The site of origin of medulloblastoma: Does the neurosurgical perspective support the current concept from molecular data?

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Abstract

**Purpose** Developmental gene expression data from medulloblastoma (MB) supported by retrospective MR imaging studies suggest that WNT-MB originate from the region of the embryonic lower rhombic lip (LRL), whereas SHH-MB and non-WNT/non-SHH-activated MB arise from cerebellar precursor matrix regions. This study aims to analyze detailed intraoperative data with regard to the site of origin (STO) and compare these findings with the hypothesized regions of origin associated with the molecular group.

**Methods** A review of the institutional database identified 58 pediatric patients who were operated on a MB at our department between 1996 and 2020 and had a detailed operative report, surgical video as well as clinical and genetic classification data available for analysis. The STO was assessed based on intraoperative findings of an expert neurosurgeon blinded to the molecular group information.

**Results** Using the intraoperatively defined STO, “correct” prediction of molecular groups was feasible in 20% of WNT-MB, 60% of SHH-MB and 71% of non-WNT/non-SHH activated MB. The positive predictive values of the neurosurgical inspection to detect the molecular group were 0.21 (95% CI 0.08–0.48) for WNT-MB, 0.86 (95% CI 0.49–0.97) for SHH-MB and 0.73 (95% CI 0.57–0.85) for non-WNT/non-SHH activated MB.

**Conclusions** The present study demonstrated a limited predictive value of the intraoperatively observed STO for the prediction of the molecular group of MB. Thus, our findings challenge the current concept of the molecular group-specific origins based on developmental gene expression data and neuroradiological STO definitions.

Introduction

Medulloblastoma (MB) is one of the most common malignant pediatric brain tumor types [1]. According to the current WHO classification of CNS tumors 2021, MB comprises the four major molecular groups, MB, WNT-activated (WNT-MB); MB, SHH-activated (SHH-MB) TP53-wildtype; SHH-MB TP53-mutant; and non-WNT/non-SHH activated MB (Group 3_4) [2–6]. These four major groups have shown to encompass further subgroups that have recently been incorporated in the most recent 5th edition of the WHO classification of CNS tumors [7].

About a decade ago, developmental gene expression data first revealed that the molecular groups originate from distinct cell lineages in the developing brain [8]. According to the emerging concept of group-specific cellular origins, WNT-MB presumably arises from the lower rhombic lip (LRL) of the embryonal brainstem, SHH-MB mainly from the cerebellar hemispheres, and non-SHH/non-WNT activated MB from the inferior cerebellar vermis [9]. Subsequent basic science research articles generated similar results and further strengthened this concept [10–12]. In addition, several studies attempted to analyze imaging characteristics of the molecular groups and defined the tumor location and origin based on neuroradiological data, delivering ambiguous results [5, 13–18]. Despite a comparably large number of
neuroradiological studies, the site of origin (STO) of MB has largely not been described from a neurosurgical perspective.

To date, the standard of care for MB in children consists of gross-total resection, followed by chemotherapy and radiotherapy in children over the age of three years [19, 20]. During surgery, most neurosurgeons generally tend to aim for gross-total resection whenever possible, although there is insufficient definitive evidence that maximizing the extent of resection is associated with improved progression-free survival and overall survival [21]. As MB is inherently situated in an area that harbors vital neurological functions, neurosurgeons are often confronted with the decision to either attempt gross-total resection or preserve neurological function with the risk of impacting the patient outcome [22]. Intraoperatively, the knowledge of the molecular group would add valuable information to optimize and tailor the neurosurgical strategy to the prognostic profile of the patient.

Based on the assumption that the molecular groups exclusively arise from distinct STOs [8, 23], we hypothesized that the intraoperative observation would enable the neurosurgeon to predict the molecular group during surgery and thus allow a risk-stratified approach. Given the fact that WNT-MB is prognostically superior in comparison with all other molecular groups, it would be arguably justifiable to opt for a subtotal resection in order to preserve neurological function [24].

However, there is still insufficient clinical evidence supporting this concept of distinct cellular origins of MB. Therefore, this study aimed to identify the STO of molecular groups from a neurosurgical perspective.

**Methods**

**Study population**

135 pediatric (aged under 18 years at time of diagnosis) patients with a histologically confirmed MB who were referred to our Department of Pediatrics and Adolescent Medicine between 1996 and 2020 were identified from an institutional database. Of these, 72 patients were operated at our Department of Neurosurgery. A detailed operative report, surgical video and/or intraoperative photos as well as clinical and genetic classification data were available for 58 patients for inclusion into the study.

Patient demographics, presence of metastases at diagnosis, treatment modalities (number of surgeries, radiotherapy, chemotherapy), tumor size, pre- and postoperative symptoms and patient outcome were extracted from the medical charts. The extent of resection was evaluated according to interdisciplinary tumor board reviews, operative reports and MRI imaging performed 72 hours postoperatively and classified as gross-total /near-total resection (GTR/NTR) or subtotal resection (STR, residual tumor > 1.5 cm²). Histopathological and molecular data were primarily obtained based on the results of a previous study at our Department of Pediatrics and Adolescent Medicine and further complemented by data from the institutional biobank. Baseline and treatment-related characteristics of the patients stratified by
molecular group are summarized in Table 1. The study was approved by the Institutional Ethics Committee (EK 1476/2021) and complies with the principles of the Declaration of Helsinki.
### Table 1
Baseline and treatment-related characteristics of the study population (n = 58) and stratified by molecular group

<table>
<thead>
<tr>
<th>Variable</th>
<th>WNT (n = 10)</th>
<th>SHH (n = 10)</th>
<th>non-WNT/non-SHH (n = 38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (50.0)</td>
<td>4 (40.0)</td>
<td>12 (31.6)</td>
<td>0.531</td>
</tr>
<tr>
<td>Male</td>
<td>5 (50.0)</td>
<td>6 (60.0)</td>
<td>26 (68.4)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, in years, median (range)</td>
<td>8 (5–17)</td>
<td>3 (0–17)</td>
<td>7 (1–16)</td>
<td>0.128</td>
</tr>
<tr>
<td>KPS at diagnosis, median (range)</td>
<td>70 (20–80)</td>
<td>70 (60–80)</td>
<td>70 (60–90)</td>
<td>0.113</td>
</tr>
<tr>
<td>Metastases at diagnosis, n (%)</td>
<td>10 (100.0)</td>
<td>9 (90.0)</td>
<td>15 (39.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M0</td>
<td>0 (0.0)</td>
<td>1 (10.0)</td>
<td>23 (60.5)</td>
<td></td>
</tr>
<tr>
<td>M+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histopathological subgroup, n (%)</td>
<td>9 (90.0)</td>
<td>0 (0.0)</td>
<td>33 (86.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Classic</td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
<td>4 (10.5)</td>
<td></td>
</tr>
<tr>
<td>LCA</td>
<td>0 (0.0)</td>
<td>10 (100.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>DNMB</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>MBEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of resection, n (%)</td>
<td>10 (100.0)</td>
<td>10 (100.0)</td>
<td>26 (68.4)</td>
<td>0.015</td>
</tr>
<tr>
<td>GTR</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>12 (31.6)</td>
<td></td>
</tr>
<tr>
<td>STR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy, n (%)</td>
<td>0 (0.0)</td>
<td>5 (50.0)</td>
<td>6 (15.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>no</td>
<td>10 (100.0)</td>
<td>5 (50.0)</td>
<td>32 (84.2)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>no</td>
<td>10 (100.0)</td>
<td>10 (100.0)</td>
<td>38 (100.0)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS at last FU, median (range)</td>
<td>90 (60–100)</td>
<td>90 (20–100)</td>
<td>80 (30–100)</td>
<td>0.077</td>
</tr>
</tbody>
</table>
### Intraoperative definition of the STO

The assessment of the epicenter and extension of the assumed origin of tumor growth was conducted based on surgical videos, operative reports and preoperative imaging by a pediatric neurosurgeon with 15 years of experience blinded to subgroup allocation. Over the entire study period, the surgical strategy at our institution has been to carefully dissect the tumor as much as feasible and get a clear anatomic understanding of the tumor margins, adherent neurovascular structures, growth pattern and eventually the STO before and during the actual resection. The anatomical features and STO of the MB were prospectively and systematically documented in the operative reports of all cases of this study.

Depending on their origin, MB follows distinct growth patterns which are largely predetermined by anatomy. Also, the intraoperatively observed displacement of anatomical structures such as the branches of the posterior inferior cerebellar artery, the posterior medullary velum and the choroid tela of the fourth ventricle caused by the tumor allow the neurosurgeon to infer on its presumed STO during the surgical dissection.

The differentiation between the assumed STO versus secondary infiltration was systematically based on the following observations: If the tumor was growing beneath the ependymal level of the ventricular floor forcing the surgeon to leave a thin layer of tumor behind, the STO was attributed to the ventricular floor. If the tumor was replacing the nodulus of the vermis with the pial surface covering the tumor border per continuatatem being just attached and/or infiltrating the ventricular wall, the STO was attributed to the vermis (Fig. 1).

### Statistical analysis
Continuous variables are reported as median and range, and categorial variables as counts and percentages. Chi-Square-tests and Fisher’s exact tests were performed to test for association between clinicopathological features and molecular groups. Wilcoxon rank-sum test and Kruskal-Wallis test were used to compare subgroups on continuous variables. Sensitivities as well as positive predictive values and 95% Wilson confidence intervals of the intraoperatively observed STO were calculated for each subgroup separately. Fisher’s exact test was used to compare the sensitivities and positive predictive values between the three molecular groups. All analyses were performed in the R Statistical Environment (Version 4.2.0.) [25]. P-values on two-sided tests < 0.05 were considered statistically significant.

Results

Intraoperative assessment

The distribution of the intraoperatively inferred STO with regard to their respective molecular group is visualized by Fig. 2 and reported in detail in Table 2.

The intraoperative observation revealed that the majority of WNT-MB (6/10 (60%)) originated from the cerebellar lower vermis with no infiltration or even adhesion of the tumor to the brainstem. The location of the tumor origin of three (30%) WNT-MB could be traced to the lateral recess of the fourth ventricle, with two tumors involving also the caudal paramedian rhomboid fossa. One (10%) WNT-MB was situated entirely within the cerebellar hemisphere, the origin was classified as hemispheric.

Six (60%) SHH-MB originated from the cerebellar hemispheres whereas 4/10 (40%) arose from the vermis. For two SHH-MB, the STO was clearly delineated in the upper vermis from where they further extended into the hemisphere.

Of 38 non-WNT/non-SHH activated MB, 27 (71%) originated from the lower vermis. The origin of the remaining 11/38 (29%) tumors was assigned to the brainstem. In 7/11 (64%) of these tumors originating from the brainstem, the origin involved a unilateral recess, with a slight tendency for the left side (4/7 (57%)). In 4/11 (36%) tumors arising from the brainstem, the STO showed clear infiltrative attachment to the caudal rhomboid fossa.

We further sought to identify differences in the baseline characteristics of patients with different STOs within the molecular groups. Notably, in WNT, SHH-activated patients with a vermian STO were younger (median age at diagnosis (range): 1 (0–3) years) than patients with a hemispheric MB (median age at diagnosis (range): 8 (1–17) years), however, this difference did not reach statistical significance (p = 0.055).

Prediction of MB subtype based on STO

Based on the hypothesis that WNT-MB arise from the LRL, SHH-MB from the cerebellar hemisphere and non-WNT/non-SHH activated MB from the inferior cerebellar vermis, prediction of molecular groups by the intraoperatively observed STO was correct in 20% for WNT-MB, 60% for SHH-MB and 71% for non-
WNT/non-SHH activated MB. The positive predictive values of the neurosurgical inspection to detect the molecular group depending on the STO were 0.21 (95% CI 0.08–0.48) for WNT-MB, 0.86 (95% CI 0.49–0.97) for SHH-MB and 0.73 (95% CI 0.57–0.85 for non-WNT/non-SHH activated MB). Thus, the positive predictive values of the intraoperatively observed STO differ significantly across the molecular groups (p = 0.002). The probability for the correct prediction of a WNT-MB based on the intraoperative observation of a tumor origin from the dorsal brainstem is significantly lower compared to SHH-MB (p = 0.016) and non-WNT/non-SHH MB (p = 0.001).

Table 2
Primary location and extension of the intraoperatively observed STO stratified by molecular group (n = 58)

<table>
<thead>
<tr>
<th>Primary location</th>
<th>Extension</th>
<th>WNT</th>
<th>SHH</th>
<th>non-WNT/non-SHH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 38)</td>
<td></td>
</tr>
<tr>
<td>Brainstem, n (%)</td>
<td></td>
<td>3 (30.0)</td>
<td>0 (0.0)</td>
<td>11 (28.9)</td>
<td>0.196</td>
</tr>
<tr>
<td>Caudal rhomboid Fossa, n (%)</td>
<td>Paramedian rhomboid</td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fossa, left lateral</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recess</td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
<td>2 (5.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right lateral Recess</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral Recesses</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right side of rhomboid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fossa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unilateral recess, n (%)</td>
<td>Left lateral Recess</td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td></td>
<td>Left lateral Recess and</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar peduncle</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right lateral Recess</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral Recesses</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar peduncle, n (%)</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres, n</td>
<td></td>
<td>1 (10.0)</td>
<td>6 (60.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar vermis, n (%)</td>
<td></td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td>27 (71.1)</td>
</tr>
</tbody>
</table>
Discussion

The cell and STO of MB have been a matter of debate ever since the characterization of this tumor entity a century ago [26–28]. Molecular analyses of tumors correlated to developmental gene expression led to the concept of a group-specific origin [8]. This concept, however, has widely not included the neurosurgical perspective which can add valuable information through direct visual inspection [8–10, 12, 13, 16, 17, 29–31]. The detailed neurosurgical data on the presumed STO of MB provided herein complement the current understanding and challenge the current concept of the molecular group-specific cells of origin to a certain extent. Especially WNT-MB, which are hypothesized to originate exclusively from the LRL, exhibit a substantial amount of variance with observed STO that also include cerebellar structures derived from the upper rhombic lip. This discordance and the resulting inability to reliably predict the molecular group based on its STO is particularly relevant when it comes to surgical decision-making accounting for risk-stratification.

Intraoperatively observed intra-group heterogeneity of STO

WNT-MB

In our cohort, only 30% of WNT-MB originated from the LRL derived structures as complying with developmental gene expression data. Moreover, we found 60% of WNT-MB to originate from the vermis and therefore to preferentially grow in the midline, in contrast to Patay et al who reported a significant proportion of WNT-MB to be characterized by a lateralized midline position in the region of the Foramen of Luschka and Perrault et al who noted that 75% were located in the cerebellopontine angle cistern [5, 13]. Consistent with other neuroradiological studies, our findings corroborate the hypothesis of Gibson et al that all MB originating from the LRL are predominantly located in the midline position [32]. Our results also confirm the rare occurrence of a hemispheric WNT-MB. In the neuroradiological analysis of 75 WNT-MB included in the HIT trial, Stock et al also reported 2/75 cases (5%) of WNT-MB with cerebellar hemispheric location as well as 3/75 WNT-tumors (8%) primarily located in the cerebellar vermis. the latter of which is a considerably lower proportion than in our present study (80%) [33].

SHH-MB

In contrast to the hypothesis that SHH-MB are derived from granule cell precursors predominantly found in the cerebellar hemispheres [12, 34], we provide further evidence that 40% of SHH-MB originate from the vermis. Teo et al were one of the first to critically address the concept of distinct cells of origin [30]. Although they concluded that midline tumors were significantly associated with WNT-MB and non-WNT/non-SHH MB as suggested by Gibson et al [8], they also showed that 47% of SHH-MB were located in the vermis, which was in contrast to the concept that SHH-MB are exclusively hemispheric [30]. Several other studies also reported that only two-thirds of SHH-MB showed lateral hemispheric location on MRI [15, 18, 32]. Moreover, Grammel et al noted that 48% of SHH-MB arose from the vermis in their neuroradiological analysis [35]. As reported by previous studies [18, 31], patients with vermian SHH-MB in our study cohort were more frequently infants, which may be due to variable genetic mutations among
different age groups [36]. Notably, two of four vermian SHH-MB were located in the upper part of the vermis as was similarly reported previously by Wefers et al and Dasgupta et al [15, 18]. In our cohort, the intraoperative observation of a hemispherically located tumor was predictive of the SHH-groups in 85% of the cases.

**Non-WNT/non-SHH activated MB**

The current literature suggests that non-WNT/non-SHH activated MB originate from precursors located in the upper rhombic lip [23, 37, 38]. As several Tp53 mutant murine models resembling Group 3 MB developed from cerebellar neuronal stem cells, these cells were also proposed to be the cell of origin of this groups [39, 40]. On the contrary, Wefers et al reported that the vast majority of non-WNT/non-SHH activated MB expanded into the fourth ventricle and had contact to the cochlear and cuneate nucleus without any evidence of intracerebellar growth [15]. Consistent with these results, Narayan et al noted that 62% of non-WNT/non-SHH activated MB tumors were located in the midline and had a tendency to contact the brainstem [32], which supports to some extent our observation that almost a third of non-WNT/non-SHH activated MB tumors intraoperatively arose from the brainstem. Although our findings elucidate the fact that a tumor originating from the vermis is highly predictive (73%) of non-WNT/non-SHH MB, vermian MB may also belong to the WNT-MB or SHH-MB.

**How does the neurosurgical observation complement the neuroradiological review?**

In the neuroradiological review of Patay et al, 8/16 (50%) WNT-MB showed a paramedian midline growth [13]. Based on this observation they speculated that these tumors do not originate from the vermis but the ventricular lateral recess lacking any intraoperative information that could possibly support this speculation, but corroborating the current developemental cell lineage concept [13]. Challenging this suggestion, the direct intraoperative inspection in our study clearly revealed that 60% of WNT-MB arose from the vermis or the cerebellar hemisphere. The ambiguous neuroradiological results given in the literature further support this notion [5]. Advanced imaging techniques combined with a radio-omics approach might enable more reliable prediction in the future. To date, the most comprehensive study using a radio-omics approach identified the relation of the tumor to the brainstem as a discriminating feature to predict the molecular group [18]. While the mean AUC for predicting WNT tumors using T2-weighted images was acceptable (0.72), there were large institutional differences in performance suggesting that more training samples of the WNT group are needed before a radio-omics approach can deliver generalizable results that may or may not support the current developemental cell lineage concept [18]. Therefore, we assume that the preoperative assessment based on neuroradiological review alone may misinterpret the site of origin and that the intraoperative evaluation may possibly serve as standard of reference to delineate the tumor origin more precisely.

**Clinical and surgical implications**
The findings of our study provide evidence of an insufficient predictive accuracy of the neurosurgical perspective to correctly detect the molecular group based on the presumed tumor origin: Only 21% of all tumors which had been intraoperatively observed to originate from the brainstem were WNT-MB according to the molecular analysis. The remaining 79% of tumors arising from the brainstem were non-WNT/non-SHH activated MB which are generally associated with poorer overall and progression-free survival [41]. Therefore, we conclude that for now, maximal safe gross-total resection should remain the aim of surgery irrespective of the observed STO. In compliance with our experience, it seems not possible to reliably identify a WNT-MB intraoperatively based on a brainstem STO as developmental gene expression data would suggest. Consequently, despite the favorable progression-free and overall survival rates of WNT-MB, subtotal resection in favor of a good neurological outcome is not justified based on neurosurgical assessments. To enable a correct diagnosis intraoperatively and define the appropriate neurosurgical strategy, it will be of utmost importance to advance the development of robust and sensitive methods of intraoperative genetic methylation classification [42]. A deeper understanding of the classification of MB based on their cellular origin might have therapeutic implications and prognostic value [29]. Thus, the present study also provides additional evidence that encourages a more controversial discussion of the concept of distinct MB group-specific cellular origins among basic researchers, neuro-oncologists, neuroradiologists, and neurosurgeons.

**Limitations**

The main limitation of the study is due to the inherent nature of retrospective analyses. While we included patients with sufficient intraoperative documentation only, the neurosurgical classification was based on retrospective evaluations of surgical reports and operative videos. Despite the attempt to be as systematic as possible in these evaluations, our results – especially with regard to the differentiation between the STO and the sites of secondary infiltration – are certainly prone to subjectivity. However, this situation is commonly encountered in neurosurgical practice and reflects a real-life scenario.

**Conclusions**

Our findings challenge the current concept of the molecular group-specific origins based on developmental gene expression data and neuroradiological STO definitions. In our series of 58 well-documented cases, the intraoperative assessment of the STO could not reliably predict the molecular group. This discordance should be critically discussed among basic researchers, neuro-oncologists, neuroradiologists and neurosurgeons. The current evidence does still not allow for intraoperative group-specific risk stratification that would enable tailoring the neurosurgical strategy to the prognostic profile of the patient.

**Declarations**

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**Competing Interests** The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions** C.D. and T.C. contributed to study conception and design. Material preparation and data collection was carried out by O.C.C, C.D., G.K., J.F., M.K., M.S., J.G., A.C. and C.H.. Statistical analyses were performed by O.C.C. Figures 1-2 were prepared by O.C.C. and C.D. The study was supervised by C.D., T.C. and K.R.. The first draft of the manuscript was written by O.C.C., C.D. and J.M.F. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Medical University of Vienna (EK 1476/2021).

**Consent to participate** Written informed consent was obtained from the parents.

**Consent to publish** The authors affirm that human research participants provided informed consent for publication of the images in Figure 1.

**References**


Figures

Figure 1

Illustrative case of a WNT-MB with vermian origin defined by intraoperative inspection a Intraoperative overview of the vermis (*), cerebellar hemispheres (**), tumor (***), and brainstem (****). The MB is replacing the nodulus of the vermis with the pial surface covering the tumor border per continuitatem, meaning that the vermian pial vessels continue over the tumor surface (^) b The same MB is lifted upwards with a dissector by the surgeon demonstrating that the MB is not infiltrating the floor of the IV.ventricle (**) let alone originating from it.
Figure 2

Distribution of intraoperatively assessed sites of origin dependent on their allocation to the molecular subgroups WNT, SHH and Group 3 and Group 4