# The effect of background parenchymal enhancement on the predictive performance of functional tumor volume measured in MRI

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## Background

Strong background parenchymal enhancement (BPE) may cause over-estimation in tumor volume measured from dynamic contrast-enhanced (DCE) –MRI.

BPE may adversely affect the predictive performance of functional tumor volume (FTV) for pathologic outcomes after neoadjuvant chemotherapy (NAC).

**Purpose:** this retrospective study
1) investigated the adverse effect of BPE on the predictive performance of FTV
2) proposed a potential solution to offset the effect.

## 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- 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



**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

All I-SPY 2 participants had series of MRI at T0 (pre-NAC), T1 (after 3 weeks of NAC), T2 (inter-regimen), and T3 (pre-surgery).

BPE was calculated as the mean enhancement compared to pre-contrast in the contralateral breast on DCE-MRI.
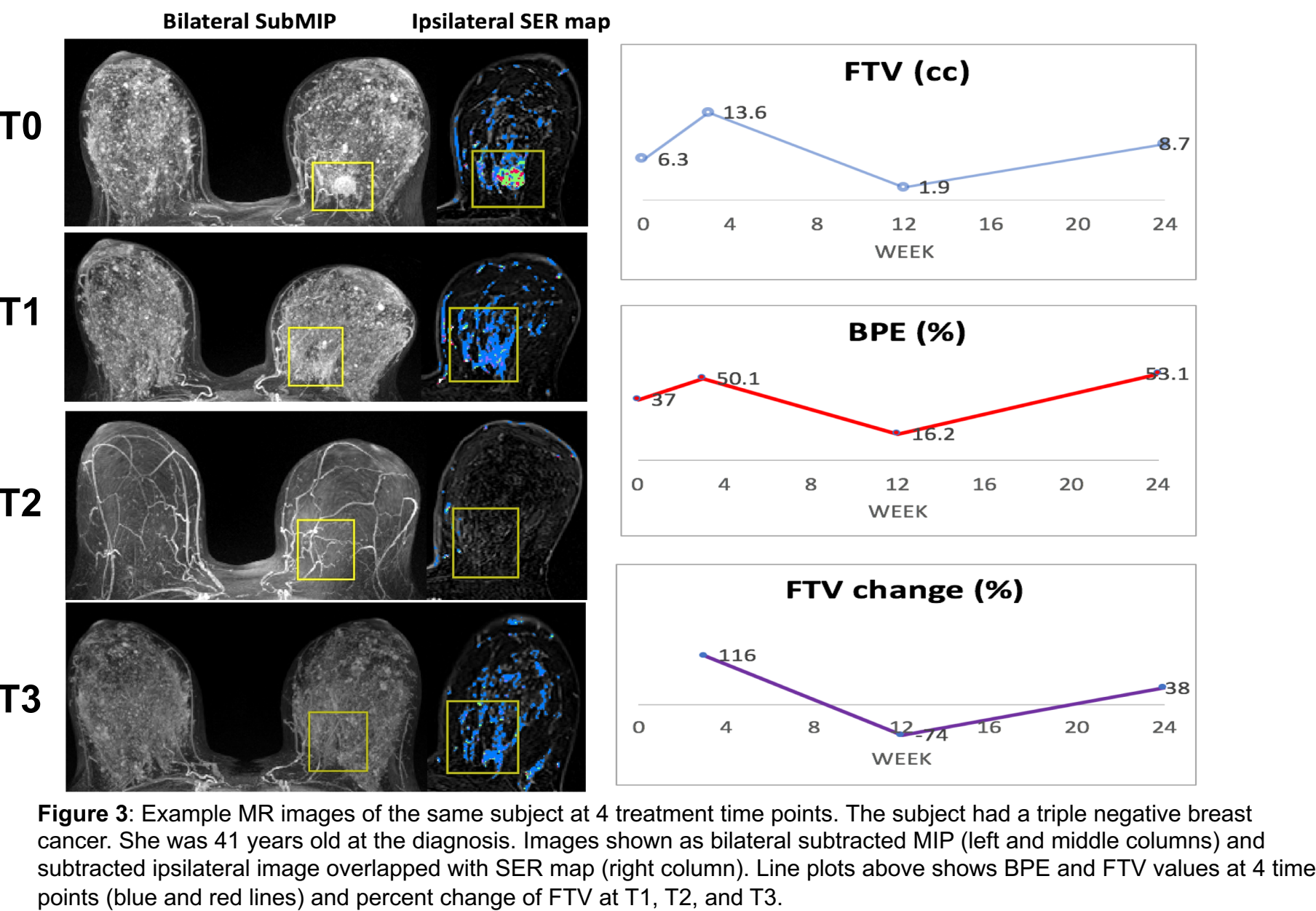
FTV was calculated by summing the voxels exceeding enhancement thresholds on DCE-MRI.



$$ SER = \frac{\Delta S_1}{\Delta S_2} $$

**Figure 2:** BPE and FTV calculations. Plot on the left shows simulated signal change after the contrast injection. The images in the middle and on the right shows the segmentation of fibroglandular tissue in the contralateral breast and tumor in the ipsilateral breast.

**Statistics:** The area under the ROC curve (AUC) was used to evaluate the predictive performance of FTV variables with and without high BPE subjects.

## High BPE effect on FTV calculation

- High BPE may cause inaccurate calculation of FTV
- This effect can adversely affect the predictive performance of FTV
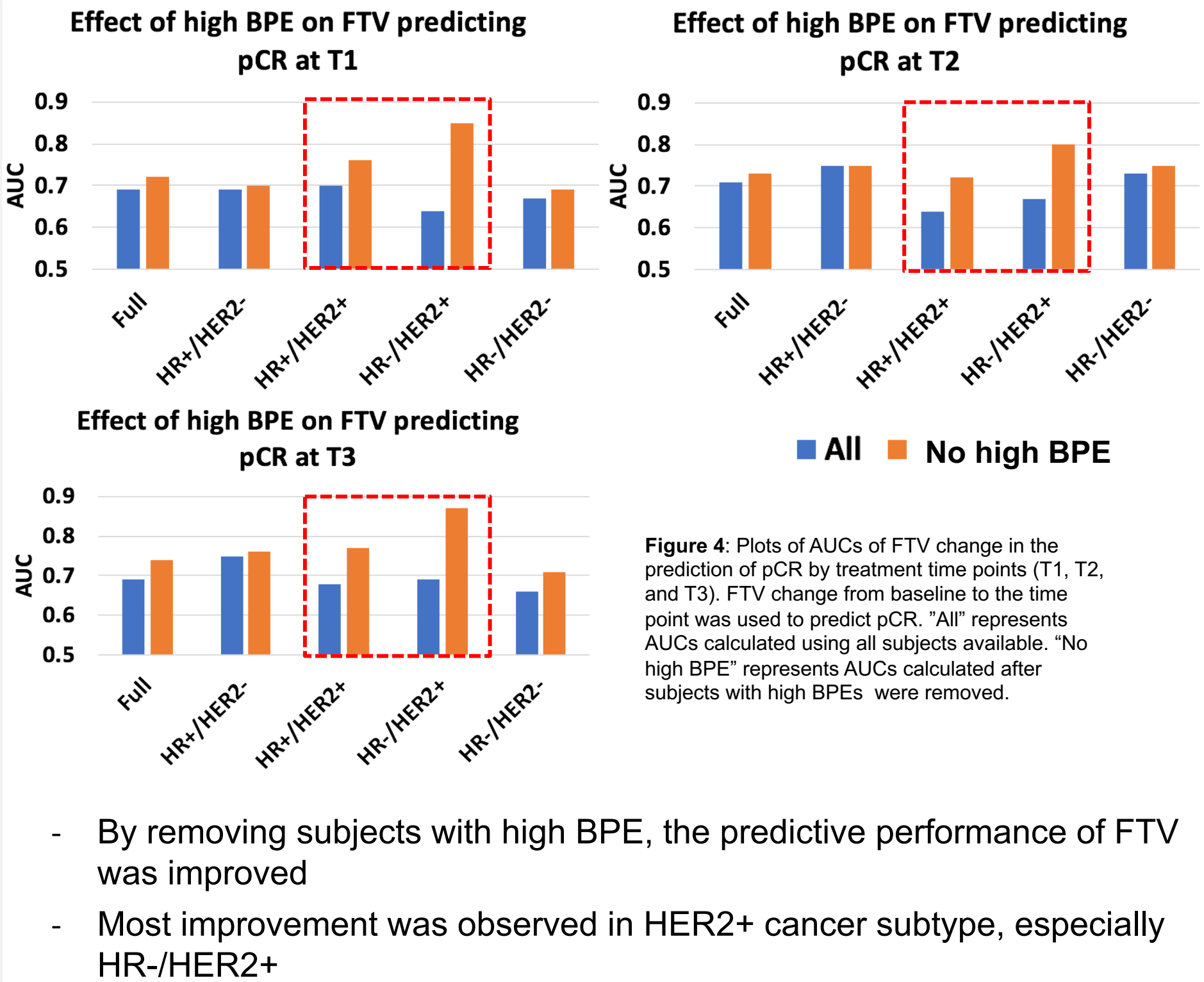- The change of BPE itself may indicate treatment response



**Figure 3:** Example MR images of the same subject at 4 treatment time points. The subject had a triple negative breast cancer. She was 41 years old at the diagnosis. Images shown as bilateral subtracted MIP (left and middle columns) and subtracted ipsilateral image overlapped with SER map (right column). Line plots above shows BPE and FTV values at 4 time points (blue and red lines) and percent change of FTV at T1, T2, and T3.

## Effect on the predictive performance



**Figure 4:** Plots of AUCs of FTV change in the prediction of pCR by treatment time points (T1, T2, and T3). FTV change from baseline to the time point was used to predict pCR. "All" represents AUCs calculated using all subjects available. "No high BPE" represents AUCs calculated after subjects with high BPEs were removed.

- By removing subjects with high BPE, the predictive performance of FTV was improved
- Most improvement was observed in HER2+ cancer subtype, especially HR-/HER2+

**Table 1.** Number of subjects and pCR rates in all and subset with no high BPE

|  | T1 | | T2 | | T3 | |
|---|---|---|---|---|---|---|
|  | All | No high BPE | All | No high BPE | All | No high BPE |
| Full | 667 (32%) | 503 (32%) | 629 (33%) | 441 (33%) | 660 (33%) | 449 (33%) |
| HR+/HER2- | 269 (17%) | 219 (17%) | 251 (17%) | 251 (17%) | 251 (17%) | 226 (17%) |
| HR+/HER2+ | 109 (37%) | 76 (34%) | 109 (39%) | 77 (38%) | 94 (36%) | 68 (34%) |
| HR-/HER2+ | 57 (65%) | 33 (64%) | 51 (69%) | 38 (63%) | 48 (71%) | 33 (70%) |
| HR-/HER2- | 233 (40%) | 174 (39%) | 218 (41%) | 154 (40%) | 207 (43%) | 139 (41%) |

**Table 2.** BPE cutoffs to define subsets with high BPE removed

|  | T1 | | T2 | | T3 | |
|---|---|---|---|---|---|---|
|  | BPE0 | BPE1 | BPE0 | BPE2 | BPE0 | BPE3 |
| Full | 31 | 23 | 27 | 17 | 26 | 19 |
| HR+/HER2- | 35 | 22 | 86 | 82 | 36 | 24 |
| HR+/HER2+ | 31 | 22 | 30 | 18 | 30 | 16 |
| HR-/HER2+ | 21 | 17 | 29 | 20 | 25 | 16 |
| HR-/HER2- | 32 | 22 | 29 | 18 | 25 | 16 |

## Potential solution

- Exclude gradual wash-out (FTVt) in FTV calculation
- AUCs of FTV calculated with SER>0.9 were improved in HER2+ subtypes
- The improvement was observed in the early treatment time point
- Consistent with prior study showing the higher SER thresholds in the optimized PE/SER thresholds for HER2+ (Li et al 2016)



**Figure 5:** Plots of AUCs of predicting pCR using FTV vs. FTV calculated with SER > 0.9. Slight improvement can be observed in the full cohort and triple negatives, while more improvement is observed in HER2+ subtypes. No improvement was observed in HR+/HER2- subtype.
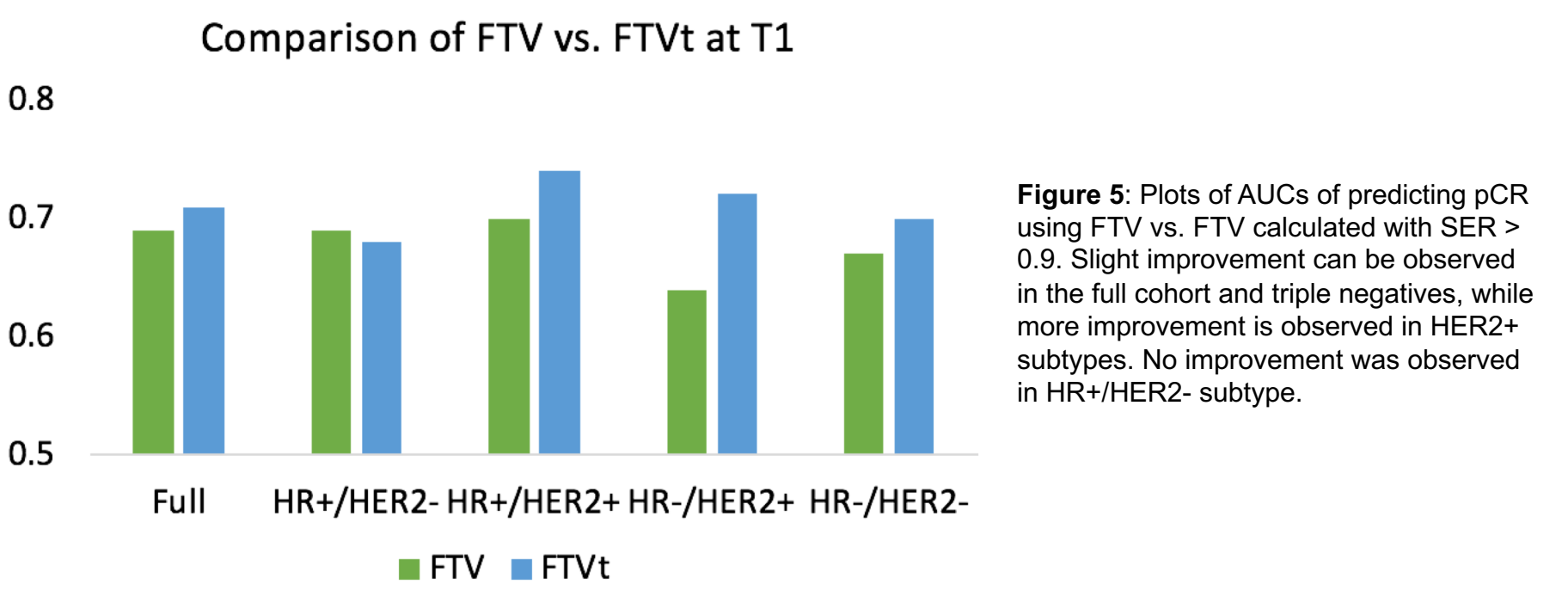
## CONCLUSIONS

- Our retrospective study showed adverse effect of background parenchymal enhancement on the functional tumor volume calculation and its prediction of pathologic complete response

- This effect may be adjusted by re-calculating functional tumor volume using a different signal-enhancement ratio threshold

- In future study, we will test the predictive performance of re-calculated functional tumor volume with subtype-specific enhancement thresholds in I-SPY 2 cohort

The right drug, the right patient, the right time… *now*.

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