Diffusion-weighted MRI Improves Imaging Prediction of Response in the I-SPY 2 TRIAL

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BACKGROUND

The I-SPY 1 TRIAL demonstrated that functional tumor volume (FTV) measured by dynamic contrast-enhanced (DCE) MRI during neoadjuvant chemotherapy (NAC) predicts both pathologic complete response (pCR) and recurrence free survival[1,2]. In addition to DCE, the I-SPY 2 TRIAL is testing whether diffusion weighted MRI (DW-MRI), a non-contrast method that characterizes water mobility and cellularity by measuring the apparent diffusion coefficient (ADC), acquired during the same MRI exam as DCE, can provide valuable distinct information about tumor response. We hypothesize that combining FTV and ADC can improve the predictive performance of breast MRI.

ELIGIBILITY/ENROLLMENT/DISPOSITION

Eligible patients include those with one of the following criteria: Stage II or III, or T4, any N, M0, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites metastasis.

A sub-cohort of 311 patients who had completed therapies with investigational or control regimens were included in this study. Table 1 shows number of patients with breast cancer subtypes defined by HR & HER2 status and patients treated with experimental vs. control regimens (Exp/ctl) in each subtype category. pCR rates in the full cohort and by subtype are also shown in Table 1.

Table 1 Patient Characteristics

	Full cohort	HR+/HER2-	HR+/HER2+	HR-/HER2+	HR-/HER2-
n	311	110	56	29	116
Exp/ctl	236/75	80/30	43/13	22/7	91/25
pCR rate	31.8%	15.5%	26.8%	55.2%	44.0%

I-SPY2's ADAPTIVE TRIAL DESIGN

I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast (FIG.1). Within each subtype, participants are assigned to one of several investigational therapies or the control regimen. Randomization probabilities are proportional to current probabilities that the respective therapies have a higher pCR rate than control rate in the respective subtypes. *The primary endpoint is pathologic complete response (pCR, no residual disease in breast or nodes) at surgery*.

The goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by hormone-receptor (HR) & HER2 status & MammaPrint (MP).

Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (< 10% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

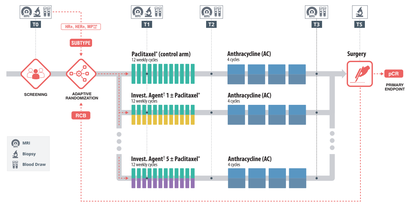

Figure 1: I-SPY2 study schema and adaptive randomization based on probabilities of agents of achieving pCR within a given subtype

MRI ACQUISITION AND QUANTIFICATION

MRI was acquired at 4 time points: pre-NAC (T0), early-treatment (T1), inter-regimen (T2), and post-NAC (T3) (FIG.1). MR imaging was performed at 1.5T or 3T, across a variety of vendor platforms. The standard breast MRI protocol included a localization scan, a T2-weighted sequence, DW-MRI, and DCE-MRI. The percent change of FTV and mean ADC at T1 (%ΔFTV1_0 and %ΔADC1_0) and T2 (%ΔFTV2_0 and %ΔADC2_0) from the pre-NAC (T0) were evaluated as predictors for pCR.

- **Functional tumor volume (FTV)** in DCE-MRI was calculated by the sum of voxels with enhancement above pre-defined thresholds (FIG.2a)
- **Apparent diffusion coefficient (ADC)** map was generated from DW-MRI with 2 b-values (b=0 and 800 s/mm^2). Mean ADC was calculated by averaging ADC values within the whole tumor ROI (FIG.2c)

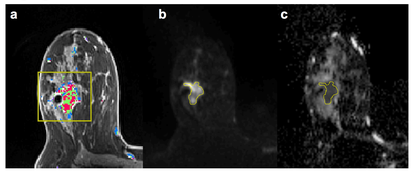

Figure 2: MR images acquired at pre-NAC (T0). (a) An axial slice from DCE-MRI. FTV was calculated by the sum of voxels with enhancement (in color) within the region-of-interests (yellow rectangular). Corresponding slices from DW-MRI (b) and ADC map (c) are shown with tumor ROI manually delineated.

Logistic regression model and area under the receiver operating characteristic curve (AUC) were used in analysis. AUCs of multivariate models were calculated using logistic regression predicted values from 10-fold cross-validation. The statistical significant level for all testing was set at 0.05.

RESULTS

❑ Univariate analysis

The values of percent change of FTV and ADC at early-treatment time point T1 (%ΔFTV1_0 and %ΔADC1_0) and at inter-regimen time point T2 (%ΔFTV2_0 and %ΔADC2_0) are plotted in FIG.3. Corresponding AUCs for predicting pCR are listed in Table 2.

Table 2 AUCs for FTV or ADC predictors alone

%ΔFTV1_0	N	AUC (95% CI)	p-value*
Full	262	0.67 (0.60, 0.74)	$8.1\times e^{-06}$
HR-/HER2-	100	0.68 (0.58, 0.79)	0.002
HR-/HER2+	22	0.59 (0.34, 0.85)	0.500
HR+/HER2-	92	0.73 (0.58, 0.88)	0.007
HR+/HER2+	48	0.70 (0.52, 0.88)	0.034
%ΔADC1_0	**N**	**AUC (95% CI)**	**p-value***
Full	262	0.59 (0.51, 0.66)	0.027
HR-/HER2-	100	0.58 (0.46, 0.70)	0.188
HR-/HER2+	22	0.62 (0.36, 0.87)	0.381
HR+/HER2-	92	0.54 (0.34, 0.73)	0.644
HR+/HER2+	48	0.63 (0.47, 0.79)	0.188
%ΔFTV2_0	**N**	**AUC (95% CI)**	**p-value***
Full	232	0.68 (0.61, 0.76)	$8.8\times e^{-06}$
HR-/HER2-	84	0.76 (0.66, 0.87)	$1.8\times e^{-05}$
HR-/HER2+	22	0.63 (0.34, 0.89)	0.346
HR+/HER2-	84	0.80 (0.67, 0.92)	0.001
HR+/HER2+	42	0.59 (0.38, 0.80)	0.459
%ΔADC2_0	**N**	**AUC (95% CI)**	**p-value***
Full	232	0.72 (0.64, 0.79)	$1.5\times e^{-07}$
HR-/HER2-	84	0.77 (0.66, 0.87)	$1.7\times e^{-05}$
HR-/HER2+	22	0.78 (0.56, 1)	0.025
HR+/HER2-	84	0.70 (0.51, 0.88)	0.030
HR+/HER2+	42	0.72 (0.53, 0.91)	0.060

*by Wilcoxon rank-sum test

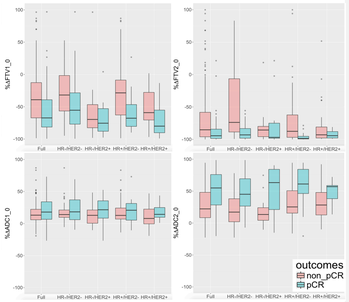

Figure 3: Box plots of FTV (top) and ADC (bottom) in percent changes at treatment time point T1 (left) and T2 (right) in patients having pCR vs. non_pCR after NAC.

- In the full cohort, both FTV and ADC percent change at T1 or T2 are strong predictors for pCR
- However, their predictive performance varied in breast cancer subtypes
- AUCs are higher at T2 than at T1

❑ Multivariate analysis

The multiple regression model combining %ΔFTV and %ΔADC showed statistically significant improvement compared to %ΔFTV and %ΔADC alone at T1. P-values of likelihood ratio test are 0.02 compared to %ΔFTV1_0 alone and $9.4\times e^{-05}$ compared to %ΔADC1_0 alone. At T2, p-values are $8.7\times e^{-05}$ compared to %ΔFTV2_0 alone and 0.002 compared to %ΔADC2_0 alone. Odds ratios of each 10% increase of %ΔFTV and %ΔADC to have non-pCR post-NAC were shown in Table 3.

Table 3 Odds ratio evaluated by logistic regression model

	%ΔFTV alone	%ΔADC alone	%ΔADC adjusted for %ΔFTV
Early-treatment (T1)	1.16 (1.07, 1.26)	0.83 (0.71, 0.95)	0.84 (0.72, 0.97)
Inter-regimen (T2)	1.28 (1.13, 1.52)	0.82 (0.75, 0.89)	0.85 (0.78, 0.92)

Note: data in parentheses are 95% confidence intervals.

AUCs for predicting pCR using %ΔFTV or %ΔADC alone, as long as using multivariate combining them and/or breast cancer subtype in the logistic regression model are listed in Table 4. The model combining %ΔFTV, %ΔADC, and subtype resulted in highest AUCs at T1 and T2. ROC curves of %ΔFTV, %ΔADC alone and the combined models with %ΔFTV + %ΔADC and %ΔFTV + %ΔADC + subtype are plotted in FIG. 4.

Table 4 AUCs for multivariate analysis

Early treatment (T1)	
Predictors	AUC (95% CI)
%ΔFTV1_0	0.67 (0.60, 0.74)
%ΔADC1_0	0.59 (0.51, 0.66)
%ΔFTV1_0 + %ΔADC1_0	0.65 (0.61, 0.70)
%ΔFTV1_0 + subtype	0.72 (0.68, 0.76)
%ΔADC1_0 + subtype	0.67 (0.63, 0.71)
%ΔFTV1_0 + %ΔADC1_0 + subtype	0.73 (0.69, 0.76)
Inter-regimen (T2)	
Predictors	AUC (95% CI)
%ΔFTV2_0	0.68 (0.61, 0.76)
%ΔADC2_0	0.72 (0.64, 0.79)
%ΔFTV2_0 + %ΔADC2_0	0.73 (0.69, 0.77)
%ΔFTV2_0 + subtype	0.78 (0.74, 0.82)
%ΔADC2_0 + subtype	0.78 (0.74, 0.82)
%ΔFTV2_0 + %ΔADC2_0 + subtype	0.80 (0.77, 0.84)

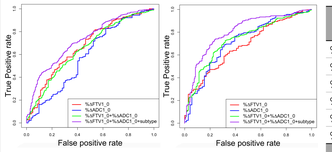

Figure 4: ROC curves of logistic regression model with single or multi- variate analysis for predicting pCR at treatment time point T1 (left) and T2 (right). The associated area under the curve (AUC) are listed in Table 4.

CONCLUSIONS

The addition of ADC to standard FTV MRI may help refine the prediction of treatment response. Further improvement can be achieved by adjusting the model for breast cancer subtype. The effect of different novel agents should be considered in future study on a larger cohort.

REFERENCES

1. Hylton et al. Radiology 2012
2. Hylton et al. Radiology 2016

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