Radiotherapy (RT) remains the mainstay of medulloblastoma treatment but its impact on neurocognitive outcome of young children is massive. In this age group, the main challenge is to limit the cost of cure by deferring, completely avoiding or at least reducing RT (field or dose) without jeopardizing survival. In the past, survival of young children with medulloblastoma was somewhat lower than in older children treated with standard craniospinal RT. Apart from the decrease of RT other causes can be discussed: differences in tumor biology, higher frequency of metastases, inclusion of others embryonal tumors such as atypical teratoid/rhabdoid tumor (ATRT) or embryonal tumor with multilayered rosettes (ETMR) with known worse prognosis.

The identification of subgroups defined molecularly represents the most fundamental advance in our understanding of medulloblastoma. The current international consensus recognizes four subgroups of medulloblastoma: wingless (WNT), sonic hedgehog (SHH), group 3 and group 4 (1). These subgroups recognized in the 2016 WHO classification of brain tumours (2) will further define research studies and clinical trials. However, most of the molecular subgrouping of medulloblastomas despite the analysis of large cohorts did not take into account informations about neither clinic-radiological characteristics nor treatment received; this left many relationships to disease outcome unresolved. Desmoplastic medulloblastomas or medulloblastoma with extensive nodularity arising in young children are associated with a good prognosis following chemotherapy treatment (3) and are characterised by SHH-activated, TP53 wild-type biology. Young patients with non-WNT/non-SHH non-desmoplastic medulloblastoma have a worse prognosis however, importantly, the prognostic significance of non-desmoplastic histology in SHH tumours requires definition.

In the Lancet Oncology, Robinson and colleagues (4) report for the first time the results of a clinical trial aiming to estimate the event-free survival with respect to subgrouping according to the methylation profiles in 76 young children with medulloblastoma. In this trial SJYC07, patients were stratified postoperatively into three risk groups. All patients were treated with induction and maintenance chemotherapy. Radiation therapy was limited to intermediate risk-patients who received focal RT. No patients received high-dose chemotherapy with stem cell support or intrathecal chemotherapy. The limitation of this study, mainly its sample power and bias towards single therapy have been carefully addressed by the authors. The strength of the study is the integration of clinical information and the histopathological central review into their substratification algorithm. Robinson and colleagues found that risk-adapted treatment did not improve event-free survival in young children with medulloblastoma. However, analysis by methylation status revealed distinct subgroups and subtypes of medulloblastoma that were associated with...
distinct outcomes. As previously reported (5-7), patients with SHH medulloblastoma had higher rates of progression free-survival compared to patients with group 3 and group 4 medulloblastoma. By contrast with other publications (5-7), the prevalence of classic medulloblastoma in SHH subgroup was very low (3 patients; 7%). As mentioned by Robinson and colleagues, this small sample size did not allow for conclusion regarding whether molecular classification outperforms morphological-based classification and molecular classification should be placed ahead of morphological classification, but should not replace it.

There is no consensus of the age cutoff for infant medulloblastoma. Some “infant studies include children up to age 3 with others extending children’s age to 4 or 5. In the SJYC07 trial, select 3–5 years old children were included in the intermediate risk group. From a cohort of 190 patients younger than 6 years of age, Robinson and colleagues found more than 70% of children younger than 3 years were in the SHH subgroup, compared with 21% in patients aged at least 3 years. As mentioned by the authors, age cutoffs in clinical trials will select certain subgroup over others. These findings should be considered in future trials and probably, the combination of age with others parameters, rather than a sharp of cutoff, might be used for therapy stratification.

Robinson and colleagues described two methylation subtypes in the SHH subgroup, which they named iSHH-I and iSHH-II. The identification of two infant SHH subgroups has been reported previously: MB_{SHH-infant} and MB_{SHH-I,shld} (6); SHH_{L} and SHH_{S} (7). In SJYC07 trial, the 5-year progression survival was 27.8% for the iSHH-I subtype compared with 75.4% for iSHH-II. The authors suggested that these patients with iSHH-II medulloblastoma benefit from reduced-intensity therapy. The prevalence of iSHH-I versus iSHH-II need to be assessed in infant cohorts to understand why different outcomes were reported with the same infant treatment strategies (8,9).

Over the last decades, improvements in next-generation sequencing approaches run on large cohorts allowed to better identify genetic predisposition to medulloblastoma. While Robinson and colleagues reported few data about genetic predisposition, in this infant cohort, Waszak et al. studied germline mutations in 110 cancer predisposition genes on 1,022 patients with medulloblastoma in a large retrospective cohort and a prospective validation cohort (10). The retrospective cohort had no age limit for inclusion and eligibility in some prospective cohorts was up to 39 years. The authors identified 6 major genes with a significant excess of damaging germline mutation for patient with medulloblastoma: APC, BRCA2, PALB2, PTCH1, SUFU and TP53. The prevalence of genetic predisposition based on these 6 genes was 5% to 6% in both cohorts with a highest prevalence of 20% in patients with SHH medulloblastoma. Except APC, all these germline mutations were mainly found in the SHH subgroup (exclusively for SUFU, PTCH1, TP53 and compound heterozygous BRCA2 mutations, mostly for others BRCA2 and PALB2 mutations).

To note, 1 infant with an APC germline mutation also developed a SHH medulloblastoma. SHH subgroup is more frequent in infants and younger children (<3 years) and in adults, and is commonly associated with the desmoplastic/nodular histology (1). Robinson and colleagues found that more than 70% of children with medulloblastoma younger than 3 years had a tumor type of the SHH subgroup. SUFU, PTCH1 and TP53 were already known to be associated with SHH medulloblastoma (11) with a high prevalence of SUFU and PTCH1 germline mutation in infants (12) and an occurrence of TP53 mutation mostly during childhood. The strengths of the study are the large size of the cohort in a single pediatric brain tumor entity that allows assessing the incidence of cancer predisposition syndrome for patients with medulloblastoma and the correlation with the tumor genome analysis. Its limitation is the lack of familial history of cancer. This study confirms that this population of infants or very young children, who mainly develop SHH medulloblastomas has the higher rate of germline predisposition to medulloblastoma. So, these patients should be counseled for a systematic genetic testing because the prevalence of germline mutation is high and the familial history of cancer and clinical signs of genetic predisposition is often absent. Anyway, broad genetic analysis on tumor and constitutional DNA might have several consequences for the affected patient and his family when it leads to identify a germline mutation. It was already known that prognosis of medulloblastoma was dependent on the underlying germline predisposition. Waszak and colleagues reported that patients with APC, BRCA2, PALB2, SUFU and PTCH1 germline mutation have excellent prognosis contrary to patients with compound heterozygous BRCA2 and TP53 germline mutations. These results are not consistent with others reports showing that patients harboring a germline mutation in SUFU gene had a worse prognosis than usually observed in SHH medulloblastoma possibly due to the high risk of local relapses (4,13). It may also have larger consequences on the family that must be taking into
account and anticipated with the parents at the time of the child genetic testing, especially when there is no familial history of cancer. It raises the question of the inherence of the pathogenic germline mutation and can lead to identify other mutation carriers among the relatives. The aim of this approach is the proposed a genetic counseling to offer an early cancer detection in unaffected mutation carriers with an adapted and structured follow-up, but it also may have psychological effects, especially when the tumor prevalence and spectrum are still unclear. Mutation in \textit{BRCA2} and \textit{PALB2}, so far known only in the context of Fanconi anemia, were identified as germline mutation in medulloblastoma with no strict association with age at diagnosis and tumors with signs of homologous recombination repair deficiency. Waszak and colleagues propose to screen them in patients with a SHH medulloblastoma following a negative test result for the others genes, or in case of family history of BRCA-associated cancers. But nothing is already known on the prevalence of these two germline mutations in medulloblastoma and international collaboration are needed to better describe the spectrum and impact of these predisposition syndromes in medulloblastoma.

The development of risk-adapted therapeutic strategies improves outcome of young children affected with medulloblastoma needs a better stratification of early childhood medulloblastoma, mainly composed with SHH medulloblastoma. It must be based on the integration of clinical, therapeutic and genetic information in addition to morphological and molecular usual data. Genetic counseling has to be offered for all young children who develop a medulloblastoma even if the familial history of cancer and clinical signs of genetic predisposition are absent. But it can also raise other questions due to the lack of our current knowledge that have to be evaluated. The best therapeutic strategies for infants with medulloblastoma are currently under discussion, particularly the question of whether patients with a germline mutation require a specific therapeutic approach. RT is probably efficient, but its use in this very young age and the genetic context is still debated because of the risk of second malignancies. Therapy with a targeted inhibitor of the SHH pathway, which is clearly involved in the malignant transformation, could offer an alternative therapeutic option to the classic chemo-RT approach and have demonstrated good efficacy as monotherapy in a subset of patients with SHH medulloblastoma (14). However, there are some limitations in patients with germline mutation: mutations in SHH pathway genes downstream of SMO (including \textit{SUFU}) can make these tumors intrinsically resistant to SMO targeting drugs (11) and these agents may induce early growth plate fusion restricting their use in these patients usually very young and not skeletally mature.

In conclusion, treatment of medulloblastoma in infants and young children will have to take into account the refinement of their biological characteristics as well as a systematic genetic enquiry in order to Taylor therapy and offer proper surveillance and genetic counselling. These two papers represent definitive milestones for our understanding of medulloblastoma in this age group.

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\section*{Footnote}
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\section*{References}
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