

DNA Repair Biomarkers in Triple Negative Breast Cancer

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INTRODUCTION

- Triple negative breast cancers are defined by a lack of expression of ER, PR and HER2 receptors
- These tumors have a high rate of local and systemic relapse following conventional therapy
- Both phenotypic and gene expression show similarities with *BRCA1* mutated tumors
- Triple negative breast cancers shows characteristics consistent with defects in DNA repair

METHODS

- 143 women were identified with triple negative breast cancers through CORIS database
- Archived, formalin-fixed, paraffin-embedded primary excision biopsies were used to create a tissue microarray (TMA)
- TMA was stained using antibodies against proteins in various DNA repair pathways including XPF, FANCD2, PAR, MLH1, and MK2
- Stained tissue was evaluated using machine-based image analysis and pathology-based scoring that represented both the intensity and quantity of positive tumor staining
- Kaplan-Meier and Cox proportional hazards were used to identify correlations between biomarker and time to recurrence
- A multiple marker model was developed by randomizing patients into training and test cohorts

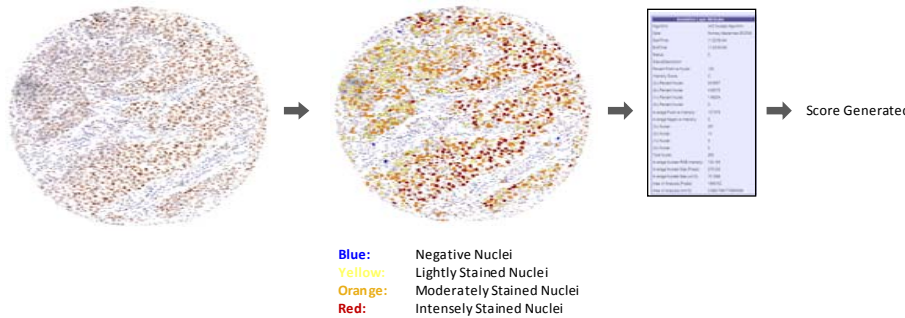


Figure 1: Customized image analysis algorithms were used to score nuclei in each core. The algorithms were optimized to score tumor nuclei while excluding most non-tumor nuclei. The data output includes measurements of intensity and quantity and was used to generate a QIM score for each core. Image analysis generated scores and pathology generated scores have been compared in multiple cancers with good correlation.

RESULTS

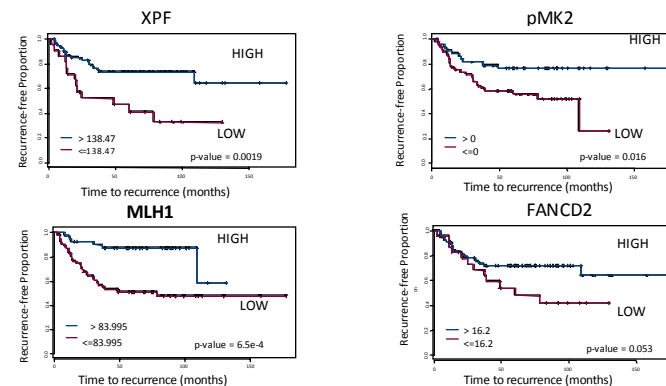


Figure 2: Single Biomarkers Discriminating Recurrence Patient Groups. Each core was scored using image analysis for XPF, MLH1, and FANCD2 and pathology-based scoring for pMK2. The cores considered non-evaluable were removed from the analysis and the remaining cores representing each patient were averaged. Univariate analysis was performed with the marker scores and the patient's time to recurrence. Each of the four markers shown above was determined to have a significant or nearly significant correlation with the patient's time to recurrence.

- 115 patients with primary treatment data were available
- Median follow up was 58 months
- Low XPF ($p=0.002$), pMK2 ($p=0.02$), MLH ($p<0.001$) and FANCD2 ($p=0.05$) was associated with shorter time to recurrence
- Training cohort \rightarrow High-risk group defined by a four marker model had a relative risk of recurrence of 3.0 ($p<0.00001$) with shorter median time to recurrence than the low risk group (13.1 months versus not reached)
- Test set \rightarrow Relative risk 2.1 ($p=0.029$) for the high-risk group with shorter median time to recurrence (14.1 months versus not reached)

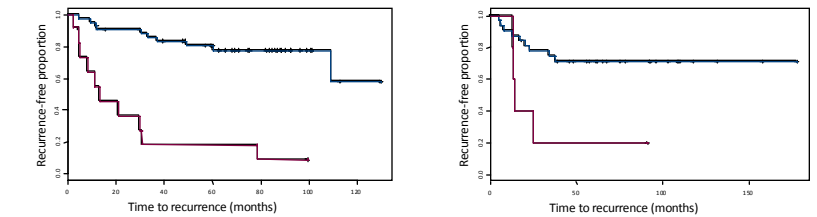


Figure 3: DNAR Initial Multi-marker Algorithm Distinguishes Recurrence Groups. Each core was scored using image analysis for XPF, PAR, and FANCD2 and pathology-based scoring for DR02. A multi-marker model was developed using multivariate analysis to distinguish and early from late recurrence group in a randomly assigned training set ($n=44$) which was then applied to a test set ($n=32$).

CONCLUSIONS

- Triple negative breast cancers show variable expression of DNA repair proteins
- Levels of four DNA repair proteins correlated significantly with recurrence free survival, and were used to develop a DNA repair profile model in a training set which was prognostic in a test set
- DNA repair biomarker panels may be useful as prognostic or predictive indicators as well as suggest possible targets for novel therapies such as PARP inhibition
- Further study of the model in another validation set with other clinical variables is warranted