

TUMOR GENE EXPRESSION PREDICTS DISTANT DISEASE-FREE SURVIVAL (DDFS) IN BREAST CANCER PATIENTS WITH 10 OR MORE POSITIVE NODES: HIGH THROUGHPUT RT-PCR ASSAY OF PARAFFIN-EMBEDDED TUMOR TISSUES

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Background: Breast cancer patients with 10 or more positive nodes have a poor prognosis, yet some survive long-term. We sought to identify predictors of DDFS in this high risk group of patients. Methods: Patients with invasive breast cancer and 10 or more positive nodes diagnosed from 1979 to 1999 were identified. RNA was extracted from three 10 micron sections and expression was quantified for 7 reference genes and 185 cancer-related genes using RT-PCR. The genes were selected based on the results of published literature and microarray experiments. Results: 79 patients were studied. Mean age was 57 yr, mean clinical tumor size was 4.4 cm, and mean number of involved nodes was 18. 54% received hormonal therapy and 80% received chemotherapy. Median follow-up was 15.1 yrs. As of Aug. 2002, 77% of patients had distant recurrence or breast cancer death. Univariate Cox survival analysis of the clinical variables indicated that number of nodes involved was significantly associated with DDFS ($p=0.02$). A multivariate model including age, tumor size, involved nodes, tumor grade, adjuvant hormonal therapy, and chemotherapy accounted for 13% of the variance in DDFS time. Univariate Cox survival analysis of the 185 cancer-related genes indicated that a number of genes were associated with DDFS (5 with $p<0.01$; 16 with $p<0.05$). Higher expression was associated with shorter DDFS ($p<0.01$) for the HER2 adaptor Grb7 and the macrophage marker CD68. Higher expression was associated with longer DDFS ($p<0.01$) for TP53BP2 (tumor protein p53-binding protein 2), PR, and Bcl2. A multivariate model including 5 genes accounted for 45% of the variance in DDFS time. Multivariate analysis also indicates that gene expression is a significant predictor after controlling for clinical variables. Eight of the 16 genes associated with DDFS here were also significantly associated by this RT-PCR assay in an independent study of a lower risk group of breast cancer patients (Esteban et al, Abstract, ASCO 2003).