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ORIGINAL ARTICLE

Prognostic factors predicting recurrence in invasive breast cancer: An analysis of radiological and clinicopathological factors

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Summary *Background/Objective:* The purpose of this study was to perform a comprehensive analysis of the radiological and clinicopathological factors that could predict recurrence of invasive breast cancer who underwent curative surgery without neoadjuvant chemotherapy.
Methods: Three hundred and sixty-four consecutive women who underwent preoperative mammography, ultrasound, and breast magnetic resonance imaging for newly diagnosed invasive breast cancers and curative surgery between January and December 2010 were included. We analyzed the radiological findings of each modality and reviewed the histopathological features. A Cox proportional hazards model was used to determine the association between the radiological and clinicopathological parameters and disease-free survival (DFS).
Results: During the median follow-up period of 5.3 years, 23 patients (6.3%) developed recurrences: locoregional recurrence in six patients, contralateral breast recurrence in three patients, and distant recurrences in 14 patients. Microcalcifications on mammography showed a tendency towards worse DFS. The multivariate Cox regression analysis showed that presence of lymphovascular invasion (LVI) ($p = 0.006$), negative progesterone receptor (PR) status ($p < 0.001$), and positive CK5/6 expression ($p = 0.015$) were independent significant variables predictive of worse DFS.
Conclusion: Understanding the prognostic factors in patients with invasive breast cancer may provide considerable practical information about future treatment strategies.

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1. Introduction

Breast cancer is a highly heterogeneous disease with diverse clinical and genetic characteristics.[1] Different subtypes of breast cancer with distinct biological features lead to different responses to various treatments. With the development of various adjuvant treatment methods including chemotherapy, endocrine therapy, and radiation therapy, the treatment outcome for patients with breast cancer has improved.[2] Nevertheless, the 10-year recurrence rate for patients with breast cancer has been reported to be as high as 25—30% for patients without axillary lymph node metastasis and approximately 75—80% for patients with axillary lymph node metastasis.[2] It is well known that recurrence is one of the independent prognostic factors for mortality.[3] As a result, studies on predictive factors for recurrence in breast cancer are considered important.

There have been several reports on potential predictive factors for recurrence and survival, including tumor size, histological type, differentiation degree of the tumor, nuclear grade, presence of lymph node metastasis, estrogen receptor (ER) and progesterone receptor (PR) status, and gene expression.[2,4—6] Although there have been only a few studies regarding the radiological factors predictive of recurrence, some reports have suggested that mammographic calcification and mammographic breast density are associated with higher rates of local recurrence.[7,8] However, the results of previous studies have been relatively inconsistent and, to date, there has been no clinical study that includes a comprehensive analysis of the clinical, histopathological, and radiological risk factors associated with recurrence in breast cancer. Thus, the purpose of this study was to perform a comprehensive analysis of the radiological and clinicopathological factors that could predict recurrence of invasive breast cancer who underwent curative surgery without neoadjuvant chemotherapy.

2. Materials and methods

The study protocols were approved by our institutional review board. Informed consent was waived owing to the retrospective design of this study.

2.1. Study population

Between January and December 2010, 419 female patients underwent curative surgery without neoadjuvant chemotherapy for newly diagnosed invasive breast cancer in our institution. Patients who met the following criteria were excluded: prior mammotome excision or excisional biopsy at an outside hospital before image analysis (n = 44); not available of pre-operative images including mammography, ultrasound (US), and magnetic resonance imaging (MRI) (n = 8) findings or immunohistochemical results (n = 2); pure ductal carcinoma in situ (n = 1). Finally, 364 patients (age range, 22—73 years; mean age, 48 years) were enrolled in the study. We scanned the medical records at our institution to determine the menopausal status for each patient.

2.2. Preoperative imaging technique and analysis

Two standard mammography views, i.e. craniocaudal and mediolateraloblique views, with additional views as necessary, were obtained using a Senographe DS unit (GE Medical Systems, Milwaukee, WI, USA). The density of the parenchyma shown on mammography was classified according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS)[9] as: a) almost entirely fatty, b) scattered areas of fibroglandular density, c) heterogeneously dense, and d) extremely dense. The breast density a and b were considered fatty breast, and c and d were considered dense breast. The lesions in the mammographic findings were classified as either calcified or noncalcified lesion.

Whole breast US examination was performed using an IU22 (Philips, Bothell, Wash) equipped with a 50-mm, high-resolution linear-array transducer with a frequency of 5—12 MHz. Each breast was scanned using both transverse and sagittal orientations, with the patient's arm raised above her head. In addition, bilateral axillae, supraclavicular fossa, and internal mammary lymphatic space were scanned for regional or metastatic lymph nodes. The lesions of the breast in the US findings were classified as mass-forming or non-mass-forming.

Breast MRI was performed with the patient in a prone position using either a 1.5T MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) or a 3T MR scanner (Skyra, Siemens Medical Solutions, Erlangen, Germany; Ingenia, Philips, Best, The Netherlands) with a dedicated, phased-array breast coil (Siemens Medical Solutions). The standard MRI protocol included the following pulse sequences: axial two-dimensional T2-weighted short tau inversion recovery turbo spin-echo pulse sequence, and precontrast- and postcontrastenhanced fat-saturated axial three-dimensional T1-weighted fast low-angle shot sequences. The contrast medium (0.2 mL/kg body weight; Magnevist, Schering, Berlin, Germany) was injected using an MRI compatible power injector (Spectris, Medrad, Pittsburgh, PA, USA) at a flow rate of 1 mL/s followed by a 20-mL saline flush. Post-processing manipulation included standard subtraction and maximum-intensity projection of images.[10] The background parenchymal enhancement (BPE) was evaluated according to the ACR BI-RADS guidelines as minimal, mild, moderate, or marked BPE.[9] MRI findings of the lesion were classified as mass or non-mass enhancement.

The imaging findings for each modality used for the patients were retrospectively reviewed, with consensus by two breast radiologists (W.J.C and S.R.J) with 9 and 5 years of clinical experience, respectively. The two radiologists were unaware of the pathological features of the tumor.

2.3. Histopathological analysis

All patients in the study group underwent mastectomy or breast conserving surgery for breast cancer. All resected specimens were histopathologically verified. For each malignant lesion, the cancer types and tumor characteristics were recorded. Information on tumor size, histological and nuclear grade, lymph node status, lymphovascular invasion

(LVI), and immunohistochemical factors was recorded for all cases. LVI was defined as the presence of tumor emboli in peritumoral lymphatic spaces, capillaries, or post-capillaryvenules. The immunohistochemical staining results for ER, PR, HER-2, HER-1, p53, CK5/6, and Ki-67 were reviewed. ER and PR status was considered positive if at least 1% of the tumor nuclei stained positive. HER-2-positive status was defined as evidence of protein over-expression using immunohistochemistry (score of 3) or gene amplification by silver in situ hybridization (SISH). The cutoff point for Ki-67 positive expression was 14%. Subtypes based on the immunohistochemical profile were categorized as follows: luminal A (ER and/or PR positive, HER-2 negative and low Ki-67); luminal B (ER and/or PR and HER-2 overexpressed and/or amplified or HER-2 negative with high Ki-67); HER-2 (ER and PR negative and HER-2 overexpressed and/or amplified); and basal-like (ER, PR and HER-2 negative).

2.4. Postoperative care and follow-up

After curative surgery, supplementary treatments such as radiation therapy, chemotherapy, or endocrine therapy were administered, as was clinically indicated on the basis of patient and tumor characteristics. The last date of data collection for follow-up was March 31, 2016. Follow-up duration was calculated from the date of surgery to the last date of follow-up, or to the occurrence of any event or death. The site of the breast cancer recurrence was classified as ipsilateral breast, contralateral breast, regional lymph node, or distant.

2.5. Statistical analysis

The primary end point was recurrence and disease-free survival (DFS). DFS was defined as the time from the date of radical treatment to the date of first breast cancer recurrence, the date of death, the last known date of no evidence of disease, or the date of most recent follow-up. Cox proportional hazards model was used to analyze the effect of clinicopathological and radiological parameters on recurrence. To identify significant risk factors, all clinically relevant variables with $P < 0.1$ in the univariate analysis were entered into a multivariate Cox regression model using backward elimination. Cumulative survival rates were analyzed by the Kaplan–Meier method for the variables that showed a significant association with DFS in the multivariate analysis. Differences in cumulative survival were assessed using the log-rank method. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software version 20.0 (SPSS, Chicago, IL) or SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

The clinicopathological characteristics of 364 patients with breast cancer are listed in Table 1. One hundred twenty-five patients underwent mastectomy and 239 patients underwent breast conserving surgery. The primary tumors consisted of invasive ductal carcinoma (n = 288),

Table 1 Clinical, pathological, and treatment-related characteristics of 364 patients with breast cancer.

Characteristics	N (%)
Age	
<45 years	120 (33.0)
≥45years	244 (67.0)
Menopause status (n = 338)[a]	
Pre-menopausal	237 (70.1)
Post-menopausal	101 (29.9)
Surgery	
Mastectomy	125 (34.3)
Breast conserving surgery	239 (65.7)
Histological type	
Invasive ductal carcinoma	288 (79.1)
Invasive lobular carcinoma	16 (4.4)
Other	60 (16.5)
Tumor size	
≤2 cm	242 (66.5)
2–5 cm	114 (31.3)
>5 cm	8 (2.2)
AJCC Stage	
I	201 (55.2)
II	137 (37.6)
III	26 (7.1)
Histological grade	
I	25 (6.9)
II	223 (61.3)
III	116 (31.9)
Nuclear grade	
I	23 (6.3)
II	222 (61.0)
III	119 (32.7)
Nodal status	
Negative	264 (72.5)
Positive	100 (27.5)
Lymphovascular invasion	
Negative	306 (84.1)
Positive	58 (15.9)
Estrogen receptor	
Negative	95 (26.1)
Positive	269 (73.9)
Progesterone receptor	
Negative	141 (38.7)
Positive	223 (61.3)
Her-2	
Negative	276 (75.8)
Positive	88 (24.2)
HER-1	
Negative	347 (95.3)
Positive	17 (4.7)
CK 5/6	
Negative	305 (83.8)
Positive	59 (16.2)
p53	
Negative	265 (72.8)
Positive	99 (27.2)
Ki-67	
≤14%	201 (55.2)
>14%	163 (44.8)

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Table 1 (*continued*)

Characteristics	N (%)
Molecular subtype	
Luminal A	231 (36.5)
Luminal B	43 (11.8)
HER-2	44 (12.1)
Basal	46 (12.6)
Receipt of breast radiation	
No	129 (35.4)
Yes	235 (64.6)
Receipt of adjuvant chemotherapy	
No	106 (29.1)
Yes	258 (70.9)
Receipt of adjuvant hormone therapy	
No	110 (30.2)
Yes	254 (69.8)
Receipt of herceptin treatment	
No	45 (12.4)
Yes	319 (87.6)

[a] Clinical information regarding the menopausal status of 26 patients was unclear because of hysterectomy (n = 14), no record (n = 7), or the presence of a Mirena device (n = 5).

microinvasive ductal carcinoma (n = 32), invasive lobular carcinoma (n = 16), and other tumors (n = 28), which included mucinous carcinoma (n = 9), tubular carcinoma (n = 7), mixed invasive ductal and lobular carcinoma (n = 5), metaplastic carcinoma (n = 3), papillary carcinoma (n = 2), mixed invasive ductal and mucinous carcinoma (n = 1), and invasive micropapillary carcinoma (n = 1).

The average follow-up period was 66 months (range, 20–74 months). At the time of analysis, 23/364 patients (6.3%) had developed recurrences. This included patients with ipsilateral breast recurrence (n = 2, microinvasive ductal carcinoma), contralateral breast recurrence (n = 3; microinvasive ductal carcinoma (n = 1), invasive ductal carcinoma (n = 2)), regional lymph node recurrence (n = 4; ipsilateral axillary lymph node (n = 2), supraclavicular lymph node (n = 1), internal mammary lymph node (n = 2)), and distant recurrence (n = 14; bone (n = 9), lung (n = 7), liver (n = 4), brain (n = 1), and adrenal gland (n = 1)). The median time to recurrence in these patients was 27.1 months.

Table 2 shows the relationship between radiological features and DFS. None of the radiological features were statistically significant; however calcified lesion on mammography had a tendency toward worse DFS compared with noncalcified lesion (HR, 2.23; $p = 0.076$). On univariate analysis of clinicopathological factors associated with DFS, menopausal status ($p = 0.024$), tumor stage ($p = 0.021$), histological grade ($p = 0.001$), nuclear grade ($p = 0.001$), LVI ($p = 0.012$), ER ($p = 0.019$), PR ($p < 0.001$), HER-2 ($p = 0.029$), CK5/6 ($p = 0.004$), Ki-67 ($p = 0.017$) status, and receipt of hormone treatment ($p = 0.024$) were found to be statistically significant factors (Table 3). Multivariate Cox regression analysis revealed that the presence of LVI (HR, 3.39; $p = 0.006$), negative PR status (HR, 6.99; $p < 0.001$), and positive CK5/6 expression (HR, 2.89; $p = 0.015$) were independent significant factors for poorer DFS (Table 4). Fig. 1 shows that there were statistically significant differences in DFS between patients with presence or absence LVI ($p = 0.009$), positive or negative PR ($p < 0.001$) and positive or negative CK5/6 ($p = 0.002$).

Table 2 Univariate analysis of radiological factors as prognostic factors for disease-free survival.

	No recurrence (n = 341)	Recurrence (n = 23)	Total (n = 364)	Hazard ratio	95% CI	*P* value
Mammography						
Parenchymal pattern						
Fatty	76 (22.3)	7 (30.4)	83 (22.8)	1.00		
Dense	265 (77.7)	16 (69.6)	281 (77.2)	0.66	0.27–1.60	0.354
Type of lesion						
Noncalcified lesion	170 (49.9)	7 (30.4)	177 (48.6)	1.00		
Calcified lesion	171 (50.1)	16 (69.6)	187 (51.4)	2.23	0.92–5.43	0.076
Ultrasound						
Type of lesion						
Mass	310 (90.9)	22 (95.7)	332 (91.2)	1.00		
Nonmass lesion	31 (9.1)	1 (4.3)	32 (8.8)	0.46	0.06–3.39	0.444
MRI						
Background parenchymal enhancement						
Minimal to mild	149 (43.7)	13 (56.5)	162 (44.5)	1.00		
Moderate to marked	192 (56.3)	10 (43.5)	202 (55.5)	0.61	0.27–1.39	0.236
Type of lesion						
Mass	234 (68.6)	19 (82.6)	253 (69.5)	1.00		
Nonmass enhancement	107 (31.4)	4 (17.4)	111 (30.5)	0.46	0.16–1.36	0.161

Numbers in parentheses represent percentages.
CI confidence interval.

Table 3 Univariate analysis of clinical and histopathological factors as prognostic factors for disease-free survival.

	No recurrence (n = 341)	Recurrence (n = 23)	Hazard ratio	95% CI	*P* value
Age					
<45years	115 (33.7)	5 (21.7)	1.00		
≥45years	226 (66.3)	18 (78.3)	1.02	0.97—1.07	0.399
Menopausal status[a]					
Pre-menopausal	227 (71.6)	10 (47.6)	1.00		
Post-menopausal	90 (28.4)	11 (52.4)	2.67	1.14—6.29	0.024
Surgery					
Mastectomy	116 (34.0)	9 (39.1)	1.00		
Breast conserving surgery	225 (66.0)	14 (60.9)	0.82	0.35—1.89	0.636
Histological type					
Invasive ductal carcinoma	270 (79.2)	18 (78.3)	1.00		
Invasive lobular carcinoma	16 (4.7)	0 (0)	∞	0.990	
Others	55 (16.1)	5 (21.7)	1.30	0.48—3.49	0.610
Tumor size					
≤2 cm	229 (67.2)	13 (56.5)	1.00		
2—5 cm	104 (30.5)	10 (43.5)	1.67	0.73—3.81	0.222
>5 cm	8 (2.3)	0 (0)	∞	0.989	
AJCC Stage					0.021
I	190 (55.7)	11 (47.8)	1.00		
II	130 (38.1)	7 (30.4)	0.94	0.36—2.41	0.889
III	21 (6.2)	5 (21.7)	3.96	1.38—11.39	0.011
Histological grade					
I/II	240	8	1.00		
III	111	15	4.23	1.79—9.98	0.001
Nuclear grade					
I/II	237	8	1.00		
III	104	15	4.07	1.72—9.59	0.001
Nodal status					
Negative	249 (73.0)	15 (65.2)	1.00		
Positive	92 (27.0)	8 (34.8)	1.45	0.61—3.41	0.400
Lymphovascular invasion					
Negative	291 (85.3)	15 (65.2)	1.00		
Positive	50 (14.7)	8 (34.8)	2.99	1.27—7.05	0.012
Estrogen receptor					
Negative	84 (24.6)	11 (47.8)	1.00		
Positive	257 (75.4)	12 (52.2)	0.37	0.17—0.85	0.019
Progesterone receptor					
Negative	122 (35.8)	19 (82.6)	1.00		
Positive	219 (64.2)	4 (17.4)	0.13	0.04—0.37	<0.001
HER-2 (c-ErbB2)					
Negative	263 (77.1)	13 (56.5)	1.00		
Positive	78 (22.9)	10 (43.5)	2.51	1.10—5.72	0.029
HER-1 (EGFR)					
Negative	325 (95.3)	22 (95.7)	1.00		
Positive	16 (4.7)	1 (4.3)	0.93	0.13—6.89	0.942
CK5/6					
Negative	291 (85.3)	14 (60.9)	1.00		
Positive	50 (14.7)	9 (39.1)	3.42	1.48—7.91	0.004
P53					
Negative	250 (73.3)	15 (65.2)	1.00		
Positive	91 (26.7)	8 (34.8)	1.46	0.62—3.44	0.390
Ki-67					
≤14%	194 (56.9)	7 (30.4)	1.00		
>14%	147 (43.1)	16 (69.6)	2.94	1.21—7.14	0.017
Molecular subtype					0.104
Luminal A	222 (65.1)	9 (39.2)	1.00		
Luminal B	38 (11.2)	5 (21.7)	3.10	1.04—9.26	0.042

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Table 3 (*continued*)

	No recurrence (n = 341)	Recurrence (n = 23)	Hazard ratio	95% CI	*P* value
HER-2	39 (11.4)	5 (21.7)	3.05	1.02–9.10	0.046
Basal	42 (12.3)	4 (17.4)	2.27	0.70–7.38	0.172
Receipt of breast radiation					
No	121 (35.5)	8 (34.8)	1.00		
Yes	220 (64.5)	15 (65.2)	1.21	0.51–2.86	0.659
Receipt of adjuvant chemotherapy					
No	98 (28.7)	8 (34.8)	1.00		
Yes	243 (71.3)	15 (65.2)	1.95	0.83–4.60	0.127
Receipt of adjuvant hormone therapy					
No	98 (28.7)	12 (52.2)	1.00		
Yes	243 (71.3)	11 (47.8)	0.39	0.17–0.88	0.024
Receipt of herceptin treatment					
No	41 (12.0)	4 (17.4)	1.00		
Yes	300 (88.0)	19 (82.6)	1.51	0.51–4.43	0.457

Numbers in parentheses represent percentages.

[a] Clinical information regarding the menopausal status of 26 patients was unclear because of hysterectomy (n = 14), no record (n = 7), or the presence of a Mirena device (n = 5).

Table 4 Prognostic factors for disease-free survival in multivariate analysis.

	Hazard ratio	95% CI	*P* value
Presence of lymphovascular invasion	3.39	1.42–8.12	0.006
Negative PR	6.99	2.37–20.83	<0.001
Positive CK5/6	2.89	1.23–6.79	0.015

CI confidence interval.

4. Discussion

In the present study, we investigated the relevance of clinical, radiological, and histopathological factors as predictors of recurrence in breast cancer. Unlike previous studies, radiological and clinicopathological parameters were all into account for prediction of recurrence. In our study, 23 patients (6.3%) experienced a recurrence during the median follow-up period of 5.3 years. Multivariate analysis illustrated only pathologic factors to be independent prognostic factors for worse DFS, which were the presence of LVI, negative PR status, and positive CK 5/6 expression. The presence of calcifications observed on mammography had a trend toward worse DFS although it did not show statistically significance.

Previous studies have shown that presence of LVI is an independent poor prognostic factor in patients with invasive breast cancer.[6,11,12] In our retrospective study, LVI was observed in 15.9% of patients (58/364); this proportion is consistent with the range of 15%–25% reported in previous studies.[11,13] A study by Colleoni et al[14] suggested that LVI significantly correlates with other prognostic features such as positive axillary lymph nodes, young age, larger tumors, high histological grade, high Ki-67, and HER-2 overexpression. Therefore, in the context of the present comprehensive examination of the prognostic value of pathological features, we concluded that LVI might have an important role in determining the outcome in patients with invasive breast cancer.

In our study, positive ER status ($p = 0.019$) and positive PR status ($p < 0.001$) status were significantly associated with longer DFS and a positive PR status ($p < 0.001$) was also an independent predictive factor for longer DFS. Positive hormone receptor expression is associated with a good prognosis; however, even though most hormone-expressing breast cancers that express both ER and PR have a good prognosis, a small minority may express either ER or PR and these cases are associated with poorer outcomes than those that express both ER and PR.[15,16] PR is a stronger prognostic and predictive marker of treatment response and DFS than ER[17] and PR as a prognostic factor in addition to ER may improve the power of ER in predicting the treatment response.

Positive CK5/6 expression ($p = 0.002$) was a significant independent predictive factor for worse DFS in this study. CK5/6 is a basal marker and basal-like breast cancer is associated with negative hormonal status and shorter DFS.[18,19] In our study, 68 patients (18.7%) had positive CK5/6 expression, and among them, recurrence was observed in 14.7% (10/68). This result is consistent with that of a previous study, which reported that basal phenotypes have a more aggressive course than non-basal phenotypes.[18]

In our study, although treatment related factors were not independent predictive factors related with recurrence in multivariate analysis, patients who undergone adjuvant hormone therapy showed significant lower recurrence ($p = 0.024$) in univariate analysis. In this study, 269 patients were ER positive cancers and 254 patients undergone adjuvant hormone therapy. Luminal subtype breast cancers are known to have more favorable prognosis. Moreover, for hormone positive breast cancer, tamoxifen has been the standard therapy for pre-menopausal women and aromatase inhibitors in post-menopausal women preventing recurrence,[20] and extending the duration of adjuvant therapy for 10 years has reduced the late recurrence.[21]

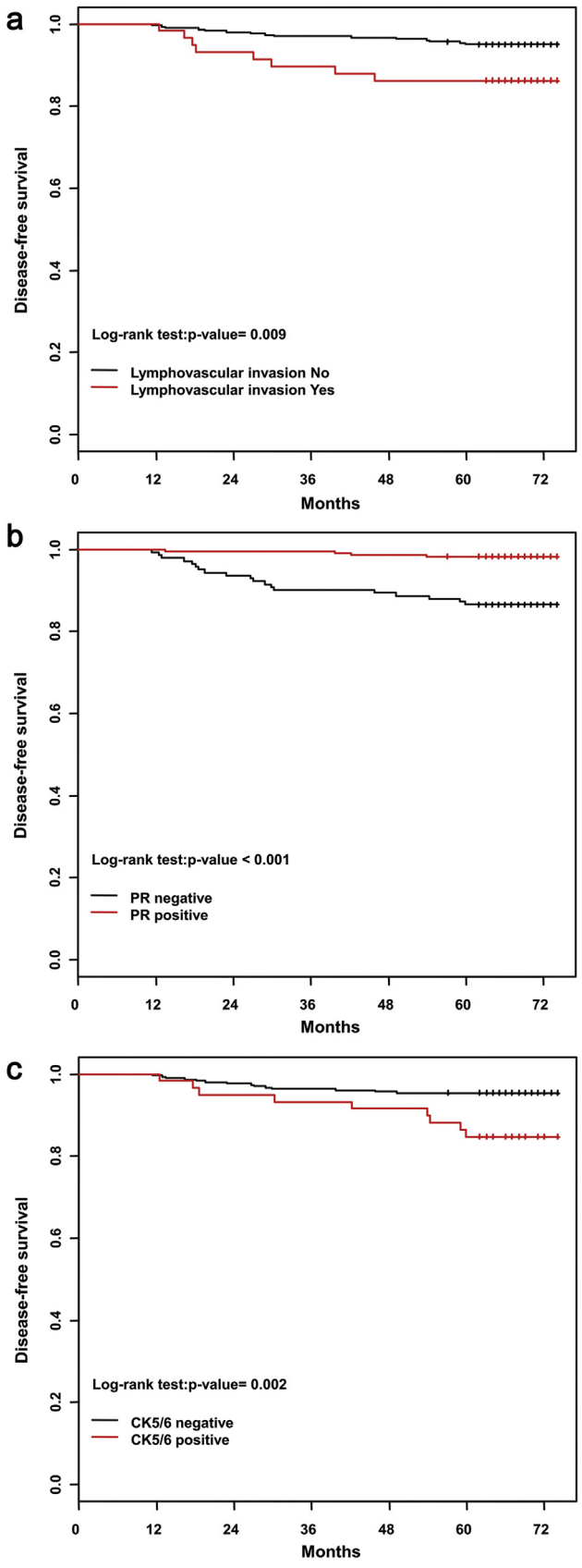

Fig. 1 Kaplan—Meier curves for disease-free survival between patients with and without lymphovascular invasion (A), patients with positive and negative progesterone receptor status (B), and patients with positive and negative CK5/6 expression (C).

There are several reports regarding the radiological features that may represent potential prognostic factors for recurrence of breast cancer. Although there were no significant radiological features capable of predicting the DFS, a trend was observed between the presence of calcifications observed on mammography and worse DFS (HR = 2.23; $p = 0.076$). Kini et al[22] demonstrated that calcifications on preoperative mammography appeared to be associated with an increased risk of local recurrence and that fine linear branching microcalcification observed on mammography was associated with a poor survival rate.[7,22] It has been suggested that "neoductgenesis" may be the underlying mechanism responsible for this worse outcome. This process promotes vascular invasion and consequently excessive lymphatic and hematogenous spread in breast cancer. It is indirectly detected by the presence of extensive fine linear branching calcifications on mammography.[7]

Our study has several limitations. First, the retrospective design and single center nature may have led to selection bias. Second, it contained a relatively small number of recurrent cases. The various prognostic factors obtained in our study need to be validated in a larger, prospective trial to refine the present scores and establish new risk factors.

In conclusion, presence of LVI, negative PR status, and positive CK5/6 expression were independent parameters of worse DFS in patients with invasive breast cancer. Breast cancers with calcification observed on mammography tended to be associated with worse DFS. Understanding the prognostic factors in patients may provide considerable practical information about future treatment strategies.

Conflict of interest

The authors declare that they have no conflict of interest.

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