Medulloblastoma (MB) is the most common malignant brain tumor in children and the one which has a narrower therapeutic index with a cure rate of 50–85% depending on risk factors, and severe sequelae in nearly all the patients. It rapidly appeared that medulloblastoma was a radio–chemosensitive tumor, exceptionally curable without radiotherapy, and only in cases of complete resection. Since the 1990s, risk stratification of medulloblastoma has been based on age, metastatic status at diagnosis, and extent of surgical resection. Then, the presence of widespread anaplasia or large cell morphology and nodular desmoplastic were added to risk-stratification criteria because they are associated with poor or favorable progression-free survival, respectively. Thus, prior to the current explosion of molecular biology, the golden standard treatment consisted of the most complete possible resection, potentially leading to cerebellar mutism and neurological sequelae, craniospinal irradiation, and more or less intensive chemother-apy, depending on risk factors [1]. This treatment strategy led to a 50–70% overall survival [2] but was associated with devastating long-term sequelae, including developmental, neurological, neuroendocrine, psychosocial deficits, and second tumors [3,4]. To better determine risk factors and to improve the therapeutic index, several multicenter randomized studies have been performed aiming to elucidate the respective role of resection extent, optimal doses of radiotherapy, notably as neuroaxis prophylaxis, and the impact of chemotherapy. The following studies have provided some certainties concerning risk factors and therapeutic strategies:

- the prognosis of metastatic medulloblastoma, which was made up of 1/3 of the cases, is far more severe, with an overall relapse free survival rate less than 50% until the end of the 1990s [5];
- the extent of resection > 1.5 cm² had a worse prognosis, with a 5-year–event free survival of 82% versus 64% in the SIOP PNET 4 study [6];
- children younger than 5 years of age have a poor prognosis except for the desmoplastic/nodular medulloblastoma or medulloblastoma with extensive nodularity, and worse long-term sequelae [7];
- for children older than 5 years, large cell or anaplastic MB have been associated with an impaired prognosis [8];
- relapsed disease patients after previous craniospinal irradiation (CSI) have very little chance of cure despite receiving very intensive salvage regimens, including megatherapy with autologous stem cell rescue [9].

In addition to these well-documented risk factors, randomized studies have also reported some important data currently used for designing new treatment strategies:

- delayed radiotherapy [10], above all in cases of a decreased dose of neuroaxis radiotherapy may have a negative impact on outcome [11];
- quality control of initial imaging is essential to avoid incorrect staging leading to include metastatic patients in average risk treatment strategies [12];
- impact of targeting radiotherapy deviation is essential [13], above all in cases of a dose-reduction regimen [12];
- it is possible to reduce the radiation therapy dose to the neuroaxis [14] and to limit the boost volume to the tumor bed rather than to the complete posterior fossa, without the use of chemotherapy [15];
- for children older than 5 classified as standard risk, the adjuvant chemotherapy associated with a 23.4 Gy of craniospinal irradiation and a boost to 55 Gy to the posterior fossa-tumor bed is considered as the standard treatment with a 5-year outcomes of approximately 80%, independent of the regimen used [16];
- high-risk patients older than 5 years treated with CSI of 36 to 39 Gy, with a boost to 55 Gy to the posterior fossa-tumor bed, followed by cisplatin–cyclophosphamide based chemotherapy has resulted in 5-year survivals of 60% to 65% across most studies [17];
- strategy based on sequential high-dose chemotherapy and CSI could compare favorably with those using high-dose radiotherapy with alkylator based regimen in children older than 5 years of age [18];
- some non-metastatic children less than 5 years of age could be cured with radiation-sparing protocols avoiding, in part, long-term radiation sequelae to the entire neuroaxis, using intensive chemotherapy which results in superior neurocognitive...
outcomes [19]. Within this age group, infants with nondesmoplastic metastatic disease (specifically group 3) continue to have poor outcomes without radiation therapy;

- although advances in proton radiation may improve functional outcomes, there will likely be a limit to this improvement in the youngest children, and the risk of secondary malignancies is unlikely to decrease [20];

- a major challenge in determining long-term functional outcomes has been a lack of long-term quality-of-life parameters in clinical trials.

1. Many questions are still pending

Many questions are still pending using conventional strategies:

- what is the optimal dose of radiotherapy on neuroaxis, whether it is associated or not with chemotherapy and according to risk factors?
- is it necessary to proceed to a new resection for a residual tumor which is in good partial response after chemotherapy?
- is it necessary to propose maintenance chemotherapy for high-risk MB?
- what is the place of neoadjuvant chemotherapy prior to any surgical resection?

2. The turning point of a new era

The current explosion of molecular data has begun to elucidate the medulloblastoma biology and is expected to lead to improved disease classification, treatment stratification, and the discovery of novel drug targets. The array-based transcriptional-profiling studies of large cohorts of primary medulloblastoma samples has represented a fundamental advance in the understanding of medulloblastoma. Current international consensus has divided medulloblastoma into at least four distinct subgroups: Wnt/Wingless (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4 medulloblastoma which have distinct cytogenetic features, genetic aberrations, gene expression profiles, stable at recurrence, and divergent phenotypes including tumor cell histology, and outcomes [21]. A group of favorable-risk patients expressing nuclear b-catenin (WNT subgroup) was identified as having survivals >90% leading to reduce craniospinal irradiation [22] with the aim of decreasing long-term neurocognitive outcome. In contrast, group 3 subgroup patients have a very poor prognosis across several studies [23]. However, substantial heterogeneity in clinical and molecular features still exists in these subgroups. Moreover, previous studies that defined the four-subgroup consensus used modestly sized cohorts and were limited in developing survival models in these patient cohorts who received heterogeneous treatment. Recent advances in epigenome research showed that epigenetic changes are common in medulloblastoma and may constitute an important class of drivers for the disease [24]. Among the most frequent mutations are those that affect genes that alter histone methylation. Thereafter, single-nucleotide polymorphism arrays and whole-genome and whole-exome sequencing have uncovered further the genetic landscape of medulloblastoma [25]. Schwalbe et al. reported recently a retrospective analysis of 428 pediatric patients with molecularly defined medulloblastoma which aimed to identify a deeper molecular substructure of the four subgroups with further clinical relevance [26]. They identified seven robust and primarily molecularly defined subgroups based on methylation profiling, characterized by distinct clinical and biological features which notably suggested that the MBSSH subgroup could be divided into 2 different groups (more or less than 3 years). These new findings could lead to the potential for further individualization of therapy for patients with Group 3 and Group 4 medulloblastoma in future studies. This integrative approach could help to simplify therapy stratification algorithms for clinical trials in an era in which knowledge about medulloblastoma biology can become too complex for viable clinical decision-making. Still more recently, it was reported that similarity network fusion (SNF) applied to genome-wide DNA methylation and gene expression data across 763 primary samples has identified very homogeneous clusters of patients, supporting the presence of medulloblastoma subtypes [27]. After integration of somatic copy-number alterations, and clinical features specific to each cluster, the authors have identified 12 different subtypes of medulloblastoma. Integrative analysis using SNF further delineates group 3 from group 4 medulloblastoma, and 2 clear subtypes of infants with Sonic Hedgehog medulloblastoma with disparate outcomes and biology. Although some response rates have been obtained, the usefulness of targeted therapy need to be confirmed within a large group of patients. For example, a reported phase II study which tested medulloblastoma response to the SHH pathway inhibitor sonidegib (LDE225) in patients having a signature of five differentially expressed genes associated with Hh pathway activation status was closed prematurely due to a poor response rate [28].

Concerning the treatment of recurrent medulloblastoma, it is urgent to search therapeutics not only for the primary tumor but also directed at the metastatic compartment and target clones resistant to conventional treatments. Advances in single-cell genomic techniques and liquid biopsies from plasma and CSF could explore the scope of intratumoral heterogeneity across the metastatic compartment. The next generation of preclinical modeling and clinical trials must take into account this clonal divergence.

The latest consensus on childhood medulloblastoma, where patients are risk stratified by various subgroups into very low risk, standard risk, high risk, and very high risk, provides a framework for the next generation of clinical trials [29]. This risk-stratification acknowledges MYC-amplified and/or metastatic group 3 and TP53-mutant SHH as being very high-risk diseases which could be an opportunity to test novel upfront approaches.

The rapid accumulation of molecular data poses the clinical challenge of applying this data in a timely manner in clinical trials. From a clinical perspective, the number of subgroups should ideally remain within a framework allowing their clinical application for stratification in the context of future clinical trials.

An integrative approach could help to simplify therapy stratification algorithms for clinical trials in an era in which knowledge about medulloblastoma biology can become too complex for viable clinical decision-making.

3. Conclusion

Medulloblastoma which was once regarded as a single-disease entity two decades ago is now recognized as being at least twelve distinct diseases that could require an individual diagnostic and therapeutic approach. The new insights obtained from molecular information combined with clinical and pathological findings could serve to improve risk-adapted treatment strategies towards individualized and thereby better therapies in future.

There is a crucial need for joint clinical trials to improve outcomes, as new medulloblastoma subtypes are identified, the patient population of each subgroup will decrease, making it more difficult to recruit sufficient numbers of patients to determine optimal therapy.

There is also a need to establish a central repository of annotated mouse models that are accessible to the international
research community, and to share preliminary high-throughout drug screening data across discovery labs to speed up the development of novel therapeutics.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


