*Original Article*

# Clinical Characteristic and Molecular Subgroups of Thai Pediatric Medulloblastomas at Queen Sirikit National Institute of Child Health

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***Objective***: To determine the correlation between clinical characteristics and molecular subgroups of medulloblastoma (MB) in Thai pediatric patients at the Queen Sirikit National Institute of Child Health (QSNICH), Thailand.

***Materials and Methods***: MB specimens operated between 2004 and 2018 were classified by Nanostring into four molecular subgroups, including Wingless signaling pathway (WNT), Sonic Hedgehog signaling pathway (SHH), Group 3, and Group 4. For the present cases, the clinical records were retrospectively analyzed.

***Results***: Twenty-two MB cases with complete clinical records were analyzed. Group 4 was the most common molecular subgroup (31.82%), followed by WNT (27.27%), SHH (22.73%), and Group 3 (18.18%). The histologic subtypes included 18, three, and one cases of classic MB, MB with extensive nodularity (MBEN), and large cell MB, respectively. All SHH MBs were found in infants. All MBENs belonged to SHH subgroup, and the large cell MB was Group 3. All six WNT MB cases did not experience tumor recurrence. Five-year cause specific survival rates were 100% in WNT, 60% in SHH, 57.1% in Group 4, and 0% in Group 3. Five-year recurrence-free survival rates were 100% in WNT, 42.9% in Group 4, and 0% in SHH and Group 3.

***Conclusion***: MB is a heterogeneous disease. Classification of MB, especially at the molecular subtype, is helpful for the management and prognostication.

***Keywords***: Medulloblastoma; Molecular subgroup

Received 24 May 2021 | Revised 27 August 2021 | Accepted 31 August 2021

**J Med Assoc Thai 2021;104(10):1648-57**

**Website:** http://www.jmatonline.com

Medulloblastoma (MB) is the most common malignant pediatric brain tumor, constituting 20% of brain tumors in children[1]. With slight variation observed among regions, the overall global incidence of MB in pediatric group is 0.44/100,000. The incidence rate of MB is highest in the Southern Europe at 0.58/100,000, while it is 0.35/100,000 in the Southeast Asia[2]. In Thailand, the incidence of MB among patients with age between 0 to 19 years is 2.8 per million person-years[3].

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**How to cite this article:**

Tadadontip P, Shuangshoti S. Clinical Characteristic and Molecular Subgroups of Thai Pediatric Medulloblastomas at Queen Sirikit National Institute of Child Health. J Med Assoc Thai 2021;104:1648-57.

doi.org/10.35755/jmedassocthai.2021.10.12989

The classification and treatment of MB have evolved from Chang's classification[4] to the clinical risk stratification system[5,6], which has been adopted worldwide as the standard practice. In 2011, Sirachainan et al reported the result of treatment of Thai MB patients with reduced-dose radiation therapy plus adjuvant chemotherapy. Comparable to the other studies, the 5-year overall survival (OS) rate was 70.4±9.5% and 49.7±13%, respectively, in the average-risk and the high-risk groups[7].

The molecular classification of MB is now playing an important role, and the current consensus of four molecular subgroups of MB that includes Wingless signaling pathway (WNT), Sonic Hedgehog signaling pathway (SHH), Group 3, and Group 4[8]. Thus far, the clinical characteristics and prognosis of MB molecular subgroups were reported from Europe, United States of America, and Canada[8,9], none has been evaluated in the Southeast Asia.

The purpose of the present study was to describe the clinical characteristic of MB, stratified into molecular subtypes, in Thai pediatric patients treated

**Table 1.** Summary of the clinicopathological features and outcome of medulloblastoma

| Molecular subgroups | WNT | SHH | Group 3 | Group 4 | Total | p-value |
|---|---|---|---|---|---|---|
| The number of cases; n (%) | 6 (27.27) | 5 (22.73) | 4 (18.18) | 7 (31.82) | 22 cases | |
| Age at diagnosis | 7 years to 13 years 11 months | 3 months to 2 years 2 months | 3 years to 11 years | 1 year 2 months to 12 years 9 months | 3 months to 13 years 11 months | 0.001 |
| Mean±SD | 9 years 10 months ± 2 years 8 months | 1 year 2 months 18 days ± 9 months 28 days | 7 years 4 months 15 days ± 3 years 3 months 15 days | 7 years 1 month ± 3 years 3 months | 6 years 6 months 24 days ± 4 years 8 months | |
| Median | 9 years 8 months | 1 year 4 months | 7 years 9 months | 7 years 6 months | 7 years 6 months 15 days | |
| Sex (male:female) | 5:1 | 2:3 | 4:0 | 5:2 | 16:6 | 0.208 |
| Number of disseminated case at diagnosis; n (%) | 1 (16) | 1 (20.00) | 1 (25.00) | 3 (42.85) | 8 (27.27) | 0.719 |
| Histological diagnosis | Classic all cases | Classic 2 cases MBEN 3 cases | Classic 3 cases Large cell 1 case | Classic 7 cases | Classic 18 cases MBEN 3 cases Large cell 1 case | |
| Loss to followed up cases; n (%) | 0 (0.00) | 1 (20.00) | 2 (50.00) | 2 (28.5) | 5 (22.72) | |
| Recurrent cases; n (%) | 0 (0.00) | 4 (80.00) | 2 (50.00) | 2 (28.5) | 8 (36.36) | See survival analysis |
| Expired cases; n (%) | | | | | 6 (27.27) | See survival analysis |
| From treatment complication | 2 (33.33) | 0 (0.00) | 0 (0.00) | 1 (14.28) | 3 (13.63) | |
| From progression of disease | 0 (0.00) | 1 (20.00) | 2 (50.00) | 0 (0.00) | 3 (13.63) | |

WNT=Wingless signaling pathway; SHH=Sonic Hedgehog signaling pathway; MBEN=medulloblastoma with extensive nodularity; SD=standard deviation

at the Queen Sirikit National Institute of Child Health (QSNICH), a public hospital under the Department of Medical Services, Ministry of Public Health, Thailand.

## Material and Methods

### Patients

The present study was a continuous study that utilized results of the previous study dealing with the molecular classification of MB conducted by Shuangshoti et al[10]. Newly diagnosed cases with known molecular subtypes classified by Nanostring operated at the QSNICH between January 2004 and December 2018 were enrolled. Medical records including demographic data, clinical risk stratification, operative note, pre- and post-operative imaging studies, treatment, and outcome, were retrospectively reviewed. Patients with incomplete medical record were excluded. The present study was approved by the Ethical Committee, QSNICH (REC.111/2563).

### Statistical analysis

Descriptive statistics were reported in terms of frequencies and percentages for qualitative data. Category variables were compared between the molecular subgroups, using either chi-squared test or ANOVA test. Kaplan-Meier method was used for survival analysis. Cause specific survival (CSS) and recurrent-free survival curves were calculated. Differences between groups were compared with log-rank test. For the CSS analysis, time to event was counted from the operative date to event or to the last visit date. All medical records were reviewed until June 2020. Events of interest were disease-related deaths whereas treatment-related deaths were counted as censored. Lost to follow-up were counted as event. For the recurrence-free survival, events of interest included tumor recurrence and lost to follow-up. Uneventful follow-up was counted as censored. Duration was calculated using DATEDIF function (Excel, Microsoft). All statistical analyses were performed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

## Results

Forty-seven MB cases were retrieved, but only 22 matched with the inclusion criteria set above. Summary of the clinicopathological features, including outcome of each molecular subgroups of MB in the present study cohort is shown in Table 1. Mean followed up time in the present group of patients was 1,479.5 days. Shortest followed up time was seven days and longest followed up time was 5,792 days.

In WNT subgroup, there were six patients. One case was found dissemination at time of diagnosis, leptomeningeal enhancement at spinal cord were

**Table 2.** Summary of clinical characteristic and outcome in WNT subgroups patients

| Case No. | Sex | Age at diagnosis | Residual tumor ($cm^2$) | Dissemination | Clinical risk | Duration of followed up | Outcome | Current condition |
|---|---|---|---|---|---|---|---|---|
| 1w | Male | 11 years 2 months | 0 | No | Average | 1 year 1 month 12 days | Expired, sepsis | |
| 2w | Male | 7 years | 0.3 | No | Average | 2 years 9 months 15 days | Followed | Healthy |
| 3w | Male | 7 years 7 months | 0 | No | Average | 3 years 6 months 8 days | Followed | Healthy |
| 4w | Male | 8 years 4 months | 1.5 | Yes | High | 5 years 7 months 28 days | Followed | Healthy |
| 5w | Female | 13 years 11 months | 0 | No | Average | 8 months 14 days | Expired, sepsis | |
| 6w | Male | 11 years 22 days | 1.5 | No | Average | 6 years 2 days | Followed | Coordination problems |

**Table 3.** Summary of clinical characteristic and outcome in SHH subgroup patients

| Case No. | Sex | Age at diagnosis | Residual tumor ($cm^2$) | Dissemination | Clinical risk | Duration of followed up | Recurrence (episode) | Outcome | Current condition |
|---|---|---|---|---|---|---|---|---|---|
| 1s | Male | 2 years 2 months | Gross total | No | High | 15 years 10 months | Local 2 episodes | Followed | Delay development, seizure, panhypopituitary |
| 2s | Female | 3 months | 2 | Yes | High | 8 years 9 months | Local 1 episode | Followed | Impair truncal balance, severe coordination problems |
| 3s | Male | 1 year 10 months | Partial removal | No | High | 4 months 21 days | Local 1 episode | Expired | |
| 4s | Female | 6 months 15 days | 0 | No | High | 7 years 8 months | Local 2 episodes | Followed | Behaviour problems and seizure |
| 5s | Female | 1 year 4 months | 0.4 | No | High | 4 years 4 months | - | Lost to followed | |

found on magnetic resonance imaging (MRI) at one month after operation. Cerebrospinal fluid (CSF) studies were negative for malignancy in all cases. Gross total or near total removal was done in all cases. Five patients were classified as average risk group. All patients were treated with chemotherapy. Regimen included Vincristine, Cyclophosphamide, Carboplatin, and Etoposide. Four cases were treated at QSNICH and two cases were treated at another hospital. The present study hospital did not have radiotherapy department, thus all patients were referred to received craniospinal radiation and conformal radiation to tumor bed at another available centers. All patients were followed up. In the first five years after diagnosis, clinical followed up and image surveillance were done at least two times a year. There was no evidence of recurrence in this groups. Two patients expired due to sepsis. The summary of clinical characteristic and outcome in WNT subgroups patients is shown in Table 2.

In SHH subgroup, there were five patients, all of them were diagnosed before three years old. There was no TP53 mutation in this group. One case was found cauda equina enhancement on MRI. For surgical management in this group, they were treated with surgical removal. Three cases had postoperative images, but two cases recorded only the degree of tumor removal on operative note and medical records. This group of patients received chemotherapy. Four patients received craniospinal radiation and conformal radiation to tumor bed when they were three years old. One patient did not receive radiotherapy due to lost to follow up. Four patients had recurrence during follow up and all were local recurrent. Two of them were treated with surgical removal and chemotherapy. One patient was treated with radiotherapy when recurrence. The other patient was treated with palliative treatment. Recurrence in these four patients occurred before they received radiation therapy. One patient expired due to tumor progression. One patient was lost follow up. Three patients who were followed had been documented about their medical condition that needed consultation and treatments such as panhypopituitary, seizure, and developmental problems. The summary of clinical characteristic and outcome in SHH subgroup patients is shown in Table 3.

There were a four-patients subgroup in Group 3 MBs in the present study. The youngest patient was three years old, and the oldest patient was eleven years old when diagnosed. One patient (25%) was found with tumor dissemination at diagnosis. Suprasellar

**Table 4.** Summary of clinical characteristic and outcome in Group 3 subgroup patients

| Case No. | Sex | Age at diagnosis | Residual tumor ($cm^2$) | Dissemination | Clinical risk | Duration of followed up | Outcome | Current condition |
|---|---|---|---|---|---|---|---|---|
| 1gr3 | Male | 7 years 8 months | 0 | No | Average | 5 months 9 days | Lost to followed | |
| 2gr3 | Male | 7 years 10 months | 0 | No | Average | 2 years 10 months 15 days | Recurrence, disseminate expired | Expired from disease progression |
| 3gr3 | Male | 3 years 23 days | 0.18 | Yes | High | 18 days | Lost to followed (referred) | - |
| 4gr3 | Male | 11 years | 0 | No | Average | 1 year 5 months 4 days | Recurrence, disseminate expired | Expired from disease progression |

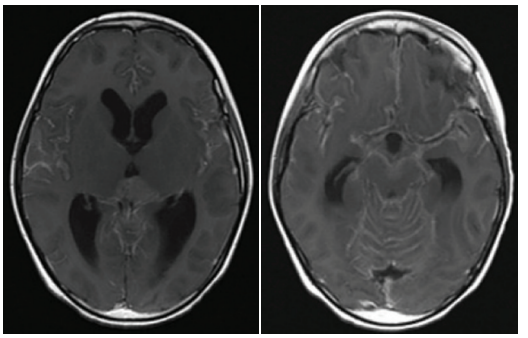

**Figure 1.** Axial MRI brain T1 with contrast performed on survillance program one years and four months after diagnosis. Showing disseminate lesions including 4th ventricle lesion, Right cerebellar hemisheric lesion, pineal lesion and leptomeningeal enhancement at basal cistern.

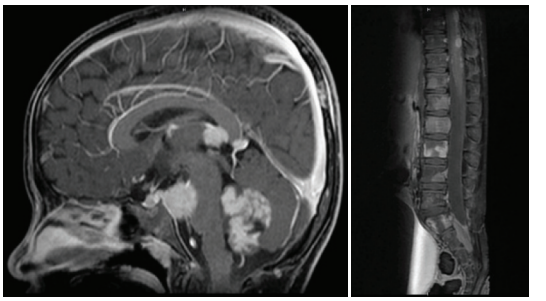

**Figure 2.** Preoperative MRI T1 with contrast images of example case demonstrated multiple mass lesion at $4^{th}$ ventricle, pre-pontine, right temporal region, pineal region and spinal cord lesion. Tumor removal was done on $4^{th}$ ventricle mass and then patient was referred to receive adjuvant therapy at the other hospital.

lesion, pial enhancement at pons, and leptomeningeal lesion at distal thecal sac were simultaneously found at diagnosis along with the fourth ventricle mass. All patients were operated. Total or near total tumor removal were done in all cases. Two patients were lost to follow up, the remaining patients were treated with craniospinal radiation and conformal radiation to tumor bed and chemotherapy. Recurrence was found in the second year of the treatment. Disseminated lesions were found at recurrence in both cases. Follow up MRIs of example cases are shown in Figure 1. Both patients expired. The summary of clinical characteristic and outcome in Group 3 subgroup patients is shown in Table 4.

There were seven patients categorized into Group 4 MB in the present study. The youngest patient was one year and two months old, the oldest was ten years and nine months old. Five patients achieved near-gross total surgical removal of tumor. One patient was left with residual tumor. One patient presented with multiple mass and was operated for one tumor removal. MRI of the brain and spinal cord of this patient is shown in Figure 2. Three patients had tumor dissemination at diagnosis. One case presented with multiple mass, one case was found malignant cell in CSF with normal MRI, and one case was found laminar enhancement at spinal cord on MRI performed during 24-hour postoperative period. Only one patient expired in this group during early postoperative period. The cause of death was pneumonia, meningitis, and sepsis. Symptoms that related with brainstem manipulation such as hypertension, facial palsy, and abducen palsy were identified in this case. Two patients were lost to follow up. Four remaining patients were treated with chemotherapy and craniospinal radiation and conformal radiation to tumor bed, except one case that was only treated with chemotherapy. One patient had spinal recurrence on surveillance MRI at the end of observation period of the present study and waited for further management. Another patient had spinal recurrence three years after diagnosis. He was treated with additional radiotherapy and then lost to follow up. One patient, having the longest period of follow up, had been diagnosed with sensorineural hearing loss (SNHL), optic atrophy, and panhypopituitary. The summary of clinical characteristic and outcome in Group 4 subgroup patients is shown in Table 5.

**Table 5.** Summary of clinical characteristic and outcome in Group 4 subgroup patients

| Case No. | Sex | Age at diagnosis | Residual tumor ($cm^2$) | Dissemination | Clinical risk | Duration of followed up | Outcome | Current condition |
|---|---|---|---|---|---|---|---|---|
| 1gr4 | Male | 7 years 6 months | 0.5 | No | Average | 3 years 6 months 6 days | Recurrence | Healthy<br>Recurrent lesion found on surveillance MRI |
| 2gr4 | Male | 5 years 1 month | 0 | CSF cytology positive | High | 3 years 11 months 19 days | Followed | Healthy |
| 3gr4 | Female | 8 years 7 months | 3×3×4 | No | High | 13 years 10 months | Followed | SNHL, optic atrophy, panhypopituitary |
| 4gr4 | Female | 1 year 2 months | 0.7 | No | High | 2 years 8 months 12 days | Followed | Healthy |
| 5gr4 | Male | 10 years | 0 | Spinal lesion | High | 16 days | Expired<br>Pneumonia, meningitis, sepsis | Postoperative hypertension, CN VI, VII palsy |
| 6gr4 | Male | 10 years 9 months | 0 | No | Average | 3 years 7 months 14 days | Recurrence<br>Lost to followed | - |
| 7gr4 | Male | 6 years 7 months | 3 masses at present Subtotal removal at posterior fossa mass | Yes | High | 7 days | Lost to followed (referred) | - |

CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; SNHL=sensorineural hearing loss; CN=cranial nerve

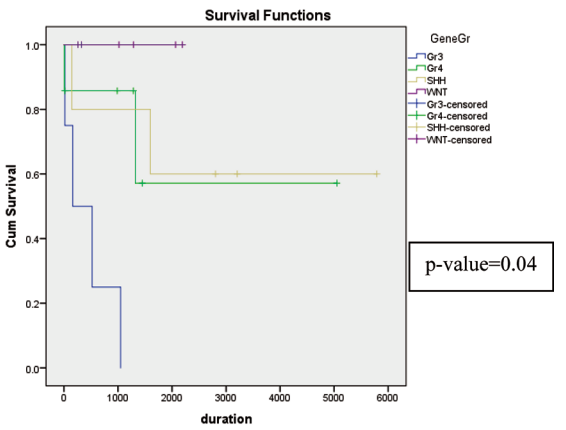


**Figure 3.** Cause specific survival curve of medulloblastoma patients in each molecular subgroup.

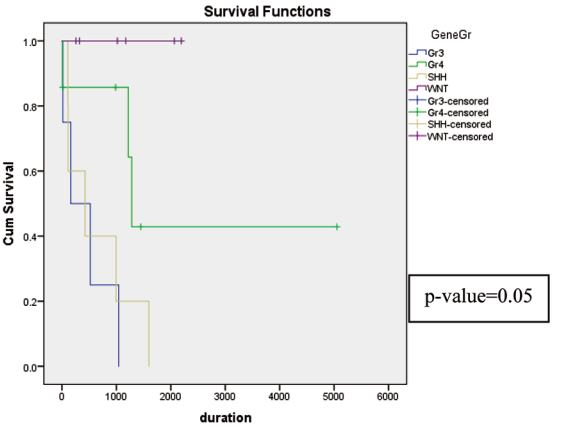


**Figure 4.** Recurrence-free survival curve of medulloblastoma patients in each molecular subgroup.

## Survival analyses

Kaplan-Meier analysis were used based on interest of the present study. First, cause specific survival analysis, expired from MB were counted as event. The present study aimed to evaluate the worst possible outcome, lost to follow up patients were counted as event. Second, recurrence-free survival analysis, recurrence was counted as event. Lost to follow up patients were counted as event in this study. Differences between each subgroup were evaluated with log-rank test. Duration was calculated in days. Cause specific survival curve is shown in Figure 3.

Cumulative cause specific survival probabilities at 2-year in each subgroup were 0.25 (standard error [SE] 0.217) in Group 3, 0.857 (SE 0.123) in Group 4, 0.8 (SE 0.179) in SHH group, and 1 in WNT group.

Cumulative cause specific survival probabilities at 5-year in each subgroup were 0 in Group 3, 0.571 (SE 0.249) in Group 4, 0.6 (SE 0.219) in SHH group, and 1 in WNT group.

For recurrence-free survival analysis. Recurrence-free survival curve were plotted and shown in Figure 4.

At 5-year duration, cumulative recurrence-free survival of WNT group was 1, Group 4 was 0.429 (SE 0.224), SHH and Group 3 were 0. There was no

**Table 6.** Summary of distribution in medulloblastoma subgroups that were reported in Asian

| Main author | Number of cases | Country | WNT (%) | SHH (%) | Group 3 (%) | Group 4 (%) |
|---|---|---|---|---|---|---|
| Tao, et al.[13] | 55 | China | 9.1 | 10.9 | 21.8 | 58.2 |
| Min, et al.[14] | 74 | South Korea | 16 | 20 | Non-WNT/SHH 64 | |
| Wu, et al.[15] | 55 | Taiwan | 13.5 | 32.7 | 28.8 | 25 |
| Kaur, et al.[16] | 87 | India | 25.3 | 17.2 | 23 | 34.5 |
| The present study | 22 | Thailand | 27.27 | 22.73 | 18.18 | 31.82 |

WNT=Wingless signaling pathway; SHH=Sonic Hedgehog signaling pathway

recurrence in WNT group in the present study. All patients in SHH and Group 3 had recurrence or lost to follow up within 1,598 days period.

## Discussion

Understanding and management of MB had been developing overtime. At present, understanding in genetic variation of MB has an important role in classification of patients and new treatment protocol has been studying for each subgroup[11]. In Thailand, classification and management of MB patients are based on clinical risk stratification systems. DNA methylation microarray analysis for MB is very limited in the present study country. Alternative method for genetic classification such as immunohistochemistry stained with appropriate protocol[10,12] are available in only a limited number of hospitals. To date, there is no study about MB molecular subgroups and clinical correlation in Thai population.

The distribution of genetic subgroups in MB in the present study showed that Group 4 formed the largest group in this study (31.82%), followed by WNT (27.27%), and SHH (22.73%). The smallest group was Group 3 (18.18%). In the international meta-analysis study conducted by Kool et al, from the 523 MB patients in all age group, Group 4 was the largest group (34%), followed by SHH (28%), Group 3 (27%), and WNT (11%). That study also demonstrated that age distribution differed dramatically in each molecular subgroup. The SHH tumors were found in infant and adult, Group 3 tumors were found in infant and children, WNT and Group 4 tumors were found in children and adult[8].

Some studies in Asian population reported a slight variation in subgroup distribution in MBs. The summary of those reports is demonstrated in Table 6[13-16].

In many studies, WNT group is described as rarest one with good prognosis, and Group 4 is the common one. However, many studies shows that the distribution have slight variation including the present study results. The cause of variation in the present study may be due to methodological errors such as low sample size. It was also a possibility that there is a true variation in subgroup distribution in each region and ethnicity.

Age distribution in the present study was concordant with the other studies since WNT and Group 4 were predominantly found in children, group 3 was found in infant and children[8,15], and SHH was described as bimodal age distribution[8,17] where infant and adult had clinical and molecular distinction[17]. TP53 mutation was found in adult SHH MB, which also had a poorer prognosis than wild type TP53 status in infant SHH[18]. Due to the case selection of the study, the authors did not have adult MB patients. All SHH MBs in the present study were infant and none of them were found with the TP53 mutation.

Gender distribution in the overall MB in the present study showed a male dominance pattern as described in another study[19]. In subgroup population, except SHH subgroup, which was equally found in male and female at a ratio of 2 to 3, also demonstrated male predominance.

In the international meta-analysis study of subgroup MB conducted by Kool et al, they found that male to female ratios were significantly different between molecular subgroups. WNT and SHH tumor occurred almost equally in male and female[8].

Most commonly found histologic subtype in the present study was classic MB in 18 out of 22 patients (81%). MB with extensive nodularity were found in three cases. All of them were infant, SHH subgroup cases. One large cell MB cases was found in an 11-year-old boy, group 3 patient. There was evidence of strong correlation between histology subtype and molecular subgroups. Most of the WNT subgroup were classic histology, SHH subgroup were associated with desmoplastic/MBEN histology, and large cell MB were found in Group 3[8]. The result of the present study followed those trends.

Frequency of dissemination at diagnoses in the

present group of patients were 16% in WNT group, 20% in SHH group, 25% in Group 3, and 42.85% in Group 4. Many studies showed that frequency of metastasis at diagnosis varied across subgroups. In study conducted by Kool et al, frequency of metastasis at diagnosis was found highest in Group 3 (30%) and Group 4 (31%). For SHH groups, metastasis was found in 17% of the infants and in 20% of the children. For WNT tumors, metastasis was detected in 9% and only in children[8]. Zapotocky et al conducted investigation in 117 MBs patients. Their interest was differential patterns of metastatic dissemination across MB subgroups. In their cohort study, frequency of metastasis at diagnosis varied significantly across the four groups. No metastasis was found in WNT tumors, 11.5% of the SHH tumors were metastasis, 30.4% of Group 4 were metastasis and 35.7% of Group 3 were metastasis. Not only frequency varied between group, but they also found that each subgroups had different pattern. All the metastatic SHH tumors in their study demonstrated nodular pattern and two of five cases of metastatic SHH tumors exhibited cerebellar nodular lesion without leptomeningeal lesion, raising suspicion of synchronous primary tumors. Metastatic Group 3 mainly exhibited laminar pattern in 16 of 18 cases (87.5%) and frequently showed that metastatic lesions were bigger than the primary tumor. Metastatic Group 4 exhibited nodular pattern in 11 of 19 cases.

They also found that suprasellar dissemination were frequently found in Group 4 tumors[20]. Not only image appearances varied between subgroups, pattern of enhancement and restricted diffusion on diffusion-weighted imaging (DWI) varied. Mata-Mbemba et al described mismatching pattern on MRI that contrast enhancement did not correlate with restriction on DWI. In their study, MRI characteristics of Primary Tumors and Metastatic Lesions in Molecular Subgroups of Pediatric MB: A Single-Center Study, mismatching pattern was found in the initial metastatic Group 4 tumors, while all the initial metastatic SHH and Groups 3 demonstrated matching pattern with contrast enhancement and restriction on DWI[21].

There was a study that focus on WNT group conducted by Stock A et al. In 35 WNT tumors, only four found dissemination at diagnosis (11.5%), with one patient showing cranial dissemination, two patients showing cranial and spinal dissemination, and one patient showing isolate spinal dissemination[22]. When only spinal enhancement on MRI was found at postoperative period without other lesion and normal CSF cytology, phenomenon of subdural enhancement after posterior fossa craniectomy for tumor removal should be considered. This phenomenon could be found in 15% after posterior fossa craniectomy with tumor removal especially when an MRI was done early in postoperative period. This lesion would spontaneously resolve on follow up MRI after four weeks[23]. The result of the present study showed the same trend with the other. Group 3 and Group 4 were the most frequently found metastatic at diagnosis in the present study, while WNT group was the less frequently found metastasis at diagnosis. Isolate spinal lesion was found in one case in WNT group, one case in SHH group and one case in Group 4. Those three cases were reviewed in aspect of ruling out post posterior fossa craniectomy subdural enhancement phenomenon. All lesions were metastasis. All lesions still appeared in the follow-up image. Diffuse laminar metastasis involving both cranial and spinal was found in one case in Group 3. Multiple nodular masses involving both cranial and spinal were found in one case in Group 4.

Difference in survival among molecular subgroups were evidenced in many studies. Results from the study conducted by Kool et al showed WNT tumors had the best outcome with a 5- and 10-year OS of 95% in children and a 5-year OS of 100% in adults. The worst outcome in all age categories was seen in patients of Group 3 tumors with infants 5- and 10-year OS at 45% and 39%, and children 5- and 10-year OS at 58% and 50%, respectively. SHH tumors clearly had a better outcome in infants with 5- and 10-year OS at 77% and 77% compared to children with 5- and 10-year OS at 68% and 51%, and adults with 5- and 10-year OS at 75% and 34%, respectively. Group 4 tumor had intermediate prognosis[8]. There was a study from Asian population conducted by Kuo-Sheng et al, Molecular-Clinical Correlation in Pediatric Medulloblastoma that studied 52 cases in Taiwan. WNT tumor had the best prognosis with 5-year OS rate at 100% and 5-year relapse-free survival (RFS) rate at 85.7%. Five-year OS rate and 5-year RFS rate in SHH group were 76.5% and 58.8%, respectively. Five-year OS rate and 5-year RFS rate in Group 4 tumors were 72.7% and 61.4%. Group 3 had the worst prognosis, 5-year OS rate and 5-year RFS rate were 60.0% and 46.7%, respectively[15]. The result of the present study followed those trends.

The WNT group in the present study had the best prognosis. Two-year and five-year CSS rate was 100% and 100%, and no recurrence was found in this group. However, two cases expired from sepsis during the course of treatment.

Two-year and five-year CSS rate of SHH group in the present study was 80% and 60%. The authors found the SHH tumors group had a high recurrence rate. Four from five patients had recurrence before 5-year follow up period. Somehow, 75% (3/4) of those who had recurrence had disease controlled after the treatment. All the SHH patients in the present study were infant and all the specimens were negative for TP53 mutation. However, survivors in this group had a long-term medical condition that needed medical attention. That maybe because this group of patients had received multiple treatment on their developing brain since very young.

Two-year and five-year CSS rate of Group 4 tumors were 85.7% and 57.1%. Five- year RFS rate was 42.9%.

In the present study, Group 3 had the worst prognosis. Longest duration of follow up was 2 years 10 month. Two patients during follow up expired due to disease progression in dissemination pattern and did not respond to treatments. The present study patients' survival duration was shorter than the other reports.

The present study had lots of limitation. Molecular subgrouping with appropriate technic were limited in this country. Most of the MB patients in Thailand were not molecular subgroup, leading to low sample size in the present study. Some of the important data such as detail of radiation treatment, a mainstay treatment was lacking. Lost to follow up problems had an impact on result of the present study too.

Overall, the present retrospective study demonstrates correlation between molecular subgroup and the clinical of pediatric MB patients. The distribution of molecular subgroups found were slightly higher proportion of WNT group compared with the previous report. That may be caused by methodologic error or there was a true variation in different ethnicities. Investigation in a larger group of patients in the present study country would show the true results. The present study results in characteristic of each subgroup and their prognoses followed the trend with the other studies.

In molecular era, some clinical risk such as metastasis was integrated into new risk stratification systems. The consensus for the new risk groups in non-infant MB were defined based on current survival rates with low risk at more than 90% survival, average or standard risk at 75% to 90% survival, high risk at 50% to 75% survival, and very high risk at less than 50% survival. The WNT subgroup and non-metastatic Group 4 tumors with whole chromosome 11 loss or whole chromosome 17 gain were recognized as low-risk tumors and may qualify for reduced therapy. High-risk strata were defined as patients with metastatic SHH or Group 4 tumors, or MYCN amplified SHH MBs. Very high-risk patients were Group 3 with metastases or SHH with TP53 mutation[24]. However, some clinical risk factor such as extent of surgery were reevaluated and found that the prognostic benefit of increased extent of resection for patients with MB was attenuated after molecular subgroup affiliation was taken into account[25].

Until now, standard treatment protocol for MB patients is based on clinical risk stratification systems. Treatment for MB based on molecular subgroup has been developing. For example, in WNT group, treatment de-escalation concept had been investigated for low risk WNT MB. The protocol aimed for reducing treatment-related toxicity, improving quality of life outcomes and maintaining a good survival rate[26]. For SHH group, target therapy for SHH pathway gene has been investigated[26-28].

Soon molecular and genetic study in each patient will be the essential information in risk stratification and planning treatment.

## Conclusion

The present study showed that when the molecular subgrouping is applied into Thai pediatric MB patients, MB is a heterogeneous disease. Nature of each subgroup followed trend with the other previous reports. Molecular subgrouping will aid clinicians in understanding course of disease in each subgroup and their prognoses. Future management of MB, including risk stratification system and treatment protocol have been developing based on molecular subgroup classification and genetics finding. In Thailand, most of the MB patients were given diagnosis and managed according to clinical risk stratification. Only a few centers can perform molecular subgroup classification. Making those test available for all MB patients in Thailand is a challenging task but crucial for development of MB caring system in Thailand.

## What is already known in this topic?

Molecular subgrouping is well studied in developed countries. Those findings show an impact in management of MB patients including prediction of prognosis and design of the future treatment.

## What this study adds?

This study is the first study about clinical

characteristic and molecular subgrouping of MB in Thailand. Until now, those tests are still limited in the authors' country. The authors hope that the result of this study will encourage health authorities to create the systems that make this test available for the Thai MB patients countrywide.


## Acknowledgements

The authors would like to express their appreciation to colleagues for their continuous support and ambition to improve the quality of treatment. The authors are deeply grateful to Shanop Shuangshoti for providing valuable advice on developing the manuscript.


## Conflicts of interest

The authors declare no conflict of interest.

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