Extent of resection and histopathology grading as a survival risk factor in a patient with medulloblastoma

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Extent of resection and histopathology grading as a survival risk factor in a patient with medulloblastoma

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ABSTRACT

Background: Medulloblastoma is a common neoplasm in the pediatric population with a poor prognosis. Incomplete resection has been reported to be related to second-look surgery and subsequent more malignant clinical course, while certain histopathological is said to have a more favorable prognosis.
Methods: This study retrospectively analyzed data from patients with medulloblastoma who underwent tumor resection in our hospital between 2016 to 2020. Histopathologic information and the extent of resection were collected. Survival analysis was done with log-rank and Kaplan-Meier to determine the overall and progression-free survival.
Results: There were 42 patients with medulloblastoma with mean overall survival of 16.5 months and a mean progression-free survival of 12.43 months. Patient with subtotal resection has the longest mean overall survival and progression-free survival compared with others. Patient with classical medulloblastoma has the longest mean overall survival and progression-free survival compared to other types of histopathology.
Conclusion: The extent of resection and histopathology grading is statistically significantly related to the outcome of a patient with medulloblastoma.

Keywords: Medulloblastoma, Extent of resection, Histopathology.
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BACKGROUND

Medulloblastoma is the most common malignant tumor in children, which causes significant morbidity.[1] The 5-year survival rate of patients with medulloblastoma in Australia and the United States is reported to be as high as 65% to 80% after various treatment modalities, including chemotherapy, radiotherapy, or combination.[2–4]

In Indonesia, on the other hand, data on medulloblastoma is limited. A Study from Jakarta found that the median survival rate of medulloblastoma patients is lower than that of other countries despite undergoing surgery, chemotherapy, or radiotherapy.[5–7] In the said study, the extent of resection was not associated with better survival.[5] Similarly, Thompson and colleagues reported that a greater extent of resection did not result in better survival for medulloblastoma of certain molecular subtypes.[8]

In our center in Surabaya, treatment for medulloblastoma is unfortunately limited to surgery and radiotherapy, while diagnostic modality does not go beyond histopathology. Through this study, we aim to determine our patient's survival rate concerning the extent of resection and histopathological type.

METHODS

This study retrospectively collected data from medical records from January 2016 to December 2020. Sex, age, the extent of resection, histopathological features, radiotherapy status, progression-free survival (PFS) and overall survival (OS) of all medulloblastoma cases were taken. Patients with incomplete data or those who did not return for an outpatient visit after surgery were excluded. Each variable was analyzed using Kaplan - Meier survival analysis to assess the effect of each variable on the outcome.

RESULT

A total of 42 patients were included in the analysis. The patients were predominantly male (54,8%), and most were older than three years old (71.4%). The most prevalent histopathologic finding was classic. Overall demographic characteristic is provided in Table 1.

This study's overall mean OS and PFS were 16.5 and 12.43 months, with median values of 17 and 13 months, respectively. Survival analysis found that 92,8% of the patients survived within one year since first having treatment in our hospital, while only 61,9% were free of progression during the same period (Table 2). The first tumor progression was seen between 6 to 8 months after initial treatment, while the earliest death was observed within the first ten months (Figure 1). In this study, none of the patients survived two years after treatment.

Table 1. **Demographic characteristic.**

Variable		N	%
SEX	Male	23	54,8
	Female	19	45,2
AGE	< 3 years	12	28,6
	years	30	71,4
TUMOR RESECTION EXTENSION	Gross Total Tumor Resection (GTR)	13	31
	Near Total Tumor Resection (NTR)	13	31
	Sub Total Tumor resection (STR)	9	19
HISTOPATHOLOGY GRADING	Partial Tumor Resection (PTR)	4	11,9
	Biopsy	3	7,1
	Classic	27	64,3
	Desmoplastic	8	19
	Anaplastic	5	11,9
	NOS	2	4,8
UNDERGONE RADIOTHERAPY	Yes	24	80
	No	6	20

Table 2. **Mean, median, and % of 1-year survival for overall Survival and progression-Free Survival.**

	Mean	Median	% of 1-year survival
OS	16,50	17	92,8%
PFS	12,43	13	61,9%

The analysis showed that the <3 years age group had lower mean and median OS and PFS of 15.66 months and 11.75 months compared to the > 3-year age group, namely 16.83 months and 12.7 months. There was no statistically significant correlation between age, OS (p-value = 0.055, 95% CI), and PFS (p-value = 0.134, 95% CI) in patients with medulloblastoma. The analysis showed that males had a slightly higher mean OS and a slightly lower mean PFS than females. The analysis showed no correlation between sex and OS (p-value = 0.658, 95% CI) and PFS (p-value = 0.96, 95% CI) in patients with medulloblastoma. Patients who underwent STR had the most prolonged mean OS and PFS, followed by GTR, NTR, PTR, and biopsy (p-value = 0.001, 95% CI).

Patients with classic medulloblastoma had the most extended mean OS (p=0.001, 95% CI) and PFS (p=0.040, 95% CI), followed by desmoplastic, anaplastic, and NOS. Patients who received radiotherapy had a longer mean OS (p= 0.003, 95% CI) and PFS (p=0.001, 95% CI) compared to patients who only underwent surgery without radiotherapy.

Subgroup analysis

Patients younger than 3-year-old were seen to fare worse (mean OS 15,66 mos; mean PFS 11,75 mos) than those older than 3 (mean OS 16,83 mos; mean PFS 12,7 mos), although these differences were not statistically significant (Table 3). Survival analysis found that the gap between the two groups started to become apparent at around 15 months for OS, while PFS for patients below 3 started dipping after eight months (Figure 2a). Based on gender, male patients had slightly better mean OS yet worse PFS than females despite not being statistically significant (Table 3; Figure 2b).

Interestingly, in contrast to our hypothesis, patients with STR had the longest mean OS and PFS (17,25 mos and 13,25 mos, respectively). Patients who underwent biopsy had the worst course in this study (mean OS 11 mos; mean PFS 7,66 mos) (Table 3; Figure 2c). Upon analysis based on histopathologic grouping, classic medulloblastoma has the best mean OS and PFS, followed by desmoplastic, anaplastic, and NOS (Table 3; Figure 2d).

Further subgroup analysis was carried out regarding the extent of resection and histopathologic findings. Patients with classic medulloblastoma who underwent GTR had the best mean, median OS, and PFS values compared to other histopathologic findings. This is also true for patients with classic medulloblastoma who underwent STR, NTR, and biopsy.

DISCUSSION

The mean value of OS and PFS in the present study was 16,5 months and 12,43 months, with a median value of 17 months and 13 months. Most patients (92,8%) survived within the first year since treatment began, yet only 61,9% were free of survival. Unfortunately, none of them reached 2-year survival. A previous study found higher OS and PFS (mean 19,1 and 15,83 months, respectively) with 50% of the subjects still alive within the first two years.[9] This difference may be due to differences in postoperative management protocols, such as delayed chemotherapy and radiotherapy.

In this study, we grouped the study sample based on age group (< 3 years and >3 years), gender, the extent of resection, and histopathology. We found that patients aged <3 years had lower mean and median OS and PFS values than those older than 3. Similarly, a previous study found that an age younger than 3 classifies as high-risk medulloblastoma, with the other factors being the presence of metastases and/or residual tumors with a size of 1.5 cm^2.[10] The present study, however, did not consider the presence of the residual tumors.

Our study showed better mean OS and PFS in patients who underwent STR. Thompson and colleagues did a large retrospective study that concluded that the extent of resection's influence on survival in medulloblastoma cases is insignificant. However, they did find that patients with specific molecular subgroups would fare better after GTR.[8] In 2018, the

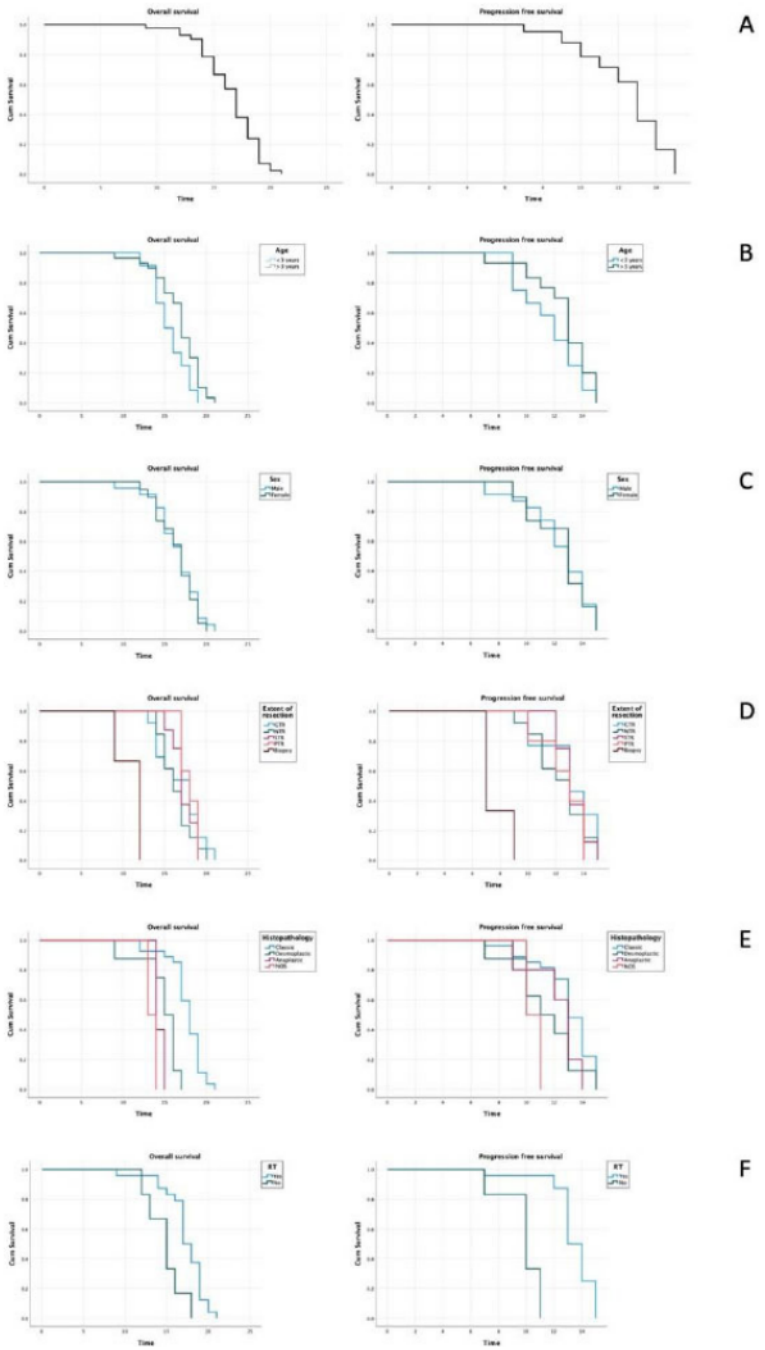

Figure 1. Kaplan-Meier Graphic for A. OS and FPS, B. OS and PFS based on age, C., OS and FPS based on sex, D. OS and FPS based on the extent of resection, E. OS and FPS based on histopathology grading, F. OS and FPS based on radiotherapy.
OS= Overall Survival, PFS= Progression Free Survival, GTR= Gross Total Tumor Resection, NTR= Near Total Tumor Resection, STR= Sub Total Tumor Resection, PTR=Partial Tumor Resection, NOS= Not Otherwise Specified.

same author did a systematic review which suggested that the relationship between the extent of resection and survival remains questionable. In that review, they found only three studies that considered molecular subgroup analysis, making their conclusion in 2016 challenging to replicate.[11] According to a study by Albright and colleagues, the extension of tumor resection was not associated with a better outcome. However, the extension of residual tumors was a prognostic factor in pediatric patients older than three years without tumor dissemination.[12] In contrast to our result, Urberuaga et al. found that patients with STR had a worse outcome than GTR.[13]

Another prognostic parameter previously mentioned as a predictor of survival is histopathology.[14] In the present study, classical medulloblastoma had the longest mean OS and PFS, followed by desmoplastic, anaplastic, and NOS medulloblastoma in this study. Anaplastic medulloblastoma had the worst survival when compared to other histopathological subtypes. Similarly, a previous study mentioned that anaplastic appearance was related to poor outcomes.[15] Kumar et al. found that desmoplastic medulloblastoma had a better outcome instead.[6] In contrast to our result, a recent meta-analysis stated that the classic subtype had the worst OS, anaplastic had the worst PFS, and desmoplastic had the best OS.[16]

Desmoplastic medulloblastoma, according to published studies, had relatively good survival that surgeons are trying to reduce the treatment that can cause morbidities such as radiotherapy or intraventricular methotrexate chemotherapy for patients less than three years. However, until now the minimal intensity and duration required for the treatment of desmoplastic medulloblastoma without radiotherapy is still unknown.[17] Histopathological parameters such as nuclear pleomorphism, degree of necrosis, proliferation index, intra-tumoral vasculature, are factors that influence the outcome of medulloblastoma patients.[13] These factors, however, were not sought further in our study.

According to the latest convention, medulloblastomas are currently classified according to molecular subgroups, namely

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Table 3. **OS and PFS analysis based on the observed variable.**

		n	OS		p-value	PFS		p-value
			Mean	Median		Mean	Median	
AGE	< 3 Years	12	15,66	15	0,055	11,75	12	0,134
	> 3 Years	30	16,83	17		12,70	13	
SEX	Male	23	16,52	17	0,658	12,39	13	0,96
	Female	19	16,47	17		12,47	13	
EXTENT OF RESECTION	GTR	13	16,84	18	0,001	13,00	13	0,001
	NTR	13	16,38	16		12,38	13	
	STR	8	17,25	17		13,25	13	
	PTR	5	18	18		12,6	13	
	Biopsy	3	11	12		7,66	7	
HISTOPATHOLOGY GRADING	Classic	27	17,63	18	0,001	12,92	13	0,040
	Desmoplastic	8	14,75	15		11,37	11	
	Anaplastic	5	14,40	14		12,2	13	
	NOS	2	13,50	13		10,5	10	
UNDERWENT RADIOTHERAPY	Yes	24	17,33	17	0,003	13,41	13	0,001
	No	6	14,83	15		9,83	10	

OS= Overall Survival, PFS= Progression Free Survival, GTR= Gross Total Tumor Resection, NTR= Near Total Tumor Resection, STR= Sub Total Tumor Resection, PTR=Partial Tumor Resection, NOS= Not Otherwise Specified

Table 4. **Subgroup analysis of the multiple variables.**

Extent of Resection and Histopathology Analysis								
		n	OS		p-value	PFS		p-value
			Mean	Median		Mean	Median	
GTR	Classic	8	18,62	18	0,001	13,28	13	0,168
	Desmoplastic	2	14,50	14		12,00	11	
	Anaplastic	2	14,00	14		10,50	9	
	NOS	1	13,00	13		11,00	11	
NTR	Classic	7	17,57	17	0,002	13,62	14	0,118
	Desmoplastic	3	15,66	16		11,50	10	
	Anaplastic	2	14,50	14		13,50	13	
	NOS	1	14,00	14		10,00	10	
STR	Classic	6	17,83	17	0,006	13,50	14	0,353
	Desmoplastic	2	16,50	16		12,50	10	
	Anaplastic	1	15,00	15		13,00	13	
	NOS	0	-	-		-	-	
PTR	Classic	4	18.25	18	-	12.5	12	-
	Desmoplastic	0	-	-		-	-	
	Anaplastic	0	-	-		-	-	
	NOS	0	-	-		-	-	
Biopsy	Classic	2	12.00	12	0.157	8.00	7	0.480
	Desmoplastic	1	9.00	9		7	7	
	Anaplastic	0	-	-		-	-	
	NOS	0	-	-		-	-	

OS= Overall Survival, PFS= Progression Free Survival, GTR= Gross Total Tumor Resection, NTR= Near Total Tumor Resection, STR= Sub Total Tumor Resection, PTR=Partial Tumor Resection, NOS= Not Otherwise Specified

WNT, SHH, group 3, and group 4,[18,19] and it is believed that each subgroup of medulloblastomas originates from different cells.[20] In a study by Eid and Heabah, the molecular subgroups had significant differences in survival rates, with the WNT subgroup having the best PFS and non-WNT/SHH showing the shortest and worst OS.[9] The meta-analysis study also stated that group 3 had the worst prognosis compared to all other medulloblastoma subgroups.[16] Most surgeons did not aggressively perform GTR surgery in this group.[10,21]

The results of the subgroup analysis of resection extension and histopathology showed that in the group of patients who underwent GTR, NTR, and STR, patients with classical medulloblastoma had significantly higher mean and mean OS values followed by desmoplastic, anaplastic, and NOS types. Most adjuvant therapy protocols classify pediatric patients with residual tumors greater than

1.5 cm^2 as high-risk cases. These cases are treated with higher doses of radiotherapy and often with additional chemotherapy. Morbidity associated with increasing the dose of radiotherapy combined with chemotherapy has been widely reported. Adjuvant therapy in pediatric patients with medulloblastoma causes severe ototoxicity in more than 18% of patients,[22] endocrinopathies in more than 50% of patients,[23] and permanent cognitive deficits in almost all patients.[24] Patients also have a 10% incidence of secondary malignancy, and this risk persists after ten years of therapy.[25] Thompson recommends safely resecting the tumor as much as possible to reduce the mass effect on critical brain structures and treat obstructive hydrocephalus.[11]

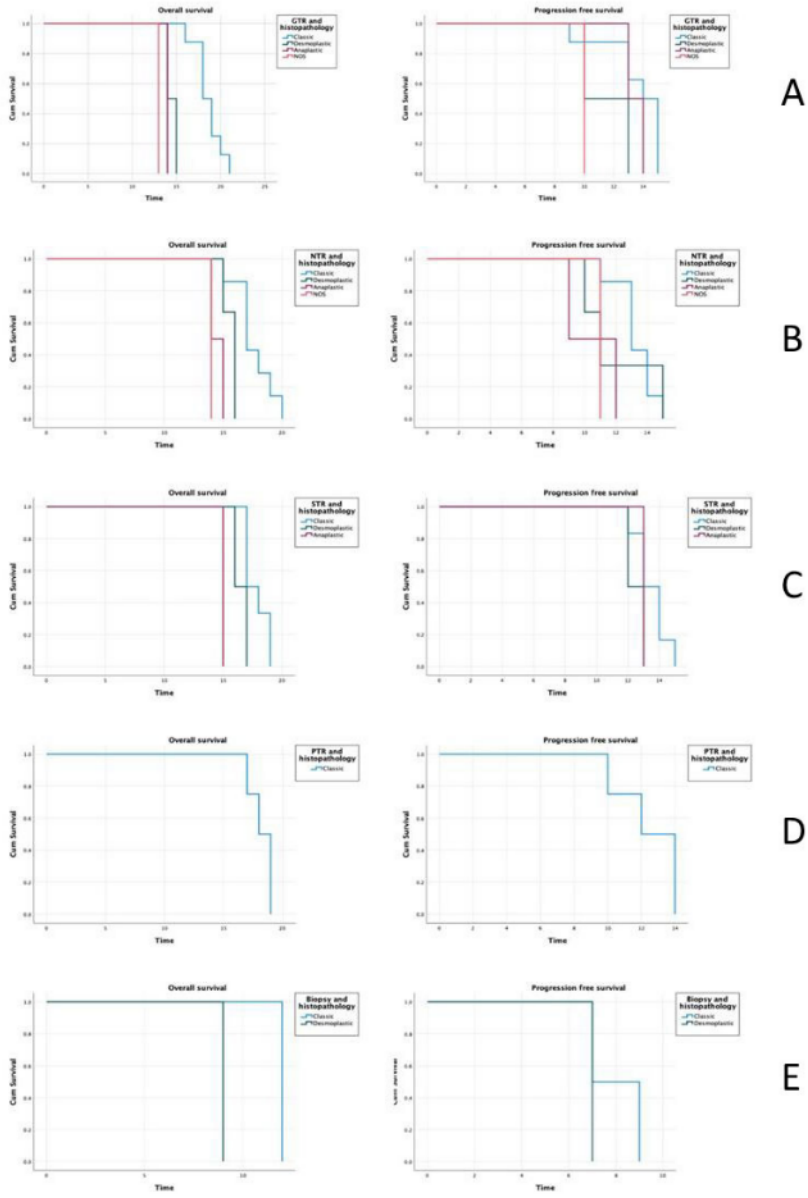

Figure 2. Kaplain-Meier Graphic for subgroup analysis.
OS= Overall Survival, PFS= Progression Free Survival, GTR= Gross Total Tumor Resection, NTR= Near Total Tumor Resection, STR= Sub Total Tumor Resection, PTR=Partial Tumor Resection, NOS= Not Otherwise Specified.

Limitation of The Study

This study was a single-center study with small sample size; patient data such as extent of resections, preoperative and postoperative tumor volumes, histopathological grading, and radiotherapy were taken through medical records, thus causing a risk of bias in the analysis.

Classification of medulloblastoma in this study was based solely on histopathology. Treatment is surgery and radiotherapy without chemotherapy. Medulloblastoma classification based on histopathology was established in 1980 and was updated in 2007 by WHO into five variants. Since 2010, the classification of medulloblastoma was based on molecular subtypes and then in 2013 the epigenetic characteristics of medulloblastoma were found. Currently, the results of an integrated analysis of intertumoral heterogeneity led to the identification of 12 different medulloblastoma subtypes.[26] The classification of medulloblastoma in Dr. Soetomo General Hospital is divided into four variants based only on histopathology grading.

CONCLUSION

Medulloblastoma patients who received treatment had a mean OS of 16.5 with 92.8% 1-year survival and a mean PFS of 12.43 with 61.9% 1-year survival.

Extended resection can affect the prognosis and outcome of medulloblastoma. Patients who underwent STR had the most extended mean OS and PFS, followed by GTR, NTR, PTR, and biopsy.

Histopathological features can affect the prognosis and outcome of medulloblastoma. Patients with classic medulloblastoma had the longest mean OS and PFS, followed by desmoplastic, anaplastic, and NOS. Patients with classical medulloblastoma who underwent GTR, NTR, and STR had a longer mean OS than other histopathologic medulloblastomas.

LIST OF ABBREVIATIONS

OS : Overall Survival
PFS : Progression Free Survival
GTR : Gross Total Resection
NTR : Near Total Resection
STR : Sub Total Resection
PTR : Partial Total Resection
NOS : Not Other Specified
WHO : World Health Organization
WNT : Wingless type
SHH : Sonic Hedgehog type

DECLARATIONS

Ethics approval and consent to participate

This study has undergone an ethical test at the ethics committee of dr. Soetomo General Academic Hospital with the ethical number 0917/113/4/VIII/2021.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on request.

Competing interests

The authors do not have any conflicts of interest to declare.

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Authors' contributions

RP and MAP designed the study and concept, defined the intellectual content, and prepared the manuscript. PL analysed the data, data acquisition and statistical analysis. AT and EAS searched the literature, clinical and experimental studies. MAP and II edited and reviewed the manuscript. All authors read and approved the final manuscript.

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