Refining neoadjuvant predictors of three year distant metastasis free survival: integrating volume as measured by MRI with residual cancer burden

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BACKGROUND

Patients achieving a pathologic complete response (pCR) following neoadjuvant therapy have significantly improved event-free survival relative to those who do not; and pCR is an FDA-accepted endpoint to support accelerated approval of novel agents/combinations in the neoadjuvant treatment of high risk early stage breast cancer. Previous studies have shown that recurrence risk increased with increasing burden of residual disease (as assessed by the RCB index). As well, these studies suggest that patients with minimum residual disease (RCB-I class) also have favorable outcomes (comparable to those achieving a pCR) within high risk tumor subtypes. In this study, we assess whether integrating RCB with MRI functional tumor volume (FTV), which in itself is prognostic, can improve prediction of distant recurrence free survival (DRFS); and identify a subset of patients with minimal residual disease with comparable DRFS as those who achieved a pCR. Imaging tools can then be used to identify the subset that will do well early and guide the timing of surgical therapy.

I-SPY 2 TRIAL

I-SPY 2: Phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast cancer

Inclusion criteria: Tumor Size ≥ 2.5cm; HR+HER2- (MammaPrint high risk), HR-HER2- or HER2+.

Primary Endpoint: Pathologic complete response (pCR).

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of increased pCR rate if tested in a neoadjuvant 300-patient phase 3 trial.

To date: 10 experimental regimens have been evaluated for efficacy.

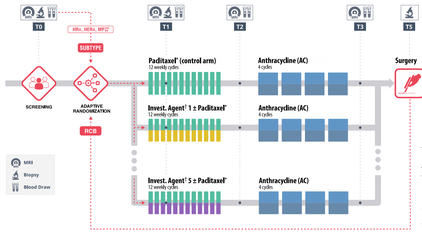


Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

Secondary Endpoints: RCB and Event-free Survival (EFS).

Methods

We performed a pooled analysis of 649 patients from the I-SPY2 TRIAL with RCB, pre-surgical MRI FTV data and known follow-up (data cutoff date: June 2018, median 2.9 years). We first assessed whether FTV predicts residual disease (pCR or pCR/RCB-I) using ROC analysis. We then applied a power transformation to normalize the pre-surgical FTV distribution; and assessed its association with DRFS using a Cox proportional hazard model adjusting for HR/HER2 subtype. We also fitted a Cox model of RCB index adjusting for subtype; and assessed whether adding pre-surgical FTV to this model further improves association with DRFS using a likelihood ratio (LR) test. For the Cox modeling, penalized splines approximation of the transformed FTV and RCB index with 2 degrees of freedom was used to allow for non-linear effects of FTV and RCB on DRFS.

MRI FTV as Predictor of Response

MRI FTV is more effective at predicting pCR/RCB-I than predicting pCR alone

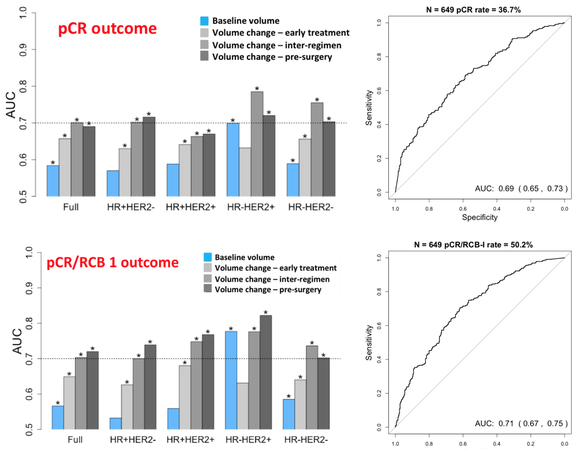


Figure 2. LEFT: AUC values for FTV prediction of pCR (top) and pCR/RCB 1 (bottom), for the full cohort and by subtype. AUC values are shown for baseline FTV (blue), change at early treatment (light gray), inter-regimen (medium gray) and pre-surgery (dark gray). RIGHT: Corresponding ROC curves for the pre-surgical change in FTV in the full cohort.

MRI FTV and RCB as Predictor of DRFS

Univariate Cox Modeling

Pre-surgical MRI FTV is significantly associated with DRFS (Wald p for linear effect <0.00001)

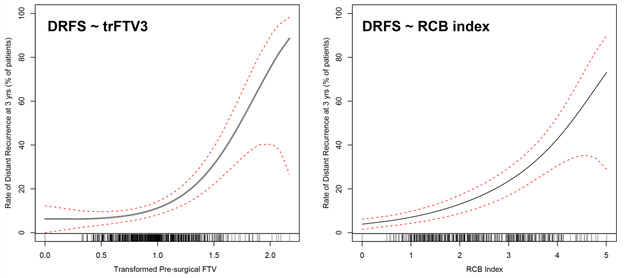


Figure 3. Association between Pre-surgical MRI FTV (FTV3), RCB and DRFS. (A-B) DRFS event rate as a function of (A) transformed FTV3 (trFTV3), and (B) the RCB index at 3 years estimated using smoothing splines approximation from Cox modeling

The RCB index is also significantly associated with DRFS (Wald p for linear effect <0.00001).

Multivariate Cox Modeling

Larger pre-surgical FTV remains associated with worse DRFS adjusting for subtype (Wald p <0.00001). Adding FTV to a model containing RCB and subtype further improves association with DRFS (LR p=0.0007).

Table 1: Multivariate Cox Modeling of DRFS as a function of trFTV3, RCB and HR/HER2 subtypes

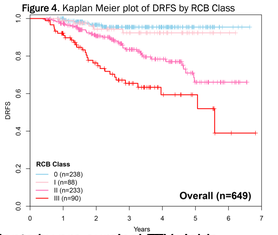
	Cox Model Coefficient	Wald test p
Transformed Pre-surgical FTV (trFTV3)		
Linear Effect	0.76	0.0164
Non-Linear Effect		0.0049
RCB Index		
Linear Effect	0.65	<0.00001
Non-Linear Effect		0.330
HR (Ref: HR-)	-0.87	0.0002
HER2 (Ref: HER2-)	-0.38	0.1765

Integrating MRI and RCB

RCB-I patients have excellent DRFS (94% at 3 years compared to 95% in the pCR group).

Association between pre-surgical FTV and DRFS is observed in the RCBII/III group but not RCB0/I group (Wald p for linear effect < 0.00001 vs. 0.539 respectively).

Figure 4. Kaplan Meier plot of DRFS by RCB Class



Further sub-division of RCB-II and RCB-III patients by pre-surgical FTV yields groups with significant differences in DRFS

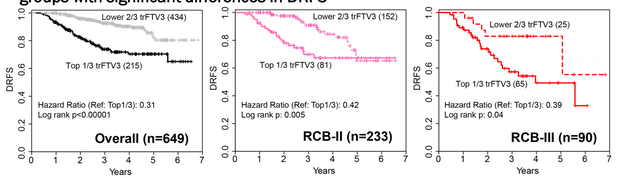


Figure 5. Kaplan Meier plot of DRFS by pre-surgical FTV (top vs lower 2/3 tertile) in all (left); RCB-II (middle) and RCB-III (right) patients

Efforts are underway to identify optimal FTV measures and dichotomizing thresholds for use in combination with pCR/RCB-I class to generate integrated RCB (iRCB) groups as a composite predictor of DRFS.

CONCLUSIONS

- Pre-surgical MRI FTV is effective at predicting minimal residual disease (RCB0/I) in the I-SPY 2 TRIAL.
- Despite the association between FTV and RCB, FTV appears to provide independent added prognostic value (to RCB and subtype), suggesting that integrating MRI volume measures and RCB into a composite predictor may improve DRFS prediction.

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