High-throughput tissue microarray analysis for the prognostic significance of cell cycle regulation and proliferation, apoptosis and angiogenesis in non-small cell lung cancer

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Background: Recent molecular studies have provided increased understanding of the biology of non-small cell lung cancer (NSCLC) and have identified molecular abnormalities responsible for the modulation of tumor growth and the prognosis. Nevertheless, the essential genetic features, along with factors for prognosis, have yet to be fully understood. This study was undertaken to investigate such immunophenotypes with regard to cell cycle regulation and proliferation, apoptosis, and angiogenesis, and their significance to patient outcome.

Design: Two hundred and nineteen NSCLC samples were assembled on tissue microarrays, and examined immunohistochemically using antibodies against p16, p21, p27, cyclin B1, cyclin E, Ki-67, caspase-3, survivin, bcl-2, VEGF and endostatin. Clinical information was obtained through the computerized retrospective database from the tumor registry.

Results: One hundred and sixty-eight patients (76.7%) were male and the mean age was 65.8 years (SD 9.9; median 67; age range 19-89). Despite previously described prognostic relevance of some of the 11 investigated molecules, many were found not to be directly associated with recurrence or survival. However, p16 and bcl-2 had an impact on 5-year survival. There was a trend for p16 immunoreactivity to be related with a good prognosis (57% vs. 42% in 5-year survival) (p=0.071). Bcl-2 expression in tumor tissue strongly correlated with a better outcome (65% vs. 45% in 5-year survival rate) (p=0.029), and the hazard ratio of death for bcl-2 positive patients was 0.42 times of that for bcl-2 negative patients (p=0.047). A multivariate analysis with Cox proportional hazards model confirmed that the lymph node status (p=0.043) and stage (p=0.003) were other independent prognostic factors.

Conclusion: The present study demonstrates that NSCLCs have heterogeneous expression of cell cycle regulatory proteins, apoptotic factors and angiogenic factors. The expressions of p16 and bcl-2 correlate with better survival, suggesting that both proteins provide prognostic information independent of TNM stage in NSCLCs.