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Original Research

Predictive Value of Breast MRI Background Parenchymal Enhancement for Neoadjuvant Treatment Response among HER2– Patients

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Abstract

Objective: Women with advanced HER2– breast cancer have limited treatment options. Breast MRI functional tumor volume (FTV) is used to predict pathologic complete response (pCR) to improve treatment efficacy. In addition to FTV, background parenchymal enhancement (BPE) may predict response and was explored for HER2– patients in the I-SPY-2 TRIAL.

Methods: Women with HER2– stage II or III breast cancer underwent prospective serial breast MRIs during four neoadjuvant chemotherapy timepoints. BPE was quantitatively calculated using whole-breast manual segmentation. Logistic regression models were systematically explored using pre-specified and optimized predictor selection based on BPE or combined with FTV.

Results: A total of 352 MRI examinations in 88 patients (29 with pCR, 59 non-pCR) were evaluated. Women with hormone receptor (HR)+HER2– cancers who achieved pCR demonstrated a significantly greater decrease in BPE from baseline to pre-surgery compared to non-pCR patients (odds ratio 0.64, 95% confidence interval (CI): 0.39–0.92, $P = 0.04$). The associated BPE area under the curve (AUC) was 0.77 (95% CI: 0.56–0.98), comparable to the range of FTV AUC estimates. Among multi-predictor models, the highest cross-validated AUC of 0.81 (95% CI: 0.73–0.90) was achieved with combined FTV+HR predictors, while adding BPE to FTV+HR models had an estimated AUC of 0.82 (95% CI: 0.74–0.92).

Conclusion: Among women with HER2– cancer, BPE alone demonstrated association with pCR in women with HR+HER2– breast cancer, with similar diagnostic performance to FTV. BPE predictors remained significant in multivariate FTV models, but without added discrimination for pCR prediction. This may be due to small sample size limiting ability to create subtype-specific multivariate models.

Key words: background parenchymal enhancement; breast cancer; HER2– breast cancer; magnetic resonance imaging; neoadjuvant chemotherapy; tumor response.

Key Messages

- Quantitative background parenchymal enhancement (BPE) of the contralateral breast decreases with neoadjuvant chemotherapy, and in HR+HER2– patients, discrimination of pathologic complete response (pCR) by BPE alone is within the range of diagnostic performance of tumor volume predictors.
- BPE predictors remained significant in multivariate FTV models but did substantially improve discrimination for pCR prediction. However, due to small sample size, we were limited in the ability to create subtype-specific multivariate models.

Introduction

Women with advanced breast cancer (stage II and III) have significant morbidity and mortality, with a 5-year disease specific survival as low as 33% (1). The neoadjuvant period provides the opportunity to noninvasively monitor tumor response to therapy with breast MRI, and redirect therapy for women who are not responding in hopes of improving their prognosis. Furthermore, the surrogate outcome pathologic complete response (pCR) has a high association with survival, accelerating the prediction of a woman's outcome to months rather than years (2). Women with advanced hormone receptor (HR)+HER2– and HR-HER2– disease in particular have relatively lower rates of pCR compared to women with HER2+ disease due to limited treatment options (3). Improving prediction of pCR in women with HER2– disease during the neoadjuvant period would provide opportunities to improve treatment selection and potentially increase the pCR rate.

The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2, ClinicalTrials.gov number NCT01042379) is an ongoing multicenter prospective randomized clinical trial framework used to monitor treatment response and assess novel investigational neoadjuvant chemotherapy (NAC) agents for breast cancer. The study uses quantitative measurement of MRI-derived tumor volume (defined as functional tumor volume [FTV]) to predict response. The prior I-SPY-1 trial demonstrated a significant association with both prediction of pCR (4) and recurrence-free survival (5) outcomes, with area under the curve (AUC) estimates for FTV regression models ranging from 0.70 to 0.84 and 0.52 to 0.72 for each outcome type, respectively.

Background parenchymal enhancement (BPE) describes the natural phenomenon observed on breast MRI in which normal breast tissue demonstrates signal enhancement related to uptake of intravenous contrast. Biologically, BPE is believed to represent tissue activated by endogenous hormones (primarily estrogen) and is dynamic in appearance over time and distribution within a woman's breast tissue. This is demonstrated by histopathologic studies that have found BPE to be correlated with increased microvascular density (6) and proliferative breast tissue (7). Additionally, single-center studies have found strong associations between BPE and subsequent primary breast cancer, with odds ratios of 2–18 (8–10). More recent studies have also demonstrated that BPE is a surrogate outcome of treatment response to chemotherapy and chemoprevention agents (11–14). BPE signal intensity decreases with treatment, and the magnitude of this decrease is associated with the degree of tumor response. The biological basis of these associations is unclear, but it has been speculated that BPE characterizes activated breast stroma that is more susceptible to malignant transformation but also to potential treatment responsiveness (9,15).

Tumor volume is a validated predictor of NAC response, but few MRI studies have evaluated the adjunctive contribution of BPE to a tumor volume model. Most studies evaluate the association of BPE alone with treatment response, but the more relevant clinical question is if BPE provides additive improvement to the more established tumor volume model. Moreover, prior studies on BPE in tumor response are based on retrospective observational studies from single institutions or rely on a qualitative definition of BPE, which is prone to issues with inter-rater reliability and measurement error (12,16).

The current study has several strengths that overcome limitations in prior studies: We analyze data from a prospective study primarily designed to evaluate MRI biomarkers; our patient cohort was evaluated for a clearly defined pathological endpoint for neoadjuvant response; and we had a consistent MRI protocol with high-quality control of acquisition. We evaluated the primary effect of BPE as well as the additive effect of BPE to a FTV tumor volume model in improving the prediction of pCR of women with HER2– advanced breast cancer enrolled in the I-SPY-2 trial.

Methods

Patient Population

In this Health Insurance Portability and Accountability Act compliant, Institutional Review Board-approved study, women 18 years of age and older diagnosed with stage II or III breast cancer and with tumor size measured ≥2.5 cm were eligible to enroll in the I-SPY 2 TRIAL (17). Biomarker assessments based on hormone (estrogen and progesterone) receptors (HR+/-) and a 70-gene assay (MammaPrint, Agendia, Amsterdam, The Netherlands) were performed at baseline and used for treatment randomization (17). Patients who had tumors that were designated as hormone-receptor positive and low risk according to the 70-gene assay were excluded. All patients provided written informed consent to participate in the study. A second consent was obtained if the patient was randomized to an experimental treatment. Enrollment occurred between 2010–2012.

Schema

Figure 1 shows the schema of the I-SPY 2 TRIAL. All breast cancers in these drug arms were HER2– by nature of the drug mechanism of action. Participants received a weekly dose of paclitaxel alone (control) or in combination with experimental NAC agents for 12 weekly cycles, followed by 4 (every 2–3 weeks) cycles of anthracycline-cyclophosphamide (AC) prior to surgery. MRI was performed before the initiation of NAC, or baseline (T0), after 3 weeks of therapy, or early treatment (T1) after 12 weeks of therapy at which patient is transitioned from a taxane-based regimen to an AC-based regimen, or inter-regimen (T2), and after neoadjuvant therapy completion and prior to surgery, or pre-surgery (T3).

Pathologic Assessment of Response

Pathologic complete response—defined as the absence of residual invasive cancer in the breast or lymph nodes at the time of surgery—is the primary endpoint of the I-SPY 2 TRIAL. All patients were classified as achieving pCR or not achieving pCR (non-pCR) at the time of definitive surgery by a trained pathologist. Patients that withdrew from the trial in mid-study were counted as non-pCR.

MRI Acquisition

MR imaging was performed using 1.5T or 3T scanners with a dedicated breast radiofrequency coil, across a variety of vendor platforms and institutions. All MRI exams within a single patient were performed using the same magnet configuration (manufacturer; field strength; breast coil model). Bilateral dynamic contrast–enhanced (DCE) MRI images were acquired in the axial orientation with the following parameters: repetition time = 4–10 ms, minimum echo time, flip angle = 10–20°C, field of view = 260–360 mm to achieve full bilateral coverage, acquisition matrix = 384–512, within-plane resolution ≤1.4 mm, slice thickness ≤2.5 mm, and slice gap = 0 mm. Gadolinium contrast agent was administrated intravenously at a dose of 0.1 mmol/kg body weight, and at a rate of 2 ml/second, followed by a 20 ml saline flush. The same contrast agent brand was used for all MRI exams for the same patient. Pre-contrast and multiple post-contrast images were acquired using identical sequence parameters. There was no delay between contrast injection and data acquisition. Post-contrast imaging continued for at least 8 minutes following contrast agent injection.

Quantitative Image Analysis

FTV was calculated from each DCE-MRI examination using a previously described semi-automated segmentation method (Figure 2) (18). BPE was assessed following manual whole-breast segmentation of the contralateral unaffected breast so that measurement would not be confounded by adjacent disease. Subsequently, enhancement was determined on a per-voxel basis using co-registered DCE sequences at two time points: pre-contrast (time 0) and the first post-contrast acquisition between 2 minutes 15 seconds and 2 minutes 30 seconds post-contrast (time 1), with S_0 and S_1 representing the corresponding signal intensities at those times. BPE was calculated as an average of early enhancement measured for all voxel of segmented fibroglandular tissue, where early enhancement is defined as $(S_1 - S_0)/S_0$.

For FTV measurements, the segmentation method calculated the volume of all tumor voxels that exceeded an early enhancement threshold of 70%. Participating sites in I-SPY 2 TRIAL could slightly adjust the early enhancement threshold to qualitatively reflect the extent of tumor, and to account for unexpected variability in MRI systems and imaging parameters. However, the FTV analysis had to be reviewed and approved by the designated breast radiologist at each site, and all FTVs in the I-SPY 2 TRIAL had to be visually approved by the Imaging Core Lab at the University of California San Francisco.

Statistical Analysis

Univariate analyses were performed with logistic regression, using predictors of absolute values of BPE and FTV at each treatment time point (e.g., absolute value of BPE at inter-regimen/T2 is notated as "BPE_2") or relative change

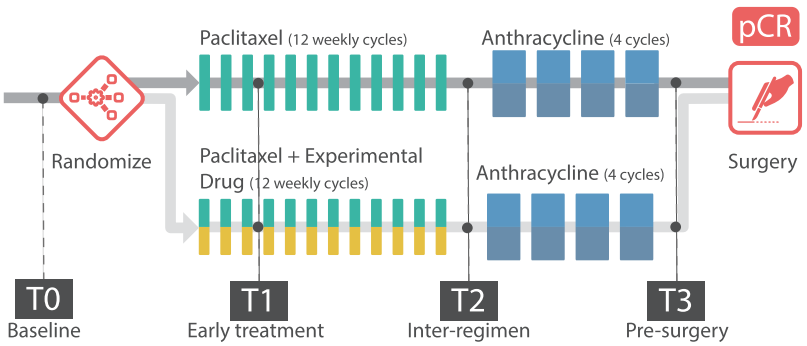

Figure 1. I-SPY2TRIAL study schema and adaptive randomization. Breast MRI was obtained at 4 different time points (T0–T3) as described. Patients were randomized to the control (paclitaxel) or the experimental drug arm (paclitaxel + experimental agent) for 12 weekly cycles followed by 4 (every 2–3 weeks) cycles of anthracycline-cyclophosphamide prior to surgery. Pathologic complete response – defined as the absence of residual cancer in the breast or lymph nodes at the time of surgery – is the primary end point of the I-SPY 2 TRIAL. Abbreviation: pCR, pathologic complete response.

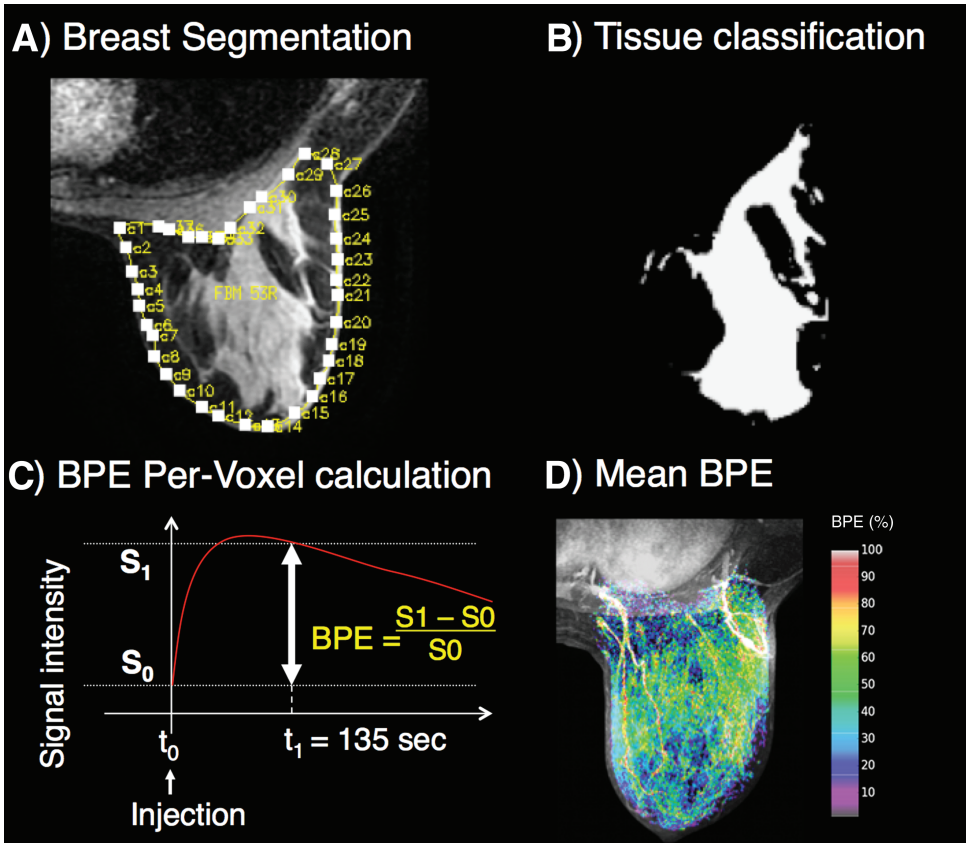

Figure 2. Process of quantitative background parenchymal enhancement (BPE) calculation. **A:** Initially, manual segmentation of the contralateral (unaffected) breast was performed. **B:** This is followed by deriving a mask classifying fibroglandular tissue and removing non-breast elements using fuzzy c-means clustering. BPE is then calculated on per-voxel basis (**C**), and an average value of all voxels is calculated to derive the final BPE estimate (**D**).

from baseline, and the treatment response outcome pCR. Relative change was calculated as change from baseline divided by baseline value. For example, relative change of BPE from baseline to early treatment (or T1) was calculated as (BPE_1 – BPE_0)/BPE_0 and notated as %ΔBPE0_1. All possible FTV or BPE predictors were evaluated as individual univariate predictors of tumor response in models stratified by HR status. We additionally estimated models including the following sets of multiple predictors: Model 1, baseline FTV and relative FTV change for each treatment time point; Model 2, the same FTV model with the corresponding baseline and BPE change variable. A final model was derived which optimized AUC by exhaustively searching all possible linear combination of FTV predictors and HR, without or with all possible BPE predictors ("Model 3" and "Model 4," respectively). For all models, an odds ratio (OR) is used to describe the strength of association with pCR. For the relative change measures ORs are reported for 10% relative change to aid interpretability. The interpretation of the OR, for example an OR of 0.9 for a relative change variable, is that for each 10% decrease in ΔFTV or ΔBPE, there is a 10% decrease in the odds of non-pCR or a corresponding 10% increase in the odds of pCR. Diagnostic performance was assessed using AUC for all models. To avoid overfitting, 10 times repeated 5-fold cross-validation AUC (cvAUC) was used for multiple predictor models. All statistical analysis was performed using the R statistical programming environment, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). A nominal value of $P < 0.05$ was considered to be statistically significant.

Results

Of the 110 women who had enrolled and received at least one MRI examination in the initial drug arms, a total of 88 women (29 with pCR, 59 with non-pCR) with 352 MRI examinations were included. A total of 22 women were excluded for the following reasons: unable to calculate BPE due to image quality issues (13 women), missing one or more MRI visits (8 women), and missing demographic information (1 woman).

Patient Characteristics

Table 1 describes the baseline characteristics of women included in this study. Women with pCR as compared to women with non-pCR were slightly younger and more

often Asian or Black/African American and pre-menopausal. Women with pCR were more commonly HR+HER2– than women with non-PCR.

Univariate Analysis of BPE

Figure 3 displays the average absolute values of BPE and FTV over time as treatment progressed. Women who achieved pCR tended to have higher absolute BPE values at baseline, which decreased more at later treatment time points than non-pCR patients (Figure 4). In contrast, women who achieved pCR tended to have lower absolute FTV values at baseline, which remained lower for all time points than non-pCR patients.

Table 2 summarizes our findings of the univariate regression analyses of all 88 women included in this study stratified by HR status. Greater decreases in BPE from baseline to inter-regimen treatment predicted a higher odds of pCR (%ΔBPE0_2; OR = 0.88 per 10% change in %BPE0_2, 95% confidence interval [CI]: 0.75–1.00, $P = 0.08$), or from baseline to pre-surgery (%ΔBPE0_3; OR = 0.87 per 10% change in predictor, 95% CI: 0.74–1.00, $P = 0.07$), than non-pCR, although the P value and AUC did not reach statistical significance at the nominal $\alpha = 0.05$ level for either predictor. Among the 43 women with HR+ breast cancer, the change in BPE from baseline to pre-surgery was statistically significant (%ΔBPE0_3; OR = 0.64 per 10% change in predictor, 95%

Table 1. Participant Characteristics[a]

	Pathologic Complete Response ($n = 29$)		Nonpathologic Complete Response ($n = 59$)	
	Mean	**IQR**	**Mean**	**IQR**
Age (years)	46.9	17.0	48.8	12.5
	n	**%**	***n***	**%**
Race				
Asian	3	10%	2	3%
Black or African American	6	21%	7	12%
White	20	69%	50	85%
Menopausal status[b]				
Pre-menopausal	20	69%	35	59%
Peri-/post-menopausal	9	31%	24	41%
Receptor subtype[c]				
HR+HER2–	7	24%	36	61%
HR-HER2–	22	76%	23	39%

Proportions calculated within each column.

Abbreviation: IQR, interquartile range.

[a]All patients received paclitaxel (control) or in combination with an experimental agent for 12 weekly cycles followed by four cycles of anthracycline-cyclophosphamide every 2–3 weeks prior to surgery.

[b]There were 20 missing values, which were categorized as pre vs. peri-/post-menopausal if age ≤55.

[c]All patients represented were HER2 receptor negative.

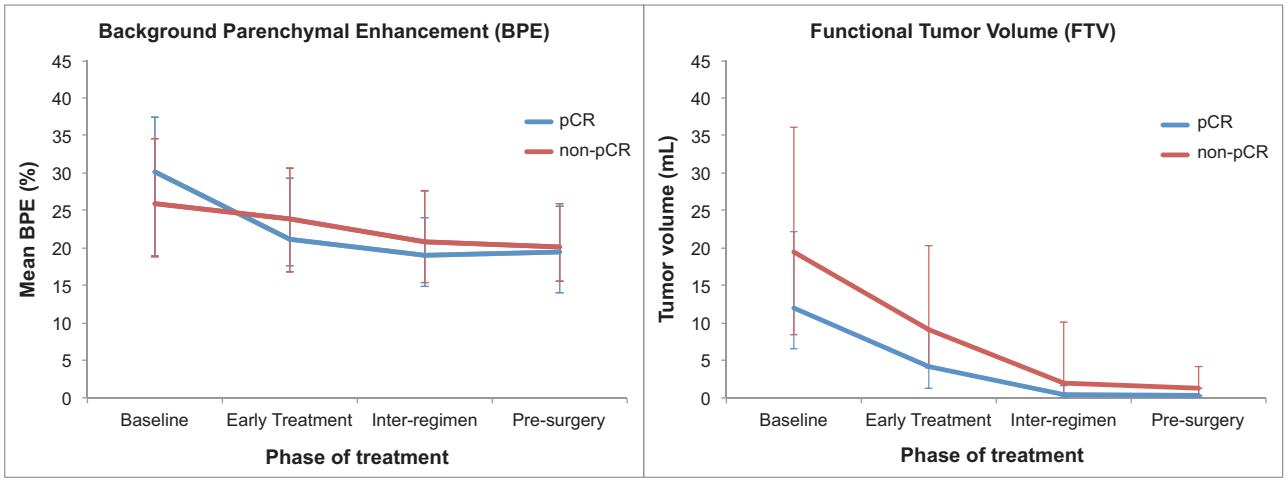

Figure 3. Plots of median values of background parenchymal enhancement and functional tumor volume through phases of treatment (errors bars represent interquartile range). Abbreviation: pCR, pathologic complete response.

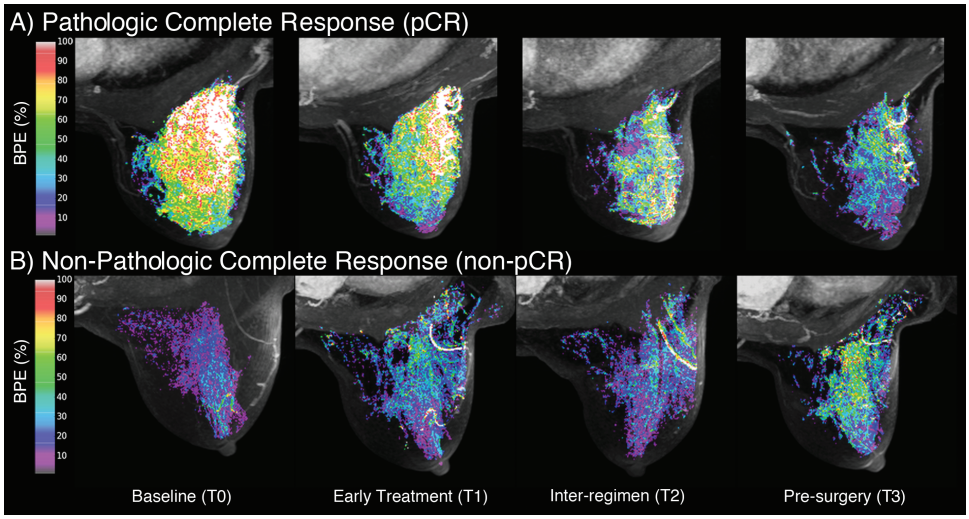

Figure 4. Spectral maximum intensity projection breast MRI of an individual woman's background parenchymal enhancement (BPE) at neoadjuvant therapy treatment time points with outcomes of pathologic complete response (pCR) **(A)** or non-pathologic complete response (non-pCR) **(B)**. Women who went on to have pCR (**A**) were more likely to demonstrate higher baseline BPE that decreased with therapy, while women who have non-pCR (**B**) had lower baseline BPE levels that decreased relatively less or did not change with therapy.

Table 2. Univariate Analyses of BPE Variables for Predicting pCR, Stratified by HR Subtype

Receptor type	**ALL**		**HR+HER2–**		**HR-HER2–**	
Total number (pCR/non-pCR)	88 (29/59)		43 (7/36)		45 (22/23)	
Predictors	**OR (95% CI)**	**AUC**	**OR**	**AUC**	**OR**	**AUC**
BPE_0	1.02 (0.99–1.05)	0.48	1.04 (0.98–1.10)	0.43	1.02 (0.98–1.07)	0.49
BPE_1	1.00 (0.96–1.04)	0.51	1.02 (0.95–1.10)	0.49	1.00 (0.95–1.07)	0.45
BPE_2	0.96 (0.91–1.00)	0.59	0.95 (0.84–1.03)	0.58	0.96 (0.90–1.02)	0.62
BPE_3	0.95 (0.89–1.01)	0.60	0.88 (0.73–1.00)	0.69	0.97 (0.89–1.05)	0.57
%ΔBPE0_1	0.99 (0.86–1.14)	0.52	0.98 (0.74–1.27)	0.54	1.04 (0.86–1.26)	0.47
%ΔBPE0_2	0.88 (0.75–1.00)*	0.60	0.82 (0.58–1.04)	0.67	0.87 (0.69–1.06)	0.59
%ΔBPE0_3	0.87 (0.74–1.00)**	0.62	0.64 (0.39–0.92)**	0.77	0.91 (0.75–1.09)	0.59

Nomenclature of predictors: _0, absolute value at pretreatment; _1 or 0_1, absolute value at early treatment or change from baseline to early treatment; _2 or 0_2, inter-regimen or change from baseline to inter-regimen; _3 or 0_3, pre-surgery or change from baseline to pre-surgery.
Abbreviations: AUC, area under the curve; BPE, background parenchymal enhancement; CI, confidence interval; HR, hormone receptor; non-pCR, non-pathologic complete response; OR, odds ratio; pCR, pathologic complete response.
*$P < 0.05$; **$P < 0.10$.

CI: 0.3–0.92, $P = 0.04$), with a corresponding AUC of 0.77 (95% CI: 0.56–0.98). In comparison, FTV univariate AUCs ranged from 0.57 to 0.80 in this population, depending on the FTV predictor used.

Multiple Predictor Analysis of BPE and FTV

Table 3 describes the results of the multiple predictor analyses, which were used to assess the additive effect of BPE to FTV-only multiple predictor models. FTV-only multiple predictor analyses demonstrated statistically significant associations across subtypes in change parameters only, with cvAUC remaining significant and estimates ranging from 0.61 to 0.72. Model 2 added BPE to Model 1, which did not lead to improved overall performance based on cvAUC.

Model 3 included all possible linear combination of FTV and HR predictors, which was then optimized by selecting the highest cvAUC value, achieving a cvAUC of 0.81 (95% CI: 0.73–0.90) with %ΔFTV0_2 and HR status. Model 4 was based on any possible combination of BPE predictors with FTV and HR predictors, which did not substantially change the cvAUC of 0.82 (95% CI: 0.74–0.92) but retained multiple BPE predictors with significant associations with pCR.

Discussion

In this study, we demonstrated that quantitative whole-breast BPE alone was predictive of pCR using change from

Table 3. Comparison of Pathologic Complete Response (pCR) Prediction Models Based on Functional Tumor Volume (FTV) Predictors only or Adding Background Parenchymal Enhancement (BPE) Predictors

Prediction model	Treatment Phase	Predictors	OR (95% CI)	cvAUC
Model 1: Pre-specified FTV variables only	Early treatment	%ΔFTV0_1	0.83 (0.71–0.95)*	0.68
		FTV_0	1.00 (0.98–1.01)	
	Inter-regimen	%ΔFTV0_2	0.54 (0.31–0.80)*	0.70
		FTV_0	1.00 (0.98–1.01)	
	Pre-surgery	%ΔFTV0_3	0.45 (0.20–0.81)*	0.63
		FTV_0	1.00 (0.98–1.01)	
Model 2: Pre-specified BPE and FTV variables only	Early treatment	%ΔFTV0_1	0.89 (0.67–0.93)*	0.68
		FTV_0	1.04 (0.98–1.01)	
		%ΔBPE0_1	1.11 (0.94–1.33)	
		BPE_0	1.00 (1.00–1.08)	
	Inter-regimen	%ΔFTV0_2	0.52 (0.28–0.80)*	0.68
		FTV_0	1.02 (0.98–1.01)	
		%ΔBPE0_2	0.97 (0.80–1.15)	
		BPE_0	1.00 (0.98–1.07)	
	Pre-surgery	%ΔFTV0_3	0.46 (0.19–0.86)*	0.61
		FTV_0	1.01 (0.98–1.01)	
		%ΔBPE0_3	0.94 (0.77–1.13)	
		BPE_0	1.00 (0.97–1.06)	
Model 3: Optimized model using any possible FTV and HR predictors	Any phase of treatment	%ΔFTV0_2	0.52 (0.29–0.78)*	0.81
		HR +	0.16 (0.05–0.44)*	
Model 4: Optimized model using any possible FTV, HR, BPE predictors	Any phase of treatment	%ΔFTV0_2	0.49 (0.26–0.80)*	0.82
		HR +	0.08 (0.02–0.29)*	
		BPE_0	1.22 (1.04–1.47)*	
		BPE_1	0.83 (0.69–0.98)*	
		%ΔBPE0_1	1.93 (1.14–3.53)*	
		%ΔBPE0_3	0.86 (0.66–1.06)	

Nomenclature of predictors: _0, absolute value at pretreatment; 0_1, change from baseline to early treatment; 0_2, change from aseline to inter-regimen; 0_3, change from baseline to pre-surgery.

Abbreviations: CI, confidence interval; cvAUC, cross-validated area under the curve (10-repeated 5-fold); HR, hormone receptor; OR, odds ratio.

*$P < 0.05$.

baseline to later treatment time points in women with HR+HER2– breast cancers who were undergoing taxane and anthracycline-based NAC regimen. Moreover, the diagnostic accuracy as measured by AUC was comparable to the predictive performance of the tumor volume measurement FTV. BPE predictors remained significantly associated with pCR when added to multivariate FTV models; however, there was no substantial improvement in discrimination.

We observed that BPE responds to neoadjuvant therapy as demonstrated by declining values as treatment progressed. Moreover, BPE had a similar diagnostic accuracy for women with HR+HER2– breast cancers as compared to FTV under univariate analysis. This is impressive in so far as BPE is measured in the contralateral unaffected breast of presumably normal fibroglandular tissue, whereas FTV is a direct measurement of the primary disease. This suggests that the reaction of normal tissue to neoadjuvant therapy as measured by BPE may represent a biomarker of treatment-responsive phenotype, with higher sensitivity to HR+ tumors. This is consistent with the theory of BPE being primarily modulated by estrogen, given higher values in pre-menopausal women and consistent decreases with hormone therapy (11). Moreover, this is consistent with multiple prior studies, which demonstrated changes in BPE in response to chemotherapy for prediction of pCR (19). However, the observed nature of subtype-specific effect has been mixed in prior studies, with some studies showing an effect of BPE only in HR+ subtypes (14,20), and some studies showing an effect in HR– subtypes (21,22).

The additive value of BPE remains uncertain based on our multiple predictor results. While retained BPE predictors had a significant association with pCR in multivariate FTV models, there was overall no substantial improvement of the cvAUC (Table 3, Model 4). However, we were unable to perform a stratified multivariate analysis within subtype due to limited sample size, which would better mirror the neoadjuvant treatment approach. Our analysis improves on prior literature by evaluating the most relevant clinical question of the additive value of BPE to tumor measurements for predicting pCR, rather than evaluating the utility of BPE prediction alone as most studies do. Changes in the primary tumor are the most direct and robust method for non-invasive

prediction of pCR (23), and the benefit of BPE is therefore most relevant when supplementing tumor models. The only prior study to evaluate the additive effect of BPE for prediction of pCR (22) found that while BPE predictors remained statistically significant in a multiple predictor model, they did not report the extent to which the OR or AUC changed relative to a univariate model.

While BPE still has the potential to be an independent marker of response, our observation of limited additive effect may be due to a variety of reasons. We had a relatively small sample size, which may have caused a strong negative bias when performing cross-validation (24). There are also no accepted definitions of quantitative BPE measurement, and thus alternative quantitative techniques (e.g., partial volume sampling or different kinetic parameterizations) should be explored to assess if they have stronger prediction and additive value to FTV models. Finally, given multiple comparisons, our statistically significant univariate BPE results may have been arguably due to chance. However, the fact that we demonstrate a continued improvement in magnitude and strength of BPE prediction with later time points in HR+ cancers indicates a consistent pattern that reduces the likelihood of results being the product of random chance.

Conclusion

In conclusion, our results suggest BPE may have subtype-specific association with pCR in women with HR+HER2– breast cancer, achieving a similar diagnostic performance to univariate prediction with FTV. However, we did not observe substantial additive improvement in predictive performance when adding BPE to an FTV model in our current study. Additional studies (with ideally larger cohorts) are necessary to replicate these effects and further understand potentially important additive effects, as well as differential effects, within subtypes.

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Conflict of Interest Statement

None declared.

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