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Original Article

High-background parenchymal enhancement in the contralateral breast is an imaging biomarker for favorable prognosis in patients with triple-negative breast cancer treated with chemotherapy

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Abstract: This study aimed to analyze the association between background parenchymal enhancement (BPE) in the contralateral breast tissue on magnetic resonance imaging (MRI) and clinicopathologic parameters in patients with unilateral breast carcinoma and to investigate its potential prognostic significance. A total of 467 patients who were pathologically confirmed to have unilateral breast cancer and underwent breast MRI were recruited to participate in this cohort study. BPE was assessed in the healthy contralateral breast. Minimal and mild levels were classified as low BPE, whereas moderate and marked levels were classified as high BPE. The effects of BPE on clinicopathologic parameters, overall survival (OS), and invasive disease-free survival (IDFS) were determined. Among the 467 patients, 327 cases were classified into the low-BPE group, whereas 140 cases were classified into the high-BPE group. The high-BPE pattern markedly correlated with age at diagnosis, menopausal status, histologic grading, and estrogen receptor status. BPE pattern did not correlate with OS and IDFS in the entire breast cancer cohort, regardless of whether adjuvant chemotherapy was received. Notably, BPE in the healthy contralateral breast on MRI is markedly related to OS and IDFS in triple-negative breast cancer (TNBC) cases who received chemotherapy. High BPE is related to chemotherapeutic benefits and can be an independent favorable prognostic factor for TNBC patients. Thus, our observations suggest that high BPE pattern can potentially be used as an imaging biomarker for relatively favorable prognosis in TNBC cases receiving chemotherapy. However, the findings need to be verified in a large-scale study.

Keywords: Breast cancer, MRI, background parenchymal enhancement, prognosis, TNBC

Introduction

Breast cancer is the most common malignancy in females, with a rising incidence rate and the highest cancer mortality worldwide [1]. An estimated 2.1 million new cases and 626,679 deaths were reported in 2018 [2, 3]. Breast carcinoma is a complex and heterogeneous disease with several subtypes that involve vastly different biologic and clinical processes [4]. Gene expression data have identified different breast carcinoma molecular subtypes with distinct phenotypes and prognoses [5]. These subtypes, identified by detecting the expression of specific biomarkers through the immunohistochemical method, include luminal (estrogen receptor [ER]- and/or progesterone receptor [PR]-positive), human epidermal growth factor receptor (HER2) (ER- and PR-negative and HER2-positive), and triple-negative breast cancer (TNBC) (ER-, PR-, and HER2-negative) [6].

TNBC is the most aggressive subtype with early relapse, distant metastasis, and poor prognosis despite appropriate radiotherapy and chemotherapy [7]. Owing to the lack of suitable targets, no endocrine or HER2-targeting therapy exists for TNBC. They tend to occur in younger premenopausal females and more commonly

among African-Americans [8]. However, not all TNBC patients have a poor prognosis. Generally, some TNBCs may experience early recurrence or distant metastasis within about three years after the cancer diagnosis, and other TNBCs with disease-free survival of more than eight years are less likely to die from breast cancer [7, 9]. Therefore, additional common biomarkers are needed to predict the long-term prognosis for breast cancer patients, particularly TNBCs.

Imaging has been widely used to investigate the potential risk for breast carcinoma in high-risk people. High breast density on a mammogram is a significantly high risk for developing breast carcinoma [10]. However, no correlation exists between breast density and overall survival (OS) in females with breast cancer [11]. Dynamic contrast-enhanced magnetic resonance imaging (MRI) can provide helpful information for evaluating the biological behavior of the tumor and breast parenchyma. The early signal increase after enhancement is described as background parenchymal enhancement (BPE), which is classified as minimal, mild, moderate, or marked in accordance with the Breast Imaging-Reporting and Data System [12]. Relevant studies indicate that patients with elevated BPE on MRI show an increased risk for breast cancer [13, 14]. Most studies on the relationship between BPE and prognosis have thus far mainly focused on the tumor or the surrounding parenchyma in the affected breast [15, 16]. Few studies have explored the association between healthy breast BPE and prognosis of patients with breast cancer during long term follow-up [17].

Considering the typical bilateral symmetry of the breasts, we hypothesized that the normal parenchymal tissue of the contralateral healthy breast is similar to that of the ipsilateral breast before tumor formation. In the current study, we examined the BPE pattern in the healthy breast of patients diagnosed with unilateral breast carcinoma on preoperative breast MRI and assessed its potential prognostic significance.

Materials and methods

Participants

The research protocol was reviewed and approved by the Ethics Committee of Qingpu Branch of Zhongshan Hospital Affiliated to Fudan University. Written informed consent was obtained from each participant. All procedures performed in this study involving human participants followed the 1964 Declaration of Helsinki and its subsequent amendments.

A total of 514 females with a pathological diagnosis of breast carcinoma who underwent preoperative breast MRI from 2007 to 2010 at the Qingpu Branch of Zhongshan Hospital Affiliated to Fudan University participated in this study. 47 cases were excluded for the following reasons: (1) receiving neoadjuvant treatment or preoperative radiotherapy (n = 20); (2) presence of other malignant tumors (n = 9); (3) incomplete clinical records (n = 6); (4) poor image quality or image could not be obtained (n = 8); (5) bilateral breast cancer (n = 4). A case series of 467 patients with pathology-confirmed diagnosis of invasive breast cancer were identified. Ultimately, 226 premenopausal patients were included in our analyses, of which 29 patients were examined in the menstrual phase (Days 1-4), 91 in the proliferative phase (Days 5-14), and 106 in the secretory phase (Days 15-30).

Clinical parameters

Data on patient age, menstrual status, tumor size, lymph node involvement, and histological grading were acquired from medical records and pathological reports. Cancer staging was conducted following the *American Joint Committee on Cancer (AJCC)*, 8th edition [18]. The levels of ER, PR, HER2, and Ki-67 expression were specified in the standardized histopathologic report. The expression was considered as ER-positive and PR-positive if more than 10% of the tumor nucleus stained positive [19]. Fluorescence *in situ* hybridization was performed to qualitatively determine HER2 expression in the equivocal evaluation by immunohistochemistry [20]. The Ki-67 index was dichotomized to low and high, with a cutoff of 20% [21].

The prognostic significance of BPE in patients with breast carcinoma was evaluated in the survival analysis, including OS and invasive disease-free survival (IDFS). OS was defined as the period from surgery to death from any cause, and IDFS referred to the period from surgery to local or regional recurrence caused by invasive breast cancer, as well as death from all

causes. Survivors were censored at the date of their last follow-up.

Imaging protocol

Preoperative breast MRI was conducted using a 1.5-T commercially available system (Discovery MR450; GE Healthcare, Waukesha, WI, USA) with an eight-channel breast phased-array coil. The MRI imaging protocols were as follows: transverse fat-saturated T2-weighted sequence (repetition time [TR]/echo time [TE]/inversion time [TI], 6360/45/150 ms; flip angle, 90°; field of view [FOV], 240 mm; matrix, 320 × 192; slice thickness, 5 mm; acquisition time, 2 min 56 s), and pre- and post-contrast transverse fat-saturated T1-weighted imaging (TR/TE/TI, 8.9/4.0/18 ms; FOV, 300 mm; slice thickness, 3 mm; flip angle, 10°; imaging matrix, 416 × 320) obtained before and 91, 182, 273, 364, and 455 s after the intravenous bolus injection of contrast agents. Rapid intravenous injection of gadodiamide (Omniscan; GE HealthCare, Marlborough, MA, USA) was performed from the right antecubital fossa at a dose of 0.1 mmol/kg with a flow rate of 2 mL/s by using an automatic injector.

MR image analysis

All MR data were retrospectively studied using image archiving and a diagnostic workstation by two senior radiology doctors with more than 10 years of MRI diagnostic experience in breast tumors. The reviewers determined that the patients were pathologically diagnosed with breast cancer but did not know the medical history and molecular subtypes. BPE was assessed in the contralateral breast to minimize the increased vascularization effects of the malignancy. In the global evaluation of BPE, a combination of enhanced volume and intensities was considered. The BPE pattern was classified into minimal (less than 25% of parenchymal enhancement), mild (25%-50% of parenchymal enhancement), moderate (51%-75% of parenchymal enhancement), or marked (more than 75% of parenchymal enhancement) by evaluating the post-contrast T1-weighted fat-saturated images at the first dynamic phase [13, 14]. When BPE classification differed between reviewers, both conducted the third assessment and reached a consensus after discussion. The patients were separated into two groups: cases with minimal and mild enhancement were assigned to the low-BPE group, whereas those with moderate and marked enhancement were assigned to the high-BPE group.

Statistical analysis

The data were statistically analyzed using SPSS 19.0 (Chicago, IL, USA) and GraphPad Prism 8.0.2 (San Diego, California, USA). The relationship between BPE classification and clinicopathologic factors was evaluated using the chi-squared method. Spearman correlation analysis was conducted for data with significant differences. Survival curves were generated using the Kaplan-Meier method, and different survival curves were compared using the log-rank test. BPE and clinicopathologic parameters were determined to identify potential prognostic factors by using univariate and multivariate Cox proportional hazard regression. *P*-value < 0.05 was considered statistically significant.

Results

Characteristics of breast cancer patients by BPE pattern

All patients in our cohort were female with a median age of 47 years (range, 23-82 years) at diagnosis. Among the 467 patients, the cases with minimal (n = 117) and mild (n = 210) BPE patterns were classified into the low-BPE group, and those with moderate (n = 98) and marked (n = 42) BPE patterns were classified into the high-BPE group. Representative images of BEP patterns are presented in **Figure 1**. The clinicopathologic parameters of all breast cancer patients are listed in **Table 1**. The majority of the patients (87.4%) received chemotherapy. BPE pattern was correlated with some of the clinicopathologic parameters. High BPE correlated significantly with age at diagnosis (P = 0.002), menopausal status (P < 0.001), histologic grading (P = 0.036), and ER status (P = 0.027). However, no apparent correlation with the remaining characteristics, including the treatment with postoperative chemotherapy and radiotherapy (**Table 1**), was indicated. Notably, no significant difference in BPE pattern distribution was found among the intrinsic subtypes of breast carcinoma (**Table 1**).

Survival analysis

The median follow-up time was 8.7 years from the date of surgery. The median follow-up time

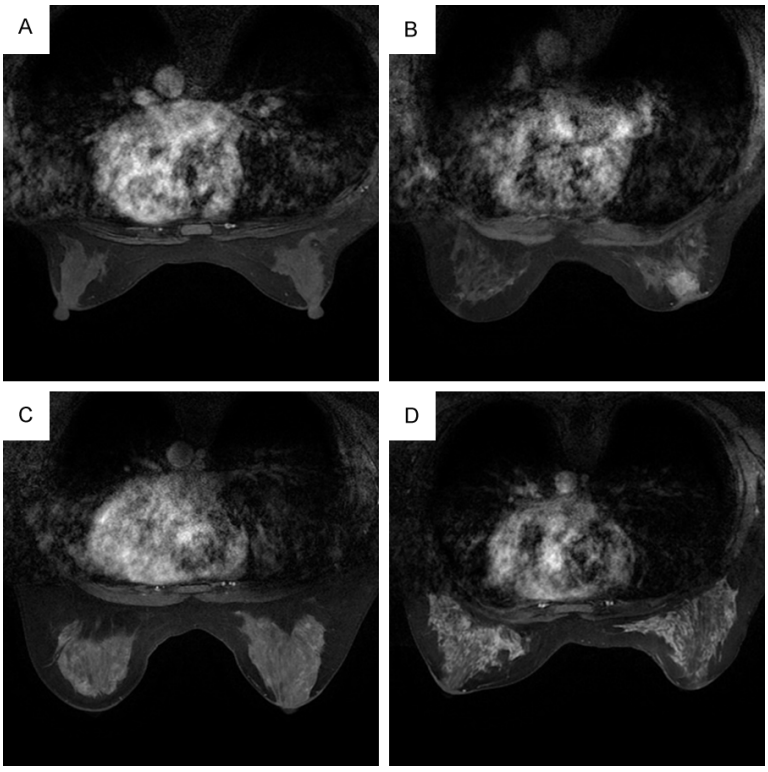

Figure 1. Representative images of varying amounts of background parenchymal enhancement (BPE), as qualitatively assessed. Post-contrast, fat-saturated T1-weighted images at the first dynamic phase showing minimal (A, left), mild (B, left), moderate (C, right), and marked (D, left) BPE in the contralateral breast.

for the low-BPE pattern was 8.7 years and that for the high-BPE pattern was 9.1 years. During follow-up, 22.3% (104 of 467) of the patients died, which consisted of 77 cases from the low-BPE group (i.e., 77 of 327 cases or 23.5%) and 27 cases from the high-BPE group (i.e., 27 of 140 cases or 19.3%). Recurrence was reported in 27.8% (130 of 467) of the patients, which consisted of 96 cases from the low-BPE group (i.e., 96 of 327 cases or 29.4%) and 34 cases from the high-BPE group (i.e., 34 of 140 cases or 24.3%). To explore the association between BPE pattern and clinical outcome, we generated survival curves by using the Kaplan-Meier estimator. These curves were compared using the log-rank statistic. When all cases were included, the BPE pattern had no statistical effect on OS (P = 0.271) or IDFS (P = 0.323) in breast cancer (**Figure 2A**, **2B**). Moreover, in cases treated with postoperative chemotherapy, no differences in OS (P = 0.187) and IDFS (P = 0.139) were observed between the low-BPE and high-BPE groups (**Figure 2C**, **2D**). However, in the subgroup analyses based on the intrinsic subtype, a high-BPE pattern exerted distinct effects on OS (P = 0.016) and IDFS (P = 0.002) in TNBC patients who received chemotherapy but not in those with other molecular subtypes (**Figure 3**). We also performed subgroup analyses on all patients on the basis of molecular subtypes regardless of whether they received chemotherapy. The results showed that the BPE pattern was not related significantly to OS or IDFS in four molecular subtypes, including TNBC (Figure S1). The aforementioned results indicate that high BPE favorably influenced OS and IDFS in TNBC cases treated with postoperative chemotherapy. In addition, the effect of BPE on radiotherapy was explored. In breast cancer patients who received radiotherapy, no significant differences in OS (P = 0.628) and IDFS (P = 0.419) were found between groups with low or high BPE (Figure S2). Subgroup analyses by molecular subtype of breast cancer also indicated that BPE exerted no significant effects on OS and IDFS in patients treated with radiotherapy (Figure S3).

Prognostic analysis

We subsequently investigated the relationship between BPE pattern and prognosis of TNBC patients who received chemotherapy. Univariate analyses indicated that TNBC patients with high BPE were more likely to exhibit marked improvement in OS and IDFS than do TNBC patients with low BPE after chemotherapy. The other variables predicting poor clinical outcomes based on the univariate analyses included enlarged tumors, advanced lymph node staging, presence of lymph node metastasis, and advanced staging in TNBC cases who received chemotherapy (**Table 2**). Moreover, multivariate statistical analyses were conduct-

Table 1. Association between BPE pattern and clinicopathological characteristics

Characteristics	All patients n = 467		Low BPE n = 327		High BPE n = 140		*P* value
	No.	%	No.	%	No.	%	
Age (years)							**0.002**
≤ 50	238	51.0	151	46.1	87	62.4	
> 50	229	49.0	176	53.9	53	37.6	
Menopausal status							**P < 0.001**
Premenopausal	226	48.4	140	42.7	86	61.1	
Postmenopausal	241	51.6	187	57.3	54	38.9	
Tumor size							0.354
T1	175	37.5	127	38.8	48	34.3	
T2	265	56.7	184	56.2	81	57.8	
T3 or T4	27	5.8	16	5.0	11	7.9	
Lymph node involvement							0.243
N0	235	50.3	171	52.2	64	45.6	
N1	114	24.4	79	24.2	35	24.8	
N2	62	13.3	44	13.5	18	12.9	
N3	56	12.0	33	10.1	23	16.7	
Lymph node metastasis							0.193
Negative	235	50.3	171	52.2	64	45.6	
Positive	232	49.7	156	47.8	76	54.4	
AJCC stage							
I	111	23.8	86	26.4	25	18.1	0.144
II	240	51.4	162	49.4	78	55.7	
III	116	24.8	79	24.2	37	26.2	
Histological grade							**0.036**
1	47	10.0	40	12.3	7	4.7	
2	162	34.7	117	35.7	45	32.2	
3	218	46.7	141	43.2	77	55.0	
Unknown	40	8.6	29	8.8	11	8.1	
ER							**0.027**
Negative	191	40.9	123	37.6	68	48.4	
Positive	276	59.1	204	62.4	72	51.6	
PR							0.400
Negative	253	54.2	173	52.8	80	57.0	
Positive	214	45.8	154	47.2	60	43.0	
HER2							0.111
Negative	334	70.3	241	73.6	93	66.4	
Positive	133	29.7	86	26.4	47	33.6	
Adjuvant chemotherapy							0.414
No	59	12.6	44	13.5	15	10.7	
Yes	408	87.4	283	86.5	125	89.3	
Adjuvant radiotherapy							0.171
No	132	28.3	85	26.0	47	33.6	
Yes	319	68.3	232	70.9	87	62.1	
Unknown	16	3.4	10	3.1	6	4.3	
Molecular subtype							0.430
Luminal A	205	43.9	148	45.3	57	40.7	
Luminal B	77	16.5	51	15.6	26	18.6	
HER2	56	12.0	35	10.7	21	15.0	
TNBC	129	27.6	93	28.4	36	25.7	

BPE, background parenchymal enhancement; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer. *P*-values that reach significance are in bold.

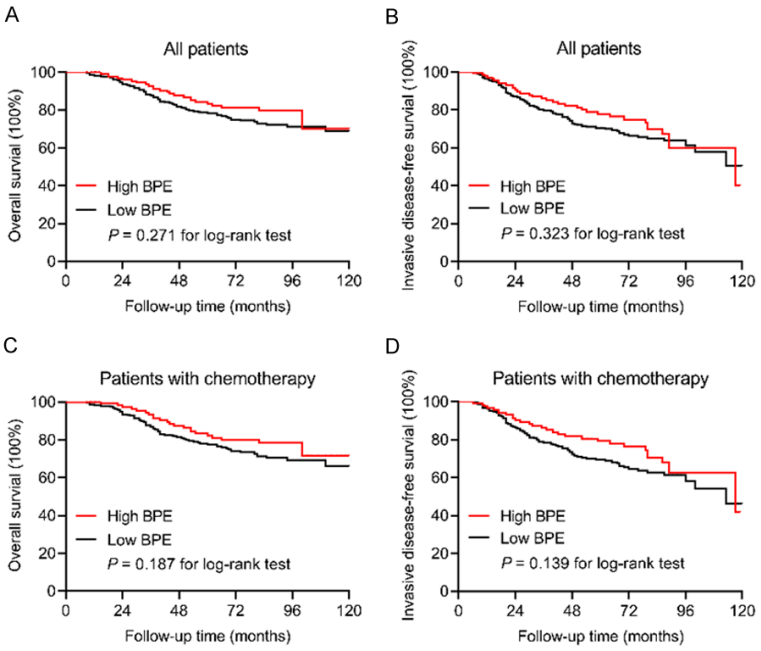

Figure 2. Association between the background parenchymal enhancement (BPE) pattern and clinical outcome in patients with breast cancer. A, B. Kaplan-Meier curves for overall survival (OS) and invasive disease-free survival (IDFS) based on the BPE pattern in all patients with breast cancer. C, D. Kaplan-Meier curves for OS and IDFS according to the BPE pattern in patients with breast cancer who received chemotherapy.

ed with the Cox proportional hazards model to adjust the aforementioned factors that showed statistical significance in the univariate analyses. Lymph node involvement was excluded from the analysis because of the repeat to lymph node metastasis and the limited sample size of the subgroup with lymph node involvement. Notably, high BPE was significantly correlated with the improvement in OS and IDFS in TNBC patients who received chemotherapy (**Table 2**; **Figure 4**). These results indicate that high BPE is related to chemotherapeutic benefits and can be an independent favorable prognostic factor for TNBC patients.

Discussion

Owing to the lack of valid molecular targets, no specific systematic treatment strategy has been established for TNBC patients. Currently, therapeutic strategies for the management of TNBC mainly depend on chemotherapy and radiotherapy. Some studies have reported that TNBC patients respond better to adjuvant chemotherapy than do patients with other molecular subtypes of breast cancer; regardless, the clinical prognosis remains poor [22]. Therefore, identifying new biomarkers that can be used to predict the effects of conventional chemotherapy can potentially improve the clinical outcome of TNBC. The present study revealed that high MRI background parenchymal enhancement in the contralateral breast predicted a relatively favorable outcome in TNBC patients who received chemotherapy.

We examined the preoperative MR images of 467 patients with unilateral breast cancer. Measurement of BPE in the contralateral normal breast was considered to reflect the enhancement of normal breast tissue around the malignant tumor in the affected breast [23]. To our knowledge, the relationship between BPE and clinicopathological parameters and outcome in breast cancer patients has been poorly investigated, and the results are inconclusive. Our results showed that BPE was related to age, menopausal status, histological grading, and ER status. Regardless, we found no significant correlation between BPE pattern and molecular subtypes of breast cancer. Our findings also showed no association between BPE pattern and survival analyses, including OS and IDFS. In the subgroup analyses, high BPE correlated with prognostic improvement in TNBC patients who received chemotherapy but not in patients with other subtypes of breast cancer. Therefore, BPE can potentially be a favorable prognostic imaging biomarker for TNBC patients receiving adjuvant chemotherapy.

Some studies revealed that parenchymal enhancement in breast MRI is influenced by cyclical hormone fluctuations in the menstrual cycle [24, 25]. Müller-Schimpfle et al. reported that participants showed higher BPE from Day 21 to Day 6 than from Day 7 to Day 20 of the menstrual cycle [26]. Kajihara et al. confirmed that BPE was relatively elevated during the luteal period [27]. Therefore, conducting an MRI

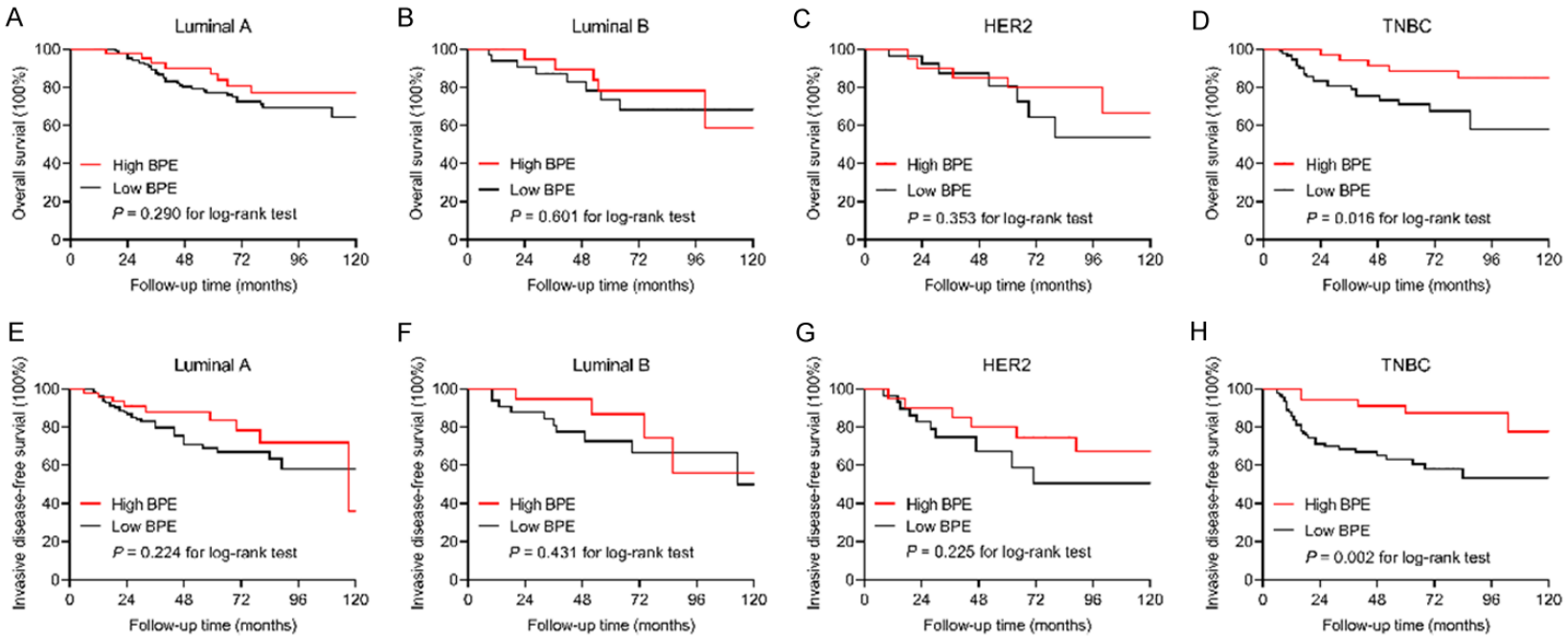

Figure 3. Prognostic significance of the background parenchymal enhancement (BPE) pattern in patients with triple-negative breast cancer who received chemotherapy. A-D. Kaplan-Meier curves for overall survival, based on the BPE pattern in patients with different molecular subtypes of breast cancer who received chemotherapy. E-H. Kaplan-Meier curves for invasive disease-free survival, based on the BPE pattern in patients with different molecular subtypes of breast cancer who received chemotherapy.

Table 2. Univariate and multivariate analyses of OS and IDFS in the TNBC patients who received chemotherapy

Parameters	Number	Univariate analysis				Multivariate analysis			
		OS		IDFS		OS		IDFS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age									
≤ 50	87	Reference		Reference					
> 50	40	1.25 (0.59-2.51)	0.537	0.74 (0.31-1.64)	0.562				
Menopausal status									
Pre	82	Reference		Reference					
Post	45	0.70 (0.40-1.21)	0.207	0.79 (0.50-1.24)	0.305				
Tumor size									
T1	44	Reference		Reference		Reference		Reference	
T2	74	2.15 (0.86-5.35)	0.095	2.08 (0.88-4.85)	0.090	0.75 (0.13-4.11)	0.751	0.72 (0.13-3.74)	0.703
T3 or T4	9	7.64 (2.47-23.72)	**< 0.001**	4.57 (1.33-15.67)	**0.016**	1.10 (0.19-7.42)	0.960	0.79 (0.10-5.67)	0.792
Lymph node involvement									
N0	73	Reference		Reference					
N1	29	1.04 (0.37-2.95)	0.940	0.76 (0.27-2.09)	0.609				
N2	14	3.02 (1.14-8.05)	**0.027**	2.19 (0.86-5.59)	0.103				
N3	11	15.23 (6.43-36.02)	**< 0.001**	7.97 (3.21-19.77)	**< 0.001**				
Lymph node metastasis									
No	73	Reference		Reference		Reference		Reference	
Yes	54	2.76 (1.33-5.62)	**0.007**	1.74 (0.86-3.41)	0.092	0.95 (0.25-3.54)	0.953	0.66 (0.21-2.21)	0.478
AJCC stage									
I	34	Reference		Reference		Reference		Reference	
II	67	1.51 (0.46-4.70)	0.449	1.67 (0.64-4.52)	0.330	2.36 (0.31-18.37)	0.415	3.06 (0.47-21.09)	0.264
III	26	6.69 (2.26-19.95)	**< 0.001**	4.54 (1.65-12.68)	**0.004**	8.63 (0.54-144.08)	0.136	10.55 (0.73-157.24)	0.089
Histological grade									
1	2	-							
2	25	Reference		Reference					
3	79	1.82 (0.60-5.35)	0.255	1.62 (0.67-4.20)	0.359				
Unknown	21	-	-	-	-				
BPE pattern									
Low	91	Reference		Reference		Reference		Reference	
High	36	0.10 (0.01-0.62)	**0.014**	0.16 (0.04-0.72)	**0.016**	0.14 (0.01-0.77)	**0.020**	0.22 (0.04-0.84)	**0.029**

OS, overall survival; IDFS, invasive disease-free survival; TNBC, triple-negative breast cancer; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; BPE, background parenchymal enhancement. *P*-values that reach significance are in bold.

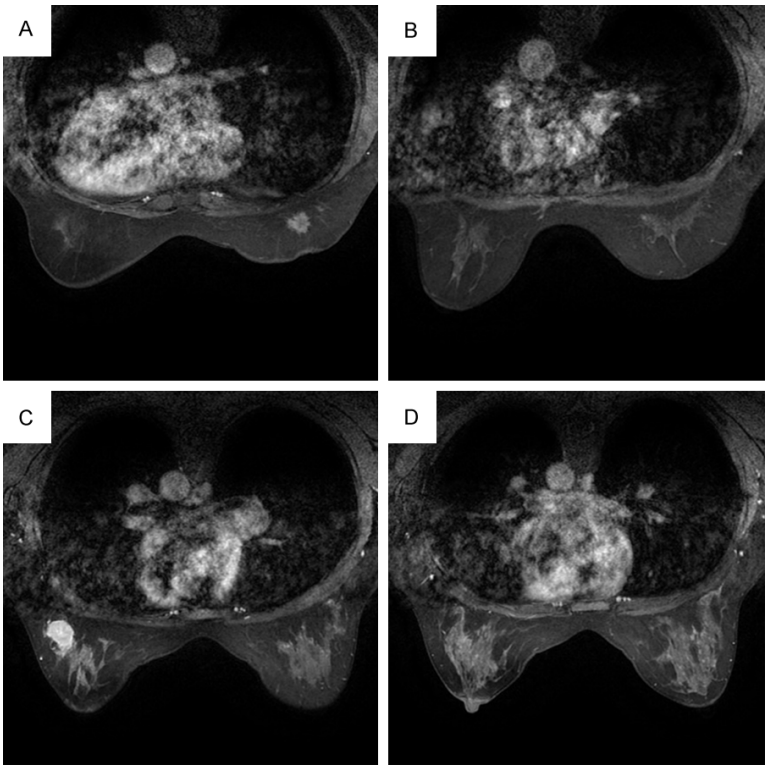

Figure 4. Pretreatment breast MRI in a 59-year-old female with triple-negative breast cancer (A, B). The fat-saturated contrast-enhanced T1-weighted images in the early phase show an irregular tumor in the lower quadrant of the right breast (A) and mild background parenchymal enhancement in the contralateral breast (B). This patient underwent adjuvant chemotherapy after surgery and experienced local-regional recurrences and lung metastases after a follow-up of 37 months. Pretreatment breast MRI in a 43-year-old female with triple-negative breast cancer (C, D). The fat-suppressed contrast-enhanced T1-weighted images in the early phase show a lobulated tumor in the upper outer quadrant of the left breast (C) and moderate background parenchymal enhancement in the contralateral breast (D). This patient received chemotherapy after surgery, and no recurrence was detected in a recent follow-up.

examination in the second week of the menstrual cycle is recommended to reduce the enhancement of normal mammary glands. The guidelines issued by the European Society of Breast Imaging indicate that the optimal time to perform a breast MRI in premenopausal women is between Day 5 and Day 12 of the menstrual cycle [28]. However, Kamitani et al. stated that breast MRI was suitable for the Asian population not only in the proliferative phase but also in the menstrual phase (Week 1) [29]. The breasts of Asian women are commonly characterized as dense or heterogeneously dense, relative to those of Western women [30, 31]. Differences in the distribution of the breast composition between Asian women and Western women might have contributed to the longer appropriate phase in premenopausal Asian women than in Western countries. However, in our analysis, MRI was not always conducted within the suggested optimal phase of the menstrual cycle to avoid delay in surgical treatment.

In the current study, the effect of BPE on healthy breast MR images was assessed for all cases. Some studies focused on tumor-induced changes in the surrounding-tumor parenchyma or evaluated BPE of the ipsilateral breast, which could be affected by increased vascularization due to the presence of breast cancer [15, 32, 33]. Verardi et al. found that increased fibroglandular vascularization was correlated with the presence of an ipsilateral malignant tumor, particularly for tumors with a diameter of more than 2 cm or exhibiting higher histological grading [34]. The healthy contralateral breast could be considered comparable to the ipsilateral breast, given the symmetry between the two breasts, and a hypothesis was formulated that the properties of the healthy parenchyma could provide useful information about breast cancer [35, 36]. Van der Velden recently reported that contralateral BPE was significantly associated with long-term outcome, particularly in ER-positive, HER2-negative invasive breast cancer patients [17]. You et al. demonstrated that the reduced BPE of the contralateral breast after two cycles of neoadjuvant chemotherapy was associated with tumor response in HER2-positive breast cancer [37]. A recent systematic review was conducted by Rella et al. to summarize evidences of the relationship between BPE in the contralateral healthy breast and breast cancer [38]. These findings indicate that the MRI assessment of BPE in the contralateral breast can prevent cancer-mediated false elevation and has the potential as a predictive and

prognostic biomarker. Therefore, the MRI assessment of BPE on contralateral breast has been proposed as a tool to refine breast cancer decision-making process.

Age and menstrual cycle have been shown to influence parenchymal enhancement [26]. Consistent with previously published studies [14, 39, 40], the current study indicated that BPE was negatively correlated with age (cut-off value of age, 50 years) and menopause in breast cancer patients. Generally, the average age of menopause in Chinese women is about 50 years [41, 42]. The extent of BPE is comparable only during the same menstrual status. The effect of age is adjusted to 50 years in the prognosis of patients with breast cancer, creating relatively homogeneous groups. This cut-off point can be used to evaluate various predictive and prognostic factors of breast cancer [43, 44]. Estrogen and progesterone levels in the body vary with the menstrual period. Estrogen may promote vasodilation and increase vascular permeability through histamine-like effects, and progesterone accelerates the proliferation of fibroglandular tissue by its mitogenic activity [24, 25, 45]. Premenopausal women usually have higher levels of estrogen and progesterone than those of postmenopausal women. Thus, the viability of mammary gland cells and local vascularity in premenopausal females are markedly higher than those in postmenopausal females, leading to a more apparent enhancement in premenopausal females than the latter [13, 46, 47]. Estrogen and progesterone levels gradually reduced with age. A previous study also suggested that parenchyma enhancement is lower in mature women than in young women [48]. However, King et al. demonstrated that menopause causes a more significant reduction in enhancement than that of age [24].

Given the correlation of the BPE pattern with serum levels of estrogen and progesterone in the body, we determined whether luminal breast cancer was more likely to show a relatively high BPE pattern than non-luminal breast cancer. A high-BPE pattern was revealed in breast cancer with ER positivity ($P = 0.027$) but not PR positivity. Luminal subtypes of breast cancer are ER-positive malignancies; thus, elevated BPE can potentially increase the risk of developing luminal-positive breast cancer. However, no correlation between BPE and intrinsic molecular subtypes was determined in the entire cohort. The results of the current study were consistent with the observations reported by Öztürk et al., Kim et al., and Li et al. [49-51]. BPE may not affect the determination of the molecular subtype. Meanwhile, Dilorenzo et al. indicated that luminal B (HER2-negative) breast cancer exhibited a significant correlation with mild BPE, and TNBC cancer showed a significant correlation with marked BPE. Mazurowski et al. also reported that the higher the ratio of lesion enhancement rate to the BPE rate, the higher the probability of breast carcinoma being luminal B [52]. Low-background parenchyma enhancement may be associated with the luminal B subtype of breast cancer. More studies should be conducted to confirm these results. For other histopathological characteristics, high BPE has been reported to be associated with tumor size, lymph node metastasis, AJCC staging, and histological grading [47, 50, 53]. The current results showed no relationship between BPE and these parameters except for histological grade. The inconsistency may be partly attributed to the differences in sample size, BPE evaluation, and study design.

A previous study reported that high parenchymal enhancement on breast MRI was associated with longer DFS time than low parenchymal enhancement [15]. The normal occurrence of mammary mesenchymal outside the tumor may influence tumor progression and reaction to treatment [54, 55]. These findings suggest that increased BPE can potentially signal an increase in microvascular density, which contributes to the delivery of more chemotherapeutic agents to a tumor, indicating an association with good response to adjuvant chemotherapy and a good prognosis [15, 56]. By contrast, Kim et al. reported that increased fibroglandular enhancement on breast MRI was related to ipsilateral relapse in breast cancer patients who underwent breast-conserving surgery [16]. Choi et al. also demonstrated that elevated BPE on MRI of the contralateral breast correlated with poor prognosis in patients with invasive breast carcinoma who received neoadjuvant chemotherapy [57]. Indeed, the relationship between BPE and clinical prognosis remains inconclusive. In the current, BPE pattern exerted no distinct effect on OS or IDFS

in patients regardless of whether they received chemotherapy.

The present study emphasizes that the prognostic significance of BPE was observed only in TNBC patients who underwent chemotherapy but not in those with other subtypes of breast cancer. Vascular endothelial growth factor (VEGF), an effective angiogenic cytokine, induces endothelial cell mitosis and increases vascular permeability and relates to increased relapse-free survival rate in breast carcinoma [58, 59]. Elevated serum levels of VEGF in TNBC have been reported, with levels up to three times greater than that in non-TNBC [60]. VEGF can convert some non-functional vessels into functional ones, allowing more chemotherapeutic drugs to kill numerous tumor cells [61]. On the basis of this assumption, BPE can be used as an imaging biomarker of vascular normalization; moreover, high BPE in the contralateral breast can be correlated with a large number of functional vessels, which are expected to deliver more cytotoxic chemotherapy agents to tumor parenchyma, consequently improving the outcome in TNBC patients.

The percentage of stromal tumor-infiltrating lymphocytes (TILs) shows a significant correlation with the obvious enhancement of tumor-adjacent parenchyma in breast cancer [62]. TILs are related to complete pathological response and good normal outcome in patients with localized breast carcinoma who received chemotherapy [63]. Wu et al. demonstrated that TILs in TNBC were significantly higher than those in HR-positive/HER2-negative breast cancer; in addition, higher TILs were associated with better prognosis and longer recurrence-free survival time in TNBC but not in other subtypes [64]. The potential explanation is that TNBC patients may benefit from TIL-mediated inflammation or immune response induced by adjuvant chemotherapy. However, Park et al. reported that increased signal enhancement surrounding the tumor on breast MRI is a biomarker for poor relapse-free survival in TNBC patients [65]. This finding contradicts the current study. The conflicting results may be partly attributed to the difference in BPE measurement methods. Park et al. used the signal enhancement ratio of normal breast tissue to tumor in their study. Another possible explanation is that the enhancement was measured around the tumor in the affected breast; the adjacent tumor vascular supply might have influenced the assessment. Further studies regarding the effect of high BPE on TNBC patients need to be conducted.

This study has several limitations. First, MRI was not always conducted within the suggested optimal phase of the menstrual cycle. Postponing the breast MRI to decrease parenchymal enhancement would result in delayed surgical treatment. However, this limitation was observed in the low-BPE and high-BPE groups in the entire cohort, likely avoiding bias. Second, this study was conducted in a single institution and included only the Asian population. MRI systems vary among different institutions. Thus, the present findings need to be verified in the multi-agency setting and other populations. Third, this research is a retrospectively observational study. Despite the relatively large sample size, the number of TNBC patients is limited. Larger prospective studies have to be conducted to confirm the influence of BPE on the clinical outcome of TNBC patients who received postoperative chemotherapy. Finally, assessment of the BPE pattern is subjective, implying dependence on the clinical expertise of the radiologist. The intra-observer and inter-observer agreement cannot be evaluated because the consensus was reached when the BPE assessment of the two radiologists differed.

Although TNBC is an aggressive subtype with poor clinical survival, some cases exhibit sensitive response to cytotoxic chemotherapy with a relatively good prognosis. Our findings revealed that BPE in the healthy contralateral breast significantly correlated with long-term outcome in TNBC patients who received chemotherapy. High parenchymal enhancement can be potentially used as an imaging marker for a favorable prognosis of TNBC patients receiving chemotherapy.

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Disclosure of conflict of interest

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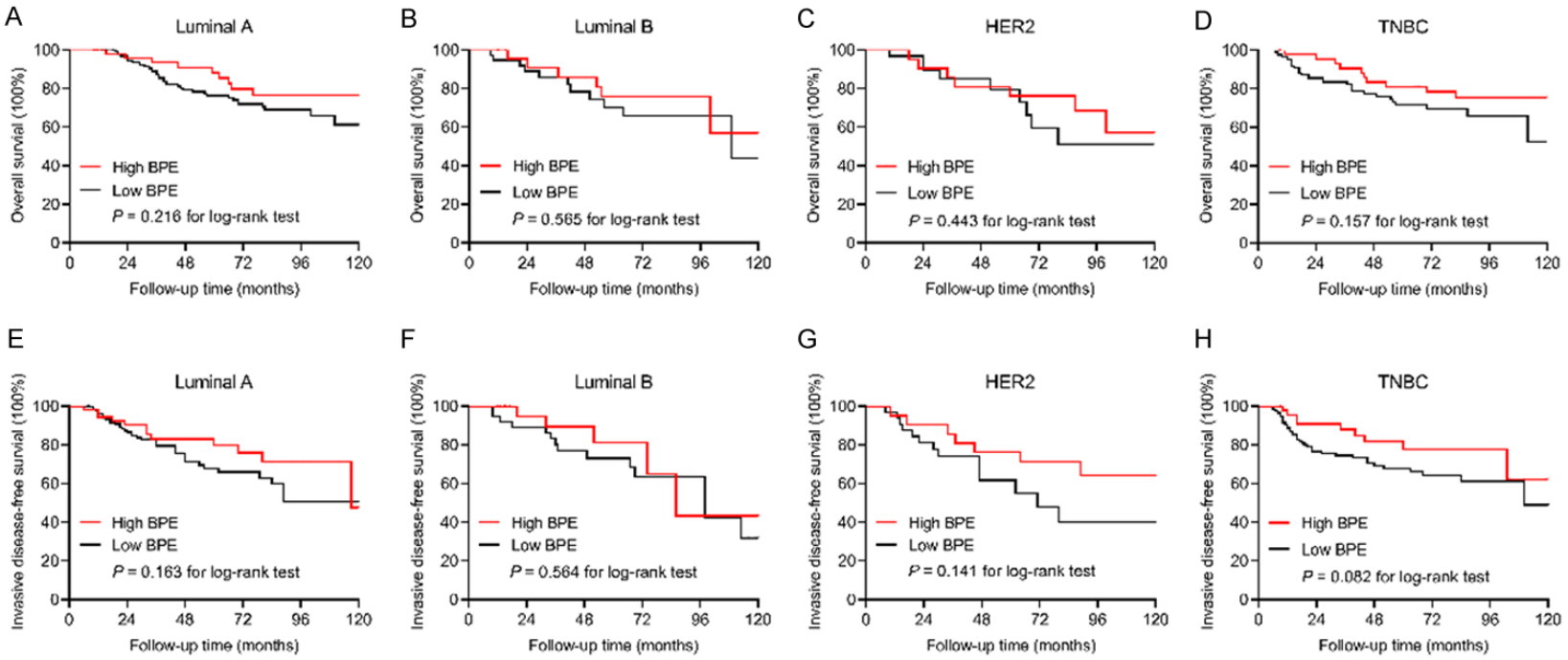

Figure S1. Kaplan-Meier curves for overall survival (A-D) and invasive disease-free survival (E-H) based on the background parenchymal enhancement (BPE) pattern in all patients with different molecular subtypes of breast cancer.

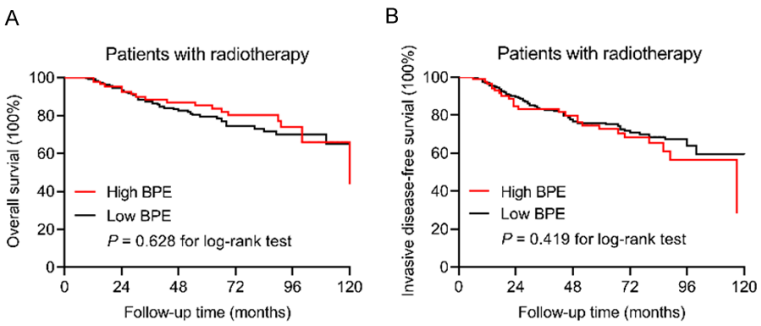

Figure S2. Kaplan-Meier curves for overall survival (A) and invasive disease-free survival (B) according to the background parenchymal enhancement (BPE) pattern in patients with breast cancer who received radiotherapy.

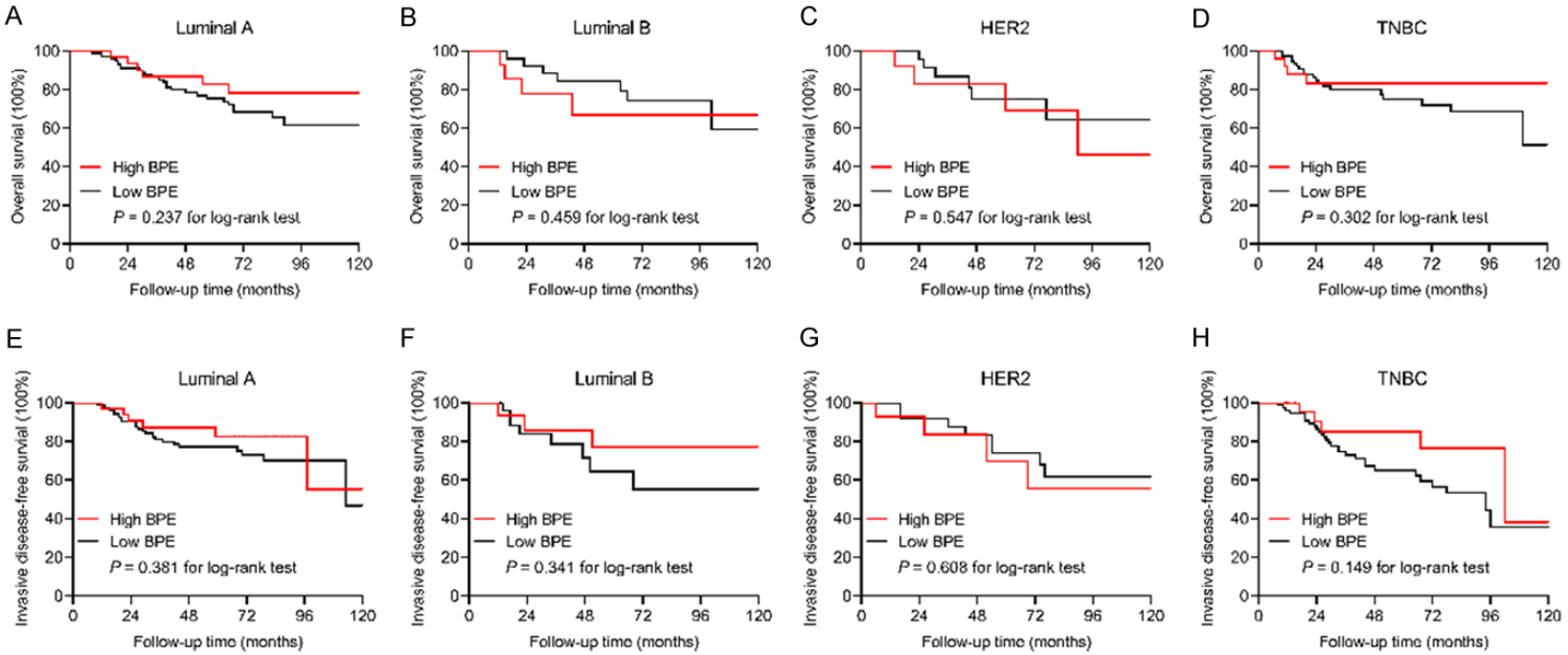

Figure S3. Prognostic significance of the background parenchymal enhancement (BPE) pattern in patients with breast cancer who received radiotherapy. A-D. Kaplan-Meier curves for overall survival, based on the BPE pattern in patients with different molecular subtypes of breast cancer who received radiotherapy. E-H. Kaplan-Meier curves for invasive disease-free survival, based on the BPE pattern in patients with different molecular subtypes of breast cancer who received radiotherapy.