High-risk breast cancer patients with RAD51-low tumors are characterized by good prognosis

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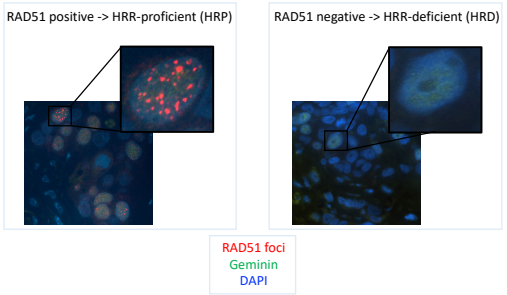
Background

Triple Negative Breast Cancer (**TNBC**) that do not achieve pathological complete response (pCR) are characterized by bad prognosis. The **RAD51 test** can identify Homologous Recombination Repair (HRR)-deficient tumors and may add prognostic value in this subset of patients, guiding post-neoadjuvant treatments in order to improve survival.



Methods

We quantified RAD51 and BRCA1 foci by immunofluorescence, content of tumor-infiltrating lymphocytes (TIL) and expression of immune markers on diagnostic tumor biopsies of **26** high-risk BC patients, admitted at the University Hospital of Parma between 01/2011 and 03/2020, and treated with neoadjuvant chemotherapy and surgery. High risk patients were defined as **TNBC** or early onset breast cancer (**younger than 35 years old**) or **gBRCA1/2-mutated** breast cancer. Functional Homologous Recombination Repair Deficiency (**HRD**) was predefined as a **RAD51 score ≤10%** (RAD51-low). Germline mutations in **HRR genes** were tested in all patients, including BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD54C, ATM, TP53 and NMN.

Results

Figure 1. A) RAD51 was successfully scored in 26/29 (90%) samples. 16/26 (**62%**) tumors were RAD51-low (**HRD**). Fourteen patients presented HRR alterations: 4 gBRCA1, 2 gBRCA2 and 2 gPALB2 mutations and 6 BRCA1-low foci, surrogate of lack of BRCA1 function likely due to promoter hypermethylation. Median **RAD51 score was 3.4 in HRR-mutated tumors** and 19.2 in HRR-WT tumors (p=.01). B) Patients with HRD tumors by RAD51 showed a trend towards **better DFS** (HR=0.28, 95% CI 0.05–1.54, p=.14).

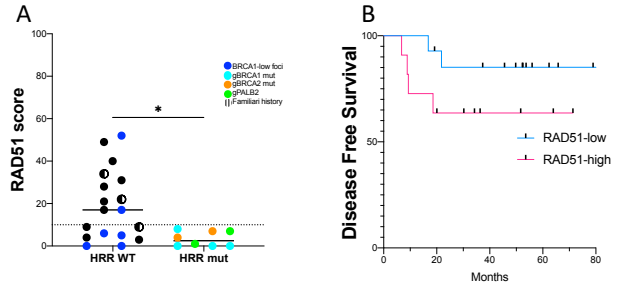


Figure 2. A) Disease-Free Survival (DFS) at 4 years was 100% for tumors that achieved pCR vs 67.5% for non-pCR tumors (p=.12). The addition of **RAD51 status to pCR** information **improved** the model **capacity to predict DFS** (ANOVA test, p=.05). B) In no-pCR subgroup, RAD51-low patients have a better DFS compared to RAD51-high.

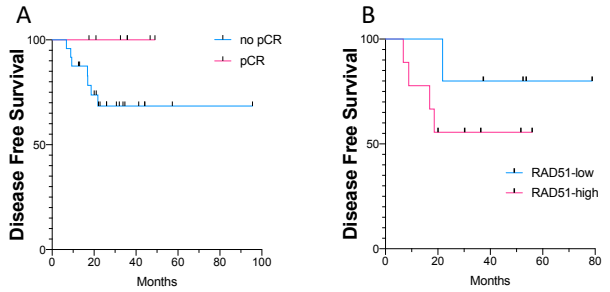


Figure 3. A) 4 out of the 5 **TIL-high** tumors in this cohort were **RAD51-low**, suggesting a crosstalk between HRD and an active antitumor immune response. B) High-TIL tumor sample. C) Low-TIL tumor sample.

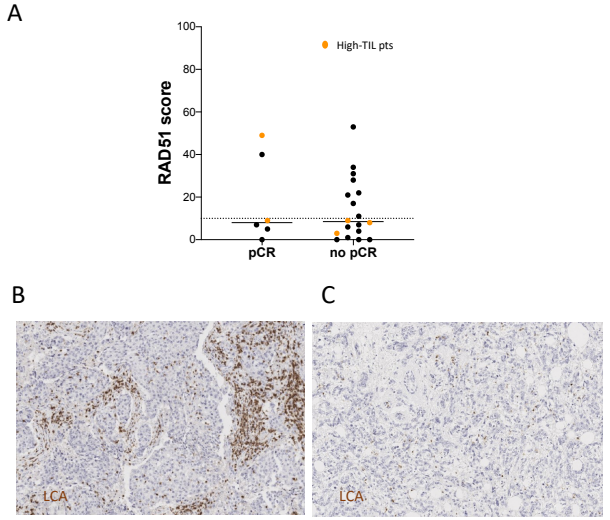


Figure 4. A) Disease-Free Survival (DFS) at 4 years was 100% for high-TIL tumors vs 65% for low-TIL tumors. B) Patients with **HRD tumors** by RAD51 showed a trend towards **better DFS** among low-TIL tumors.

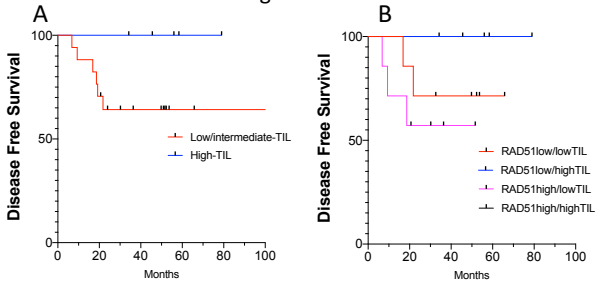
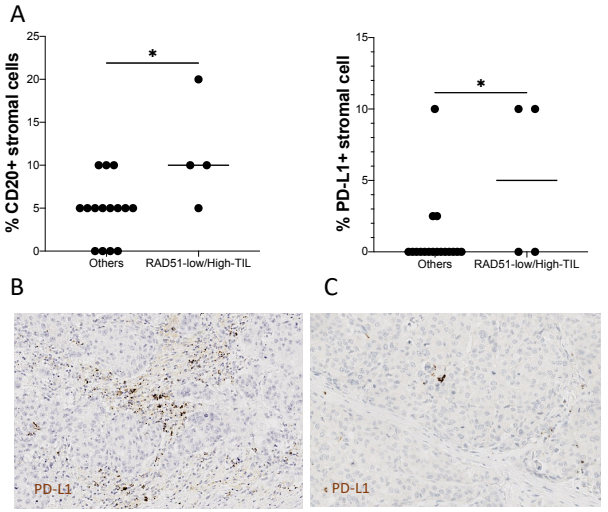


Figure 5. A) **RAD51-low/TIL-high** tumors had **higher CD20+** TIL (p=.01), lower CD3+ TIL (p=.02), **higher PD-L1** Combined Positive Score (p=.03), and a trend towards higher PD1+ TIL (p=.05); no statistically significant differences were found in FOXP3+ TIL. B) PD-L1-high tumor sample. C) PD-L1-low tumor sample.



Moreover, only 1 out of 4 **RAD51-low/TIL-high** tumors achieved pCR but **none of them relapsed**.

Conclusions

- **The RAD51 test is able to identify HRR-altered tumors, beyond gBRCA1/2 mutations, and to select a cohort of RAD51-low patients with better prognosis in a platinum-free neoadjuvant chemotherapy setting.**
- **Biomarker analyses on treated paired tumors and on a larger cohort of patients are ongoing.**

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