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Long-term Survival in Breast Cancer Patients Is Associated with Contralateral Parenchymal Enhancement at MRI: Outcomes of the SELECT Study

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

See also the editorial by Honda and Iima in this issue.

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Background: Several single-center studies found that high contralateral parenchymal enhancement (CPE) at breast MRI was associated with improved long-term survival in patients with estrogen receptor (ER)–positive and human epidermal growth factor receptor 2 (HER2)–negative breast cancer. Due to varying sample sizes, population characteristics, and follow-up times, consensus of the association is currently lacking.

Purpose: To confirm whether CPE is associated with long-term survival in a large multicenter retrospective cohort, and to investigate if CPE is associated with endocrine therapy effectiveness.

Materials and Methods: This multicenter observational cohort included women with unilateral ER-positive HER2-negative breast cancer (tumor size ≤50 mm and ≤three positive lymph nodes) who underwent MRI from January 2005 to December 2010. Overall survival (OS), recurrence-free survival (RFS), and distant RFS (DRFS) were assessed. Kaplan-Meier analysis was performed to investigate differences in absolute risk after 10 years, stratified according to CPE tertile. Multivariable Cox proportional hazards regression analysis was performed to investigate whether CPE was associated with prognosis and endocrine therapy effectiveness.

Results: Overall, 1432 women (median age, 54 years [IQR, 47–63 years]) were included from 10 centers. Differences in absolute OS after 10 years were stratified according to CPE tertile as follows: 88.5% (95% CI: 88.1, 89.1) in tertile 1, 85.8% (95% CI: 85.2, 86.3) in tertile 2, and 85.9% (95% CI: 85.4, 86.4) in tertile 3. CPE was independently associated with OS, with a hazard ratio (HR) of 1.17 (95% CI: 1.0, 1.36; $P = .047$), but was not associated with RFS (HR, 1.11; $P = .16$) or DRFS (HR, 1.11; $P = .19$). The effect of endocrine therapy on survival could not be accurately assessed; therefore, the association between endocrine therapy efficacy and CPE could not reliably be estimated.

Conclusion: High contralateral parenchymal enhancement was associated with a marginally decreased overall survival in patients with estrogen receptor–positive and human epidermal growth factor receptor 2–negative breast cancer, but was not associated with recurrence-free survival (RFS) or distant RFS.

Supplemental material is available for this article.

Upon indication of early breast cancer, treatment typically consists of surgery followed by radiation therapy and/or adjuvant systemic therapy to optimize local and regional control. One subtype of adjuvant systemic therapy is endocrine therapy, which is exclusively prescribed to patients with estrogen receptor (ER)–positive breast cancer. Endocrine therapy is a cornerstone in the treatment of ER-positive breast cancer and has reduced mortality and recurrence rates (1); however, patients are at risk for adverse effects, including fatigue, sexual dysfunction, and cognitive and musculoskeletal symptoms (2).

There is growing concern about overtreatment with adjuvant systemic therapy (including endocrine therapy) (3), as increasingly more patients with a more favorable prognosis are prescribed adjuvant systemic therapy (4). The likely benefits of omitting (or extending) treatment need

Abbreviations

CPE = contralateral parenchymal enhancement, DRFS = distant RFS, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, OS = overall survival, RFS = recurrence-free survival

Summary

In patients with estrogen receptor–positive and human epidermal growth factor receptor 2–negative breast cancer, contralateral parenchymal enhancement at preoperative MRI was associated with overall survival, but not with recurrence-free survival or distant recurrence-free survival.

Key Results

- In this retrospective study in 1432 patients with breast cancer, contralateral parenchymal enhancement (CPE) was independently associated with overall survival (hazard ratio [HR], 1.17; $P = .047$), but not with recurrence-free survival (HR, 1.11; $P = .16$) or distant recurrence-free survival (HR, 1.11; $P = .19$).
- The effect of endocrine therapy on survival could not be accurately estimated; hence, the potential association between endocrine therapy efficacy and CPE could not be reliably estimated either.

to outweigh the potential harm, and personalization tools can aid in clinical decision-making. However, there are currently no clinically validated personalization tools for endocrine therapy beyond the expression of the ER (5), and there is an unmet need to tailor endocrine therapy to individual patients.

A number of studies have investigated parenchymal enhancement at MRI as a predictor of outcome in breast cancer (6–13). However, there is considerable heterogeneity in the definition of parenchymal enhancement (14), outcome measures (13), and patient study population (6,9,12,15,16). This heterogeneity has led to partially conflicting results, and none of these features have been clinically implemented.

A number of single-center observational studies have investigated a specific measure of parenchymal enhancement called contralateral parenchymal enhancement (CPE). This measure differs from background parenchymal enhancement because it is derived from late perfusion as opposed to early perfusion. CPE was a derivative of the stromal enhancement ratio (the ratio of enhancement of parenchymal tissue around the tumor) in the original study (11). High CPE was associated with improved long-term survival in patients with ER-positive breast cancer and may be predictive of endocrine therapy efficacy (11,12,17). However, results are conflicting, and this association between CPE and long-term outcome was not reproducible in a cohort of Asian women (16). Thus far, all studies investigating CPE as a prognostic (or predictive) marker were single-center studies, often with a relatively short follow-up period (11,12,16). Hence, there is currently no consensus on the association between parenchymal enhancement and patient outcome.

Using a large multicenter retrospective cohort of women with unilateral, early, ER-positive, and human epidermal growth factor receptor 2 (HER2)–negative breast cancer, this study aimed to validate whether CPE at MRI is associated with long-term survival independent of standard clinical-pathologic prognostic factors, and whether it is related to endocrine therapy effectiveness.

Materials and Methods

Study Design and Patients

The SELECT (Stromal Enhancement on Breast MRI as Biomarker for Survival with Endocrine Therapy) study is a retrospective multicenter observational cohort study that included patients with unilateral ER-positive HER2-negative breast cancer who were diagnosed from January 2005 to December 2010 in 10 Dutch hospitals and who underwent preoperative MRI. The study was funded by the Dutch Cancer Society (grant 10755). None of the data have previously been published. At the study design phase, a priori power analyses showed that we needed to include 215 overall survival (OS) events and 312 recurrence-free survival (RFS) events (approximately 1500 patients) for sufficient statistical power, so that the study will have 90% power to detect CPE hazard ratios (HRs) of 0.64 for OS and 0.69 for RFS at a two-sided alpha of 5%, which are conservative estimates compared with the original (unstandardized) HRs of 0.22 for OS and 0.27 for RFS (11,12). The study was performed with a waiver from the institutional review board of the University Medical Center Utrecht. In every participating center, all patients with breast cancer who underwent preoperative MRI from January 2005 to December 2010 were identified (Fig 1). The inclusion criteria were unilateral ER-positive HER2-negative breast cancer, a tumor size less than or equal to 50 mm, and less than or equal to three positive lymph nodes ($n = 1432$). Patients with a history of breast cancer ($n = 36$ [2.5%], which breast was previously affected is unknown) or a benign enhancing lesion in the contralateral breast ($n = 65$ [4.5%]) were identified and included in the analysis. All breast cancers in our analyses were deemed new primary breast cancers. Whether or not preoperative MRI was performed, and the type or length of therapy prescribed, was at the discretion of the multidisciplinary team at each hospital per the standard clinical care at that time (Dutch guidelines recommended 5 years of endocrine therapy). Survival analysis was performed to investigate if parenchymal enhancement was associated with long-term patient survival, and secondly, whether parenchymal enhancement was associated with endocrine therapy effectiveness.

Clinical-Pathologic Data and Survival Outcomes

Lists of patients who underwent preoperative MRI at the participating hospitals were linked to the Dutch Cancer Registry and Pathology Registry (18) to obtain clinical-pathologic and follow-up data. Patient data were collected from April to October 2020 and were shared between the Dutch Cancer Registry, Pathology Registry, participating hospitals, and the researchers through a trusted third party (ZorgTTP) using pseudonymization to ensure that no patient-identifying data were received by the researchers. Clinical-pathologic data pertaining to tumor characteristics were based on the surgical tumor specimen. A tumor was deemed ER-positive if greater than 10% of nuclei stained positive for ER (19). Standard patient outcomes were used, including OS, RFS, and distant RFS (DRFS), as defined by Hudis et al (20).

MRI Protocol

Dynamic contrast-enhanced MRI was performed with a 1.5-T or a 3-T scanner from either Philips, Siemens, or GE Healthcare, although one patient was scanned with a 1-T MRI system (Panorama HFO; Philips). Table S1 gives an overview of the different imaging parameters used at the different hospitals. The flip angle ranged from 10° to 25°, repetition time ranged from 3.0 msec to 18.6 msec, and echo time ranged from 1.1 msec to 4.8 msec. Different types of contrast agents were used, including Gadovist (Bayer), Magnevist (Bayer), Dotarem (Guerbet), ProHance (Bracco), and Omniscan (GE Healthcare). Timing of the MRI examination relative to the menstrual cycle was at the discretion of the participating hospital.

Image Processing to Quantify Parenchymal Enhancement

Parenchymal enhancement (ie, CPE) was defined and quantified according to previously reported methods (11). In short, to calculate CPE, field inhomogeneities were corrected and the fibroglandular tissue of the contralateral breast was segmented on T1-weighted images. In the original single-institution study, segmentations were performed only on non–fat-suppressed images (11). To account for unavailability of non–fat-suppressed images and to account for differences in MRI acquisition parameters, two additions were implemented. First, to segment the fibroglandular tissue in fat-suppressed images, a deep learning–based segmentation model was developed by training an attention-gated U-Net (Fig 2). Second, MRI scans were harmonized to account for differences in the flip angle and repetition time between different MRI acquisitions (21).

CPE was calculated using the following equation applied to the region of interest as defined by the

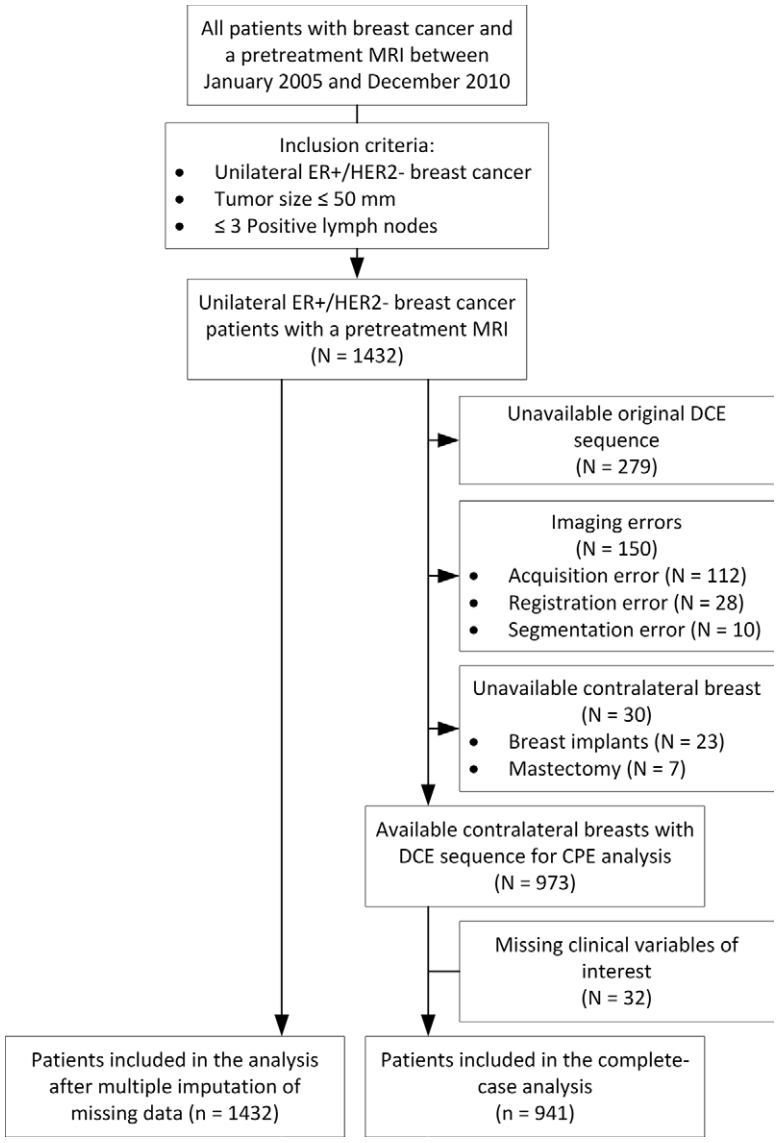

Figure 1: Flowchart shows patient inclusion. Missing MRI or clinical-pathologic data were multiply imputed. CPE = contralateral parenchymal enhancement, DCE = dynamic contrast enhanced, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2.

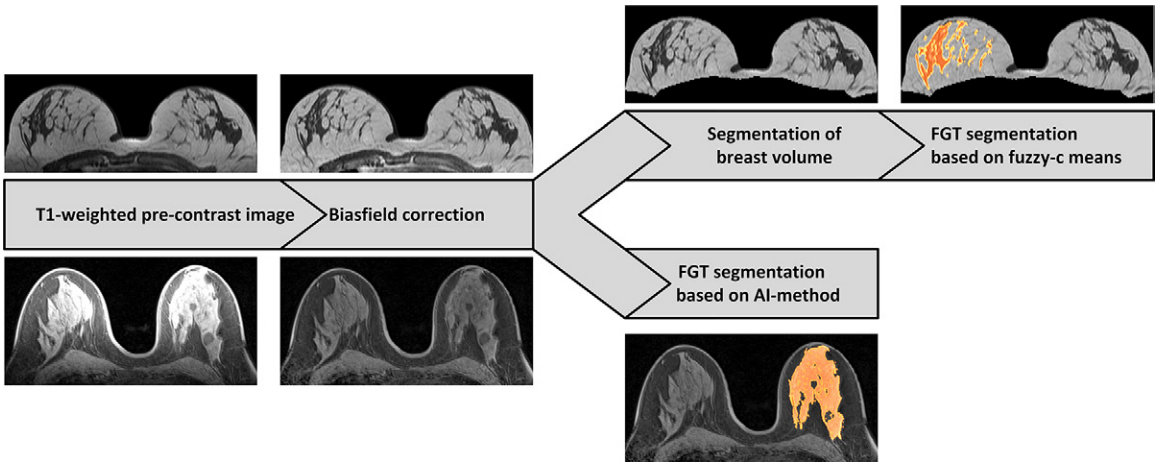

Figure 2: Schematic shows the processing pipeline for fibroglandular tissue (FGT) segmentation of non–fat-suppressed and fat-suppressed precontrast T1-weighted MRI scans. AI = artificial intelligence.

fibroglandular tissue segmentation in the contralateral breast: $(S_{late} - S_{early})/S_{early}$, where S_{early} and S_{late} represent the signal intensities of the corresponding voxels in the early and late enhancement images, respectively (11,12,17). CPE is the ratio of enhancement between the late and early postcontrast images and does not have a unit. CPE is a continuous variable. Conforming to the original definition of CPE, the early enhancement images were selected to be those closest to 90 seconds after contrast agent injection, and the late enhancement images to be those closest to 270 seconds after the early image (Table S1). To account for patient motion between early and late enhancement, deformable image registration was performed (22). Lastly, the top 10% most enhancing voxels, according to the aforementioned equation, were averaged to calculate CPE. Image analysis was centralized and performed at the researchers' facility.

Image processing was implemented using Python (version 3.7.6; Python Software Foundation) and MeVisLab (version 3.0.2; MeVis Medical Solutions).

Multiple Imputation

Missing data of interest (ie, CPE and clinical-pathologic variables) (Fig 1) were multiply imputed based on substantive model compatible fully conditional specification (23). CPE could not be calculated in 459 patients due to unavailable original dynamic contrast-enhanced MRI data (n = 279), imaging errors (n = 150), or unavailable healthy breast tissue (n = 30). The number of imputations was based on the percentage of cases with missing values (34%) (24), and we used 50 iterations (which were sufficient to reach convergence between imputation sets). Results of the imputations were checked by exploring the multiply imputed values and investigating the convergence over iterations between imputation sets (25).

Survival Analysis

Standard descriptive statistics were used to describe the overall population and subgroups based on CPE tertiles, mainly for visual assessment using Kaplan-Meier analysis and because it was done in previous publications (12,17). The association between CPE and the different survival outcomes (OS, RFS, DRFS) was investigated with a multivariable Cox proportional hazards regression model. CPE was analyzed as a continuous variable in the multivariable Cox proportional hazards regression analysis and standardized such that one unit increase in CPE represents 1 SD in the survival analyses. On the basis of its known nonlinear relation with patient outcome, age was modeled using a restricted cubic spline with four knots (26). Additionally, survival was stratified according to CPE tertile and visualized using Kaplan-Meier curves from which 10-year absolute survival differences between CPE tertiles were derived. The potential association between CPE and long-term survival was determined by testing whether the addition of CPE to the base model containing the standard clinical-pathologic variables (ie, age, tumor size and grade, number of positive lymph nodes, and treatment with endocrine therapy and/or chemotherapy) improved the model fit using the multivariable Wald test for each of the survival outcomes (23,27,28). Similarly, to investigate whether CPE was associated with endocrine therapy effectiveness, we tested whether the addition of the interaction term between CPE and endocrine therapy improved model fit (23,27,28). Age was included in all survival analyses, but the HR is not provided due to the fact that it was (nonlinearly) modeled as a spline. The P values provided for the multiply imputed data are based on the multivariable Wald test comparing the model with and without the specified variable. To quantify the model fit of the survival models, we calculated R^2, and to quantify the discriminative ability of the survival models, we calculated the concordance statistic (C statistic). A Fisher z transformation was applied to the R^2 values, and the C statistics were transformed to the logit scale before pooling of the multiply imputed results. Both values were back-transformed afterward. The analyses were performed on the full data after multiple imputation (n = 1432) and based on complete cases (n = 941).

Statistical Analysis

Correlation between CPE and age was based on the Pearson correlation coefficient. Statistical analyses were performed by two authors (M.A.A.R. and S.G.E.) using R (version 4.0.2; The R Foundation), with the smcfcs (version 1.4.2) (23) and rms (version 6.0.1) packages. Coefficient estimates are reported with their corresponding 95% CIs. A two-tailed $P < .05$ was considered indicative of a statistically significant difference.

Results

Table 1 shows the baseline characteristics for the entire patient cohort (n = 1432) and stratified according to CPE tertile. The median CPE for each tertile (after multiple imputation and before standardization) was 0.36 (range, 0.11–0.47; n = 477) for tertile 1, 0.57 (range, 0.47–0.67; n = 478) for tertile 2, and 0.81 (range, 0.67–1.7; n = 477) for tertile 3. The median age was 54 years (IQR, 47–63 years). The correlation between CPE and age was −0.43 (95% CI: −0.47, −0.37; $P < .001$).

There were 220 OS events over a median follow-up of 10.3 years (IQR, 9.5–11.5 years), 292 RFS events over a median follow-up of 9.1 years (IQR, 6.7–10.1 years), and 261 DRFS events over a median follow-up of 10.2 years (IQR, 9.4–11.4 years) (Table 1). Figure 3 shows the Kaplan-Meier survival curves for each outcome according to CPE tertile. Absolute differences in the survival outcome after 10 years for OS were 88.5% (95% CI: 88.1, 89.1) in tertile 1 (lowest CPE), 85.8% (95% CI: 85.2, 86.3) in tertile 2, and 85.9% (95% CI: 85.4, 86.4) in tertile 3 (highest CPE). For RFS, these were 77.7% (95% CI: 76.9, 78.5) in tertile 1, 78.1% (95% CI: 77.4, 78.9) in tertile 2, and 76.3% (95% CI: 75.5, 77.0) in tertile 3. For DRFS, absolute differences in survival after 10 years were 84.7% (95% CI: 84.1, 85.3) in tertile 1, 83.5% (95% CI: 82.9, 81.8) in tertile 2, and 81.8% (95% CI: 81.2, 82.4) in tertile 3.

The association between CPE and the three survival outcomes was investigated using a multivariable survival analysis that included standard clinical-pathologic variables and CPE (Table 2). CPE was standardized such that one unit increase in CPE represents 1 SD. Notably, the estimated HR of adjuvant endocrine therapy was not found to be associated with OS (HR, 1.17 [95% CI: 0.7,4 1.53]; P = .72), RFS (HR, 1.04 [95% CI: 0.77, 1.42]; P = .79), or DRFS (HR, 1.09 [95% CI: 0.78, 1.53];

Table 1: Overview of Baseline Characteristics for All Patients and according to CPE Tertile

Characteristic	All Patients (*n* = 1432)	CPE Tertile 1 (*n* = 324)	CPE Tertile 2 (*n* = 325)	CPE Tertile 3 (*n* = 324)
Age (y)*	54 (47–63)	58 (51–65)	53 (48–63)	50 (45–58)
Tumor size (mm)*	15 (11–21)	15 (11–22)	15 (12–22)	15 (11–21)
Tumor grade				
1	496 (35)	128 (40)	100 (31)	107 (33)
2	649 (45)	153 (47)	151 (47)	148 (46)
3	226 (16)	37 (11)	60 (19)	57 (18)
Unknown	61 (4)	6 (2)	14 (4)	12 (4)
No. of positive lymph nodes				
0	945 (66)	217 (67)	213 (66)	197 (61)
1	308 (22)	66 (20)	74 (23)	79 (24)
2	109 (8)	24 (7)	26 (8)	31 (10)
3	70 (5)	17 (5)	12 (4)	17 (5)
Systemic treatment				
No adjuvant systemic treatment	469 (33)	120 (37)	85 (26)	91 (28)
Only chemotherapy	42 (3)	8 (3)	9 (3)	7 (2)
Only endocrine therapy	324 (23)	79 (24)	74 (23)	69 (21)
Endocrine and chemotherapy	597 (42)	117 (36)	157 (48)	157 (49)
Radiation therapy				
Yes	515 (36)	114 (35)	105 (32)	121 (37)
No	917 (64)	210 (65)	220 (68)	203 (63)
CPE				
Median*	0.6 (0.4–0.7)	0.4 (0.3–0.4)	0.6 (0.5–0.6)	0.8 (0.7–0.9)
Unknown	459 (32)	0	0	0
Overall survival				
Event	220 (15)	40 (12)	57 (18)	58 (18)
Follow-up (y)*	10.3 (9.5–11.5)	10.1 (9.5–10.9)	10.0 (9.4–10.9)	10.3 (9.4–11.4)
Recurrence-free survival				
Event	292 (20)	60 (19)	68 (21)	74 (23)
Follow-up (y)*	9.1 (6.7–10.1)	9.0 (6.7–9.9)	9.0 (6.9–10.0)	9.2 (6.2–10.2)
Distant recurrence-free survival				
Event	261 (18)	54 (17)	62 (19)	67 (21)
Follow-up (y)*	10.2 (9.4–11.4)	10.0 (9.4–10.9)	10.0 (9.3–10.8)	10.2 (9.3–11.3)

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. Due to unavailability of CPE for a number of patients (*n* = 459), not all patients are included in the overview stratified according to CPE tertile. All patients (*n* = 1432) are included in the survival analyses after multiple imputation of missing data. CPE = contralateral parenchymal enhancement.

* Data are medians, with IQRs in parentheses.

P = .61). CPE was significantly associated with OS (HR, 1.17 [95% CI: 1.0, 1.36]; *P* = .047), meaning that patients with high CPE (2 SDs above the mean or the extreme upper limit) were estimated to have a 1.87 (ie, 1.17^4) higher hazard of dying compared with patients with low CPE (2 SDs below the mean or the extreme lower limit). CPE was not associated with RFS (HR, 1.11 [95% CI: 0.96, 1.27]; *P* = .16) or DRFS (HR, 1.11 [95% CI: 0.95, 1.3]; *P* = .19). CPE was not associated with endocrine therapy effectiveness in OS (*P* = .36), RFS (*P* = .95), or DRFS (*P* = .93). The addition of CPE to the survival models marginally increased the R^2 values and the C statistics (Table 2).

Analysis of women with complete clinical and imaging variables (*n* = 941) showed comparable results. CPE was only associated with OS (HR, 1.18 [95% CI: 1.01, 1.38]; *P* = .04), but not with RFS (HR, 1.12 [95% CI: 0.97, 1.28]; *P* = .13) or DRFS (HR, 1.12 [95% CI: 0.97, 1.3]; *P* = .13). We were also unable to adequately estimate the effect of endocrine therapy on OS (HR, 1.0 [95% CI: 0.66, 1.53]; *P* = .99), RFS (HR, 1.0 [95% CI: 0.69, 1.45]; *P* = .98), or DRFS (HR, 1.05 [95% CI: 0.7, 1.57]; *P* = .81) in the group of patients for whom there was complete data. A detailed overview of the survival analysis in the complete case analysis is available in Table S2.

Discussion

In the current study, we aimed to validate a previously defined quantitative measure of contralateral parenchymal enhancement (CPE) in a large patient population (patients with early estrogen receptor [ER]–positive human epidermal growth factor receptor 2 [HER2]–negative breast cancer) with a long follow-up. Three studies have specifically investigated CPE in a similar patient population, two of which observed that high CPE was associated

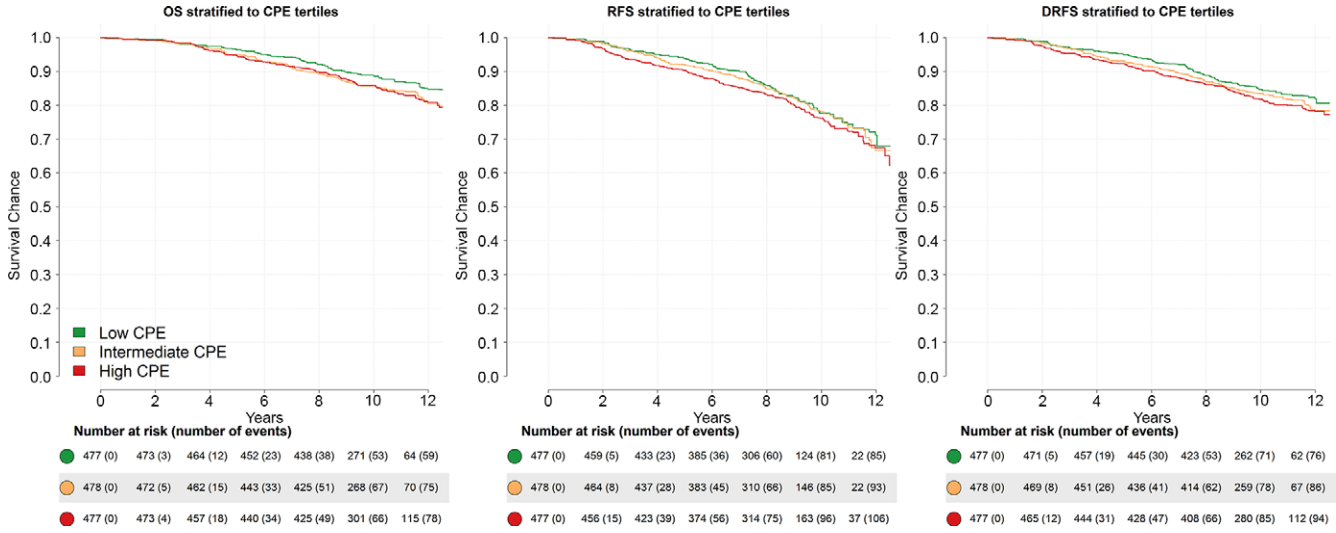

Figure 3: Kaplan-Meier survival curves show overall survival (OS), recurrence-free survival (RFS), and distant RFS (DRFS) according to contralateral parenchymal enhancement (CPE) tertile (low, intermediate, high). Note that the overall number of events for each outcome was less than the total number of outcomes because follow-up was restricted to 12 years (the maximum follow-up of 90% of the patients).

Table 2: Multivariable Survival Estimates and C Statistics according to Survival Outcome

Measure	OS	*P* Value	RFS	*P* Value	DRFS	*P* Value
Hazard ratio						
CPE	1.17 (1.0, 1.36)	.047	1.11 (0.96, 1.27)	.16	1.11 (0.95, 1.3)	.19
Age (y)	Nonlinear	<.01	Nonlinear	<.01	Nonlinear	<.01
Tumor size (mm)	1.02 (1.0, 1.03)	.02	0.97 (0.93, 1.02)	<.01	1.02 (1.01, 1.04)	<.01
Tumor grade 1	Ref		Ref		Ref	
Tumor grade 2	0.89 (0.64, 1.23)	.48	0.9 (0.68, 1.19)	.46	0.91 (0.68, 1.23)	.55
Tumor grade 3	1.63 (1.1, 2.43)	.02	1.4 (0.99, 1.98)	.06	1.47 (1.02, 2.12)	.04
No. of positive lymph nodes	1.16 (0.99, 1.37)	.07	1.15 (0.99, 1.32)	.06	1.21 (1.05, 1.4)	.01
Chemotherapy	1.01 (0.67, 1.53)	.95	0.83 (0.59, 1.17)	.28	1.02 (0.7, 1.48)	.92
Endocrine therapy	1.17 (0.74, 1.53)	.72	1.04 (0.77, 1.42)	.79	1.09 (0.78, 1.53)	.61
No. of events	220	…	292	…	261	…
R^2						
Model fit (without CPE)	0.087 (0.036, 0.139)	…	0.074 (0.022, 0.126)	…	0.078 (0.026, 0.129)	…
Model fit (with CPE)	0.091 (0.039, 0.143)	…	0.076 (0.024, 0.128)	…	0.08 (0.028, 0.132)	…
C statistic						
Discriminative ability (without CPE)	0.685 (0.648, 0,682)	…	0.644 (0.609, 0.678)	…	0.662 (0.628, 0.696)	…
Discriminative ability (with CPE)	0.688 (0.65, 0.729)	…	0.648 (0.614, 0.682)	…	0.664 (0.632, 0.698)	…

Note.—Data in parentheses are 95% CIs. CPE was standardized and the hazard ratio should be interpreted per SD increase. Age was included in all survival analyses, but the hazard ratio is not provided because it was nonlinearly modeled as a spline. CPE = contralateral parenchymal enhancement, DRFS = distant RFS, OS = overall survival, RFS = recurrence-free survival.

with improved survival (11,12) and one of which, performed in an Asian population, did not find an association (16). This large, retrospective, multicenter observational cohort study showed that higher CPE on preoperative dynamic contrast-enhanced MRI scans is statistically significantly associated with decreased long-term overall survival in patients with unilateral ER-positive HER2-negative breast cancer after correction for standard clinical-pathologic variables. However, the observed associations of CPE were of small effect size, which limits the clinical impact. CPE was not associated with recurrence-free survival (RFS) or distant RFS, which raises the question of whether the relationship between CPE and survival is actually related to breast cancer or due to other causes. One other possibility is that the association is partly due to differences in cardiac function, as CPE is related to perfusion (ie, poor cardiac function could be related to differences in CPE). The direction of the association was opposite from what was previously observed in patients treated with adjuvant endocrine treatment (11,12), although it was consistent with a more recent study investigating prognosis after neoadjuvant endocrine treatment, where a high pretreatment CPE was also observed to be associated with decreased prognosis after treatment (17).

Endocrine therapy was not observed to be associated with any survival outcome after multivariable correction in our observational data. It is well established that endocrine therapy

is associated with a decreased rate of recurrence and is a cornerstone in the treatment of ER-positive breast cancer (29). A similar issue was encountered in the development of the online prognostic tool, PREDICT (30), where the HR of endocrine therapy could not be adequately determined from observational data. This suggests that in observational data, even after multivariable adjustment for confounders, subgroups are somehow still dissimilar through unobserved or inadequately accounted for confounders (ie, residual confounding by indication), such as socioeconomic status. This complicates the analysis; because we were unable to adequately estimate the effect of endocrine therapy on survival, the estimated association between CPE and endocrine therapy effectiveness may not have been accurately modeled either.

There are several differences between previous studies investigating CPE and our study (the SELECT study) that may have led to the differences in results. First, there were differences in patient and tumor characteristics in previous studies compared with the SELECT study. The original single-center studies consecutively included patients based on eligibility for breast-conserving surgery (11,12). In the study by Shin et al (16), only patients with negative lymph node disease were included and all patients were treated with endocrine therapy. Thus, there were differences in treatment regimens and axillary load. Second, studies were performed in different time periods. For instance, the study performed in the Netherlands by van der Velden et al (11) included patients primarily diagnosed in the early 2000s (2000–2008), whereas the SELECT study included patients who were primarily diagnosed in the late 2000s (2005–2010). Several changes took place during the interim time period; aromatase inhibitors were introduced for postmenopausal women (31), taxanes were added to the chemotherapy regimen (32), and, in 2008, guideline recommendations for endocrine therapy were extended in the Netherlands (32). Different effects of aromatase inhibitors and taxanes on parenchymal enhancement have been reported compared with tamoxifen and nontaxane chemotherapy (33,34). The SELECT study included more patients (n = 1432) with a longer follow-up (10–15 years). It is likely that the differences in association between CPE and survival between SELECT and other studies can be attributed to a combination of these factors. Lastly, a possible confounder that may have affected both CPE and survival is high (genetic) risk of breast cancer. If high-risk breast cancer is (also) associated with high CPE, then this may (partly) explain the opposing results, assuming that patients at high risk for breast cancer were underrepresented in the original studies (and well or overrepresented in the current study). The results of our analyses suggest limited clinical relevance for CPE due to the conflicting results, limited predictive ability of survival, and the fact that CPE was not associated with endocrine therapy efficacy. Additional research is needed to investigate the role of CPE, alone and in combination with other imaging features, as a personalization tool to judge clinical relevance and contemplate possible clinical implementation.

This study had several strengths. We included a large number of patients from multiple centers based on a sample size analysis. We used state-of-the-art techniques to pool data from 10 centers that had different MRI acquisitions (21). Our estimates take into consideration intercenter variability and reflect the clinical reality (hospitals use MRI systems from different vendors and different acquisition protocols), leading to realistic expectations for clinical implementation. While other studies investigating parenchymal enhancement and survival generally have a more limited follow-up period (median follow-up of approximately 7 years) (11,12), this study included long-term follow-up of patients with early ER-positive HER2-negative breast cancer (median follow-up of approximately 10 years).

This study also had several limitations. We were unable to accurately estimate the effect of endocrine therapy on survival after multivariable adjustment; due to this, we were also unable to reliably estimate a possible association between endocrine therapy efficacy and CPE. Although we were able to pool MRI data from 10 centers, we were only able to correct for repetition time and flip angle (21). Remaining intercenter variability (eg, differences in contrast timing or contrast T1 relaxation times) may still have affected the results. Another limitation is that there was a relatively large proportion of missing data, which could have introduced increased variability and decreased statistical power. However, missing data were multiply imputed and complete data analysis showed comparable results. We did not have data on the timing of the MRI examination relative to a patient's menstrual cycle; however, this is unlikely to have affected the results because CPE was not associated with menstrual cycle in a previous study (12).

In conclusion, in this large multicenter retrospective study, we have observed that contralateral parenchymal enhancement (CPE) at MRI was associated with decreased long-term overall survival in patients with unilateral, early, estrogen receptor (ER)–positive, and human epidermal growth factor receptor 2 (HER2)–negative breast cancer. CPE was not associated with recurrence-free survival (RFS), distant RFS, or endocrine therapy effectiveness. Our current data do not suggest a clinical role for CPE. Additional research is needed to determine if CPE at breast MRI can be used to help select the best therapy for patients with ER-positive HER2-negative breast cancer.

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