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Risk stratification of childhood medulloblastoma in the molecular era: The Current Consensus

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Abstract

Historical risk stratification criteria for medulloblastoma rely primarily on clinicopathological variables pertaining to age, presence of metastases, extent of resection, histological subtypes and in some instances individual genetic aberrations such as *MYC* and *MYCN* amplification. In 2010, an international panel of experts established consensus defining four main subgroups of medulloblastoma (WNT, SHH, Group 3 and Group 4) delineated by transcriptional profiling. This has led to the current generation of biomarker-driven clinical trials assigning WNT tumors to a favorable prognosis group in addition to clinicopathological criteria including *MYC* and *MYCN* gene amplifications. However, outcome prediction of non-WNT subgroups is a challenge due to inconsistent survival reports. In 2015, a consensus conference was convened in Heidelberg with the objective to further refine the risk stratification in the context of subgroups and agree on a definition of risk groups of non-infant, childhood medulloblastoma (ages 3–17). Published and unpublished data over the past five years were reviewed, and a consensus was reached regarding the level of evidence for currently available biomarkers. The following risk groups were defined based on current survival rates: low risk (>90% survival), average (standard) risk (75–90% survival), high risk (50–75% survival) and very high risk (<50% survival) disease. The WNT subgroup and non-metastatic Group 4 tumors with whole chromosome 11 loss or whole chromosome 17 gain were recognized as low risk tumors that may qualify for reduced therapy. High-risk strata were defined as patients with metastatic SHH or Group 4 tumors, or *MYCN* amplified SHH medulloblastomas. Very high-risk patients are Group 3 with metastases or SHH with *TP53* mutation. In addition, a number of consensus points were reached that should be standardized across future clinical trials. Although we anticipate new data will emerge from currently ongoing and recently completed clinical trials, this consensus can serve as an outline for prioritization of certain molecular subsets of tumors to define and validate risk groups as a basis for future clinical trials.

Keywords

medulloblastoma; subgroups; WNT; SHH; Group 3; Group 4; p53; genomics; outcomes

Background

Over the past ten years, our understanding of medulloblastoma biology has dramatically increased, primarily through advances in integrated genomics.[4, 23, 32, 44, 53, 57] In 2010,

at a consensus conference in Boston, Massachusetts, it was agreed upon by a medulloblastoma working group that there are at least four principal transcriptional subgroups of medulloblastoma.[53] These four subgroups termed WNT, SHH, Group 3 and Group 4 are now accepted as being distinct biological entities and ongoing efforts are underway to tailor therapy for each of these groups, and assess whether this approach can improve outcomes. A subsequent consensus meeting in Perth, Australia, defined the diagnostic criteria for the four subgroups.[17] The WHO consensus conference held in June 2015 has recognized the importance of these biological groups and will introduce the following genetically defined entities of medulloblastoma in the revised WHO classification of CNS tumors to be published in 2016: WNT, SHH-TP53 wildtype, SHH-TP53 mutant, Non-Wnt/Non-SHH. It was recognized that Group 3 is more related to Group 4 than WNT and SHH with some overlapping features, and therefore these two groups were introduced as provisional entities within Non-SHH/Non-WNT medulloblastomas, where the subgrouping is unequivocal. Also, the SHH expression/epigenetic group was recognized to contain two different entities, the SHH-TP53 wildtype and SHH-TP53 mutant, which, due to vastly divergent clinical outcomes, are to be separately diagnosed in the future. Ongoing efforts are underway to tailor therapy for each of these entities, and assess whether this approach can improve outcomes.

The WNT subgroup is characterized by activation of the WNT pathway and commonly harbors mutations in exon 3 of *CTNNB1* and monosomy chromosome 6.[6, 12, 22, 53] Otherwise, WNT tumors harbor remarkably few genomic alterations. Patients under the age of 16 with WNT tumors have an excellent prognosis when treated with surgery and craniospinal irradiation. Adult WNT tumors may be higher risk as shown in the PNET4 study and retrospectively in a study of adult medulloblastoma. [5][45] The diagnosis of WNT tumors can be established by several methods, the most accurate being sequencing exon 3 of *CTNNB1*, DNA methylation profiling or gene expression profiling.[39] A combination of both immunohistochemistry for nuclear beta-catenin and FISH or DNA copy number array profiling demonstrating monosomy 6 can also be used to reliably identify WNT tumors.[39] [11, 17]

The SHH subgroup is characterized by activation of the SHH pathway. The tumors commonly harbor mutations in components of the SHH pathway, specifically *PTCH*, *SMO* and *SUFU*. [21] A proportion of SHH tumors exhibit amplification of *MYCN* and *GLI2*, and mutations in *TP53*, frequently associated with anaplastic morphology. SHH tumors arise across all age groups and constitute the predominant tumor type in young children (<3 years of age) and adults, however, *TP53* mutations are highly enriched in children aged 3–17 constituting a higher risk group with significantly worse outcomes.[62] SHH pathway inhibitors, specifically SMO inhibitors have gone through Phase I and II clinical trials for relapsed medulloblastoma and have shown some response, although loss of sensitivity after initial response was frequently observed.[47]

The overall outcome is intermediate depending on the age group. Young children have a more favorable outcome, while patients with *TP53*-mutated SHH medulloblastoma do poorly.[22, 62] Compared to the other subgroups, SHH tumors more frequently recur locally in the original resection cavity.[18, 43]

Group 3 is characterized by recurrent *MYC* amplifications, where approximately 20% of cases harbor a *MYC* amplicon.[22] Other frequent events in Group 3 include isochromosome 17q, activation of *GFI1A/GFI1B* and *OTX2* amplifications.[33, 34] The subgroup has a remarkably low number of recurring single nucleotide variants and is represented by a series of recurrent DNA copy number gains or losses of chromosomal arms or of whole chromosomes.[31] Group 3 are frequently metastatic, and overall outcome, particularly for those harboring *MYC* amplifications, is worse compared to the other subgroups. Group 3 patients recur most frequently with metastatic dissemination and a tumor bed devoid of disease.[43]

Although Group 4 is the most common subgroup, it remains the least well biologically characterized.. The most common aberration is isochromosome 17q, followed by amplifications of *MYCN*, duplications of *SNCAIP* and loss of 11q.[34, 49] Recurrent single nucleotide variants in *KDM6A* are found in approximately 10% of patients.[19, 31, 40, 46] Group 4 medulloblastomas occur most frequently in children and teenagers and approximately 30% are metastatic at diagnosis.[31] Irradiated Group 4 patients recur most frequently with metastatic dissemination and a tumor bed typically devoid of disease.[43]

Most of the clinical trials over the past 20 years for non-infants (i.e. those aged >3 years at diagnosis treated upfront with chemotherapy and craniospinal irradiation) have risk stratified therapy according to clinical, not biologic, criteria. On these, five-year survival rates for ‘average risk’ (“standard risk” in Europe) medulloblastoma are over 80% and approximately 60% for high-risk disease.[13, 14, 26, 36, 51, 55] The most recent generation of completed clinical trials used a clinical risk stratification that defines high-risk medulloblastoma as non-infants with residual disease >1.5cm² or metastatic dissemination with large-cell/anaplastic histology, [26, 60] The newest generation of biologically-informed clinical trials, specifically PNET5, SJMB12 and the planned COG study, are evaluating therapy de-escalation for patients with WNT tumors, and excluding *MYC* and *MYCN* amplified tumors from the average risk strata. Currently, only the SJMB12 trial enrolls high-risk patients on a biologically informed trial, and there are no open trials for high-risk non-infants in Europe.

Since publication of medulloblastoma subgroups further investigations have identified high-risk subgroups within subgroups.[53] To further refine risk stratification of medulloblastoma, a working group convened in Heidelberg, Germany, in June 2015 by reviewing the collective experience and generating a consensus towards a putative new classification for non-infants. Specifically, several consensus points were defined and a proposed risk stratification scheme was generated as a guide for the design of further validation studies, and the next generation of clinical trials in children. Stratification of adult medulloblastoma patients was not addressed. The risk stratification scheme that was agreed upon defined four risk groups based on survival across several cohorts: low risk (>90% survival), standard risk (75–90% survival), high risk (50–75% survival) and very high risk (<50% survival).

General design of the next generation of clinical trials

The following points were agreed to be principles guiding medulloblastoma treatment going forward (Table 1).

Molecular Subgrouping

In the design of the next generation of clinical trials, all tumors should be molecularly subgrouped in real time and diagnosed according to the revised WHO classification for brain tumors (2016).

There was a strong consensus that all patients should be offered enrolment into molecularly informed clinical trial and that reductions in therapy should not be considered off-study. Neuropathologists involved in the diagnostics of these patients should diagnose all patients according the WHO guidelines and need to be clearly engaged in this process. Clinical trial design needs to take into account local and preferably national consortia to obtain funds necessary to conduct the molecular analysis. This will obviously be a requirement once the update of the WHO classification is published in early 2016, which recognizes most of the molecular subgroups as distinct entities.

The methods of subgrouping have previously been defined by the Medulloblastoma working group, with a particular emphasis on WNT patients; the core principles being that subgroup assignment should be reached based on two independent validated analytical methods performed in accredited diagnostics laboratories.[16, 17] Specifically, WNT tumors should be identified by two of the following markers: nuclear beta-catenin accumulation, monosomy 6 (whole chromosome loss) by FISH or SNP/MIP array, a *CTNNB1* mutation, WNT pattern by DNA methylation or by gene expression.[16, 17] Caution should be exercised in the case of using either nuclear beta-catenin or monosomy 6 alone for the diagnosis of a WNT tumor as it has been previously shown that these markers are prognostic only in the WNT subgroup and are occasionally observed in the other subgroups.[16, 39] In addition, immunohistochemistry of beta-catenin alone may lead to an incorrect diagnosis of a WNT subgroup due to patchy nuclear accumulation in some WNT cases.[16]

SHH, Group 3 and Group 4 patients can be identified using either genome-wide methylation, expression array methods, or limited panels such as the 22 gene nanoString signature.[35] Immunohistochemistry based classification has also been used, principally to detect the WNT and SHH subgroups although it has been agreed that this should not be used in isolation in future clinical trials.[10]

Currently, two open studies, PNET5 (NCT02066220) and SJMB12 (NCT01878617) are enrolling patients across Europe and North America/Australia respectively and stratifying patients based on their molecular biology. Both studies are evaluating a reduction in the intensity of therapy for average risk WNT patients with a reduction of CSI to 18Gy in PNET5 and 15Gy in SJMB12. Moreover, SJMB12 is evaluating the use of Vismodegib as maintenance therapy in SHH patients, and the addition of Pemetrexed and Gemcitabine for select Group 3 and 4 patients.

Prospective collection of tissues

In order to allow for molecular subgrouping, but also inform the field with respect to future discoveries, fresh-frozen and paraffin-embedded tumor tissue, cerebrospinal fluid and blood should be collected on all patients. The collection of these tissues should ideally be mandated as part of any current or future clinical trial but also part of any registries outside of a clinical trial such as the biological arm of COG studies. Funding for clinical trials should take collection of tissues into account.

The benefits of collecting tissues including CSF and blood include the ability for identification of risk loci and novel risk stratification methods using CSF. Moreover, collection of blood allows for identification of germline syndromes after appropriate human genetic counseling of the families, many of which are not currently identified, and as such their true incidence is unknown (e.g. Gorlin Syndrome, Li-Fraumeni Syndrome, Fanconi Anemia, Rubinstein-Taybi, biallelic mismatch-repair deficiency). Additional efforts to collect tissue prospectively at relapse including post-mortem examinations will be essential to understand the mechanisms of treatment resistance and should be considered in the design of Phase II clinical trials at recurrence.

Central review

Several previous cooperative studies have shown clearly that central review of neuroimaging is an important prognostic marker. Indeed, in the closed A9961 study of average risk medulloblastoma, one of the most significant predictors of poor outcome was misreading of MRI scans or histology as discovered on retrospective central review.[36] Incomplete staging or central review was also a negative prognostic factor in the European PNET4 trial. [26]

Real-time central neuropathological review alongside molecular, genetic and immunohistochemical marker evaluation is also crucial to exclude morphological mimics such as atypical teratoid rhabdoid tumor (AT/RT), embryonal tumor with abundant neuropil and true rosettes (ETANTR)/embryonal tumor with multilayered rosettes (ETMR) and small cell gliomas are identified.[26]

Accurate real-time radiation planning is also important to improve survival rates as demonstrated in the SIOP/UKCCSG PNET3 and A9961 studies.[8, 54]

As such, we advocate strongly for real-time central review of MRI scans, radiation planning and pathology for patients considered for a clinical trial or registry.

Questionable value of extent of resection as a high-risk marker

Extent of resection is currently identified as a high-risk marker. Specifically, most protocols identify a residual tumor of 1.5cm² as being high risk warranting intensification of craniospinal irradiation to 36Gy. However, this is predominantly based on the COG-921 trial, which was conducted in the pre-MRI era, and was based on the limit of detection by CT scanning.[60] Moreover, the question of near-total resections (0–1.5cm²) has not been re-visited for the past 25 years. Work from the Hospital for Sick Children in Toronto that studied 787 clinically annotated and molecularly subgrouped medulloblastomas

demonstrated that near total resection poses no additional survival risk to gross total resection, and that the prognostic benefit of a subtotal resection is attenuated after accounting for molecular subgroup affiliation. [56] The PNET4 study of non-metastatic medulloblastoma identified residual disease $>1.5\text{cm}^2$ on postoperative MRI as a marker of worse prognosis.[26] However, PNET4 included only a small population of patients with incomplete resection ($\geq 1.5\text{cm}^2$, $n=31$ of 338), subgrouping for subtotal resected patients has not been reported and outcomes with 23.4Gy were not worse than those reported with 36Gy.[5] These limitations currently preclude further interpretation of the extent of resection data derived from PNET4 in a subgroup-dependent context.

Furthermore, there is a paucity of supportive evidence that intensifying therapy to the craniospinal axis improves local control in the setting of subtotal resections. Indeed, aggressive resection of the final tumor remnants may cause considerable neurological morbidity when adherent to crucial brainstem structures.[7] As such, consensus of the group was that a near total resection should be considered acceptable and equivalent to a gross total resection for staging purposes. The group advocates that maximal safe surgical resection should always be attempted; however, neurosurgeons should be advised to weigh the risks of aggressive resections particularly given the accepted prognostic equivalence of near total resection to gross total resection. The use of $>1.5\text{cm}^2$ residual as a marker for high risk medulloblastoma requiring intensified craniospinal irradiation clearly needs to be questioned and properly re-evaluated in future clinical trials.

Inclusion of functional and quality of survival measures of outcome

Several studies have shown that the long-term cognitive and quality of survival outcomes for survivors of medulloblastoma are frequently dismal.[29, 30] Various prospective clinical trials over the past 20 years including the recent high-risk COG/POG studies 9031, 9961 and 99701 did not include functional and quality of life measures. Consensus was reached underlining the importance of functional and quality of survival measures studies, and early evidence suggests that quality of survival outcomes may be related to tumor clinico-biological features.[2, 3, 20]

Currently, there is no consensus regarding standardized measures of functional and quality of survival outcomes, and most studies include suboptimal and inconsistent evaluations. A group of particular concern are younger children currently considered high risk and treated with 36–39Gy of craniospinal irradiation. As such, prospective measures evaluating quality of life, cognitive function and other aspects of toxicity need to be included in all clinical trials. International harmonization of these measures needs to be urgently conducted moving forward for adequate evaluation of both quality of life and cognitive function.

Recurrent Medulloblastoma

Several studies have shown in both medulloblastoma and other childhood cancers that significant genetic changes occur in the tumor at recurrence. Although subgrouping remains stable at recurrence, there is a high degree of clonal selection, whereby the dominant clone at recurrence is rarely the dominant clone seen at diagnosis, likely reflecting the selection for resistant clones from treatment.[18, 28, 43] Moreover, it has been previously shown in

medulloblastoma that irradiated Group 3 and 4 patients recur most frequently with metastatic dissemination, with a tumor bed frequently devoid of disease.[43] This suggests that future targeted therapies at recurrence based on target identification of the tumor at diagnosis may fail due to absence of the target at recurrence, or absence of the target in the metastatic compartment[59]. In addition, radiation induced high-grade gliomas may falsely be diagnosed as late medulloblastoma recurrences.[37, 43] As such, the group consensus is that recurrent tumors should be re-biopsied before using targeted therapy, if two years beyond initial diagnosis to exclude a radiation induced high-grade glioma or if the diagnosis is in doubt.

Identification of Familial Syndromes

Several studies have shown that SHH tumors frequently occur in patients harboring familial syndromes, notably germline mutations in *PTCH1* (NBCCS/Gorlin syndrome), *TP53* (Li-Fraumeni syndrome) and *SUFU*. [15, 21, 52, 62] These patients require unique screening for secondary malignancies, and genetic counseling for the family.[58] These syndromes have potential treatment implications, particularly patients with germline *PTCH1* mutations who have a near universal development of basal cell carcinoma if irradiated. Mutations of *TP53* are frequently germline in the childhood / adolescent population.[62] Patients with the Li-Fraumeni syndrome have a dismal outcome due to particularly aggressive primary tumors and the high risk for secondary malignancies in survivors. As such, we advocate that all pediatric patients diagnosed with SHH tumors be offered genetic counseling in order to have their tumor and germline samples sequenced for *TP53*, *PTCH1*, *SUFU* in real-time and that these mutations are reportable.

Future Risk Stratification

Currently in North America and Australia, clinical risk stratification divides patients over age three into average/standard risk and high risk. High risk is defined in those patients with residual disease (either metastatic, CSF positive (M+) or local residual disease above 1.5cm² (R+)). In Europe, in addition to patients with M+ or R+ disease, patients with large-cell and/or anaplastic pathology and/or *MYC* or *MYCN* gene amplification are excluded from average risk trials (e.g. the current PNET5 study), based on clinical, histopathological and biological studies from previous trials (e.g. PNET3).[11] The issue of residual disease is addressed above. However, several studies over the past five years have identified molecular markers, which may provide additional layers of information to allow for more robust risk stratification together with the previously used criteria.[5, 39, 48–50] Several published and unpublished studies were reviewed and a consensus was reached regarding a new proposed risk classification scheme. (Figure 1)

Low Risk (>90% survival)

Several studies globally both prospective and retrospective have shown that non-metastatic WNT patients under the age of 16 have an excellent survival independent of the protocol they have been treated with. Indeed, the prospective PNET3, PNET4 and SJMB96 studies and retrospective data from the MAGIC consortium, Heidelberg, Boston, Mumbai and Toronto have shown that non-metastatic WNT patients treated with surgery, radiation +/-

chemotherapy have excellent survival rates.[4, 5, 12, 25, 32, 39, 44, 48] Within the completed PNET4 study, and retrospective analyses of adult medulloblastoma, WNT patients over the age of 16 may not be a low-risk group, and have been excluded from PNET5.[5, 45] The ongoing SJMB12 and PNET5 clinical trials are currently evaluating de-escalation of therapy for this group of patients. WNT patients with incomplete resections are likely low-risk.[56]

The low incidence of metastatic dissemination and large cell and/or anaplastic pathology in WNT patients precludes any clear recommendation, and as such their risk stratification remains indeterminate.

A subset of average risk Group 4, specifically those patients harboring loss of chromosome 11 and/or whole gain of chromosome 17 can also be considered low risk. A retrospective study of cytogenetic prognostication from the MAGIC consortium showed that approximately a third of Group 4 patients harbor loss of Chromosome 11 and 5% harbor whole gain of chromosome 17, both with excellent survival.[49] It was reported by the group from St. Jude that preliminary data soon to be submitted for publication that appears to supports a >90% survival in this group. Although patients with metastatic dissemination and Chromosome 11 loss or whole gain of chromosome 17 also fare well, they were all undoubtedly treated as high-risk patients with 36Gy of craniospinal irradiation. As such, it was agreed that only non-metastatic Group 4 patients with Chromosome 11 loss could potentially be considered low risk based on currently available data. This observation warrants urgent validation in prospective cohorts to help guide future clinical trials.

Standard Risk (75–90% survival)

Clinical trials from several cooperative groups from SIOP, COG and St. Jude's have shown that outcomes for average / standard risk medulloblastoma exceed 80% five-year survival. [13, 26, 36] Most non-metastatic SHH patients fall into this category with the notable exception being *TP53*-mutated SHH patients who have a near uniformly poor prognosis independent of metastatic dissemination.[42, 62]

Group 3 patients were previously identified as an overall poor prognostic group, although initial retrospective studies revealed transcriptome defined subsets of Group 3 patients that have a better outcome.[22, 49] Unpublished data presented from the HIT2000 cohort, St Jude and an institutional cohort from the Hospital for Sick Children suggest that non-metastatic Group 3 patients, who received craniospinal radiation, do not necessarily have an inferior prognosis compared to other standard risk patients.[39, 42] Amplification of *MYC* has been reported to be a marker of poor prognosis although the relevance of *MYC* amplification in non-metastatic Group 3 is indeterminate.

Group 4 medulloblastoma comprise almost 50% of irradiated, non-infant childhood medulloblastoma. Unpublished data presented from the HIT studies, St Jude, UK research cohort and the published MAGIC consortium and Toronto Hospital for Sick Children institutional cohort suggest that non-metastatic Group 4 (without Chromosome 11 loss) can be considered standard risk.[49] Amplification of *MYCN* is mainly restricted to SHH and Group 4 patients, but has been shown in two studies to be a marker of poor prognosis only in

SHH (frequently co-occurring with *TP53* mutations).[21, 22, 24, 49] As such, it was the consensus of the group across non-metastatic patients currently classified as average risk; non-*TP53* mutated and non-*MYCN* amplified SHH, non-*MYC* amplified Group 3 and Group 4 without chromosome 11 loss should be considered average/standard risk. (Figure 1)

High Risk (50–75% survival)

Across several biologically informed cohorts including the MAGIC consortium, UK research cohort, St Jude studies, and HIT2000, metastatic dissemination remains a marker of poor prognosis. Patients with *MYCN* amplified SHH medulloblastomas fall into this category as well, regardless of metastatic dissemination.[22, 24, 49] Current high-risk protocols result in survival rates between 50–65% and the vast majority of these patients are non-WNT patients, but furthermore, it has been shown in previous studies that treatment of metastatic patients with reduced dose craniospinal irradiation results in a significantly poorer survival.[36] As such, metastatic non-infant *TP53* wildtype SHH and metastatic Group 4 patients should continue to be considered high-risk patients. Non-metastatic *MYCN* amplified SHH patients should also be included in this group.

Very High Risk (<50% survival)

Two groups have been identified across several studies as being very high risk, notably *TP53* mutated SHH and *MYC* amplified, metastatic Group 3.[4, 49, 62]

Patients with *TP53* mutated SHH medulloblastomas, which are almost always characterized by anaplastic morphology, are of particular interest and warrant significant discussion as they harbor significant numbers of germline *TP53* mutations as part of Li-Fraumeni Syndrome in the childhood age group.[21, 41, 62] Germline *TP53* mutated SHH patients almost always fail therapy. However, in pooling data from both European and North American centers, despite near universal fatal outcomes irrespective of treatment, there was a small subset of long-term survivors who eventually died of secondary tumors. As such, the consensus of the group was that all SHH tumors should be screened for somatic and germline *TP53* mutations after appropriate genetic counseling. Currently there are incomplete data on the frequency and outcome of somatic *TP53* mutated SHH tumors.

Those patients harboring germline *TP53* mutations should be prioritized for novel therapies, in the context of rigorous clinical trials across several international sites / trials groups. One potential option, suggested based on evidence that patients with germline *TP53* mutations are prone to secondary tumors, is the omission of external beam irradiation. [58] It should be noted that there is currently no evidence to support either approach; specifically, only very anecdotal evidence exists at the unpublished case report level to support that Li-Fraumeni patients treated with chemotherapy only potentially survive. Other potential novel therapies for this group that were discussed including lithium as a radiosensitizer.[61] In light of their universally poor prognosis, broad consensus was achieved that new treatment approaches are urgently warranted. As this group is a rare subset of medulloblastoma patients, we would advocate that a multinational approach is needed, including centers in both Europe and North America. Moreover, patients with *TP53* mutated SHH tumors almost always harbor downstream lesions of *SMO* such as *GLI2* and/or *MYCN*; and as such are not predicted to

respond to SMO inhibitors.[21] As there are currently no targeted therapies available in this group, research groups worldwide should prioritize *TP53* mutated SHH tumors for evaluation of novel therapeutic strategies.

Metastatic Group 3 patients have been shown in several studies to have a poor prognosis, including the MAGIC consortium, HIT2000 and the UK research cohort, particularly those harboring a *MYC* amplification. As such, new and novel therapies are urgently required. This group should be prioritized for new upfront therapies in multicenter clinical trials. Further studies are required for identification of specific agents active against this group. Specific agents discussed included bromodomain inhibition, aurora kinase inhibition and histone deacetylases inhibitors.[1, 9, 18, 27, 38]

Indeterminate Groups and Unanswered Questions

The lack of consistent data precluded recommendations for risk stratification and a sufficient definition of certain patient cohorts. These groups are outlined in Figure 1 and warrant further discussion, as insufficient or conflicting data exist in the literature.

Patients with *MYC* amplifications have been suggested to have a poor prognosis overall, but a recent report from the PNET4 study suggests that survival was 100% in all four non-anaplastic non-metastatic patients with FISH confirmed *MYC* amplifications with follow-up times of 4–7 years.[5] As such, we feel it is premature to generally consider non-metastatic *MYC* amplified patients as high risk. In addition, although criteria have been set within some trials group (e.g. the SIOP group [5, 11]), no consensus definition was reached regarding the detection cut-off for *MYC* or *MYCN* amplification, with respect to copy number and frequency of amplified cells by FISH or by array-based technologies. This needs to be addressed urgently by cooperative groups, particularly when array-based methods of copy number determination are becoming more widespread in clinical laboratories around the world.

The prognostic implications of two 2007 WHO defined morphological patterns of medulloblastoma, melanotic medulloblastoma and medulloblastoma, could not be determined due to their rare incidence. We feel these patients should be risk-stratified as per current recommendations. The same holds true for the prognostic relevance of anaplastic and/or large cell histology. Conflicting reports exist regarding the prognostic relevance of anaplastic and/or large cell histology. Furthermore, identification of these morphological entities does not inform as to the biology of the tumor. Several high risk entities listed above, specifically *TP53* mutated SHH and *MYC* amplified Group 3, are frequently large cell medulloblastomas or diffusely anaplastic, however the significance of anaplasia and/or large cell histology in WNT and Group 4 is currently unclear. Currently in European and in COG protocols, presence of anaplasia and/or large cell histology excludes patients from enrolment in standard risk protocols because of data from previous studies indicating their impact as predictors of a poor outcome, but stratifying all patients with this tumor characteristic as high risk remains controversial. As such, further investigation should be undertaken to reach a conclusion regarding the prognostic role of histological variants within the molecular subgroups.

Isochromosome 17q constitutes a very controversial cytogenetic marker with several conflicting studies.[49][18], [5] Indeed, a large study from the MAGIC consortium reporting subgroup-specific cytogenetic prognostication suggests it may be a high risk marker in Group 3, however, in light of the paucity of corroborating and validating data, this requires further study.

Finally, an issue that warrants special consideration is the boundary between Group 3 and 4. It has been recognized that using current molecular subgrouping strategies, an indeterminate but small fraction of tumors overlap between Group 3 and 4. One key unresolved issue is how to both reconcile those cases that are indeterminate, specifically how they will be stratified in the context of clinical trials. It was the opinion of the group, that the overlap is small and likely represents at most 10% of Group 3 and 4 assignments, but should be clearly addressed in the design of any high risk trial to avoid excluding this subset of patients from enrollment in innovative clinical trials. The WHO classification 2016 will classify Group 3 and 4 together as non-WNT/non-SHH, and has introduced the provisional subentities Group 3 and group 4 when there is an unequivocal call of one of these groups. Further delineation of substructures within the four epigenetic/expression subgroups is required to adequately address this issue.

Future Directions

Currently, no molecularly informed high-risk medulloblastoma studies are open through either of the two major cooperating consortiums in Europe (SIOP) or North America (COG). A randomized high-risk multi strata trial is currently being planned in Europe, which will evaluate the role of high dose chemotherapy and hyperfractionated *versus* standard radiotherapy. Patients with SHH tumors and *TP53* germline mutations will be excluded from the trial. The trial is unique with respect to randomization since the treatment arms will be biologically balanced regarding the distribution subgroups and other relevant prognostic biomarkers. In addition, the design will allow flexibility for novel biologically targeted agents to be evaluated when they become available. Incorporation of biological studies into all future prospective trials will be required to properly integrate new and novel therapies into clinical trials. International collaboration across the Atlantic will be required to rapidly translate knowledge into clinical care. High-risk medulloblastoma has been a neglected entity in international clinical trials and the proposed classification has been developed to potentially help guide the development of further investigations and the next generation of clinical studies. Importantly, this classification provides a framework to more accurately define high-risk patients, who urgently require the development of new and novel therapies to improve outcome.

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	WNT	SHH	Group3	Group4	Other
LR	<16y			All of the following: - Non-metastatic - Chr. 11 loss	
SR		- TP53 wt (somatic or germline) - No MYCN amplification - Non-metastatic	All of the following: - No MYC amplification - Non-metastatic	All of the following: - Non-metastatic - No Chr. 11 loss	
HR		One or both: - Metastatic - MYCN amplification		Metastatic	
VHR		TP53 mutation (metastatic or non-metastatic)	Metastatic		
Unknown	Metastatic		Non-metastatic with MYC amplification Significance of anaplasia isochromosome 17q	Significance of anaplasia	Melanotic medulloblastoma Medulloblastoma Boundary between Group 3/4 Definition of MYC & MYCN amplification

Figure 1. Proposed risk stratification for non-infant childhood medulloblastoma. LR – low risk, SR – standard risk, HR – high risk, VHR – very high risk.

Table 1

Proposed consensus for the design of the next generation of clinical trials

1. Subgrouping: All patients should be treated on a molecularly informed clinical trial. All tumors subgrouped by genome wide methylation array or other validated methods using at least 2 techniques as part of initial clinical workup
2. Tissue collection: Snap frozen and paraffin embedded tumor tissue, blood and CSF should be collected on all patients
3. Central review: Real-time neuroimaging, neuropathological diagnostics and radiotherapy planning for clinical trial or registry
4. Treatment-related side effects: Quality of life measures and neuropsychological outcomes including short, medium and long term is a high priority and should be evaluated in all patients
5. <i>TP53 mutations in SHH medulloblastoma:</i> <i>TP53</i> mutated SHH patients have a very poor prognosis and new treatment options are needed especially if germline <i>TP53</i> mutation
6. Genetic predisposition: All families with pediatric patients carrying SHH tumors should be offered genetic counseling. Tumors should be sequenced for somatic and germline mutations of <i>TP53</i> , <i>PTCH</i> , and <i>SUFU</i> as part of the diagnostic process in accredited laboratories.
7. Need to re-biopsy: Recurrent tumors should be re-biopsied before using targeted therapy or 2 years beyond initial diagnosis or diagnosis is in doubt
8. Extent of resection: Neurosurgeons should aim for maximal safe removal: NTR (to be defined) is acceptable and prognostically equivalent to GTR for staging
9. Non-metastatic WNT medulloblastoma: All WNT properly subgrouped < 16 years old have excellent prognosis and should be treated with reduced radiation/chemotherapy

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