Minimising Immunohistochemical False Negative ER Classification Using a Complementary 23 Gene Expression Signature of ER Status

BACKGROUND: Expression of the oestrogen receptor (ER) in breast cancer predicts benefit from endocrine therapy. Minimising the frequency of false negative ER status classification is essential to identify all patients with ER positive breast cancers who should be offered endocrine therapies in order to improve clinical outcome. In routine oncological practice ER status is determined by semi-quantitative methods such as immunohistochemistry (IHC) or other immunoassays in which the ER expression level is compared to an empirical threshold. The clinical relevance of gene expression-based ER subtypes as compared to IHC-based determination has not been systematically evaluated. Here we attempt to reduce the frequency of false negative ER status classification using two gene expression approaches and compare these methods to IHC based ER status in terms of predictive and prognostic concordance with clinical outcome.

METHODOLOGY/PRINCIPAL FINDINGS: Firstly, ER status was discriminated by fitting the bimodal expression of ESR1 to a mixed Gaussian model. The discriminative power of ESR1 suggested bimodal expression as an efficient way to stratify breast cancer; therefore we identified a set of genes whose expression was both strongly bimodal, mimicking ESR expression status, and highly expressed in breast epithelial cell lines, to derive a 23-gene ER expression signature-based classifier. We assessed our classifiers in seven published breast cancer cohorts by comparing the gene expression-based ER status to IHC-based ER status as a predictor of clinical outcome in both untreated and tamoxifen treated cohorts. In untreated breast cancer cohorts, the 23 gene signature-based ER status provided significantly improved prognostic power compared to IHC-based ER status (P=0.006). In tamoxifen-treated cohorts, the 23 gene ER expression signature predicted clinical outcome (HR=2.20, P=0.00035). These complementary ER signature-based strategies estimated that between 15.1% and 21.8% patients of IHC-based negative ER status would be classified with ER positive breast cancer.

CONCLUSION/SIGNIFICANCE: Expression-based ER status classification may complement IHC to minimise false negative ER status classification and optimise patient stratification for endocrine therapies.

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