Relationship between tumor gene expression and recurrence in stage II/III colon cancer: Quantitative RT-PCR assay of 757 genes in fixed paraffin-embedded (FPE) tissue.

Background: As an initial step in developing a better method of assessing prognosis following potentially curative surgery for colon cancer, we performed an exploratory gene identification study.

Methods: RNA was extracted from three 10-micron sections of the FPE tumor tissue obtained at the initial diagnosis from 353 patients entered between 1977 and 1984 into the surgery-only or surgery-plus BCG arms of NSABP C-01/C-02. Expression was quantified for 757 cancer-related and reference genes with RT-PCR.

Results: Blocks from 270 patients were evaluable after pre-specified exclusions: 128 were stage II and 142 were stage III. All patients had > 5-year follow up. In univariate Cox proportional hazard analyses, 148 genes exhibited a nominally significant (unadjusted p-value <0.05) linear association with recurrence-free interval (RFI) (7 genes p<0.001, 66 genes 0.001<p<0.01; 75 genes 0.01<p<0.05). False discovery rate calculations suggest that about 25% of the 148 genes are expected to be false positives. Higher expression was associated with shorter RFI for 118 genes including SERPINB5, DUSP1, AKT3, TIMP1, ANXA2, RHOB (p< 0.001) and with longer RFI for 30 genes including BRCA1 (p<0.001). The relationship between gene expression and RFI was similar for stage II and stage III patients for 143 of the 148 genes found to be significant. The largest cluster of genes is functionally related to extracellular matrix remodeling. The magnitude of the hazard ratios is similar to that observed in the early Oncotype DX studies in breast cancer and should allow clinically useful separation into low/intermediate/high risk groups.

Conclusions: Quantitative RT-PCR assay of FPE colon cancer tissue can be used to identify large numbers of genes associated with RFI in patients with stage II and III colon cancer. If these results are confirmed by additional studies in progress, this technique has promise to improve selection of colon cancer patients for adjuvant chemotherapy.

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