	9.5%	8	16.3%	12	13.2%	0.041	0.010	0.27
DTC de-tection	Negative	63	78.8%	18	75.0%	6	54.5%	39	86.7%	45	80.4%			
	Positive	17	21.3%	6	25.0%	5	45.5%	6	13.3%	11	19.6%	0.26	0.057	0.57
Radio-therapy	No	68	60.2%	31	60.8%	30	71.4%	7	35.0%	37	59.7%			
	Yes	45	39.8%	20	39.2%	12	28.6%	13	65.0%	25	40.3%	0.38	0.023	1.0
Chemo-therapy	No	93	82.3%	51	100%	32	76.2%	10	50.0%	42	67.7%			
	Yes	20	17.7%	0	0%	10	23.8%	10	50.0%	20	32.3%	< 0.001	< 0.001	< 0.001
Endo-crine therapy	No	62	54.9%	26	51.0%	28	66.7%	8	40.0%	38	58.1%			
	Yes	51	45.1%	25	49.0%	14	33.3%	12	60.0%	26	41.9%	0.14	0.11	0.57
Tamoxi-fen	No	74	65.5%	27	52.9%	32	43.2%	15	20.3%	47	75.8%			
	Yes	39	34.5%	24	47.1%	10	23.8%	5	25.0%	15	24.2%	0.030	0.039	0.017
Aroma-tase in-hibitor	No	97	86.6%	49	98.0%	37	88.1%	11	55.0%	48	77.4%			
	Yes	15	13.4%	1	2.0%	5	11.9%	9	45.0%	14	22.6%	0.089	< 0.001	0.001
Trastuz-umab	No	103	91.2%	51	100%	35	83.3%	17	85.0%	52	83.9%			
	Yes	10	8.8%	0	0%	7	16.7%	3	15.0%	10	16.1%	0.003	0.011	0.002

* Grade is given either as Nottingham histological grade for invasive cancer or nuclear grade for DCIS according to CAP guidelines

College of American Pathologists (CAP) protocols [14,15] 2013 updates (3.2.0.0) available at www.cap.org. ER and PR status were available from routine pathology for all samples using antibodies NCL-ER-6F11 (Novocastra Laboratories, UK) and PgR 636 M3569 (DAKO, Hamburg, Germany) for ER and PR, respectively. HER2 immunohistochemistry (IHC) was performed using rabbit monoclonal antibody SP3 (Cell Marque Co., Rocklin, CA). A surrogate of the molecular subtypes of breast cancer was defined based on receptor status combinations according to the following groups: TNBC (triple negative), HER2-like (ER negative/HER2 positive), Luminal (ER positive/HER2 negative), and Luminal-HER2 (ER positive/HER2 positive) [13,16,17]. All assessments were made blinded with respect to clinical patient data.

Detection of disseminated tumor cells in bone marrow

Disseminated tumor cell (DTC) detection was performed according to a validated immunocytochemical assay with anti-cytokeratin (CK) antibodies A45-B/B3 (AS Diagnostics, Germany) and AE1/AE3 (Chemicon by Millipore, USA) as described [18].

Statistical analysis

χ^2 and Fisher's Exact Test were used to determine significance of categorical variables. All p-values are two-sided and 0.05 was

Table 3 Comparison of tumor cell dissemination with age and receptor status.

Parameter		Total		DTC negative		DTC positive		p-value
Age	Age ≤ 50	22	28.2%	19	31.1%	3	17.6%	
	Age > 50	56	71.8%	42	68.9%	14	82.4%	0.37
HER2 status	Negative	54	68.4%	45	72.6%	9	52.9%	
	Positive	25	31.6%	17	27.4%	8	47.1%	0.15
ER status	Negative	21	26.6%	14	22.6%	7	41.2%	
	Positive	58	73.4%	48	77.4%	10	58.8%	0.14
PR status	Negative	35	44.3%	23	37.1%	12	70.6%	
	Positive	44	55.7%	39	62.9%	5	29.4%	**0.026**
Molecular subtype	TNBC	12	15.2%	9	14.5%	3	17.6%	
	HER2	9	11.4%	5	8.1%	4	23.5%	
	Luminal	42	53.2%	36	58.1%	6	35.3%	
	Luminal-HER2	16	20.3%	12	19.4%	4	23.5%	0.23

used a significance level. Follow-up information was available for 43 patients with DCIS and 40 patients with T1a tumors. Relapse of any kind (secondary DCIS or invasive cancer) was used as an endpoint. Follow-up data for those women in whom the envisaged end point was not reached were censored as of the last follow-up date. Subjects with missing values were excluded from the analyses. A Cox proportional-hazards model was used to examine the effects of covariates on relapse free survival. The effect of each individual variable was assessed with the use of the Wald test and described by the hazard ratio, with a 95 percent confidence interval (95% CI). We also constructed Kaplan-Meier curves and used the log-rank test to determine the univariate significance of the variables. All analyses were performed using SPSS Statistics Version 22 (IBM Corp.).

Results

Clinical characteristics of DCIS and invasive breast cancer patients

We analyzed a cohort of 145 patients which underwent surgical resection for either DCIS or invasive breast cancer between January 2004 and November 2011 at the Breast Unit of the Goethe University Hospital in Frankfurt. Clinical parameters of the patients are given in **Table 1**. Median age was 57 years, the majority of patients (64.8%) had ER positive disease and only 4.8% displayed primary metastasis at diagnosis. About one third of the patients (36.6%) were diagnosed with DCIS without invasive disease.

Comparison of clinical parameters and biomarkers between DCIS and invasive breast cancers

We first compared clinical parameters of the DCIS patients with those showing invasive breast cancer. We also included an additional comparison of patients with DCIS and the subgroup of patients with T1a invasive cancers (tumor size ≤ 5 mm). As shown in **Table 2** we did not detect significant differences between patients with DCIS and invasive cancers regarding patients' age, hormone receptor and HER2 status, as well as the use of radiotherapy and endocrine therapy for adjuvant treatment. The proportion of "high nuclear grade" tumors was larger in DCIS (68.8%) compared to tumors with high histological grade among invasive cancers (32.9%; $p < 0.001$), but it should be noted that "grade" refers to different definitions in the two types of samples (nuclear grade for DCIS and Nottingham histological grade for invasive breast cancer, respectively). We also applied a simplified classification of molecular subtypes of breast cancer based on receptor status of ER and HER2 [13, 16, 17]. Using this classification we found a higher number of HER2-like cancers among T1a tumors (38.1%) compared to both DCIS (12.5%) and to larger invasive tumors (8.2% for T1b–T4). In contrast the number of Luminal-HER2-like (ER+/HER2+) cancers was lower in T1a tumors (9.5%) than in DCIS (25.0%) or T1b–T4 tumors (16.3%). These differences were significant both for T1a tumors compared to DCIS ($p = 0.041$) and between all three groups ($p = 0.010$; **Table 2**). In patients with pure DCIS no adjuvant chemotherapy or trastuzumab treatment were used. We also compared the proportion of patients displaying tumor cell dissemination in the bone marrow at primary diagnosis. Interestingly, the frequency of DCIS with disseminated tumor cells (25.0%) did not significantly differ from that of invasive breast cancer (19.6%; $p = 0.57$). Despite caution should be taken because of the very small sample size in our study, this observation supports previous results of early dissemination and systemic spread already in pre-invasive disease [18–21].

Comparison of tumor cell dissemination with age and receptor status

We next compared the presence of disseminated tumor cells with receptor status of ER, PR, and HER2 as well as age. Since numbers were too small in separate subgroups of patients with either DCIS or invasive cancer the analysis was performed in the complete cohort only. As given in **Table 3** we observed a significant association of a negative PR status with disseminated tumor cell detection (70.6 vs. 37.1%, $p = 0.026$; **Table 3**). Associations with age, ER status, HER2 status, and molecular subtype were not significant.

Prognostic factors in DCIS and T1a invasive breast cancer

We next compared the relationship of clinical parameters and biomarkers with prognosis of patients with either DCIS or invasive cancer. For homogeneity we included only invasive cases with a tumor size ≤ 5 mm (T1a) in this analysis. Follow-up information was available for 43 patients with DCIS and 40 patients with T1a tumors. Median follow up was 47 months and 40 months for DCIS and T1a tumors, respectively. Relapse of any kind (secondary DCIS or invasive cancer) was used as an endpoint. **Table 4** shows results of univariate Cox regression analysis for relapse free survival according to different parameters. Results are presented separately for the groups of DCIS patients and

Table 4 Univariate Cox regression of relapse free survival in DCIS and T1a breast cancer according to clinical parameters and biomarkers.

Parameter	DCIS				T1a				DCIS + T1a			
	Num-bers	HR	95% CI	p-value	Num-bers	HR	95% CI	p-value	Num-bers	HR	95% CI	p-value
Age (≤ 50 vs. > 50)	8 vs. 34	0.04	0–4950	0.59	13 vs. 27	0.42	0.05–3.8	0.44	21 vs. 61	0.39	0.05–3.08	0.37
ER (negative vs. positive)	16 vs. 27	7.0	0.72–68.3	0.094	20 vs. 20	53.1	0.04–$8*10^4$	0.28	36 vs. 47	11.4	1.4–91.2	**0.022**
PR (negative vs. positive)	18 vs. 24	4.9	0.50–46.9	0.172	24 vs. 16	37.3	0.01–$3*10^5$	0.42	42 vs. 40	7.07	0.88–56.7	0.066
HER2 (negative vs. positive)	16 vs. 9	0.54	0.03–8.65	0.66	19 vs. 20	0.37	0.04–3.3	0.37	35 vs. 29	0.40	0.08–2.09	0.28
Grade (high vs. low/interm) *	30 vs. 8	31.2	0–4×10^6	0.57	7 vs. 26	2.6	0.16–42	0.50	37 vs. 34	1.65	0.30–9.0	0.56
DTC detection (negative vs. positive)	14 vs. 4	0.004	0–3×10^6	0.60	4 vs. 4	n. a.	n. a.	n. a.	18 vs. 8	0.01	0–2382	0.47

* Grade is given either as Nottingham histological grade for invasive cancer or nuclear grade for DCIS according to CAP guidelines

the T1a cases, respectively, as well as for both groups combined. None of the parameters were significant in the analysis within these rather small cohorts of DCIS and T1a tumors. However, we detected a trend for negative ER status (HR 7.0, 95% CI 0.072–68.3; p = 0.094 for DCIS, and HR 53.1, 95% CI 0.04–8×10^4; p = 0.28 for T1a, respectively) which became significant in the combined cohort (HR 11.4, 95% CI 1.4–91; p = 0.022). Also for PR a trend was observed in the combined cohort (HR 7.1, 95% CI 0.88–57; p = 0.066). We additionally studied these two parameters in Kaplan-Meier-analysis as shown in **Fig. 1**. Here the log-rank test was applied resulting in a significant difference in survival for ER in the group of patients with T1a tumors (p = 0.046; **Fig. 1 b**) and in the combined cohort (p = 0.004; **Fig. 1 c**) and a strong trend for patients with DCIS (p = 0.053; **Fig. 1 a**). PR showed a significant difference in the combined cohort (p = 0.032; **Fig. 1 f**) and a small trend for DCIS (p = 0.13; **Fig. 1 d**) and T1a (p = 0.17; **Fig. 1 e**) patient subgroups.

Discussion

In the present study we obtained markedly similar characteristics when comparing a cohort of patients with either DCIS or invasive cancer. A strength of our study is the use of pure DCIS as selection criteria in contrast to many analyses which failed to distinguish DCIS with (or in the presence of) invasive carcinoma from cases of pure DCIS [3] as well as the inclusion of only very small invasive breast cancer in the comparison of prognosis. Limitations however include the retrospective design of the analysis and the small sample size. It should be noted that many comparisons are clearly underpowered. Therefore our inability to detect significant differences should not be taken as indication that there are none when sample size is increased. On the other hand similarity between DCIS and invasive breast cancer has already been reported. Especially synchronous and metachronous invasive cancer harbor similar genetic aberrations as found in the DCIS [4]. Grade and ER status was also associated between index DCIS and secondary cancer in a comparison of 150 secondary breast cancers from 2636 patients with DCIS [22]. Theories of progression from DCIS to IBC mainly focus either on acquired behaviour e.g. through clonal selection or on non-genetic mechanisms e.g. driven by microenvironment [4]. Several gene expression profiling studies have demonstrated remarkably similar gene expression patterns between premalignant, preinvasive and invasive breast cancer [23–27] suggesting that progression from in situ to invasive disease is not necessarily driven by specific redundant genetic aberrations in DCIS cells [4]. More complex branched models of evolution may be much closer to reality with multiple mutational events driving multiple routes to invasive cancer [3,4,26]. Consequently the clarification of driving events will be complicated but emerging technologies could hint to the design of future studies [4]. One interesting aspect of our comparison between patients with DCIS and invasive cancer refers to the observation that no significant difference was found regarding the detection of disseminated tumor cells. This result seems counterintuitive and sample size is again an issue here. But beside potential technical and statistical issues similar data have been obtained before [18–21,28] suggesting that profound but undetectable dissemination may occur very early.

Our results also hint towards a better prognosis of luminal type tumors both in DCIS and invasive breast cancer. In a recent systematic review [29] several previous studies were assembled which have analyzed the relationship of ER expression in DCIS and recurrence. Four of 16 studies reported a positive prognostic value of ER status. However, heterogeneity between studies and methods was rather large and no prospective studies are available. It is also not clear whether observed effects are mainly based on pure prognosis or a predictive value of ER for response to endocrine therapy. Sample sizes in subgroups of treatment are small (e.g. in our study only one quarter of the patients did not receive endocrine treatment) and numbers of events are low. One of the largest studies performed a nested case-control study based on 324 relapses among 1162 DCIS patients without endocrine treatment [30]. Negative ER status and positive HER2 status were associated with a higher risk in that study. A report applying an immunohistochemical (IHC) surrogate to define the basal-like subgroup among 392 DCIS observed a non-significant trend for higher recurrence [31]. In a presentation at the San Antonio

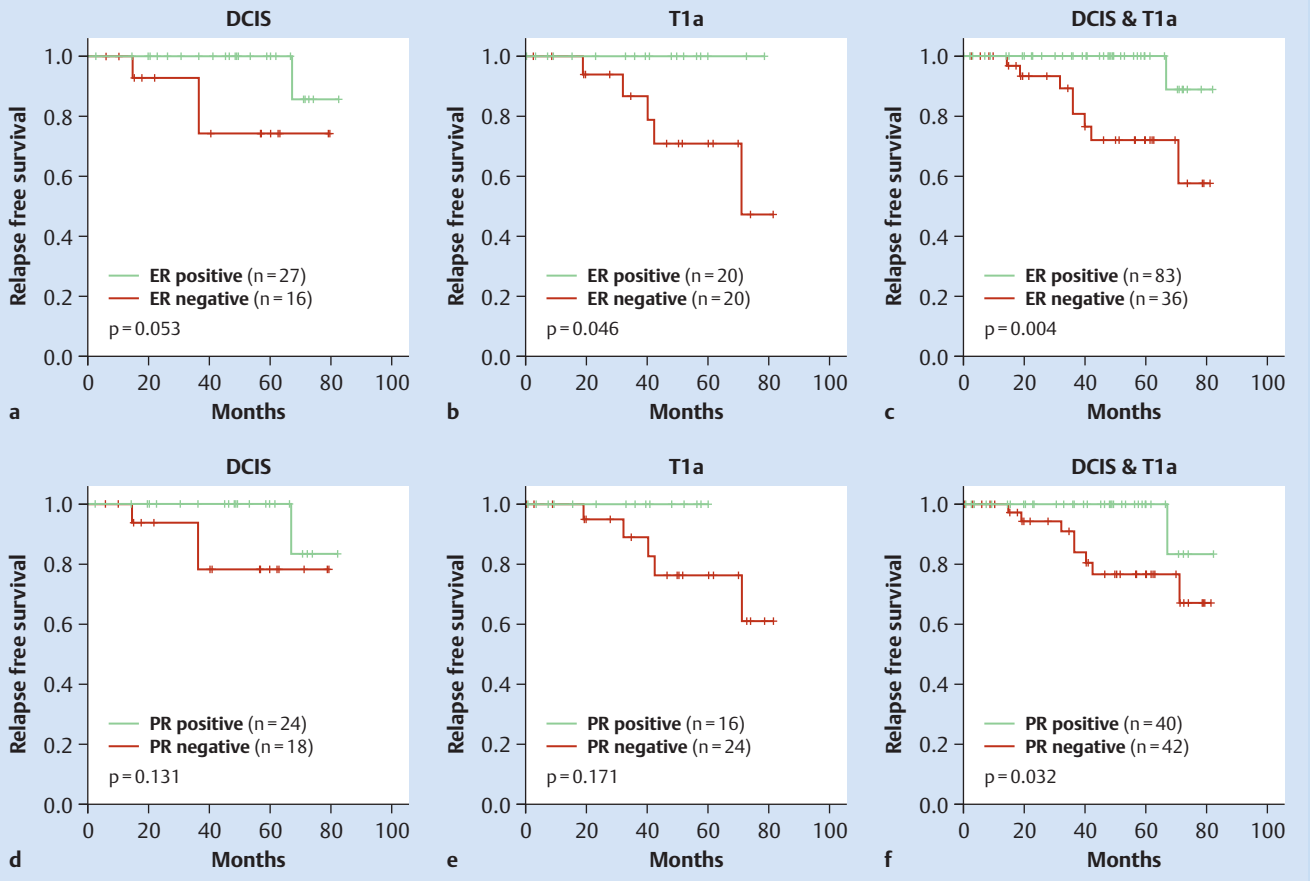

Fig. 1 a to **f** Prognosis of DCIS and T1a invasive breast cancer according to hormone receptor status. Kaplan-Meier analysis of relapse free survival according to ER status (**a, b, c**) and PR status (**d, e, f**) are presented for DCIS cases (**a, d**), T1a invasive breast cancers (**b, e**), and the combined cohorts (**c, f**). Any relapse (secondary DCIS or invasive cancer) was used as endpoint. P-values from log-rank test are given.

Breast Cancer Symposium 2012 the same approach we used for IHC molecular subtype surrogates was applied to categorize 314 patients with DCIS [13]. The frequencies of the respective subtypes were similar to our analysis (given in parentheses): 42.4% Luminal (43.8%), 28.0% Luminal-HER2 (25.0%), 15.9% HER2 (12.5%), and 13.7% TNBC (18.8%). A good prognosis was detected mainly for the Luminal subgroup (hazard ratios > 14 compared to the other groups; $p < 0.02$). When we analyzed all subtypes separately in our cohort samples size in the individual groups was very small and the prognostic effect did not exceed that of ER status alone (not shown). Nevertheless, other researchers also reported an increased risk of recurrence in the HER2-like and Luminal-HER2 groups [32]. Taken together, since IHC surrogates are readily available they represent an attractive pragmatic approach for studies on risk assessment of molecular subtypes of DCIS [1]. Clearly validation datasets are needed to establish whether this marker panel could replace traditional risk factors or be amalgamated into a model or nomogram.

Conclusions for Practice

Despite effective therapy many patients with DCIS are either over- or undertreated because of the paucity of precise models to predict recurrence or progression. The combination of clinical and molecular factors may help to build such models. A luminal phenotype seems to be characterized by a favourable prognosis but needs to be validated in further studies.

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Conflict of Interest

None.

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