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Association between Parenchymal Enhancement of the Contralateral Breast in Dynamic Contrast-enhanced MR Imaging and Outcome of Patients with Unilateral Invasive Breast Cancer[1]

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Purpose: To retrospectively investigate whether parenchymal enhancement in dynamic contrast material–enhanced magnetic resonance (MR) imaging of the contralateral breast in patients with unilateral invasive breast cancer is associated with therapy outcome.

Materials and Methods: After obtaining approval of the institutional review board and patients' written informed consent, 531 women with unilateral invasive breast cancer underwent dynamic contrast-enhanced MR imaging between 2000 and 2008. The contralateral parenchyma was segmented automatically, in which the mean of the top 10% late enhancement was calculated. Cox regression was used to test associations between parenchymal enhancement, patient and tumor characteristics, and overall survival and invasive disease–free survival. Subset analyses were performed and stratified according to immunohistochemical subtypes and type of adjuvant treatment received.

Results: Median follow-up was 86 months. Age ($P < .001$) and immunohistochemical subtype ($P = .042$) retained significance in multivariate analysis for overall survival. In patients with estrogen receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative breast cancer ($n = 398$), age ($P < .001$), largest diameter on MR images ($P = .049$), and parenchymal enhancement ($P = .011$) were significant. In patients who underwent endocrine therapy ($n = 174$), parenchymal enhancement was the only significant covariate for overall survival and invasive disease–free survival ($P < .001$).

Conclusion: Results suggest that parenchymal enhancement in the contralateral breast of patients with invasive unilateral breast cancer is significantly associated with long-term outcome, particularly in patients with estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer. Lower value of the mean top 10% enhancement of the parenchyma shows potential as a predictive biomarker for relatively poor outcome in patients who undergo endocrine therapy. These results should, however, be validated in a larger study.

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Breast cancer is no longer considered to be a single disease but is categorized in three different subtypes according to immunohistochemistry (IHC) (1): estrogen receptor positive (and human epidermal growth factor receptor 2 [HER2] negative, independent of progesterone receptor status), HER2 positive (independent of estrogen receptor and progesterone receptor status), and "triple negative" (estrogen receptor negative, progesterone receptor negative, and HER2 negative).

Different treatment plans are advised for the different IHC subtypes, including endocrine therapy for estrogen receptor–positive HER2-negative tumors, anti-HER2 therapy for HER2-positive tumors, and cytotoxic therapy for estrogen receptor–positive HER2-negative tumors, HER2-positive tumors, and triple-negative tumors. Nonetheless, variation still exists in treatment outcome within breast cancer subtypes. This may be due to de novo and acquired resistance to endocrine therapy (2). Hence, additional biomarkers for obtaining a more patient-specific prediction of treatment outcome are desirable.

Imaging techniques have been used to analyze risk factors of the microenvironment in vivo prior to treatment. A well-established risk factor is mammographic breast density (3); women with relatively more parenchyma are at higher risk of developing breast cancer. Although pretreatment density is related to the risk of developing breast cancer, it is not related to survival of women with breast cancer (4). Dynamic contrast material–enhanced magnetic resonance (MR) imaging of the breast allows assessment of the functional behavior of the tumor and the parenchyma. An increase in enhancement of the parenchyma has been associated with an increased odds ratio to develop breast cancer (5). Studies on the association between MR imaging and outcome of patients with breast cancer have thus far focused primarily on the tumor itself or on tumor-induced changes in the surrounding parenchyma (6,7). It remains unknown whether properties of the healthy parenchyma are associated with therapy outcome.

Given the typical symmetry between left and right breast, we hypothesize that the parenchyma of the healthy contralateral breast is comparable to that of the ipsilateral breast before tumorigenesis. The purpose of this retrospective study was to determine whether parenchymal enhancement of the contralateral breast of patients with unilateral invasive breast cancer was associated with therapy outcome.

Advances in Knowledge

- Top 10% parenchymal enhancement in the contralateral breast of patients with invasive unilateral breast cancer is significantly associated with long-term outcome, particularly in patients with estrogen receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer (n = 398; overall survival [OS] hazard ratio, 0.03; 95% confidence interval [CI]: 0.00, 0.44; P = .011).
- In patients with estrogen receptor–positive, HER2-negative breast cancer who are undergoing endocrine therapy (n = 174), lower top 10% enhancement of the parenchyma in the contralateral breast is the only significant covariate in Cox regression and shows potential as a predictive biomarker for relatively poor outcome (OS hazard ratio, 0.00; 95% CI: 0.00, 0.06; $P < .001$).

Materials and Methods

Patient Cohort

Data were acquired after approval of the institutional review board and receipt of written informed patient consent. Financial support was provided in part by Guerbet, Villepinte, France. The authors had full control of the data and the information submitted for publication. A subset of 596 consecutive women with unilateral invasive breast cancer who participated in the prospective Multimodality Analysis and Radiological Guidance IN breast conServing therapy, or MARGINS, trial (2000–2008) was included for a retrospective analysis. In the MARGINS trial, the patients eligible for breast-conserving therapy on the basis of conventional imaging and clinical assessment were recruited for additional preoperative breast MR imaging. Proof of breast cancer was acquired by using image-guided fine-needle aspiration or core biopsy. Treatment plans were established in consensus by a multidisciplinary team of breast cancer specialists. Patients who underwent previous breast surgery (22 of 596 patients, 4%), those whose study records were incomplete (26 of 596 patients, 4%), or those whose image acquisition or image registration failed (17 of 596 patients, 3%) were excluded, after which 531 patients remained. Part of these data have been investigated in previous studies

Implication for Patient Care

- Contralateral parenchymal enhancement has the potential to serve as a biomarker to guide therapy selection in patients with estrogen receptor–positive, HER2-negative breast cancer.

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Abbreviations:
CI = confidence interval
HER2 = human epidermal growth factor receptor 2
IDFS = invasive disease–free survival
IHC = immunohistochemistry
OS = overall survival

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Conflicts of interest are listed at the end of this article.

that focused on tumor staging at MR imaging (94 of 531 patients [18%] [8]; 515 of 531 patients [97%] [9,10]; 140 of 531 patients [26%] [11]). Timing of the MR imaging to the menstrual cycle was not performed in the MARGINS trial, because it could lead to delay of surgery. The mean age at diagnosis ± standard deviation was 56 years ± 10.

Clinical Covariates

Clinical covariates investigated were age at diagnosis, largest tumor diameter on MR images, histologic grade, IHC subtype, adjuvant systemic therapy, tumor type, and axillary load. The largest tumor diameter on MR images was measured in three orthogonal directions by a dedicated breast MR imaging radiologist (C.E.L., with more than 10 years of experience), after which the largest of the three measurements was obtained. Histologic grade was assessed according to the Bloom and Richardson method (12). Tumors were classified as estrogen receptor positive or progesterone receptor positive if more than 10% of the cells were stained positive. Tumors were classified as HER2 positive when scored at least 3 at IHC or when in situ hybridization demonstrated gene amplification. Adjuvant systemic therapy was "yes" when a patient underwent cytotoxic, hormonal, or anti-HER2 therapy or a combination of these. Tumor type was stratified into invasive ductal carcinoma, invasive lobular carcinoma, or other invasive carcinoma. Axillary load was stratified into three groups: no positive lymph nodes, one to three positive lymph nodes, or four or more positive lymph nodes.

MR Imaging

MR images were acquired by using a 1.5-T imaging unit (Magnetom; Siemens, Erlangen, Germany) with a dedicated double breast array coil (CP Breast Array, four channels; Siemens). An unenhanced coronal fast low-angle shot three-dimensional T1-weighted image was acquired. A bolus (14 mL) of gadolinium-based contrast material (Prohance; Bracco-Byk Gulden, Konstanz, Germany) was administered at 3 mL/sec by using a power injector, followed by a bolus of 30 mL of saline solution. Subsequently, four consecutive contrast-enhanced series were acquired. The imaging parameters were acquisition time of 90 seconds, repetition time (msec)/echo time (msec) of 8.1/4.0, flip angle of 20°, voxel size of 1.35 × 1.35 × 1.35 mm, and field of view of 310 mm.

Image Processing

The processing of the MR images consisted of two main steps: parenchymal segmentation and calculation of enhancement. Processing was implemented by using the Insight Segmentation and Registration Toolkit and Visualization Toolkit (Kitware, Clifton Park, NY) and MeVisLab software (MeVis Medical Solutions, Bremen, Germany).

Parenchymal segmentation.—Parenchyma on MR images was fully automatically segmented in three dimensions. The following steps were performed: *(a)* Correction of field inhomogeneities was conducted by adopting Nick's nonparametric nonuniform intensity normalization Insight Toolkit implementation for MR imaging bias field correction (13). *(b)* Deformable registration of the postcontrast time series to the precontrast time series was performed by adopting a custom-developed method (14). *(c)* Segmentation of the breast volume was conducted by adopting a custom-developed breast segmentation tool (15), thus yielding the breast mask. Incorrect breast masks were manually corrected (B.H.M.v.d.V., a biomedical engineer with 2 years of experience in breast MR imaging postprocessing). The breast mask was applied to the bias field–corrected precontrast time series to restrict the region of interest for subsequent calculations to the breast. *(d)* Segmentation of the parenchyma was performed by using fuzzy c-means clustering (16) with two classes at threshold value of 0.5, thus yielding the parenchymal mask. The number of voxels in the parenchymal mask divided by the number of voxels in the breast mask was calculated automatically in three dimensions and was defined as the "percentage of dense tissue." An example of the image processing is displayed in Figure 1.

Calculation of enhancement.—Each voxel in the parenchyma at breast MR imaging typically shows a continuous increase in signal intensity over time after contrast material injection (Fig 2), albeit with differences in the rate of the signal intensity increase between voxel locations. For each location, consider the signal intensity at two time points (S_1 and S_4) on the time versus signal intensity curve, where S_1 corresponds to the image intensity in the first postcontrast acquisition and S_4 to the intensity in the fourth (last) postcontrast acquisition. The late enhancement is then calculated as $(S_4 - S_1)/S_1$ for every voxel location in the parenchyma of the contralateral breast (by using the parenchymal mask, Fig 1d). These values are subsequently sorted from high to low in a list, and the mean of the top 10% of the list is calculated, denoted as $\overline{\mathrm{LE}}_{90^+}$.

The decision to focus on the top 10% was made a priori. The rationale to focus on the top 10% comes from the hypothesis that parenchymal enhancement may be a measure of hormone sensitivity, and while heterogeneity may exist across the parenchyma, the sensitivity of the parenchyma as a whole will be determined by its most sensitive parts.

Statistical Analysis

SPSS version 20.0 (IBM, Armonk, NY) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. To assess the likelihood of a potential bias caused by exclusion of patient data, the variation in predicted survival between the included patients and the excluded patients was tested by using the Nottingham Prognostic Index (17) and the Fisher exact test. When the Nottingham Prognostic Index was unknown because the largest diameter on MR images, the axillary load, or the histologic grade was missing, the difference between the other covariates was tested for significance by using the Mann-Whitney *U* test for largest diameter on MR images or the Fisher exact test for axillary load and histologic grade. The images of patients in whom image-to-image registration failed were inspected visually

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Figure 1

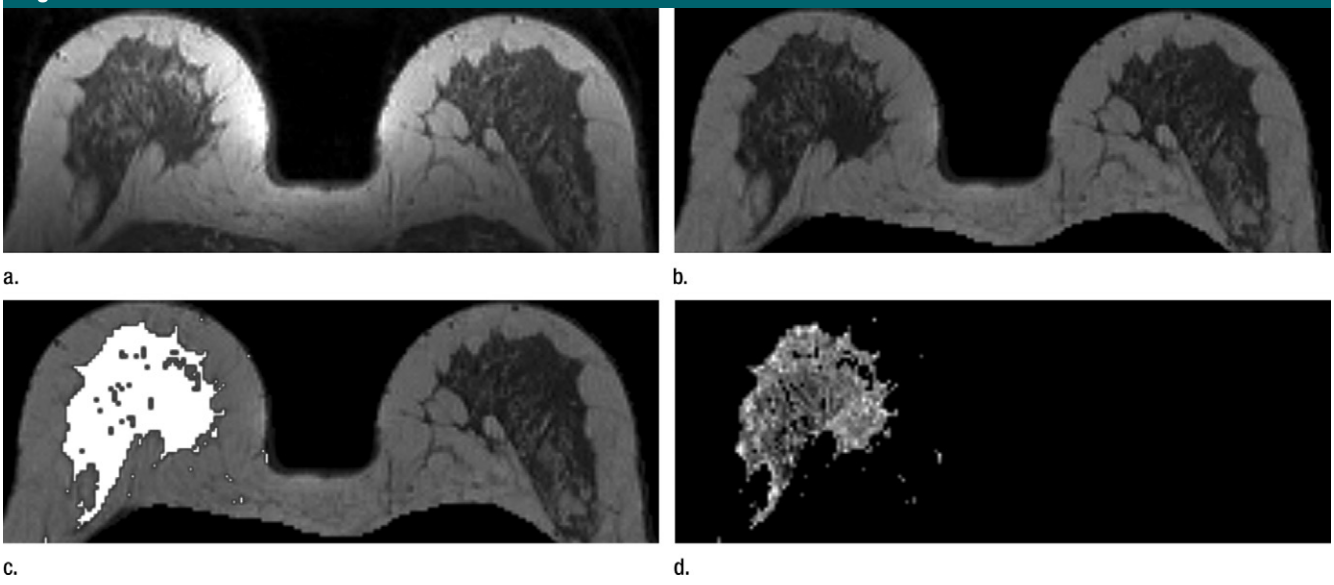


Figure 1: Transverse T1-weighted MR images in a 56-year-old woman with invasive ductal carcinoma in the left breast. **(a)** Precontrast MR image without fat suppression, **(b)** result of bias field correction and applying the breast mask, **(c)** segmented contralateral parenchyma (white overlay), and **(d)** late enhancement in the contralateral parenchyma mask are shown (higher signal intensity denotes higher late enhancement values).

Figure 2

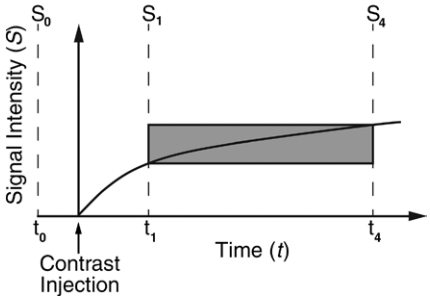


Figure 2: Schematic illustration of the continuous increase in signal intensity (vertical axis) over time (horizontal axis) in the breast parenchyma after contrast material injection. Box illustrates late enhancement, which is the relative enhancement between the first postcontrast acquisition (S_1) and the last postcontrast acquisition (S_4). t_0 = time of the precontrast series, t_1 = time of the first postcontrast series, t_4 = time of the last (fourth) postcontrast series.

(B.H.M.v.d.V.) for potential underlying causes, such as high parenchymal density. Continuous covariates were tested for normality by using the Kolmogorov-Smirnov test. Variation of covariates between IHC subtypes was tested by using one-way analysis of variance, Kruskal-Wallis, and Fisher exact tests for continuous normal, continuous nonnormal, and categorical distributions, respectively. Survival analysis was performed for overall survival (OS) and invasive disease–free survival (IDFS). Follow-up time was the number of months between the date of diagnosis and the date of last follow-up, moment of loss to follow-up, or moment of an event. We adopted the standardized end point definitions from Hudis et al (18). In short, events for OS included death from all causes. Events for IDFS included death from all causes, as well as recurrence except for ductal carcinoma in situ. Patients without an event were censored at the last date of follow-up, regardless of whether they were scheduled for future follow-up or whether they had been lost to follow-up. The covariates tested were the clinical covariates, as well as percentage of dense tissue and $\overline{LE}_{90^+}$ (Table 1). Univariate analysis was performed by using Kaplan-Meier estimators and log-rank tests. Continuous covariates were dichotomized at the median. Covariates with a significance level of $P < .2$ in univariate analysis were included in multivariate analysis. Cox regression with stepwise backward feature selection by using the likelihood ratio was used (probability-to-removal, 0.1; $P < .05$). Subset analyses conducted by using similar procedures were performed per IHC, per systemic treatment type, and per combination of IHC subtype and systemic treatment type. To test the robustness of the set of variables in the final model, we also performed Cox regression with forward feature selection (probability-to-enter, 0.1; $P < .05$).

Results

Patient Cohort

Patient and tumor characteristics are summarized in Table 1. The median follow-up was 86 months (range, 3–150 months). The Nottingham Prognostic Index of the excluded patients was not significantly different from that of the included patients ($P = .618$). In patients in which we were not able to calculate the Nottingham Prognostic Index, the other covariates were not significantly different ($P > .103$).

Table 1

Baseline Characteristics of the Patient Cohort

Characteristic	All ($n = 531$)	Estrogen Receptor Positive, HER2 Negative ($n = 398$)	HER2 Positive ($n = 67$)	Triple Negative ($n = 66$)	*P* Value*
Age (y)†	56 ± 10	57 ± 10	53 ± 10	54 ± 12	.008
Largest tumor diameter on MR images (mm)‡	18 (5–90)	17 (5–90)	21 (8–73)	23 (5–60)	<.001
Histologic finding					<.001
Invasive ductal carcinoma	418 (79)	298 (75)	63 (94)	57 (86)	
Invasive lobular carcinoma	75 (14)	71 (18)	2 (3)	2 (3)	
Other invasive carcinoma	38 (7)	29 (7)	2 (3)	7 (11)	
Histologic grade					<.001
Grade I	173 (32)	166 (42)	2 (3)	5 (8)	
Grade II	227 (43)	186 (47)	32 (48)	9 (14)	
Grade III	131 (25)	46 (12)	33 (49)	52 (79)	
Axillary load					.086
No positive lymph nodes	344 (65)	265 (67)	34 (51)	45 (68)	
1–3 positive lymph nodes	155 (29)	110 (28)	29 (43)	16 (24)	
Four or more positive lymph nodes	32 (6)	23 (6)	4 (6)	5 (7)	
Adjuvant systemic therapy					<.001
Yes	265 (50)	175 (44)	50 (75)	41 (62)	
No	266 (50)	223 (56)	17 (25)	25 (38)	
Chemotherapy					
Yes	169 (32)	92 (23)	36 (54)	41 (62)	
No	362 (68)	306 (77)	31 (46)	25 (38)	
Endocrine therapy					
Yes	210 (40)	174 (44)	36 (54)	0 (0)	
No	321 (60)	224 (56)	31 (46)	66 (100)	
Anti-HER2 therapy					
Yes	23 (4)	0 (0)	22 (33)	1 (2)	
No	508 (96)	398 (100)	45 (67)	65 (98)	
Percentage of dense tissue‡	0.11 (0.04–0.50)	0.11 (0.04–0.50)	0.12 (0.05–0.36)	0.10 (0.04–0.37)	.160
$\overline{LE_{90^+}}$‡	0.46 (0.10–1.13)	0.46 (0.10–1.11)	0.44 (0.20–1.13)	0.47 (0.18–1.09)	.856

Note.—Values are numbers of patients with percentages in parentheses, unless specified differently.

* Significance levels for differences in covariates between IHC subtypes.

† Data are means ± standard deviations.

‡ Data are medians, with ranges in parentheses.

In nine of 531 patients (2%) in whom image-to-image registration failed, no underlying systemic reason for this failure was found (such as high parenchymal density). Percentage of dense tissue ($P = .160$), $\overline{LE_{90^+}}$ ($P = .856$), and axillary load ($P = .086$) were not significantly different between IHC subgroups. The other covariates were significantly different (Table 1).

Survival Analysis

An event occurred in 51 of 531 patients (10%) for OS (Fig 3) and in 73 of 531 patients (14%) for IDFS; 480 of 531 patients (90%) were censored for OS, and 458 of 531 patients (86%) were censored for IDFS. Hazard ratios, 95% confidence intervals (CIs), and significance levels from univariate analysis for OS and IDFS are summarized in Table 2. Covariates entered in multivariate Cox regression for OS were age, largest tumor diameter on MR images, histologic tumor grade, axillary load, IHC subtype, and $\overline{LE_{90^+}}$. Covariates entered for IDFS were largest tumor diameter on MR images, histologic tumor grade, IHC subtype, and $\overline{LE_{90^+}}$. Age and IHC subtype retained significance after multivariate analysis for OS, and IHC subtype retained significance for IDFS (Table 3). Forward feature selection yielded similar results.

Survival Analysis Stratified to IHC Subtype

Age, largest tumor diameter on MR images, percentage of dense tissue, and $\overline{LE_{90^+}}$ were entered in multivariate analysis for OS in the estrogen receptor–positive, HER2-negative subgroup. Age, $\overline{LE_{90^+}}$, and largest tumor diameter on MR images retained

Figure 3

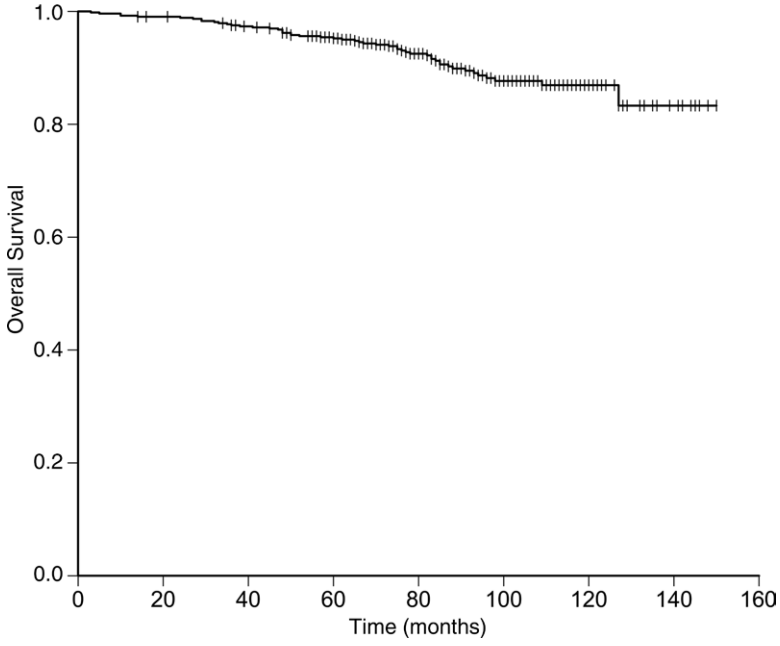


Figure 3: Graph of OS in the studied patient population (n = 531; 51 events). Symbols illustrate censored data.

significance. For IDFS, age and $\overline{LE_{90^+}}$ met the entry criterion. Age retained significance, and $\overline{LE_{90^+}}$ showed a trend (Table 3). In the HER2-positive subgroup, $\overline{LE_{90^+}}$ and axillary load were the covariates that met the entry criterion for IDFS and OS; axillary load retained significance. In the triple-negative subgroup, axillary load was the only covariate that met the entry criterion for IDFS (none for OS). Multivariate Cox regression for the triple-negative subgroup did not retain covariates in the final model. Forward feature selection yielded similar results.

Survival Analysis Stratified to Treatment Type

In the subgroup that underwent adjuvant endocrine therapy, $\overline{LE_{90^+}}$ was the only significant covariate after Cox regression for both OS and IDFS. IHC subtype showed a trend for IDFS. In the group of patients who did not undergo endocrine therapy, age and IHC subtype retained significance for OS. For IDFS, histologic grade retained significance. In the subgroup that underwent adjuvant systemic therapy, $\overline{LE_{90^+}}$ showed a trend for OS. An overview that contained all subgroups is presented in Table 3. Forward feature selection yielded similar results.

Survival Analysis Stratified to IHC Subtype and Treatment Type

$\overline{LE_{90^+}}$ was the only significant covariate after Cox regression for both OS and IDFS in the subgroups of patients with estrogen receptor–positive, HER2-negative breast cancer who underwent adjuvant endocrine therapy and/or adjuvant chemotherapy (Table 4). Patients with low $\overline{LE_{90^+}}$ had significantly (P = .014) worse OS compared with patients with high $\overline{LE_{90^+}}$ (Fig 4). In the subgroup of patients with estrogen receptor–positive, HER2-negative breast cancer who did not undergo adjuvant systemic therapy, age was the only significant covariate after Cox regression for both OS and IDFS (Table 4). In the HER2-positive group and the triple-negative group, Cox regression did not retain covariates in the final model. Forward feature selection yielded similar results.

In total, 83 of 174 patients (48%) with estrogen receptor–positive, HER2-negative cancer underwent endocrine therapy without additional chemotherapy. Of these patients, 42 of 83 patients (51%) were in the low-enhancement group. Five of these 42 patients (12%) had an OS event. In the high-enhancement group, two of 41 patients (5%) had an OS event (P = .433). For IDFS, six of 42 patients (14%) had an event in the low-enhancement group, and four of 41 patients (10%) had an event in the high-enhancement group (P = .738).

Discussion

In 531 patients with unilateral invasive breast cancer, the 10% most enhancing part of the parenchyma in the contralateral breast was found to be associated with long-term patient outcome, particularly in patients with estrogen receptor–positive, HER2-negative breast cancer. Patients with lower enhancement values had less favorable therapy outcome than those with higher enhancement values.

The 10% most enhancing parenchyma was associated with long-term survival in patients who underwent systemic therapy, especially in those who underwent endocrine therapy. In the patients who did not undergo systemic therapy, outcome was mainly related to age. These associations were found in the estrogen receptor–positive, HER2-negative group, but not in the other subgroups. These results are still significant if the P value for significance is adjusted for multiple testing by using Bonferroni correction ($P < .0028$). It should be recognized, however, that we had few patients with follow-up of 10 years; thus, long-term outcomes will need confirmation.

These findings may be explained as follows. The menstrual cycle has been shown to influence parenchymal enhancement (19,20). This effect is not prominent in all women, which suggests differences in hormone sensitivity of the parenchyma. Hence, parenchymal enhancement may be considered a measure of hormone sensitivity. Increased lifetime exposure to estrogen

Table 2

Univariate Kaplan-Meier Analysis and Log-Rank Tests for OS (51 Events) and IDFS (73 Events) in 531 Patients

	OS		IDFS	
Covariate	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Age	1.80 (1.04, 3.12)	.037	1.53 (0.84, 2.11)	.216
Largest tumor diameter on MR images	1.75 (1.01, 3.03)	.052	1.58 (1.00, 2.50)	.055
Histologic finding		.558		.575
Invasive ductal carcinoma	Reference		Reference	
Invasive lobular carcinoma	0.77 (0.35, 1.70)		0.72 (0.37, 1.38)	
Other invasive carcinoma	0.51 (0.18, 1.51)		0.72 (0.30, 1.78)	
Histologic tumor grade		.164		.173
Grade I	Reference		Reference	
Grade II	1.07 (0.56, 2.03)		1.15 (0.67, 1.97)	
Grade III	1.79 (0.86, 3.71)		1.69 (0.92, 3.12)	
Axillary load		.186		.282
No positive lymph nodes	Reference		Reference	
1–3 positive lymph nodes	1.01 (0.55, 1.87)		0.95 (0.57, 1.57)	
Four or more positive lymph nodes	1.89 (0.78, 4.56)		1.76 (0.68, 4.55)	
Adjuvant systemic therapy (yes vs no)	0.79 (0.46, 1.37)	.403	1.15 (0.73, 1.82)	.552
IHC subtype		.035		.034
Estrogen receptor positive, HER2 negative	Reference		Reference	
HER2 positive	0.80 (0.36, 1.79)		0.63 (0.32, 1.23)	
Triple negative	2.20 (0.93, 5.18)		1.86 (0.90, 3.83)	
Percentage of dense tissue	0.70 (0.40, 1.21)	.207	0.79 (0.50, 1.24)	.305
$\overline{LE_{90^+}}$	0.49 (0.28, 0.84)	.013	0.65 (0.41, 1.03)	.072

Note.—Numbers in parentheses are 95% confidence intervals. Continuous covariates are split on the median; the group containing values smaller than or equal to the median is the reference group ("Reference").

results in increased risk of breast cancer (21). Antihormonal (endocrine) therapy may be most effective for women with parenchyma that reflects high hormone sensitivity. This hypothesis is supported by our finding of significantly higher survival in patients with high parenchymal enhancement and estrogen receptor–positive, HER2-negative tumors who are undergoing endocrine therapy.

The effectiveness of endocrine therapy is known to differ among patients, and the treatment has side effects (2). Effectiveness of endocrine therapy has been associated with changes in breast density at mammography before and after treatment (22). However, to assess these mammographic changes, a follow-up period after treatment is required. Our findings suggest a pretreatment association between enhancement and outcome in the patients undergoing endocrine therapy.

Patients with estrogen receptor–positive, HER2-negative breast cancer who did not undergo chemotherapy in addition to endocrine therapy (42 of 83 patients [51%]) succumbed more often from breast cancer (five of 42 patients [12%]) when they had low parenchymal enhancement than when they had high parenchymal enhancement (two of 41 patients [5%]). Despite the fact that these differences in survival between enhancement groups could not yet be shown to be significant, it is tempting to hypothesize that patients with estrogen receptor–positive, HER2-negative breast cancer benefit less from chemotherapy in addition to endocrine therapy when they have high parenchymal enhancement.

Research on parenchymal enhancement includes background parenchymal enhancement and signal enhancement ratio. Background parenchymal enhancement takes into account the total signal intensity increase in the parenchyma and is typically divided in four incremental categories (23). Increased background parenchymal enhancement has been associated not only with decreased sensitivity in the detection of detect breast cancer (24) but also with an increased odds ratio regarding development of breast cancer (5,25). Signal enhancement ratio is the signal intensity ratio of the first postcontrast acquisition level minus the precontrast acquisition level and the last postcontrast acquisition level minus the precontrast acquisition level (26). Relatively high signal enhancement ratio values around the tumor have been associated with more ipsilateral recurrence in patients with ductal carcinoma in situ (7). Increase in near-tumor signal enhancement ratio has also been associated with increased microvessel density (27). To our knowledge, association between

Table 3

Multivariate Cox Regression Models for OS and IDFS in All Patients, Stratified according to IHC Subtype and Adjuvant Therapy Type

	OS		IDFS	
Covariate	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
	All Patients ($n = 531$)			
Age	1.05 (1.02, 1.08)	<.001		
IHC subtype				
Estrogen receptor positive, HER2 negative	Reference	.042	Reference	.039
HER2 positive	0.98 (0.38, 2.52)	.963	0.62 (0.27, 1.46)	.375
Triple negative	2.47 (1.28, 4.79)	.007	1.86 (1.05, 3.30)	.035
	Stratified according to IHC Subtype			
Estrogen receptor positive, HER2 negative ($n = 398$)				
Age	1.08 (1.04, 1.12)	<.001	1.03 (1.00, 1.06)	.043
Diameter	1.02 (1.00, 1.04)	.049		
$\overline{LE_{9}}$	0.03 (0.00, 0.44)	.011	0.19 (0.03, 1.35)	.096
HER2 positive ($n = 67$)				
Axillary load				
No positive lymph nodes	Reference	.077	Reference	.055
1–3 positive lymph nodes	2.09 (0.19, 23.12)	.549	1.14 (0.16, 8.07)	.899
Four or more positive lymph nodes	12.25 (1.09, 138.08)	.043	8.57 (1.20, 60.92)	.032
	Stratified according to Treatment Type			
Adjuvant systemic therapy administered ($n = 266$)				
$\overline{LE_{9}}$	0.14 (0.01, 1.33)	.087		
IHC subtype				
Estrogen receptor positive, HER2 negative			Reference	.067
HER2 positive			0.61 (0.21, 1.76)	.359
Triple negative			2.11 (1.00, 4.46)	.050
Adjuvant systemic therapy not administered ($n = 265$)				
Age	1.11 (1.06, 1.16)	<.001	1.05 (1.01, 1.08)	.009
Axillary load				
No positive lymph nodes			Reference	.031
1–3 positive lymph nodes			1.48 (0.62, 3.57)	.381
Four or more positive lymph nodes			78.85 (7.83, 794.26)	<.001
Chemotherapy not administered ($n = 362$)				
Age	1.09 (1.05, 1.14)	<.001		
Endocrine therapy administered ($n = 210$)				
$\overline{LE_{9}}$	0.00 (0.00, 0.08)	<.001	0.01 (0.00, 0.17)	.002
IHC subtype				
Estrogen receptor positive, HER2 negative			Reference	.093
HER2 positive			0.18 (0.02, 1.33)	.093
Triple negative			NA	NA
Endocrine therapy not administered ($n = 321$)				
Age	1.05 (1.01, 1.09)	.009		
IHC subtype				
Estrogen receptor positive, HER2 negative	Reference	.020		
HER2 positive	2.09 (0.69, 6.31)	.192		
Triple negative	2.97 (1.40, 6.32)	.005		
Histologic tumor grade				
Grade I			Reference	.065
Grade II			1.73 (0.87, 3.44)	.121
Grade III			2.26 (1.11, 4.59)	.024

Table 3 (continues)

Table 3 (continued)

Multivariate Cox Regression Models for OS and IDFS in All Patients, Stratified according to IHC Subtype and Adjuvant Therapy Type

	OS		IDFS	
Covariate	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Anti-HER2 therapy not administered (*n* = 508)				
Age	1.05 (1.02, 1.08)	.001		
IHC subtype				
Estrogen receptor positive, HER2 negative	Reference	.041	Reference	.065
HER2+	1.06 (0.38, 3.01)	.908	0.78 (0.31, 1.96)	.596
Triple negative	2.51 (1.29, 4.86)	.006	1.90 (1.07, 3.37)	.029

Note.—Numbers in parentheses are 95% CIs. The final model with hazard ratio and 95% CI after backward feature selection is shown per subgroup. In subgroups not shown, Cox regression did not retain covariates in the final model. "Reference" indicates the reference group. NA = not applicable.

Table 4

Cox Regression Model at the Final Step after Multivariate Analysis for OS and IDFS, Stratified according to Adjuvant Treatment Type and IHC Subtype

	OS		IDFS	
Parameter	Covariate	Hazard Ratio	Covariate	Hazard Ratio
Estrogen receptor positive, HER2 negative				
Adjuvant systemic therapy				
Received (*n* = 174, 18 OS events, 22 IDFS events)	$\overline{LE_{90^+}}$	0.00 (0.00, 0.06) [<.001]	$\overline{LE_{90^+}}$	0.01 (0.00, 0.17) [.002]
Not received (*n* = 224, 16 OS events, 30 IDFS events)	Age	1.13 (1.07, 1.20) [<.001]	Age	1.05 (1.01, 1.09) [.009]
Adjuvant chemotherapy				
Received (*n* = 92, 11 OS events, 12 IDFS events)	$\overline{LE_{90^+}}$	0.00 (0.00, 0.02) [<.001]	$\overline{LE_{90^+}}$	0.00 (0.00, 0.05) [.001]
Not received (*n* = 306, 23 OS events, 40 IDFS events)	Age	1.11 (1.06, 1.16) [<.001]	Age	1.04 (1.00, 1.07) [.039]
Adjuvant endocrine therapy				
Received (*n* = 174, 18 OS events, 22 IDFS events)	$\overline{LE_{90^+}}$	0.00 (0.00, 0.06) [<.001]	$\overline{LE_{90^+}}$	0.01 (0.00, 0.17) [.002]
Not received (*n* = 224, 16 OS events, 30 IDFS events)	Age	1.13 (1.07, 1.20) [<.001]	Age	1.05 (1.01, 1.09) [.009]

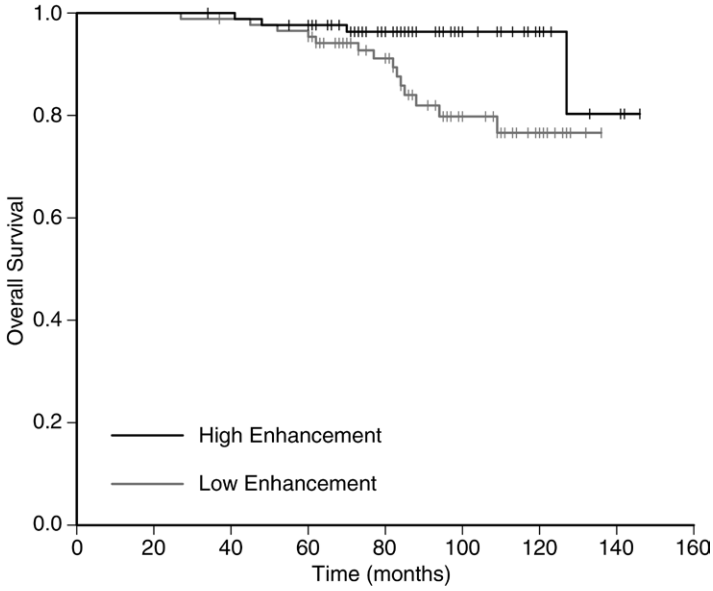
Note.—Numbers in parentheses are 95% CIs. Numbers in brackets are *P* values. The final model with hazard ratio and confidence interval after backward feature selection is shown per subgroup. In subgroups not shown, Cox regression did not retain covariates in the final model.

enhancement of healthy parenchyma in patients with unilateral breast cancer and outcome has not yet been reported. It is tempting to hypothesize that the association found in the current study may also play a future role in optimizing the selection of women in screening programs.

Parenchymal enhancement has also been researched in a neoadjuvant chemotherapy setting. Background parenchymal enhancement was found to decrease before and after neoadjuvant chemotherapy (28). Relatively high signal enhancement ratio values around the index tumor prior to treatment (29) and after one cycle of chemotherapy (6) have been associated with longer disease-free survival. We are currently investigating how the 10% most enhancing parenchyma is associated with outcome in a neoadjuvant chemotherapy setting. The fact that the enhancement is especially associated with outcome in the group of patients with estrogen receptor–positive, HER2-negative breast cancer may be a promising addition to current risk assessment in neoadjuvant chemotherapy, because changes in tumor size were shown to be less effective to monitor tumor response in the estrogen receptor–positive, HER2-negative subgroup than in other subgroups (30).

Our study has some limitations. First, MR imaging was not always performed in the recommended menstrual window. Postponing the MR imaging to correct for effects due to the menstrual cycle would lead to undesired delay of

Figure 4



Numbers at risk									
High Enhancement	87	87	86	83	60	27	16	4	0
Low Enhancement	87	87	85	83	58	31	13	0	0

Figure 4: Graph of OS in patients with estrogen receptor–positive, HER2-negative breast cancer who were undergoing adjuvant endocrine therapy ($n = 174$, 18 events, $P = .014$). The mean top 10% contralateral enhancement is dichotomized on the median. There were 87 of 174 patients in the high-enhancement group (four events, 5%) and 87 of 174 patients in the low-enhancement group (14 events, 16%). Symbols illustrate censored data.

surgery. However, this limitation was present in both groups of patients (events and no events). Hence, we considered it unlikely that this limitation biased our results. Second, all MR imaging originated from a single institution and one type of imaging unit. Differences in MR imaging hardware and protocols exist between institutions, however, requiring further validation of our findings in a multi-institutional setting. We chose the 10% threshold in analogy with the observation that the distinction between benign and malignant lesions on breast MR images can only be made effectively when the region of interest is in the most enhancing part of the tumor (31). At the 10% threshold, the calculation typically involves thousands to tens of thousands of parenchymal voxels, thus yielding sufficient statistics to minimize the effect of noise on the MR images. It is possible that the results may be somewhat improved by searching for the precise optimal threshold, but such strategy would add an additional degree of freedom to this retrospective analysis, thus lowering the power of our statistics. We limited the potential effect of intra- and interobserver variations between readers by developing a fully automated method to assess the parenchymal enhancement in the contralateral breast. The $\overline{LE_{90^+}}$ feature is relatively straightforward to compute by using the description provided. It allows implementation in a computer program for researchers and clinicians in other institutes. Third, 65 of 596 patients (11%) were excluded. Although these exclusions could cause a potential bias, we examined differences in prognostic markers between included patients and excluded patients (ie, tumor size, tumor grade, number of positive lymph nodes, Nottingham Prognostic Index) and were unable to find reasons to assume a systematic difference in survival outcome between these two groups. Last, this is a retrospective explorative study. Although a relatively large number of patients have been included, validation in larger populations is required to further elucidate on the effect of breast cancer subtype.

In conclusion, our results suggest that parenchymal enhancement in the contralateral breast of patients with invasive unilateral breast cancer is significantly associated with long-term outcome, particularly in patients with estrogen receptor–positive, HER2-negative breast cancer. Lower top 10% enhancement of the parenchyma shows potential as a predictive biomarker for relatively poor outcome in patients who undergo adjuvant endocrine therapy.

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