A three-gene signature captures the timing marks to locate-regional recurrence in luminal-like breast cancer

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BACKGROUND
Luminal-like BC cases are defined by the positive primary tumor immunostaining of estrogen (ER) and/OR progesterone receptor (PR) and absence of HER2 over-expression[1].

Gene expression profiling (GEP)-based prognostic signatures are rapidly integrated into clinical decision-making for systemic management of breast cancer patients. However, its application to loco-regional risk assessment is relatively underdeveloped[2,3].

AIM
To characterize luminal-like BC patients at risk of loco-regional relapse by gene expression profiling, developing a genomic classifier able to discriminate between early and late recurrent cases and to improve the predictive capability of conventional clinico-pathological features.

MATERIAL AND METHODS

Study population
Two retrospective independent cohorts (training-testing) of luminal-like BC recurring at different time points after surgery:
• Cohort A (training): 60 consecutive recurrent patients (diagnosis time: 2001-2017) at Istituti Clinici Maugeri
• Cohort B (testing): 51 consecutive recurrent patients (diagnosis time: 2003-2017) at Fondazione IRCCS Istituto Nazionale dei Tumori (IIT)

Gene expression
• Microarray analysis was performed with Clarion D Assay;
• Raw data normalization using the sst RMA algorithm

Statistical analysis
• Identification of differentially expressed genes (DEG) according to relapse time (≤ 5 years vs >5 years) through the Kruskal-Wallis test, and by applying the False Discovery rate (FDR) adjustment and Fold Change (FC) criteria [i.e., FDR ≤ 0.05 and FC ≥ 2] in Cohort A and confirmed in Cohort B
• Principal Component Analysis to combine the confirmed genes into the PCCs score and training and then applied to testing
• Prognostic performance investigation on in-silico datasets and on Cohort C (101 prospectively collected ER-positive, node- and HER2-negative cases from patients receiving only loco-regional treatment, with relapse-free survival outcome data at INT)

RESULTS

Study population
Cohorts A and B included patients with ER-positive breast cancer, developing a LRR. The two cohorts were well balanced for all the clinical characteristics considered with the unique exception of Ki67.

GEP analysis and PCC score development
• 70 DEGs on Cohort A (Figure 1A) and 4 (out of 70 genes, Figure 1B) confirmed on Cohort B, named ITGB1, CSTB, XG2Y and CCDC91
• 1st Principal Component score (PCCscore), statistically significant associated with relapse time (Figure 1C) in the training (p-value: < 0.001) and testing set (p-value: 0.005)
• Performance, in terms of ROC curves (Figure 1D), of the clinical model (i.e. age, hormone status and therapy) significantly improved by including the PCCscore, reaching an AUC value of 0.878 (95% CI: 0.810-0.945)

Figure 1.

Figure 2.

CONCLUSION
Our 3-gene signature represents a new exploitable tool to aid treatment choice in patients with luminal-like breast cancer at risk of developing early recurrence.