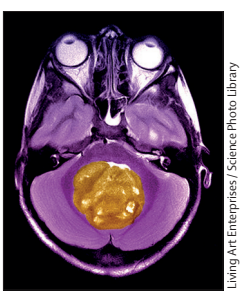
Interrogating molecular data for medulloblastoma risk stratification



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Medulloblastoma is the most common malignant paediatric brain tumour, with an incidence between 2·34 and 5·96 per million population.[1] Early studies on medulloblastoma biology were largely inconclusive because of its molecular heterogeneity and the small size of the cohorts analysed. By contrast, more recent studies, based on a large number of internationally collected cases, have produced a deeper understanding of the molecular events that characterise medulloblastoma. Indeed, on the basis of gene expression, genetic aberrations, and DNA methylation, medulloblastoma is now classified into several molecular subgroups.[2–5] The 2016 WHO Classification of Tumors of the Central Nervous System[6] combines molecular and histological features for an innovative integrated diagnosis, thus allowing stratification of patients into four prognostic risk categories: favourable, standard, high, and very high risk.[3]

The standard-risk medulloblastoma category is heterogeneous, comprising 50–60% of patients with medulloblastoma and encompassing SHH-activated *TP53*$^{wild\text{-}type}$ and groups 3 and 4, in the absence of high-risk features (ie, *MYC* amplification, anaplastic histology, or metastasis at diagnosis). The therapeutic regimen for standard-risk medulloblastoma includes radiotherapy followed by chemotherapy, with a 5-year progression-free survival of 75–85%. However, surviving patients have a heavy burden of long-term severe endocrine and neurological sequelae.[7] Therefore, there is urgent need for identification of patients with good prognosis who could benefit from therapy de-escalation, which maintains curative potential while minimising adverse effects.

To this aim, the pan-European SIOP PNET 5 clinical trial (NCT02066220) is testing a reduced treatment scheme for the favourable-risk category, which consists of patients with WNT-positive medulloblastoma younger than 16 years. Unfortunately, patients meeting these inclusion criteria account for only roughly 8% of all medulloblastomas.

In *The Lancet Oncology*, Tobias Goschzik and colleagues[8] did a whole chromosomal aberration analysis of standard-risk medulloblastoma and investigated the association between molecular features and progression-free survival, taking advantage of available samples from the completed pan-European HIT-SIOP PNET 4 trial,[9] with the intent of improving prognosis prediction. They found a new prognostic genetic biomarker signature—defined as at least two events among chromosome 7 gain, chromosome 8 loss, and chromosome 11 loss—associated with good prognosis (5-year progression-free survival of 100% in the HIT-SIOP PNET 4 cohort) in patients with non-WNT/non-SHH standard-risk medulloblastoma.

The identified risk stratification scheme was a more solid model with respect to previous ones, allowing reallocation of a subset of patients with standard-risk medulloblastoma into a favourable-risk group. Crucially, the proposed risk stratification applies to 51% of standard-risk medulloblastomas, and thus to 25–30% of all patients with medulloblastoma. Consequently, these findings increase the number of patients who could be enrolled for therapy de-escalation in future clinical trials.

As mentioned, methylation and gene expression analyses have produced an immense amount of important data that provided deep insight into the molecular events that underlie pathogenesis and laid the foundation for the development of targeted therapies.[2–5] Data from genomic analyses are in clinical use for patient risk stratification, with molecular genomic biomarkers (ie, *TP53* mutational status and *CMYC* or *NMYC* amplification) being an integral element of the latest WHO classification.[6] Goschzik and colleagues generated a whole chromosomal aberration signature that can group patients who share the same prognosis, even though they are classified in different molecular subgroups.[8] Indeed, the identified whole chromosomal aberration signature-positive class included patients with $MB_{Grp4\text{-}LowRisk}$[3] and Group3 and Group4 subgroups VI and VII.[4] Important points that strengthen the reported results[8] are clinical evidence of the proven utility of molecular data investigation, use of a strictly defined and well-characterised population (HIT-SIOP PNET 4 trial cohort) for generation of the data, and validation of the proposed model in an

For more on the **SIOP PNET 5 trial** see https://clinicaltrials.gov/ct2/show/NCT02066220

independent patient cohort with matched demographic characteristics.

Another class of molecular biomarkers that should be considered for implementation of stratification risk models in medulloblastoma is non-coding RNAs. microRNAs and long non-coding RNAs have been shown to be important regulators of medulloblastoma biology, and could represent valuable biomarkers for risk stratification and targeted therapy.[10]

In conclusion, this study[8] provides a tool for immediate clinical application. Although these results require validation in a controlled multicentre study, they set the foundation that is needed to improve genomic patient characterisation for more accurate risk stratification in routine clinical settings.

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