Molecular prognostic factors for distant metastasis in premenopausal women with HR+ HER2- early breast cancer

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Background

Breast cancer in premenopausal patients (vs. postmenopausal patients) has unique gene expression patterns. Our research focused on premenopausal patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), early breast cancer (EBC), and the molecular drivers of distant metastases after a standard adjuvant treatment.

Method

Total RNA of primary tumor FFPE specimens was extracted using the miRNeasy FFPE kit (Qiagen, Germany). Gene expression profiling was done using the Nanostring nCounter assay system (Nanostring technology, USA) with Breast Cancer 360 panel (BC360B) which includes 776 genes across 48 biological signatures, and analyzed following the panel-specific processing protocol (BC360 data analysis). The GSEA (Gene Set Enrichment Analysis) analysis of 751 genes was performed in the GSEA 4.1.0 software following the instructions and a FDR q-value less than 0.25 was considered significant. The gene expression between groups was further analyzed and compared by using limma package in R. Survival analysis was performed with Cox regression model and curve was drawn with Kaplan-Meier Function in SPSS 23.0. A p-value less than 0.05 was considered as significant.

Results

Clinical features

Between patients who developed metastasis (M+), and patients who did not (M-), tumor size, tumor grade, pT, pN were differentially distributed, ALND (axillary lymph node dissection) and chemotherapy were more often applied in patients who developed metastasis and most patients received radiotherapy (85.6%).

Differential Expression of BC360™ signatures and GSEA

Four BC360TM signatures were differentially expressed between groups: ROR, PGR, claudin-low, mammary stemness. These four signatures were associated with survival (Fig.4B) (p < 0.05).

Top differentially expressed genes

Among tested 758 genes, 22 top differentially expressed genes (DEGs) were identified based on p-value and logFC (fold change). Univariate survival analysis suggested that 19 of them were survival relevant (p < 0.05) (Table 2). According to multivariate analysis, LP2, SCUBE2, and IBSP were independent prognostic factors, even when compared with tumor node status and tumor stage (Table 3) (Fig.6).

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