·小儿神经外科·

基于分子分型的个体化治疗在儿童髓母细胞瘤治疗中的应用

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【摘要】 **目的**　探讨基于肿瘤分子分型的个体化治疗在儿童髓母细胞瘤治疗中的临床价值。**方法**　2017年12月至2019年12月共23例髓母细胞瘤患儿均予手术切除并经术后病理检查证实诊断，并行肿瘤基因检测，根据肿瘤分子分型进行术后5年生存率风险分层并予以个体化放化疗，记录肿瘤切除率、术后并发症、对放化疗的反应以及肿瘤复发情况。**结果**　23例髓母细胞瘤患儿分子分型为WNT型3例、SHH型7例、Group3型5例和Group4型8例，基于上述分子分型，风险分层为低危组（5例）、标危组（8例）、高危组（5例）和极高危组（5例）。肿瘤全切除20例，次全切除3例。术后3例脑积水加重，2例出现小脑缄默，3例出现呛咳、面瘫等神经系统症状，经对症治疗后缓解。根据风险分层术后辅以相应放化疗方案。术后平均随访（15.15±3.45）个月，低危组和标危组放化疗耐受程度较强，未见肿瘤复发；高危组和极高危组放化疗后出现明显骨髓抑制和消化道症状，经对症治疗后缓解，高危组有2例、极高危组有3例肿瘤复发。**结论**　根据髓母细胞瘤的分子分型进行风险分层更加精准，基于该分子分型的个体化治疗方案可以避免临床过度治疗或治疗不足，值得临床推广。

【关键词】 髓母细胞瘤；　儿童；　基因分型技术；　精准医学

Application of individualized therapy based on molecular classification in the treatment of medulloblastoma in children

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【**Abstract**】 **Objective**　To explore the clinical efficacy of individualized therapy based on molecular classification in the treatment of medulloblastoma in children. **Methods**　The clinical data of 23 children with medulloblastoma confirmed by pathology after surgery from December 2017 to December 2019 were analyzed retrospectively. The 5-year survival rate risk was stratified according to tumor molecular classification, and individualized chemoradiotherapy were given. Chemoradiotherapy response, postoperative complications and tumor recurrence were recorded. **Results**　There were 23 cases of medulloblastoma. The tumor molecular genes were classified as WNT type 3 cases, SHH type 7 cases, Group3 type 5 cases and Group4 type 8 cases. The patients were divided into 4 groups according to the results of molecular classification as risk factors: low risk group (n = 5), standard risk group (n = 8), high risk group (n = 5) and very high risk group (n = 5). Total tumor resection was performed in 20 cases, subtotal resection in 3 cases. Three cases with hydrocephalus aggravated after surgery, 2 cases with cerebellar silence, 3 cases with cough paralysis and other neurological symptoms, which were relieved after symptomatic treatment. Individualized treatment (radiotherapy + chemotherapy) was carried out according to the risk stratification. The mean postoperative follow-up period was (15.15 ± 3.45) months. The tolerance of radiotherapy and chemotherapy in the low risk group and the standard risk group was strong, and no tumor recurrence was observed. After radiotherapy and chemotherapy, the high risk group and the very high risk group showed obvious bone marrow suppression and gastrointestinal symptoms, which were relieved after symptomatic treatment, and there were 2 cases in the high risk group and 3 cases in the very high risk group occuring tumor recurrence. **Conclusions**　The risk stratification based on molecular classification is more accurate, and

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the individualized therapy could avoid excessive or insufficient clinical treatment, which is worthy of clinical promotion.

【Key words】 Medulloblastoma; Child; Genotyping techniques; Precision medicine

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髓母细胞瘤是儿童最为常见的中枢神经系统恶性肿瘤，是导致儿童脑肿瘤死亡的主要原因，以外科手术辅以术后放化疗的综合方案为其主要治疗方法，经此治疗后患儿长期生存率可达60%～70%[1-2]。在2016年WHO中枢神经系统肿瘤分类第四版修订版中，髓母细胞瘤分为4个分子亚型，即WNT型、SHH型、Group3型和Group4型。基于上述分子分型，将肿瘤术后5年生存率的风险分层分为低危组（生存率＜90%）、标危组（生存率75%～90%）、高危组（生存率50%～75%）、极高危组（生存率＜50%，表1）[3]，并根据新的风险分层制定个体化治疗方案（表2）[4-7]。复旦大学附属儿科医院近2年收治23例髓母细胞瘤患儿，基于其分子分型进行风险分层并采取个体化治疗，取得一定疗效，以期为临床改善髓母细胞瘤患儿预后提供参考。

对象与方法

一、研究对象

1. 纳入标准 （1）术前完善头部CT和（或）MRI检查，明确颅后窝实性占位性病变，并经术后病理证实为髓母细胞瘤。（2）年龄＜16岁。（3）所有患儿监护人均对手术方案和风险知情并签署知情同意书。（4）本研究经复旦大学附属儿科医院道德伦理委员会审核批准。

2. 排除标准 （1）术前头部CT和（或）MRI显示颅后窝囊实性占位性病变。（2）颅后窝实性占位性病变切除术后经病理排除髓母细胞瘤诊断。

3. 一般资料 选择2017年12月至2019年12月在我院神经外科行手术切除并经术后病理证实的髓母细胞瘤患儿共23例，男性16例，女性7例；年龄2～10岁，平均（5.45±2.15）岁；病程12～78 d，平均为（20.25±6.05）d；临床表现为头痛、呕吐等颅内高压（15例）和步态不稳等共济失调症状（8例）。术前头部CT显示颅后窝稍高密度混杂肿物，其中2例可见不同程度钙化；头部和脊椎MRI显示颅后窝边界相对清晰的肿物，T_1WI呈低信号、T_2WI呈高信号，增强扫描肿物明显强化。肿瘤最大径3.55～6.68 cm，平均（5.15±1.20）cm；肿瘤位于小脑蚓部14例，小脑半球7例，脑桥小脑角区2例；肿瘤发生脊髓播散2例次，合并不同程度幕上脑室扩张17例次，脑室旁水肿13例次。

二、研究方法

1. 手术治疗 （1）脑积水分流术：本组有13例患儿因头痛、呕吐等颅内高压症状明显，术前先行脑积水分流术，其中5例行脑室-腹腔分流术、8例行脑室外引流术。（2）肿瘤切除术：13例术前行脑积水分流术的患儿颅内高压症状缓解、病情平稳后，以及10例术前未行脑积水分流术的患儿均行颅后窝实性占位性病变切除术。患儿俯卧位，气管插管全身麻醉，有6例肿瘤位于小脑半球的患儿行经枕下旁正中入路，余17例肿瘤位于颅后窝的患儿行经枕下正中入路，常规颅后窝骨瓣开窗，“Y”形剪开硬脑膜，切开小脑蚓部，显露肿瘤，先瘤内减压，再分离肿瘤周围，最后完整切除肿瘤，若肿瘤粘连严重可部分残留，术中注意保护重要神经血管以及脑干等重要结构。

2. 基因检测 本组23例患儿均经术后病理证实为髓母细胞瘤（WHOⅣ级）。进一步进行肿瘤分子基因检测。将手术留取的新鲜肿瘤标本大小约为5 mm×5 mm×5 mm，置于含RNAlater保护液的组织保存管中，送检北京泛生子基因科技有限公司，采用高通量第二代测序技术（NGS）行基因检测。结果显示，WNT型3例，SHH型7例，Group3型5例，Group4型8例。

3. 放化疗方案 根据肿瘤分子分型结果，低危组5例、标危组8例、高危组5例、极高危组5例。各风险分层组均于术后3～4周接受个体化放化疗方案。（1）放射治疗：年龄＜3岁和分子分型为SHH型伴*TP53*基因突变的患儿，无需放射治疗而直接药物化疗。年龄≥3岁和其他分子分型的患儿，先行放射治疗，低危组和标危组患儿接受全脑和全脊髓照射（23.40 Gy），颅后窝肿瘤部位增加照射剂量，总剂

表1 基于髓母细胞瘤分子分型的术后5年生存率风险分层方案[3]

Table 1. Risk stratification project of 5-year survival rate after surgery based on molecular classcification of medulloblastoma[3]

分子分型	低危组(生存率<90%)	标危组(生存率75%~90%)	高危组(生存率50%~75%)	极高危组(生存率<50%)
WNT型	无肿瘤转移	无	无	无
SHH型	无	无肿瘤转移、*TP53*野生型、无*MYCN*基因扩增	肿瘤转移、*TP53*野生型,或无肿瘤转移但伴*MYCN*基因扩增	*TP53*突变型
Group3型	无	无肿瘤转移、无*MYC*基因扩增	无	肿瘤转移、伴*MYC*基因扩增
Group4型	无肿瘤转移但伴第11号染色体缺失	无肿瘤转移、无第11号染色体缺失	肿瘤转移	无

表2 根据髓母细胞瘤风险分层制定的个体化治疗方案[4-7]

Table 2. Individualized treatment based on the new risk stratification of medulloblastoma[4-7]

风险分层	手术切除	放射治疗		药物化疗
		<3岁或SHH型伴*TP53*基因突变	≥3岁	
低危组	最大程度手术切除肿瘤,保留重要神经功能,必要时可残留肿瘤	无	全脑和全脊髓照射剂量为23.40 Gy,颅后窝增加照射剂量,总剂量为54.00~55.80 Gy	顺铂+长春新碱+环磷酰胺联合化疗6个疗程
标危组				顺铂+长春新碱+环磷酰胺联合化疗8个疗程
高危组				顺铂+长春新碱+环磷酰胺+依托泊苷联合化疗10个疗程
极高危组				顺铂+长春新碱+环磷酰胺+依托泊苷+大剂量甲氨蝶呤联合化疗10个疗程

量为54.00~55.80 Gy;高危组和极高危组予全脑和全脊髓照射(36.00~39.60 Gy),颅后窝肿瘤部位增加照射剂量,总剂量54.00~55.80 Gy。(2)药物化疗:放射治疗结束后3~4周开始药物化疗。低危组予顺铂(75 mg/m^2,第1天)+长春新碱(1.50 mg/m^2,第1、7和14天)+环磷酰胺(1000 mg/m^2,第21~22天)的联合化疗方案,28 d为一疗程,共治疗6个疗程;标危组患儿采用同样化疗方案,共治疗8个疗程;高危组患儿在该化疗方案的基础上加用依托泊苷(2.50 mg/kg,第1~3天),加强化疗10个疗程;极高危组患儿在高危组化疗方案的基础上加用大剂量甲氨蝶呤(5 g/m^2,第1~2天)加强化疗10个疗程(表2)。

4.观察指标 术后观察肿瘤切除率并记录术后并发症(如脑积水、小脑缄默、神经系统症状等);个体化放化疗后观察患儿对放化疗的耐受程度并记录放化疗不良反应(如骨髓抑制和消化道症状等);术后每3个月随访头部增强MRI、每6个月随访头部和全脊椎增强MRI,观察有无肿瘤复发和转移。

结 果

本组23例患儿中20例肿瘤全切除,3例肿瘤次全切除(残留体积<1.50 cm^3)。术后3例患儿脑积水加重,再次行脑室-腹腔分流术,颅内高压症状缓解;2例出现小脑缄默,未予特殊治疗,2~3个月后症状自行缓解;3例出现呛咳、面瘫等神经系统症状,康复治疗3~5个月后症状缓解。放化疗期间,低危组和标危组患儿对化疗方案耐受性较强,骨髓抑制和消化道症状不明显;高危组和极高危组患儿药物化疗后出现明显的骨髓抑制(血红蛋白、白细胞计数和血小板计数下降)以及恶心、呕吐等消化道症状,皮下注射重组人粒细胞因子2~5 μg/kg增加白细胞数目、头孢曲松80 mg/kg预防感染和输血(红细胞悬液和血小板悬液1 U)支持治疗,均缓解。

术后随访3个月至2年,平均(15.15±3.45)个月。低危组和标危组未见肿瘤复发(图1)。高危组有2例分别于术后8和14个月肿瘤复发,1例二次手术切除复发肿瘤,再予以极高危组化疗方案,即顺铂+长春新碱+环磷酰胺+依托泊苷+大剂量甲氨蝶呤联合化疗10个疗程;1例放弃治疗,死亡。极高危组有3例肿瘤复发,2例于术后2和3个月因复发和广泛脑脊液播散,死亡;1例于术后1年复发,放弃治疗,死亡(图2)。

讨 论

髓母细胞瘤是儿童最常见的恶性脑肿瘤,约占儿童中枢神经系统肿瘤的20%。虽然髓母细胞瘤患儿的术后生存率显著升高,但现有的治疗策略往往忽略患儿的个体差异,如何利用患儿的个体差异进行更精准的治疗,从而减少不良反应、改善患儿

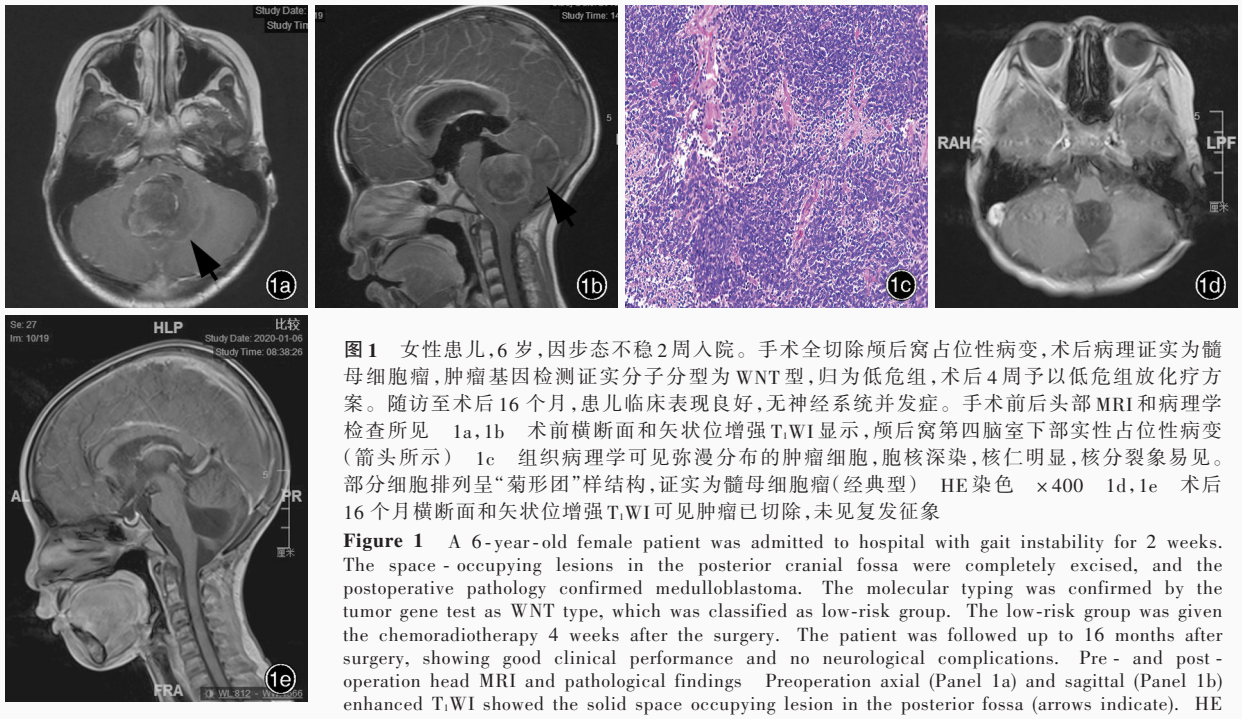

图1 女性患儿，6岁，因步态不稳2周入院。手术全切除颅后窝占位性病变，术后病理证实为髓母细胞瘤，肿瘤基因检测证实分子分型为WNT型，归为低危组，术后4周予以低危组放化疗方案。随访至术后16个月，患儿临床表现良好，无神经系统并发症。手术前后头部MRI和病理学检查所见 1a，1b 术前横断面和矢状位增强T_1WI显示，颅后窝第四脑室下部实性占位性病变（箭头所示） 1c 组织病理学可见弥漫分布的肿瘤细胞，胞核深染，核仁明显，核分裂象易见。部分细胞排列呈"菊形团"样结构，证实为髓母细胞瘤（经典型） HE染色 ×400 1d，1e 术后16个月横断面和矢状位增强T_1WI可见肿瘤已切除，未见复发征象

Figure 1 A 6-year-old female patient was admitted to hospital with gait instability for 2 weeks. The space-occupying lesions in the posterior cranial fossa were completely excised, and the postoperative pathology confirmed medulloblastoma. The molecular typing was confirmed by the tumor gene test as WNT type, which was classified as low-risk group. The low-risk group was given the chemoradiotherapy 4 weeks after the surgery. The patient was followed up to 16 months after surgery, showing good clinical performance and no neurological complications. Pre- and post-operation head MRI and pathological findings Preoperation axial (Panel 1a) and sagittal (Panel 1b) enhanced T_1WI showed the solid space occupying lesion in the posterior fossa (arrows indicate). HE staining showed diffuse distribution of tumor cells, hyperchromatic nuclei, and obvious nucleoli. The mitotic figures were common to see. Some cells were arranged in "chrysanthemum-shaped" cluster, indicated classical type medulloblastoma (Panel 1c). × 400 Sixteen months after surgery, axial (Panel 1d) and sagittal (Panel 1e) enhanced T_1WI showed no recurrence.

预后，成为目前研究方向。

随着分子技术的不断发展，2016年WHO中枢神经系统肿瘤分类第四版修订版将髓母细胞瘤分为4种分子亚型，即WNT型、SHH型、Group3型、Group4型。WNT型最为罕见，约占全部髓母细胞瘤的10%，好发于儿童和青少年，*CTNNB1*基因的稳定突变是最常见的遗传改变[8]。该亚型较少发生肿瘤转移，预后优于其他亚型。SHH型在婴儿期和青春期发病率最高，约占30%，通常发生于小脑半球外侧，约20%的患儿确诊时已发生转移[9]。该亚型在髓母细胞瘤中胚系突变发生率最高，常见*TP53*基因突变，易并发多种家族性肿瘤（Li-Fraumeni综合征，包括软组织肉瘤、乳腺癌、脑肿瘤、白血病等），且生存率较低[10]。Group3型约占全部髓母细胞瘤的25%，仅发生于婴儿和儿童，该亚型预后最差，常伴肿瘤转移扩散，*MYC*基因扩增可导致预后不良[11]。Group4型约占全部髓母细胞瘤的35%[12]，可发生于所有年龄阶段，总体预后中等，但潜在的发病机制尚不清楚，起源细胞亦未确定。本组患儿的分子分型为WNT型3例（13.04%）、SHH型7例（30.43%）、Group3型5例（21.74%）、Group4型8例（34.78%），与相关文献报道的各分子分型比例相近[8-9,11-12]。

传统观点认为，根据确诊年龄、脑脊液播散和肿瘤切除程度，可以将髓母细胞瘤分为标危组和高危组[13-14]。2016年，Ramaswamy等[3,15]提出一种基于肿瘤分子分型的新的风险分层方案（表1），主要以术后5年生存率为定义标准并考虑疾病异质性和分子亚群信息，分为4个风险分层组，即极高危组（生存率<50%）、高危组（生存率50%～75%）、标危组（生存率75%～90%）和低危组（生存率>90%）。转移性Group3型伴*MYC*基因扩增和SHH型伴*TP53*基因突变的患儿预后较差，应归入极高危组；转移性或*MYCN*基因扩增的SHH型和Group4型伴脑脊液播散的患儿，为高危组；无*MYCN*基因扩增和无*TP53*基因突变的SHH型、无*MYC*基因扩增的Group3型和无第11号染色体缺失的Group4型患儿，归入标危组；非转移性WNT型和非转移性Group4型患儿，为低危组。

根据新的风险分层，髓母细胞瘤患儿先常规手术切除肿瘤。手术目的是最大程度降低颅内压，在不引起严重神经系统并发症的前提下，尽可能多地切除肿瘤。研究显示，基于现有的肿瘤分子分型，手术切除程度与术后生存率无关联性[16-17]。本组23例患儿中3例因肿瘤与脑干粘连严重，予次全切

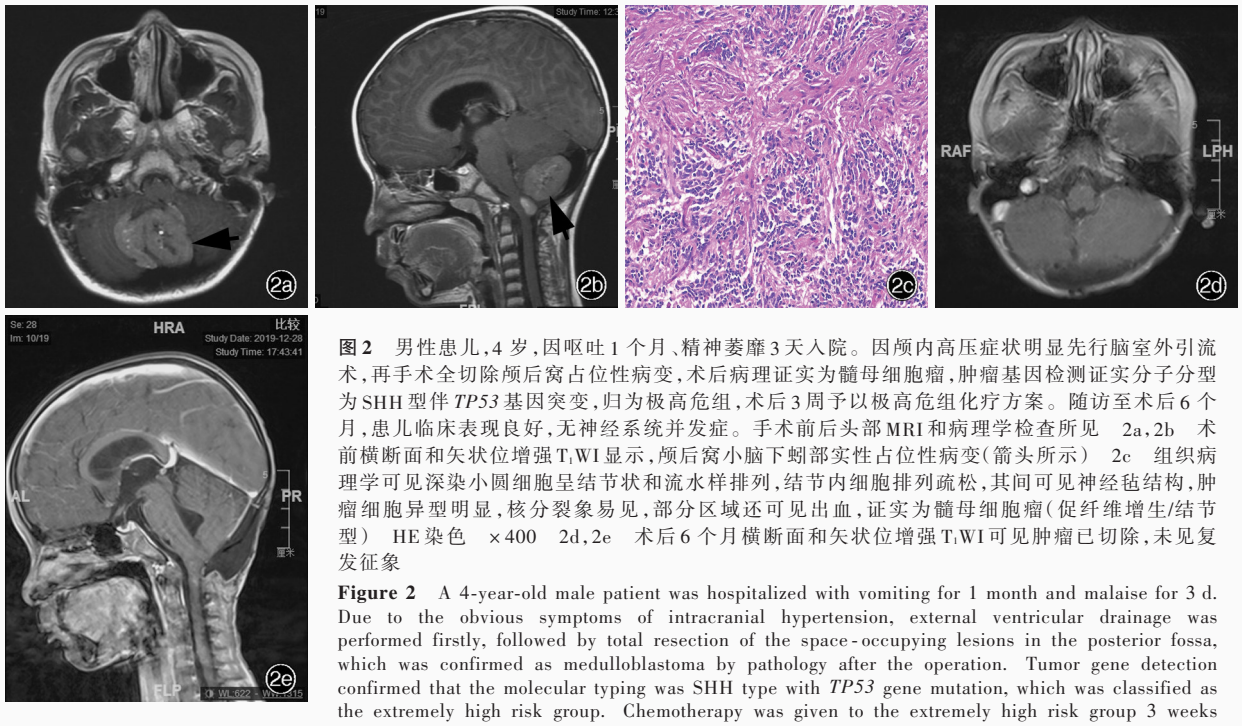

图2　男性患儿，4岁，因呕吐1个月、精神萎靡3天入院。因颅内高压症状明显先行脑室外引流术，再手术全切除颅后窝占位性病变，术后病理证实为髓母细胞瘤，肿瘤基因检测证实分子分型为SHH型伴*TP53*基因突变，归为极高危组，术后3周予以极高危组化疗方案。随访至术后6个月，患儿临床表现良好，无神经系统并发症。手术前后头部MRI和病理学检查所见　2a，2b　术前横断面和矢状位增强T_1WI显示，颅后窝小脑下蚓部实性占位性病变（箭头所示）　2c　组织病理学可见深染小圆细胞呈结节状和流水样排列，结节内细胞排列疏松，其间可见神经毡结构，肿瘤细胞异型明显，核分裂象易见，部分区域还可见出血，证实为髓母细胞瘤（促纤维增生/结节型）　HE染色　×400　2d，2e　术后6个月横断面和矢状位增强T_1WI可见肿瘤已切除，未见复发征象

Figure 2　A 4-year-old male patient was hospitalized with vomiting for 1 month and malaise for 3 d. Due to the obvious symptoms of intracranial hypertension, external ventricular drainage was performed firstly, followed by total resection of the space-occupying lesions in the posterior fossa, which was confirmed as medulloblastoma by pathology after the operation. Tumor gene detection confirmed that the molecular typing was SHH type with *TP53* gene mutation, which was classified as the extremely high risk group. Chemotherapy was given to the extremely high risk group 3 weeks after the operation. The patient was followed up to 6 months after the operation, showing good clinical performance and no neurological complications. Pre- and post-operation head MRI and pathological findings　Pre-operation axial (Panel 2a) and sagittal (Panel 2b) enhanced T_1WI showed the solid space occupying lesion in the posterior fossa (arrows indicate). HE staining showed hyperchromatic small round cells were arranged in a nodular and fluid-like manner, and the cells in the nodules were arranged loosely, during which the nerve flet structure could be seen. The tumor cells were clearly shaped and the mototic figures were common to see, and bleeding was also seen in some areas, confirmed fibrogenic/nodulartype medulloblastoma (Panel 2c).　×400　Six months after surgery, axial (Panel 2d) and sagittal (Panel 2e) enhanced T_1WI showed no recurrence.

除肿瘤致部分残留，1例肿瘤复发致死亡，2例未见肿瘤复发和转移。

通常术后3～4周开始放射治疗，延迟放射治疗有可能降低术后生存率[18]。研究显示，年龄＜3岁或SHH型伴*TP53*基因突变的患儿不宜放射治疗，这是由于放射治疗可引起神经内分泌功能障碍或继发肿瘤再次生长[7,19]。年龄≥3岁的低危组和标危组患儿接受全脑和全脊髓放射治疗，照射剂量为23.40 Gy，颅后窝肿瘤部位照射剂量增加，总剂量为54.00～55.80 Gy；高危组和极高危组患儿接受全脑和全脊髓放射治疗，照射剂量为36.00～39.60 Gy，颅后窝肿瘤部位照射剂量增加，总剂量达54.00～55.80 Gy[19]。

药物化疗是术后标准辅助治疗方案，可以提高生存率，尤其对于不能放射治疗的患儿，药物化疗尤为重要[6]。低危组患儿予以6个疗程的顺铂＋长春新碱＋环磷酰胺联合化疗；标危组将该化疗方案延长至8个疗程；高危组在该化疗方案的基础上加用依托泊苷，加强化疗10个疗程；极高危组在高危组化疗方案的基础上再加用大剂量甲氨蝶呤，必要时行鞘内化疗[20-22]。低危组和标危组患儿对药物化疗方案的耐受性较强，骨髓抑制不明显；高危组和极高危组患儿药物化疗后出现明显的骨髓抑制，表现为血红蛋白、白细胞计数和血小板计数下降，皮下注射重组人粒细胞因子2～5 μg/kg增加白细胞数目、头孢曲松80 mg/kg预防感染和输血（红细胞悬液和血小板悬液1 U）支持治疗，均缓解。高危组和极高危组患儿总体治疗时间较低危组和标危组明显延长。

随访期间，低危组和标危组患儿预后良好，复查MRI未见肿瘤复发征象。高危组有2例分别于术后8和14个月肿瘤复发，1例放弃治疗，死亡；1例二次手术切除复发肿瘤，再予以极高危组化疗方案，即顺铂＋长春新碱＋环磷酰胺＋依托泊苷＋大剂量甲氨蝶呤联合化疗10个疗程。极高危组有2例分别于术后2和3个月因肿瘤复发和广泛脑脊液播散死亡，1例术后1年肿瘤复发，放弃治疗而死亡。尽管本研究随访时间较短，不能完全评估预后，但就

目前的治疗随访结果看，低危组和标危组对治疗耐受性较强，无明显神经功能障碍，预后良好，随访中无肿瘤复发和转移病例。高危组和极高危组虽然放化疗剂量较大、疗程较长、不良反应较多，但患儿多可耐受，总体疗效较好[23-24]。

综上所述，基于肿瘤分子分型的个性化治疗更加具有针对性，可以减少治疗相关不良反应，值得临床推广。尽管髓母细胞瘤的临床治疗取得了良好进展，而肿瘤转移和复发仍是儿童髓母细胞瘤死亡的主要原因，针对此类患儿，靶向治疗可能是新的治疗方向，尚待进一步探究。

利益冲突 无

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·小词典·

中英文对照名词词汇（四）

微小RNA　microRNA（miRNA）
无进展生存期　progression free survival（PFS）
无事件生存率　eventfree survival（EFS）
戊型肝炎病毒　hepatitis E virus（HEV）
细胞角蛋白　cytokeratin（CK）
细胞外基质　extracellular matrix（ECM）
细胞周期素D2　cyclin D2（CCND2）
线粒体DNA　mitochondrial DNA（mtDNA）
线粒体脑肌病　mitochondrial encephalomyopathy（ME）
线粒体脑肌病伴高乳酸血症和卒中样发作
mitochondrial encephalomyopathy with lactic academia and stroke-like episodes（MELAS）
腺苷脱氨酶　adenosine deaminase（ADA）
效应性T细胞　effector T cell（Teff）
心源性栓塞　cardioembolism（CE）
信号传导与转录激活因子6
signal transducer and activator of transcription 6（STAT6）
Ⅰ型单纯疱疹病毒　herpes simplex virus-1（HSV-1）
虚拟现实　virtual reality（VR）
血管周围间隙　perivascular spaces（PVS）
［Virchow-Robin间隙　Virchow-Robin spaces（VRS）］
循环肿瘤细胞　circulating tumor cells（CTCs）