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Definition of Disease-Risk Stratification Groups in Childhood Medulloblastoma Using Combined Clinical, Pathologic, and Molecular Variables.

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Abstract

PURPOSE Medulloblastomas are heterogeneous and include relatively good-prognosis tumors characterized by Wnt pathway activation, as well as those that cannot be successfully treated with conventional therapy. Developing a practical therapeutic stratification that allows accurate identification of disease risk offers the potential to individualize adjuvant therapy and to minimize long-term adverse effects in a subgroup of survivors. **METHODS** Using formalin-fixed paraffin-embedded (FFPE) tissue for immunohistochemistry, fluorescent in situ hybridization, and direct sequencing to identify tumors with a Wnt pathway signature and those harboring copy number abnormalities (CNAs) of potential prognostic significance (MYC/MYCN amplification, CNAs of chromosome 6 and 17), we evaluated clinical, pathologic, and molecular outcome indicators and stratification models in a cohort (n = 207) of patients with medulloblastoma 3 to 16 years of age from the International Society of Pediatric Oncology CNS9102 (PNET3) trial. **Results** Metastatic disease and large-cell/anaplastic (LC/A) phenotype were the clinicopathologic variables associated with poor progression-free survival (PFS). Nuclear immunoreactivity for β -catenin, CTNNB1 mutation, and monosomy 6 all identified a group of good-prognosis patients. MYC amplification was associated with poor outcome, but other CNAs were not. Low-risk medulloblastomas were defined as β -catenin nucleopositive tumors without metastasis at presentation, LC/A phenotype, or MYC amplification. High-risk medulloblastomas were defined as tumors with metastatic disease, LC/A phenotype, or MYC amplification. Low-risk, standard-risk, and high-risk categories of medulloblastoma had significantly ($P < .0001$) different outcomes. **CONCLUSION** Integrating assays of molecular biomarkers undertaken on routinely collected diagnostic FFPE tissue into stratification schemes for medulloblastoma alongside clinical and pathologic outcome indicators can refine current definition of disease risk and guide adjuvant therapy.

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