Background: The current prognosis of medulloblastoma in children is better because of technological advancements and improvements in treatment strategies and genetic investigations. However, there is a lack of studies that focus on medulloblastoma in Thailand. The aims of our study were to conduct a survival analysis and to identify the prognostic factors of pediatric medulloblastoma.

Materials and Methods: Fifty-five children, with medulloblastoma, were eligible for analysis between 1991 and 2015. We retrospectively reviewed both the clinical and the histological data. Survival curves were constructed using the Kaplan–Meier method. For comparisons of dichotomous factors, between groups, the log-rank test was used to determine survival. The Cox proportional hazard regression model was used to identify the univariate and multivariate survival predictors.

Results: The mortality rate was 49.1% in this study. The median follow-up time was 68.8 months (range: 1–294 months). The 5-year overall survival rate and median survival time were 53.8% (95% CI 38.7–66.7) and 80 months (95% CI 23–230), respectively. Univariate analysis revealed children <3 years of age, hemispheric tumor location, high risk according to risk stratification, and patients who did not receive radiation therapy affected the prognosis. In multivariable analysis, hemispheric tumors (hazard ratio [HR] 2.54 [95% CI 1.11–5.80]; P = 0.01) and high risk groups (HR 3.86 [95% CI 1.28–11.60]; P = 0.01) influenced death. Finally, using conditional inference trees, the study showed that hemispheric tumor locations are truly aggressive in behavior, whereas risk stratification is associated with the prognosis of midline tumors.

Conclusions: Hemispheric medulloblastoma and high-risk groups according to risk stratification were associated with poor prognosis.

Keywords: Brain tumor, conditional inference trees, medulloblastoma, outcome

INTRODUCTION

Medulloblastoma is a malignant tumor, which frequently arises within the cerebellum. This type of tumor is one of the most common brain tumors occurring in children. The incidence in children varies from 4.0 to 4.9 per 1,000,000 person per year. Medulloblastoma is classified as grade IV in the World Health Organization classification because of its aggressive behavior. Unfortunately, the tumor tends to metastasize through the subarachnoid space. Thirty-two percent of patients showed cerebrospinal fluid (CSF) dissemination at diagnosis.

Various factors have been studied to identify significant prognostic factors such as age, staging of disease, risk stratification, and molecular biology. The risk stratification system is classified by significant factors such as age and residual tumor along with metastasis, which are generally grouped into two groups. The
high-risk group has a significantly poorer prognosis than that of the average-risk group.\cite{9} Within the histology, the desmoplastic variant is correlated with a better outcome compared to that of the others.\cite{6} Furthermore, the current consensus on molecular subgroups of medulloblastoma is that there are four molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4.\cite{7} In children, as well as adults, WNT tumors clearly have the best outcome compared with others. The WNT tumor was reported to have a 5-year overall survival (OS) time of 95% and 100% in children and adults, respectively.\cite{8} The treatment of medulloblastoma is carried out by a multidisciplinary management team that includes surgeons, radiologists, and chemotherapists. Currently, the treatment paradigm following risk stratification has improved the survival rate.\cite{6}

Three articles in the literature from Thailand have focused on medulloblastoma. In 1974, Shuangshoti and Panyathanya\cite{9} reported that about one-fourth of tumors occurred in children, and medulloblastoma was the second most common posterior fossa tumor. Janjindamai et al.\cite{10} studied the clinical characteristics of primary brain tumors in children in 1997. Subsequently, medulloblastomas were found in 14.5% of posterior fossa tumors.\cite{10} In 2011, Sirachainan et al.\cite{11} reported the outcomes of medulloblastoma in children treated with reduced-dose radiation therapy coupled with adjuvant chemotherapy. The average-risk group had a 5-year survival rate, which was better than the high-risk group (70.4% vs. 49.7%).\cite{11} The aims of our study were to identify the factors that intervene with the outcomes.

**Subjects and Methods**

**Study population**

The medical records of children younger than 15 years and diagnosed with medulloblastoma at our institute over a period of 24 years (January 1, 1991, to September 16, 2015) were retrieved for the study. The inclusion criteria were all patients categorized into average- or high-risk groups according to the risk stratification.\cite{4} Patients who had lost medical records, preoperative size, residual tumor size, and other characteristics of medulloblastoma were reviewed by two neurosurgeons. The locations of the tumors were then categorized into two groups. The midline group described the medulloblastomas at the vermis, or when the center of the tumor was clearly identified at the midline in at least two plains of magnetic resonance imaging (MRI). The other tumors were grouped into a non-midline category (Figure 1).

Several ways to assess the extension of the disease included an MRI of the brain for intracranial leptomeningeal seeding, an intraoperative finding of leptomeningeal seeding, CSF cytology, whole-spinal MRI, bone marrow aspiration, and plain chest film. M0 was defined as negative studies on the whole-spinal MRI, or microscopic examination of CSF cytology according to the risk stratification.\cite{4} Finally, the living status of the patients was assessed from the civil registration database.

**Statistical analysis**

The mean, with standard deviation, was calculated for descriptive purposes. Survival curves were constructed using the Kaplan–Meier method. For comparisons of dichotomous factors between groups, the log-rank test was used to determine the prognostic value for survival. The Cox proportional hazard regression model was used to identify the univariate and multivariate predictors of survival. In multivariate analysis, stepwise regression was used to check whether factors deserved to be included in the model. A P-value of less than 0.05 was considered as statistically significant and all tests were two tailed. The statistical analysis was performed using the R version 3.4.0 software (R Foundation, Vienna, Austria). In addition, the package coin was used for the function of survival test\cite{12} and the package partykit was used for creating conditional inference trees.\cite{13}

**Results**

**Patient characteristics**

The baseline characteristics of the patients are presented in Table 1. The mean age of the study population was 7.05 (±3.9) years. The percentage of male patients was 54.5%. Two-thirds of the patients (67.2%) had increased
intracranial pressure symptoms. Cerebellar impairment was found in 23.6% of the patients.

The tumor characteristics are described in Table 1. From the histology, most of the medulloblastomas in this study were of a classical subtype (87.3%). The other subtypes were desmoplastic (7.3%), medulloblastoma with other differentiation (3.6%), and large cell/anaplastic (1.8%). The mean diameter of the tumors was 4.6 (±1.2) cm, and 60% of the tumors extended into the aqueduct of Sylvius, foramen of Magendie, and foramen of Luschka. Preoperative hydrocephalus was found in 21.8% of the patients. Most tumors (78.2%) were located in the vermis. Half of the patients were observed with metastasis at diagnosis. Consequently, seven patients had positive CSF cytology. Two patients were observed with gross tumor seeding: one was detected to have intracranial nodular seeding and the other had intracranial leptomeningeal dissemination on a cranial MRI, but had no evidence of spinal metastasis. The whole-spinal MRI was used to evaluate metastatic staging in 54 patients; 17 patients (31.4%) had spinal metastasis. The one patient who was not sent for a whole-spinal MRI had positive CSF cytology.

### Treatment and outcome

Treatment and outcomes are described in Table 2. Microscopic surgery was the first-line management for all patients in this study. However, only 30.9% succeeded in resection of the entire tumor. Therefore, 14 (25.5%) were classified into the average-risk

| Table 1: Baseline characteristics of the medulloblastoma patients |
|---|
| **Factor** | **Medulloblastoma**<br>**(n = 55)** |
| **Sex (%)** | Male | 30 (54.5) |
| Female | 25 (45.5) |
| **Age (years)** | | |
| Mean age (SD) | 7.05 (± 3.9) |
| <3 | 10 (18.2) |
| ≥3 | 45 (81.8) |
| **Clinical presentation** | | |
| Increased intracranial pressure | 37 (67.2%) |
| Headache | 30 (54.5%) |
| Cerebellar signs | 13 (23.6%) |
| Increased head circumference | 4 (7.3%) |
| Alteration of consciousness | 3 (5.5%) |
| Other | 5 (9.1%) |
| **Tumor location** | | |
| Vermis (midline) | 43 (78.2%) |
| Hemisphere | 12 (21.8%) |
| **Preoperative hydrocephalus** | 12 (21.8%) |
| **Histology** | | |
| Classical medulloblastoma | 48 (87.3%) |
| Desmoplastic subtype | 4 (7.3%) |
| Large cell-anaplastic subtype | 1 (1.8%) |
| Medulloblastoma with other differentiation | 2 (3.6%) |
| **Mean tumor size (SD) (cm)** | 4.6 ± 1.2 |
| **Tumor extension** | | |
| Tumor size <3 cm | 2 (3.6%) |
| Tumor size ≥3 cm | 6 (10.9%) |
| Tumor size ≥3 cm with extension into the aqueduct of Sylvius, foramen of Magendie, foramen of Luschka, or tumor cause hydrocephalus | 33 (60.0%) |
| Tumor size ≥3 cm invading brain stem | 8 (14.5%) |
| Tumor size ≥3 cm extending through aqueduct to third ventricle, midbrain, or down past of foramen magnum | 6 (10.9%) |
| **Metastasis** | | |
| No metastasisa | 28/55 (50.9%) |
| Microscopic tumor cells found in CSF | 7/39 (17.9%) |
| Gross seeding in subarachnoid space or ventricle | 2/55 (3.6%) |
| Spinal metastasis | 17/54 (31.4%) |
| Extraneuroaxial metastasisb | 0/55 (0) |

SD = standard deviation

a No metastasis is defined according to postoperative risk stratification and treatment of medulloblastoma; metastatic investigations were MRI of the whole spine or CSF cytology.
b Evaluated via bone marrow aspiration and chest plain film. All were sent for chest plain film, but 23 patients were sent to bone marrow aspiration.

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Figure 1: Axial (A) and sagittal (B) T1-weighted gadolinium-enhanced MRI showing a midline medulloblastoma. Axial (C) and coronal (D) T1-weighted gadolinium-enhanced MRI showing a left hemispheric medulloblastoma
group, whereas 41 patients (74.5%) were in the high-risk group. Postoperatively, adjuvant therapies were considered according to the risk stratification. The percentages of patients who received radiation therapy in addition to chemotherapy were 76.4% and 74.5%, respectively. Thirteen patients (23.6%) refused to have radiation therapy, whereas 14 (25.5%) refused chemotherapy. The mortality rate was 49.1% from this study.

**Survival analysis**

In this study, the mean follow-up time was 68.8 months (range: 1–294 months). The overall median survival time of medulloblastoma was 80 months (95% CI 23–230) [Figure 2]. The 5-year OS rate was 53.8% (95% CI 38.7–66.7). In addition, medulloblastoma at the vermis had a higher 5-year OS rate compared to the other group (60.4% [95% CI 42.7–74.2] vs. 31.2% [95% CI 0.08–57.84]). The 5-year OS rate was 84.4% (95% CI 50.4–95.9) in the average group and 42.8% (95% CI 26.1–58.5) in the high-risk group. In addition, the median survival times of the average- and high-risk groups were 147 and 24 months, respectively.

Using univariate analysis, the significant factors associated with death were children younger than 3 years (hazard ratio [HR] 2.88 [95% CI 1.19–6.95]; \(P = 0.01\)), non-midline location (HR 2.49 [95% CI 0.11–5.58]; \(P = 0.02\)), size of residual tumor ≥1.5 cm\(^2\) (HR 2.49 [95% CI 1.13–5.52]; \(P = 0.02\)), high-risk group (HR 3.50 [95% CI 1.19–10.26]; \(P = 0.02\)), and children who did not receive radiation therapy (HR 2.00 [95% CI 0.87–4.60]; \(P = 0.01\)) [Table 3].

Patients who were ≥3 years had a better survival rate than patients <3 years (log-rank test; \(P = 0.01\)) [Figure 3A]. The survival probability in the older children group (55.0%) was significant compared to the group of younger children (29.0%). Tumor location was one of the significant predictors for vermis tumors, which had a better probability than the non-midline tumors (60.4% vs. 31.2%). The Kaplan–Meier survival curves of the two groups were obviously different (log-rank test; \(P = 0.02\)) [Figure 3B]. In univariate analysis, the size of the residual tumor was an important factor in the prognosis. The group with a residual tumor size ≥1.5 cm\(^2\) had a significantly worse survival probability than the other group with a residual tumor size <1.5 cm\(^2\) (72.9% vs. 37.7%) (log-rank test; \(P = 0.01\)) [Figure 3C]. The 5-year survival rates in the average- and high-risk groups were 84.4% and 42.8%, respectively. Between the two groups, the survival rate was significantly different (log-rank test; \(P = 0.01\)) [Figure 3D].

Independent prognostic factors were identified by multivariable regression analysis (Cox proportional hazards regression model). With backward elimination, significant factors associated with death were both hemispheric tumors (HR 2.54 [95% CI 1.11–5.80]; \(P = 0.01\)) and high-risk group (HR 3.86 [95% CI 1.28–11.60]; \(P = 0.01\)) [Table 3].

With the conditional inference trees (CTree) in Figure 4, tumor location and risk stratification were significant covariates that predicted prognosis for vermis medulloblastoma. Moreover, risk stratification was insignificant in the condition of hemispheric medulloblastoma, which was a very poor prognosis.
Discussion
Because of the lack of information on brain tumors in Thailand, especially on medulloblastoma,[9-11] this study focused on the prognosis and survival of children diagnosed with medulloblastoma within Thailand. Fifty-five patients were enrolled for the analysis. Clinical characteristics were comparable with previous studies.[14,15] Nevertheless, the severity of disease, in our study, tended to be more aggressive. More than half of the patients had metastatic disease compared with previous studies.[15,16] In addition, the mean tumor size was larger than 4 cm in diameter, which is an enormous size to be found in the posterior cranial fossa. Postradiation therapy of meningioma was found in seven patients. Sugden et al.[17] also found that radiation therapy in children increased the risk for meningioma.

Prognosis in our study was parallel compared with previous studies. Sirachainan et al.[11] reported that the 5-year OS rate in children with medulloblastoma was 60.6%, whereas patients in this study had a 5-year OS rate of 53.8%. To the best of our knowledge, this is the first study to identify midline medulloblastoma that was significantly associated with a better prognosis than that of hemispheric tumors. However, Rutkowski et al.[16] reported that hemispheric tumors had a better 8-year OS rate than the midline tumor in univariate analysis although the adjusted HR of this factor was not significant in multivariable analysis.

Recently, Jiang et al.[18] classified medulloblastoma into three groups according to location and fourth-ventricle infiltration. Tumor infiltration to the fourth ventricle was one of the independent prognostic factors, whereas tumor location was insignificant in multivariable analysis.[18] Controversially, tumor localization is still being discussed as to which position of the tumor has a better prognosis. Meanwhile, the implication of tumor location had been linked with molecular pathways. The current

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**Table 3: Cox proportional regression estimating HR for death**

| Factor                        | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                               | HR (95% CI)         | P-value               | HR (95% CI)         | P-value               |
| Sex                           | Ref                 |                       | Ref                 |                       |
| Male                          | 1.14 (0.54–2.41)    | 0.71                  | 2.54 (1.11–5.80)    | 0.01*                 |
| Female                        | Ref                 |                       |                     |                       |
| Age (year)                    | Ref                 |                       | Ref                 |                       |
| ≥3                            | 2.88 (1.19–6.95)    | 0.01*                 |                     |                       |
| <3                            | 0.55 (0.12–2.35)    | 0.42                  |                     |                       |
| Tumor diameter (cm)           | Ref                 |                       | Ref                 |                       |
| <3                            | 2.49 (1.11–5.58)    | 0.02*                 | 2.49 (1.13–5.52)    | 0.02*                 |
| ≥3                            | 1.41 (0.34–3.84)    | 0.82                  |                     |                       |
| Tumor location                | Ref                 |                       | Ref                 |                       |
| Midline                       | 2.49 (1.11–5.58)    | 0.02*                 | 2.54 (1.11–5.80)    | 0.01*                 |
| Non-midline                   | 1.14 (0.34–3.84)    | 0.82                  |                     |                       |
| Histology group               | Ref                 |                       | Ref                 |                       |
| Classical                     | 1.64 (0.63–4.23)    | 0.30                  |                     |                       |
| Nonclassical                  |                      |                       |                     |                       |
| Hydrocephalus                 | Ref                 |                       | Ref                 |                       |
| No                            | 3.50 (1.19–10.26)   | 0.02*                 | 3.86 (1.28–11.60)   | 0.01*                 |
| Yes                           | 2.00 (0.87–4.60)    | 0.10                  |                     |                       |
| Residual tumor (cm²)          | Ref                 |                       | Ref                 |                       |
| <1.5                          | 2.49 (1.13–5.52)    | 0.02*                 |                     |                       |
| ≥1.5                          | 1.60 (0.63–4.07)    | 0.32                  |                     |                       |
| Postoperative risk stratification | Ref               |                       | Ref                 |                       |
| Average                       | 3.50 (1.19–10.26)   | 0.02*                 | 3.86 (1.28–11.60)   | 0.01*                 |
| High                          | 2.00 (0.87–4.60)    | 0.10                  |                     |                       |
| Radiation therapy             | Ref                 |                       | Ref                 |                       |
| Yes                           | 1.60 (0.63–4.07)    | 0.32                  |                     |                       |
| No                            |                      |                       |                     |                       |
| Chemotherapy                  | Ref                 |                       | Ref                 |                       |
| No                            | 1.60 (0.63–4.07)    | 0.32                  |                     |                       |
| Yes                           |                      |                       |                     |                       |

*Statistically significant result*
A consensus is that medulloblastoma has four molecular subtypes (WNT, SHH, group 3, and group 4).\(^{[19]}\) WNT medulloblastoma has the best outcome.\(^{[8,20]}\) Furthermore, Gibson et al.\(^{[21]}\) reported 12 medulloblastomas from a mouse model that had WNT-subtype medulloblastoma that arose from the midline of the brain stem, whereas SHH-subtype medulloblastoma originated from the cerebellar hemisphere.

Although this study has a limitation in molecular data, the significant factor in this study may be the first evidence, which revealed an association between clinical and molecular parameters. As a result, the WNT signaling pathway scheme requires future study. In multivariable analysis, the other independent prognostic factors associated with survival were risk stratification.\(^{[4]}\) In this study, the 5-year OS rates of the average- and high-risk groups were 84.4% and 42.8%, respectively. With treatment strategies, the 5-year OS rates of the average- and high-risk groups were 58%–85% and 32%–70%, respectively.\(^{[11,22-26]}\)

In the literature, several factors in medulloblastoma improved the survival rate such as histology variants, metastasis, and chemotherapy. The limitations were that the number of samples in this study was limited. Numerous patients were omitted because of unavailable preoperative imaging. Histologically, the desmoplastic/nodular variants reported the best prognosis, whereas large cell/anaplastic variants had a poor prognosis.\(^{[27,28]}\) Thus, the majority of the tumors were classical medulloblastoma. Desmoplastic/nodular and large cell variants were also rare. Differences of survival rates between histology variants were insignificant in this study.

Although a retrospective study has limitations, the strength of this study is the fact that we searched for information from computer-based medical records and the civil registration database. Thus, the follow-up duration was extended in this study to a maximum of 24 years from credible databases. Diagnostic genotypes of tumors were limited in the study; however, phenotype and clinical presentation directly related with genetic variations. So, using conditional analysis obviously showed that hemispheric medulloblastomas are truly aggressive in behavior. To the best of the authors’

Figure 3: OS rates of children with medulloblastoma according to prognostic factors using the Kaplan–Meier curves and log-rank tests. (A) Children who were ≥3 years old (solid line) and children who were <3 years old (dashed line). (B) Vermis tumor (dashed line) and hemispheric tumor (solid line). (C) Residual tumor <1.5 cm\(^2\) (solid line) and ≥1.5 cm\(^2\) (dashed line). (D) Average group (solid line) and high-risk group (dashed line)
knowledge, few studies have rarely made mention as to the location of tumors in medulloblastoma.

CONCLUSIONS

In summary, the authors provided results that were comparable with previous studies in tumor localization, which is one of the potential prognostic factors. Interestingly, these results are in concordance with molecular studies showing that WNT-subtype medulloblastomas usually arise at the midline and have a good prognosis.[29] Midline tumors with tumorigenic molecular alterations should be studied prospectively in the future. Likewise, we found different treatment outcomes according to the risk stratification. A prospective study should be able to provide a comprehensive outcome assessment of multidisciplinary management in clinical implications.

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Conflicts of interest

There are no conflicts of interest.

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