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Subgroup-directed stratification of risk in infant medulloblastoma

Hicks, D.\textsuperscript{1}, Rafiee, G.\textsuperscript{1}, Schwalbe, E.C.\textsuperscript{1,2}, Howell, C.I.\textsuperscript{1}, Lindsey, J.C.\textsuperscript{1}, Hill, R.M.\textsuperscript{1}, Smith, A.\textsuperscript{1}, Crosier, S.\textsuperscript{1}, Joshi, A.\textsuperscript{3}, Robson, K.\textsuperscript{4}, Wharton, S.\textsuperscript{5}, Jacques, T.\textsuperscript{6}, Williamson, D.\textsuperscript{1}, Bailey, S.\textsuperscript{1}, Clifford, S.C.\textsuperscript{1}

\textsuperscript{1} Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, U.K.
\textsuperscript{2} Northumbria University, Newcastle upon Tyne, U.K.
\textsuperscript{3} Department of Neuropathology, Royal Victoria Infirmary (RVI), Newcastle University Teaching Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
\textsuperscript{4} Nottingham University Hospitals NHS Trust, Nottingham, UK
\textsuperscript{5} Sheffield University, Sheffield, UK
\textsuperscript{6} UCL Institute of Child Health and Great Ormond Street Hospital, London, UK

The molecular pathology of infant medulloblastoma (iMB) has not been systematically characterised, particularly in relation to the consensus molecular subgroups or outcomes, to inform contemporary treatments, risk-stratification and clinical trials. We assembled 208 iMBs (0-5yrs) with full central clinical and pathological review, subgroup assignation, and comprehensive profiling of copy-number and mutational features. iMB represented a three-subgroup disease with MB\textsubscript{SHH} and MB\textsubscript{Grp3} predominant (41% each; MB\textsubscript{Grp4}, 17%). MB\textsubscript{SHH} significantly associated with DN/MBEN pathology (72% (50/69); p=6.8x10\textsuperscript{-19}), but also contained classic (CLA; n=15) and LCA (n=4) tumours (28%; 19/69) throughout the age-range. Multivariate survival analysis identified sub-total resection (STR; HR 6.3, p=3.1x10\textsuperscript{-5}) and DN/MBEN (HR 0.1, p=0.004) as independent prognostic factors, however metastatic (M+) disease and other established biological features were not associated with outcome. A novel MB\textsubscript{SHH} survival model defined CLA/LCA and/or STR tumours as very high-risk (44% (27/61); 10yr OS, 24%), with 18.8-fold relative-risk compared to favourable-risk totally-resected DN/MBEN disease (56% (34/61); 10yr OS, 93%). MB\textsubscript{Grp3} was strongly associated with LCA (23%, 14/62) and MYC amplification (19%, 12/62). Presence of either feature defined a very high-risk group (27% (18/62); 10yr OS, 23%), with common rapid progression on current therapies and an 11.7-fold relative-risk than remaining MB\textsubscript{Grp3} tumours (73% (45/62); 10yr OS, 74%; standard-risk). Only MB\textsubscript{SHH} DN/MBEN tumours showed potential of rescue at relapse following initial therapy (56% survival post-relapse); other relapses were almost universally fatal. Combined diagnostic assessment of iMB subgroup, pathology and molecular biomarkers will be essential to direct improved risk-stratified therapies, and novel approaches for very high-risk patients.