

Age, Tumor Grade, and Mitosis-Karyorrhexis Index Are Independently Prognostic of Outcome in Neuroblastoma: An International Neuroblastoma Risk Groups Project

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Background: Criteria for COG neuroblastoma risk stratification includes both age and by the age-linked International Neuroblastoma Pathology Classification (INPC) system, confounding the prognostic contribution of age. Previous studies demonstrated the prognostic value of histologic category and individual morphologic features, and these criteria were incorporated in the International Neuroblastoma Risk Group Classification (INRG) system in lieu of INPC. We analyzed the INRG database to determine if these histologic features retained prognostic significance in patients diagnosed between 2003-2016. We also compared risk-group treatment assignment using individual morphologic features versus INPC.

Methods: Cohort 1 patients were diagnosed 1990-2002 (n=2746) and Cohort 2 patients were diagnosed 2003-2014 (n=5012). Associations between established prognostic factors versus MKI and grade of differentiation were assessed by chi-square tests. In cohort 2, Cox proportional hazards models of EFS were used for survival tree regression and multivariable analysis of age, grade, MKI, and diagnostic category.

Results: Undifferentiated grade and high MKI were statistically significantly associated with stage 4 disease, MYCN amplification, diploidy, and age >18mon. The 4 final subgroups of the survival tree analysis ("terminal nodes") of cohorts 1 and 2 were identical: <18mon with low/intermediate MKI; <18mon with high MKI; ≥18mon with poorly/undifferentiated tumors, and ≥18mon with differentiating tumors. In separate multivariable analyses of both cohorts, age, INSS stage, MYCN, ploidy, and grade were independently statistically significantly prognostic. Of the 4821 patients in cohort 2 with sufficient data for COG treatment assignment, the same treatment assignment was made using either INPC or grade plus MKI in all but 7 patients (all > 5 years of age with stage 3 differentiating tumors.)

Conclusions: Incorporating grade plus MKI in lieu of INPC results in nearly identical COG risk-based treatment assignment. Because INPC classifies tumors from patients >5 years as UH, analysis of grade of differentiation in this cohort has the potential to refine treatment stratification, especially for those with stage 3 neuroblastoma. As new criteria are evaluated for future iterations of risk stratification systems, statistical methods should eliminate the confounding of INPC and age by using MKI and grade instead of INPC.