Original Article

Risk Factors Associated with Post-therapeutic Outcome for Medulloblastoma: An Experience from Indonesia

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Abstract

Context: The prognosis of medulloblastoma is better in patients who underwent complete treatment consisting of surgery, radiotherapy, and chemotherapy. However, the realization of such multidiscipline management is quite challenging in developing countries, including Indonesia. Until now, no study on the management of medulloblastoma has ever been conducted in Indonesia. **Aims:** The authors aimed to study the characteristics, management, and mortality outcome of medulloblastoma patients in Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia. **Subjects and Methods:** This study was based on medical record and registry of 44 medulloblastoma patients who underwent tumor removal in Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia, between 2011 and 2018. **Statistical Analysis Used:** Cox regression analysis was utilized to determine the relationship between patients' demography, tumor characteristics, and treatment, with mortality. **Results:** The incidence of mortality was 84.1% and median months' survival time (95% confidence interval [CI]) was 13 (8.67–17.32). Gross total removal (GTR) was performed in 43.2% of all tumor removal surgery. Only 50% of all patients completed radiotherapy, and 6.8% concluded multimodalities treatment (surgery, radiotherapy, and chemotherapy). Significant statistical association between age, gender, and extent of resection with mortality was identified (HR [95% CI] for age: 0.44 [0.22–0.88], gender: 0.001 [0.000–0.27; REF: female], and biopsy: 31.52 [1.09–910.56; REF: GTR]). **Conclusions:** The survival rate of medulloblastoma in Indonesia is inferior to that previously reported in other studies. There is no unusual characteristic contributing to neoteric risk factor. The authors surmise that insufficient multidisciplinary management for the disease, consisting of suboptimal tumor resection, the absence of risk stratification, and incomplete postsurgical treatment (radiotherapy and chemotherapy) resulted in such outcome.

Keywords: *Age, extent of resection, gender, medulloblastoma, mortality*

Introduction

Medulloblastoma is widely known as the most prevalent malignant brain tumor in pediatric patients and comprises the highest preponderance among embryonal tumors in adult population.[1,2] Its current prognosis, compared to other central nervous system neoplasms, is superior with 30-year overall survival (OS) of 70.2%.[3] Tumor removal surgery and cerebrospinal fluid (CSF) diversion, together with radio- and chemotherapy, are the current standard management of medulloblastoma, with the dosages of the latter two being determined through postsurgical risk stratification.[4,5]

Earlier risk stratification criteria utilize age, residual tumor size, and presence of metastases, while more recent fieldworks incorporate four types of molecular features of medulloblastoma – WNT, SHH, Group 3, and Group 4, resulting in finer adjustments of radiotherapy dosages and chemotherapy regiments.[4-10]

Nevertheless, since consensus on the management of medulloblastoma is mostly based on previous scientific efforts conducted in developed countries, this refinement may not be able to be readily applied in developing countries due to various socio-economic reasons.[4-8] Indonesia, a developing country currently ranked as the world's fourth-most populous, surprisingly has only managed to report a scant number of studies on medulloblastoma, mostly in forms of case studies.[11-13] No population-based study on the characteristics, management, and post-therapeutic outcome of medulloblastoma has

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ever been initiated here. The authors aimed to investigate the association between the various characteristics and management methods of medulloblastoma with post-therapeutic outcomes among patients managed in one national referral hospital located in Jakarta, Indonesia.

Subjects and Methods

Subjects

This retrospective, medical record-based study focused on medulloblastoma patients who underwent tumor removal surgery at Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia, from the year 2011 to 2018 (n = 44). Subjects with incomplete presurgical imaging data (n = 13) and insufficient postsurgical management (radio- or chemotherapy, [n = 22, 13 of which also have incomplete presurgical imaging data]) were excluded from further analysis. The Institutional Review Board of the Faculty of Medicine, University of Indonesia, has approved the study protocol.

Determination of medulloblastoma

Diagnosis of medulloblastoma is determined through histopathology examination (presence of small round undifferentiated cells with pleomorphism, with/without high mitotic count, and presence of Homer Wright rosettes) conducted by the Department of Pathology in Dr. Cipto Mangunkusumo National Referral Hospital, Indonesia. Samples were obtained during tumor removal surgery performed by a neurosurgeon of the Department of Neurosurgery in Dr. Cipto Mangunkusumo National Referral Hospital.

Variables and outcome

Information regarding age (<3, 3–18, or >18 years old), gender (male or female), presurgical imaging profile (tumor size (the biggest diameter of <3 cm or ≥3 cm), tumor location (midline or hemispheric), presence of cystic component (yes or no), brainstem involvement (yes or no), extent of tumor resection/EoR (gross total removal (GTR), near-total removal, or biopsy), timing of CSF diversion (prior to or simultaneous with tumor removal, or none), postsurgical management (radio- and/or chemotherapy), and survival time (management-to-death months) were obtained. Furthermore, reasons for the abandonment of postsurgical management (declined, dropout, or death) were acquired since the authors perceived this to be important to describe subjects' socio-economic background. The study outcome was post-therapeutic mortality.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (minimum–maximum), where applicable, and categorical variables as proportions. Cox regression analysis was utilized to determine the association between independent variables with mortality, with reference groups for each variable were as follows: age (younger age), gender (female), tumor size (<3 cm), tumor location (midline), presence of cystic component (no), brainstem involvement (no), EoR (GTR), and CSF diversion (prior to tumor removal). All analyses were performed using IBM Statistical Product and Service Solution (SPSS) software version 19.0 (Chicago, Illinois, USA). A two-tailed $p<0.05$ was considered to be statistically significant.

Results

Subjects' characteristics

The study subjects' characteristics are presented in Table 1. From the year 2011 to 2018, there were 44 medulloblastoma patients recorded to have undertaken tumor removal surgery. Subjects' median age (minimum–maximum) was 7 (1–38) years, with 79.5% belonged to the 3–18 years old age group and 65.9% were male, with a male-to-female ratio of 1.9:1. Presurgical imaging profiles were as follows: 65.9% of cases had tumor diameter ≥3 cm, 63.6% of cases exhibited tumor in the midline, 38.6% revealed cystic component, and 27.3% displayed brainstem involvement. Regarding management, 43.2% of subjects undertook GTR surgery, with 47.7% underwent simultaneous CSF diversion and removal tumor. Multimodality therapy, consisted of surgery, radio- and chemotherapy, was performed in 6.8% of subjects, with its median months' survival time (95% confidence interval [CI]) of 35 (0.00–71.67).

Table 2 lists the reasons for the abandonment of postsurgical management. Declining radiotherapy was the main cause for abandonment, constituting 36.4% of its population. Most subjects prefer alternative treatment, believe that no further treatment is necessary after total resection of tumor, or had socio-economic issues, each of which amounts to 9.1% of all patients who rejected radiotherapy.

Subjects' survival analysis

Table 3 shows the results for Cox regression survival analysis. Of all variables, compared to reference groups, older age, male, and biopsy displayed significant and independent association with postsurgical mortality, with HRs (95% CI) of 0.44 (0.22–0.89), 0.001 (0.00–0.28), and 31.51 (1.09–910.56), respectively. Kaplan–Meier plots for gender and EoR are presented in Figures 1 and 2, respectively.

Discussion

In this study, older age and male gender were found to be negatively associated with post-therapeutic mortality. On the contrary, a biopsy was found to be positively associated with post-therapeutic mortality. To the authors' knowledge, this is the first-ever population-based, outcome-related study on the management of medulloblastoma in Indonesia.

Table 1: Characteristics of the study sample (*n*=44)

Variable	*n* (%)
Demography	
Age (years), median (minimum-maximum)	7 (1-38)
Age (years)	
<3	6 (13.6)
3-18	35 (79.5)
>18	3 (6.8)
Gender	
Male	29 (65.9)
Female	15 (34.1)
Presurgical imaging*	
Tumor size (cm)	
<3	2 (6.4)
≥3	29 (93.6)
Tumor location	
Midline	28 (91.3)
Hemispheric	3 (9.7)
Cystic component	
Present	17 (54.8)
Absent	14 (45.2)
Brainstem involvement	
Present	12 (28.7)
Absent	19 (61.3)
Management	
Extent of resection	
Gross total removal	19 (43.2)
Near-total removal	8 (18.2)
Biopsy	17 (38.6)
CSF diversion	
Prior to tumor removal	18 (40.9)
Simultaneous with tumor removal	21 (47.7)
No CSF diversion	5 (11.4)
Postsurgical management	
Radiotherapy and chemotherapy	3 (6.8)
Radiotherapy only	19 (43.2)
No radiotherapy and/or chemotherapy	22 (50.0)
Mortality	
Yes	37 (84.1)
No	7 (15.9)
Mortality, median months' survival time (95% CI)	
All patients	13 (8.67-17.32)
Surgery only	5 (1.93-8.06)
Surgery and radiotherapy	29 (0.00-58.88)
Surgery, radiotherapy, and chemotherapy	35 (0.00-71.67)

*Missing data (*n*=13). CI – Confidence interval; CSF – Cerebrospinal fluid

Age

The relationship between age and post-therapeutic outcome has been identified from previous studies, with younger age being proven to present with worse prognosis, despite of the completion of postsurgical radio- and chemotherapy management.[14-18] Moreover, subsequent research by Children Cancer Group (CCG942, CCG923, CCG921) also highlighted worse prognosis in patients aged <3 years old.[9]

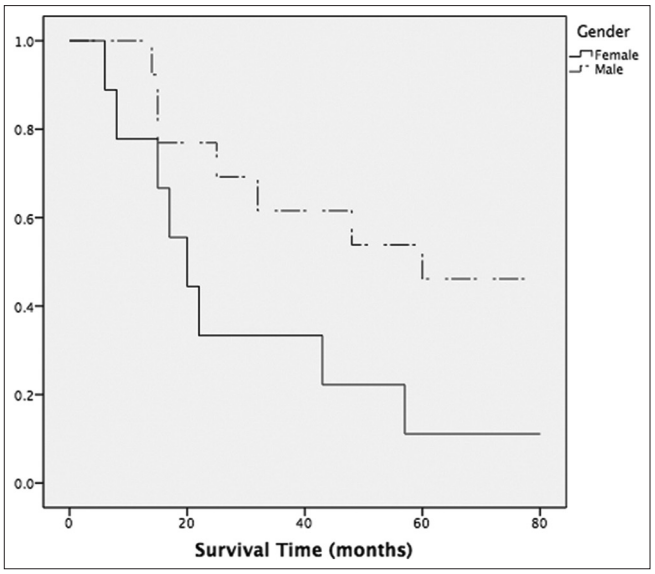

Figure 1: Kaplan–Meier plot for gender

In the current study, the median age of study subjects was shown to be lower compared to those reported in China (median years (minimum–maximum) of 10 (1–49) years) and India (mean years ± SD of 12.3 ± 8.7).[17,19] The authors ruminated on several mechanisms that may explain this finding. First, the practice of withholding radiotherapy for patients aged <1.5 years old and lessening radiotherapy dosage for patients aged 1.5–3 years old may be accounted as one of the affecting issues.[20] Next, mutations of the suppressor of fused homolog gene, protein patched homolog 1 gene, and tumor protein p53 gene, more prevalent in those aged <3 years old, were known to inflict worse prognosis due to increased risk of relapse.[21]

Extent of resection

EoR had been proven to be a significant prognostic factor of mortality in previous studies on both patients with complete and incomplete radiotherapy.[15,22] Furthermore, it was found to be significantly associated with 5-year progression-free survival.[23,24] Within this study, the proportion of biopsy is only slightly different with those of GTR (38.6% vs. 43.2%). The authors perceived that this might be responsible for the 31.5 times higher odds for postsurgical mortality when compared to GTR. Surgeon's preference to perform more biopsy in this study is based on the experience in Indonesia that larger EoR would prolong the duration of surgery and mechanical ventilation, particularly in those with a poor presurgical clinical condition, due to limitations in the postsurgical intensive care. This is contrary with the proposed target of surgery in medulloblastoma, which is maximum safe resection to lessen compression toward brainstem and eliminate CSF blockage and cytoreduction.[5,25]

Gender

Although other studies have not determined gender to be a significant prognostic factor for mortality, the female

Table 2: Reason for abandonment of postsurgical management

Reason	*n* (%)
Declined radiotherapy	8 (36.4)
Prefers alternative treatment	2 (9.1)
Believes that no further treatment is necessary after total resection of tumor	2 (9.1)
Socioeconomic issues	2 (9.1)
Believes that the disease is incurable	1 (4.5)
Unknown	1 (4.5)
Dropout from radiotherapy	6 (27.3)
Prefers to continue with alternative treatment	2 (9.1)
Socioeconomic issue	2 (9.1)
Unknown	2 (9.1)
Death	6 (27.3)
Unknown	2 (9.1)

Table 3: Cox regression survival analysis

Variable	Hazard ratio (95% CI)	*p*
Age	0.44 (0.22-0.88)	0.022*
Gender	0.001 (0.00-0.27)	0.015*
Tumor size	0.004 (0.00-2.50)	0.094
Tumor location	N/A	
Cystic component	2.79 (0.19-41.94)	0.458
Brainstem involvement	31.39 (0.07-14648.98)	0.272
Extent of resection		
Near-total removal	3.22 (0.03-358.11)	0.627
Biopsy	31.52 (1.09-910.56)	0.044*
CSF diversion	81.51 (0.47-14301.48)	0.095

CI – Confidence interval; CSF – Cerebrospinal fluid; N/A – Not applicable, *-($p<0.05$)

was found to have better outcomes compared to their male counterpart.[15,17,23,26] Ciucci *et al*. proved that estrogen has an important role in the inhibition of tumor cell cycle progressivity, decelerating its growth in female patients.[27] In this study, contrasting result was found, where the male has 60% lower odds of mortality than the female. This discrepancy could be incited by the different preeminent male:female ratio in this study compared to its antecedent investigations in Southeast Asia (1.9:1 vs. 1.2:1).[14,28]

The circumstances in Indonesia

In this initial study performed in Indonesia, the incidence of mortality within postsurgical medulloblastoma patients was shown to be as high as 84.1%. Their median survival time (median months [95% CI]: 13 [8.67–17.32]) was lower compared to those observed in two other developing countries, India (mean months ± SD: 49.22 ± 19.01) and Thailand (median months [95% CI]: 80 [23–230]).[14,29] While no neoteric independent factors found to be associated with this poor survivability, the authors postulated several matters in the management of medulloblastoma in Indonesia that might contribute to this finding.

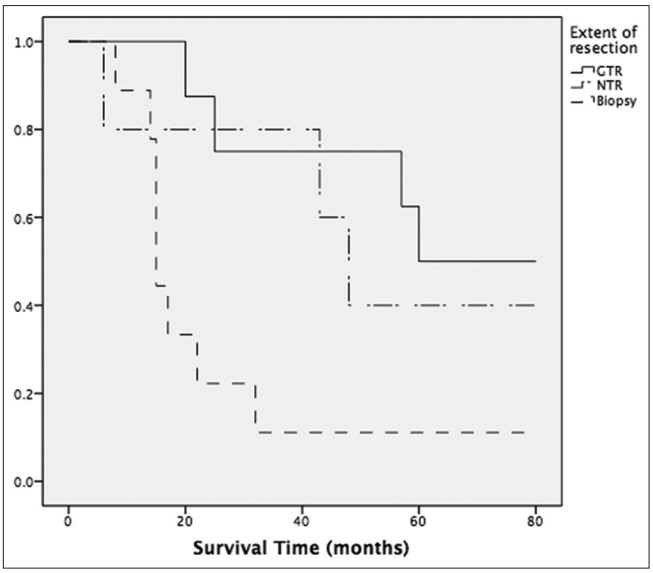

Figure 2: Kaplan–Meier plot for extent of resection

In contrast with other developing countries, for example, China, India, and Thailand, until now, neurosurgical care in Indonesia has not been able to implement the current postsurgical risk stratification in its medulloblastoma management protocol.[12,16,27,30] The finite health insurance coverage and lack of advanced ancillary studies availability have negatively impacted the ability to perform the standard evaluation of postsurgical residual tumor, presence of metastases, and molecular subtype histopathology, all of which are necessary for the determination of risk stratification.[4-10] Government officials and other partaking disciplines as public health policymakers ought to refine the national health-care insurance coverage to improve this situation.

In this study, only 50% of patients continued to undertake radiotherapy. The survival time of this patient group within the current study (median months [95% CI]: 29 [0.00 - 58.88]) was higher compared with other similar studies where only surgery and radiotherapy were implemented as standard treatment, with survival time ranging from 18 months to median months (95% CI) of 25 (6–61).[15,31] The difference in median survival time between differing treatments modalities was noticeable [Table 1], and was considered to be lower than that found in a number of recent single-center research conducted in other developing countries, although their reasons to abandon further postsurgical radiotherapy were homogenous with those elaborated in here.[14-16,19,32] This should instill a better understanding and knowledge transfer between neurosurgeons and medulloblastoma patients and their families in Indonesia since most reasons stated were due to the insufficiency of disease comprehension. Strategies to resolve socio-economic issues, for example, lack of financial strength to pay for accommodation and transportation residing outside main cities, should be discussed with both central and regional government

officials.

Another important issue that should be considered is chemotherapy. Surgery alone resulted in 0% 5-year OS, while radiotherapy could increase the percentage to 50%, and inclusion of chemotherapy would produce 70%–80% 5-year OS.[4,20,32] All patients aged <3 years old are determined to undergo chemotherapy.[33] In this study, only 6.8% of patients completed chemotherapy, whereas 13.6% of all patients were aged <3 years old. The current tenet in our hospital states that the pediatrician is responsible for administering chemotherapy. Better collaboration between the neurosurgeon and other related disciplines, involving referral policy and standardized chemotherapy protocol, is mandatory.

Strength and limitation

This is the first population-based study on the characteristics, management, and post-therapeutic outcome of medulloblastoma in Indonesia. Previous publications coming from this country consisted only of singular case studies.[12,13] The research was ensued in a national referral hospital, with medulloblastoma patients referred from Sumatra, Borneo, Java, Sulawesi, Maluku Islands, Papua, and other smaller islands. Therefore, the population of this study is representative of all cases throughout Indonesia. Nevertheless, as a research being held in a developing country, difficulties in data collection were present, such as missing presurgical imaging material.

Conclusions

Older age and male gender were found to be negatively associated with post-therapeutic mortality, while the biopsy was found to be positively associated with post-therapeutic mortality. Age and EoR were already determined as independent prognostic factors in previous investigations; meanwhile, gender-associated mortality found is contrary to preceding literature and clinical reports, with insufficient theoretical basis provided to support the finding in this study.[915,17,22,23,26,27,30]

The survival time of medulloblastoma in Indonesia is inferior to other countries. For the reason that there was no novel prognostic factor found in this study, refinement of treatment strategies should ensue. Most reasons for treatment abandonment involve inadequate knowledge of the disease. Consequently, standardized informed consent regarding course of the disease and its management should be devised. Policy discussions with government officials concerning augmenting national health-care insurance coverage for postsurgical risk stratification examinations and facilitating patients residing outside main cities (other prominent reason in treatment abandonment) should be assembled.

The incidence of under-age 5 mortality in Indonesia is high, accounted for 25/1000 live births, with the consideration that another populous developing country such as China is only at 11 deaths/1000 live births (with quintupled population compared to Indonesia).[11] Therefore, better management for diseases mostly affecting pediatric patients should be instilled, including medulloblastoma. Maximum safe resection with proper intensive care and implementation of postsurgical treatment using risk stratification and proper dosage of radiotherapy and chemotherapy for each group should be the standard procedure of medulloblastoma management in Indonesia.

Future work

A prospective study should be carried out, analyzing more possibilities for prognostic factor, such as clinical manifestations, presence of metastases, and molecular subtypes, with more outcomes (e.g.: functional status and progression-free survival).

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Conflicts of interest

There are no conflicts of interest.

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