A Nine-Gene Signature Predicting Clinical Outcome in Malignant Melanoma

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Conventional histopathological and clinical staging is largely inadequate for predicting clinical outcome of malignant melanoma. Molecular prognostic markers are not available. We identified a nine-gene signature which is closely associated with survival of melanoma patients.

To identify prognostic genes we correlated gene expression profiles of 136 primary melanomas with patient overall survival using Cox regression analysis: Based on previous gene expression profiling data, we analyzed expression of 92 candidate genes in 38 primary melanomas (training cohort), using real-time reverse-transcriptase polymerase chain reaction (RT-PCR). Expression of selected genes was analyzed in an extended group of 91 melanomas (study cohort). The resulting prognostic gene signature was validated using an independent set of 45 melanomas (validation cohort).

Expression of 11 of the 92 genes correlated with patient survival in the training cohort. A risk score, based on expression of nine of these genes (KRT9, SPINK7/ECG2, KBTBD10, DCD, HES6, COL6A6, PIP, SCGB1D2, SCGB2A2) or any subgroup thereof, predicted patient overall survival in the study cohort ($p = 0.0004$, hazard ratio 3.83), independently of conventional AJCC 2002 staging. Almost all patients (study cohort: 95.4%, validation cohort: 93.8%) with low-risk score and low/intermediate-risk AJCC stage were classified correctly as long-term survivors.

The prognostic value of the signature-based score is its ability to identify patients at low risk, not identified by AJCC staging. The clinical value of the score is that two thirds of patients (29/45, 64%) with intermediate AJCC-based prognosis were reclassified, based on a low-risk score, to a long-term survival probability of approximately 95%.