Lack of background parenchymal enhancement suppression in breast MRI during neoadjuvant chemotherapy may be associated with inferior treatment response in hormone receptor positive breast cancer

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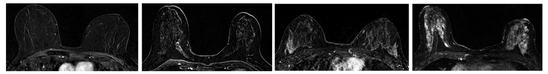
Background

Background Parenchymal Enhancement (BPE) in Breast MRI

- Contrast enhancement of "normal" fibroglandular tissue
- Symmetric degree and distribution for both breasts
- Visual assessment in BI-RADS (4-point scale)
- Quantitative measurement in contralateral breast to avoid including tumor area
- Associated with breast cancer survival[1], treatment response to neoadjuvant chemotherapy (NAC)[2,3] and future breast cancer risk[4]



Minimal BPE | Mild BPE | Moderate BPE | Marked BPE

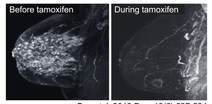
Radiographics 2014; 34: 234–47

BPE & Hormonal status

Hormonal status significantly affects the degree of BPE, potentially due to the association with mammary vascularity and activity[5–9].

- menstrual cycle
- lactation
- menopause
- hormone replacement therapy
- hormone therapy

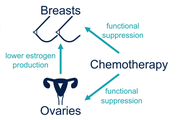
(tamoxifen, aromatase inhibitors) etc.

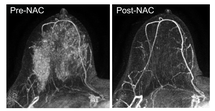


Breast J. 2012 Dec; 18(6) 527-534

Suppression of BPE during NAC

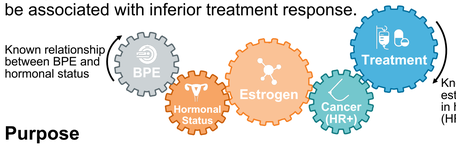
In most patients undergoing NAC, BPE may be suppressed by the nonspecific anti-proliferative effects of chemotherapy on normal breasts and/or ovaries[5,10]. However, some patients exhibit equivalent or even stronger BPE post-NAC compared to pre-NAC.





Hypothesis

We hypothesized that non-suppressed BPE in post-NAC may be associated with inferior treatment response.



Purpose

This study aimed to investigate the association between BPE suppression and treatment response as defined by pathologic complete response (pCR).

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; HR+HER2– MammaPrint (MP) high risk, HR–HER2– or HER2+

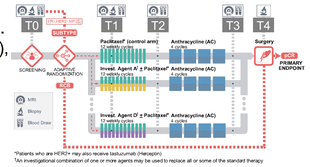
Primary Endpoint: Pathologic complete response (pCR)

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

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 ado-trastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

Methods

Patients

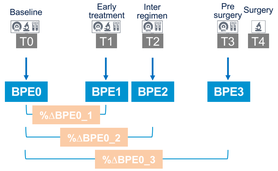
988 patients from 9 completed/graduated drug arms with pathological outcome

Dynamic enhanced MRIs at four time points during NAC

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

BPE0, BPE1, BPE2 and BPE3
→ BPE at each treatment time point

%ΔBPE0_1, %ΔBPE0_2 and %ΔBPE0_3
→ Percent change of BPE from T0 at T1, T2 and T3

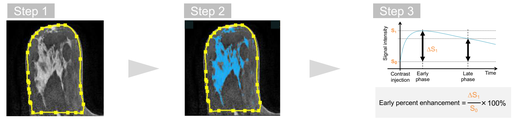


Study cohort

- MRIs with poor image quality and poor BPE calculation were excluded from the analysis
- Two subgroups based on hormone receptor status (HR+, HR−)

Methods

Automated Quantitative Measurement of BPE



Step 1 Fully automatic segmentation of contralateral breast
Step 2 Differentiation of fibroglandular tissue from fat
Step 3 Mean early (~150s post-contrast injection) percent enhancement of the central 50% of the axial slices

BPE Suppression at T1, T2 or T3

Binary indicator of whether or not BPE was suppressed in comparison with T0

%ΔBPE < 0 → **Suppressed**
%ΔBPE ≥ 0 → **Non-suppressed**

Quality Score & High-quality Set

- Quality of automated differentiation of fibroglandular tissue
- Visual assessment by a radiologist using three point scoring (score 2 = good, score 1 = adequate, score 0 = poor)
- High-quality set: %ΔBPE0_1, %ΔBPE0_2, and %ΔBPE0_3 calculated from BPE0, BPE1, BPE2 and BPE3 with quality score 2 or 1

Statistical Analysis

Chi-squared test or Fisher's exact test was used to examine the association between BPE suppression and pCR

Results

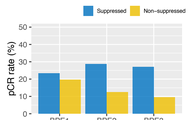
Study Cohort (High-quality set)

Time points	Analyzable BPE: Quality score 2	Analyzable BPE: Quality score 1	Analyzable BPE: Quality score 0	Unanalyzable BPE†	BPE not available‡	High-quality set of %ΔBPE*
T0 (BPE0)	104	519	347	18	2	
T1 (BPE1)	78	475	385	19	33	479 (48)
T2 (BPE2)	75	439	369	22	85	437 (44)
T3 (BPE3)	65	436	375	14	100	415 (42)

Data represent the number of exams. Data in parentheses are percentages of 988.
† Exams where automated segmentation failed to accurately define contralateral breast
‡ MRI not scanned or rejected by I-SPY2 Imaging Core Lab
* %ΔBPE0_1, %ΔBPE0_2, and %ΔBPE0_3 calculated from BPE0, BPE1, BPE2 and BPE3 with quality score 2 or 1

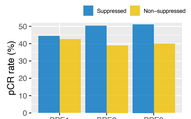
Results

HR+	pCR rate (%)	No. of pCR patients	No. of non-pCR patients	Total No. of patients	P value
HR+ cohort (n = 536)	22.8	122	414	536	
HR+ cohort in High-quality set					
BPE at T1 (n = 272)					
Suppressed	23.4	47	154	201	0.52
Non-suppressed	19.7	14	57	71	
BPE at T2 (n = 251)					
Suppressed	28.7	56	139	195	0.01*
Non-suppressed	12.5	7	49	56	
BPE at T3 (n = 238)					
Suppressed	27.0	53	143	196	0.02*
Non-suppressed	9.5	4	38	42	



- pCR rates lower for non-suppressed BPE at every visit
- Statistically significant difference at T2 (p=0.01) and T3 (p=0.02)

HR−	pCR rate (%)	No. of pCR patients	No. of non-pCR patients	Total No. of patients	P value
HR− cohort (n = 452)	44.7	202	250	452	
HR− cohort in High-quality set					
BPE at T1 (n = 207)					
Suppressed	44.4	68	85	153	0.81
Non-suppressed	42.6	23	31	54	
BPE at T2 (n = 186)					
Suppressed	50.3	73	72	145	0.20
Non-suppressed	39.0	16	25	41	
BPE at T3 (n = 177)					
Suppressed	51.1	70	67	137	0.22
Non-suppressed	40.0	16	24	40	



- pCR rates were slightly lower for non-suppressed BPE
- No statistically significant difference

Conclusions

- Our results confirmed our hypothesis in HR+ breast cancer: non-suppressed BPE at T2 and T3 showed association with inferior treatment response.
- The contrasting results in HR+ and HR– cohort may reflect the influence of functional hormone suppression on treatment response.
- About half of the exams were excluded from BPE analysis. Improvements in image quality and automated image processing may increase yield.

Acknowledgements:

- With grant support from **NIH U01 CA225427** and **NIH R01 CA132870**.
- With support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835), Safeway, an Albertsons Company, William K. Bowes, Jr. Foundation, Breast Cancer Research Foundation, UCSF, GMU, the Biomarkers Consortium, Salesforce, OpenClinica, Formedix, Natera, Hologic Inc., TGen, Illumina, CCS Associates, Berry Consultants, Breast Cancer Research – Atwater Trust, Stand up to Cancer, California Breast Cancer Research Program, and Give Breast Cancer the Boot, IQVIA, Genentech, Amgen, Pfizer, Merck, Seattle Genetics, Daiichi Sankyo, AstraZeneca, Dynavax Technologies, Puma Biotechnology, AbbVie, Madrigal Pharmaceuticals (formerly Synta Pharmaceuticals), Plexxikon, Regeneron and Agendia. Sincere thanks to our DSMB, Independent Agent Selection Committee, our patients, advocates and investigators.

References:

1. Eur Radiol 28:4705–4716, 2018 **2.** Eur Radiol 26:1590–1596, 2016 **3.** Transl Oncol 8:204–209, 2015 **4.** J Clin Oncol JCO1800378, 2019 **5.** Radiographics 34:234–247, 2014 **6.** Radiology 203:137–144, 1997 **7.** Radiology 203:145–149, 1997 **8.** Breast J 11:236–241, 2005 **9.** AJR Am J Roentgenol 204:669–673, 2015 **10.** Radiology 277:687–696, 2015