Predictive value of breast MRI background parenchymal enhancement for neoadjuvant treatment response among HER2- patients

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Background

- Background parenchymal enhancement (BPE) describes normal breast tissue uptake of intravenous contrast on breast MRI
- BPE as an imaging biomarker may predict pathologic complete response (pCR) to neoadjuvant chemotherapy. Additionally, BPE may give additive prediction to MRI-measured functional tumor volume (FTV) models
- HER2- disease has limited treatment options, and MRI may have greater impact for improving for patient selection
- We systematically explored models of quantitative whole breast BPE for prediction of pCR to neoadjuvant chemotherapy in the I-SPY 2 trial using a manual segmentation approach of the whole breast

I-SPY 2 TRIAL

I-SPY 2: A multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents as neoadjuvant therapy for high-risk breast cancer

Inclusion criteria: Tumor Size ≥ 2.5cm; hormone-receptor (HR)+HER2- MammaPrint (MP) high risk, HR-HER2-. HER2+ patients were not included in this substudy.

Primary Endpoint: Pathologic complete response (pCR)

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HR and HER2 status, and MP

Regimens may leave the trial for one of four reasons: Futility (< 10% probability of success) ; Maximum sample size accrual (with probability of success ≥ 10% and < 85%) ; Graduation (≥ 85% predictive probability of success) ; or as recommended by the independent DSMB

To date: 11 experimental regimens have been evaluated for efficacy

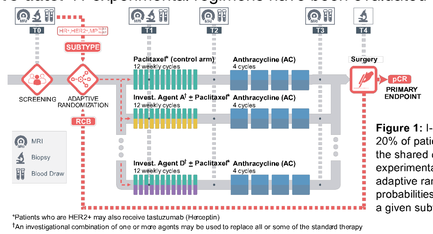


Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

*Patients who are HER2+ may also receive tastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

Methods

- Subjects were identified who initially enrolled in the I-SPY 2 drug arms (all HER2- cancers) using a prospective protocol (Figure 1)
- Women underwent breast MRI and were evaluated for BPE using a manual segmentation approach of the contralateral breast (Figure 2)

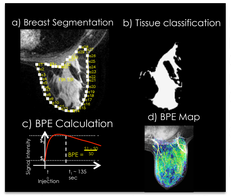
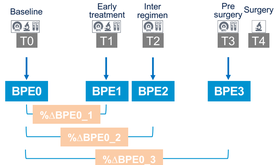


Figure 2: MRI segmentation was manually performed of the whole contralateral breast (Figure 2a), and tissue classification was performed using fuzzy c-means clustering (Figure 2b). Values of BPE were calculated on a per-voxel basis using the equation $(S_1 - S_0)/S_0 \times 100\%$, where S_0 represents the precontrast acquisition and S_1 represents the early postcontrast acquisition (Fig. 2c).

- Logistic regression, stratified by hormone receptor (HR) subtype, was performed using 1) univariate models of BPE predictors alone (Figure 3) and 2) multivariate models using all possible combinations of BPE, FTV predictors and HR status. Additive benefit for multivariate models was evaluated by estimating change in the 5-fold cross-validated area under the curve (AUC) for overall diagnostic performance

Figure 3: Schema of predictors used in regression models based on MRI protocol acquired at four time points during neoadjuvant therapy:

T0: baseline
T1: early-treatment
T2: inter-regimen
T3: pre-surgery



RESULTS

- A total of 352 MRIs in 88 women (29 pCR, 59 non-pCR) were identified
- Women with pCR were more often HR+ than non-PCR (24% vs. 61%)
- Women who achieved pCR tended to have higher absolute BPE values at baseline, which decreased more at later treatment time points (Fig 4)
- Univariate models (Table 1) demonstrated that women with HR+ cancers who achieved pCR demonstrated a significantly greater decrease in BPE from baseline to pre-surgery compared to non-pCR patients (OR = 0.64, 95% CI = 0.39-0.92, p-value = 0.04).
- The associated BPE AUC was 0.77 (95% CI 0.56-0.98), comparable to the range of FTV AUC estimates.

RESULTS

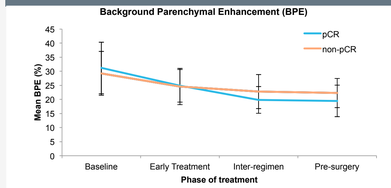


Figure 4: Plots of average values of background parenchymal enhancement (BPE) through phases of treatment (errors bars represent interquartile range)

Table 1: Univariate analyses of BPE variables, stratified by HR subtype

Receptor type	ALL		HR+		HR-	
Total No. (pCR / non-pCR)	88 (29 / 59)		43 (7 / 36)		45 (22 / 23)	
	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

Table 2: Prespecified multivariate analyses of FTV/BPE variables

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 & 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)	

■ $p < 0.05$; ■ $p < 0.10$

RESULTS

- Prespecified multivariate analyses demonstrated significant associations in %Δ change parameters only. cvAUC ranged from 0.61-0.72 (Table 2)
- Optimized multivariate models performed best (Table 3), with the highest AUC of 0.81 (95% CI 0.73-0.90) was achieved with combined FTV predictors and HR, while adding BPE to FTV and HR models had an estimated AUC of 0.82 (95% CI 0.74-0.92).

Table 3: Optimized multivariate analyses of FTV/BPE variables

Prediction Model	Treatment phase	Predictors	OR (95% CI)	cvAUC
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)	

CONCLUSIONS

- Quantitative whole breast BPE of the contralateral breast decreases with neoadjuvant chemotherapy
- In HR+HER2- patients, univariate diagnostic performance of BPE alone is within the range of diagnostic performance of tumor volume for prediction of pathologic complete response (pCR).
- In this preliminary HER2- cohort, BPE did not show significant improvement in diagnostic performance when added to a multiple predictor tumor volume model, although further study is warranted (see PD9-04 and PD9-05)

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