Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.2(2023). p.73-9; DOI: https://doi.org/10.14238/pi63.2.2023.73-9

Original Article

Predictors of mortality in children with neuroblastoma

Rusida Harjayanti Sanindya Arum, Kristia Hermawan, Pudjo Hagung Widjajanto, Sutaryo

Abstract

Background Neuroblastoma is an extracranial solid tumor originating from neural crest cells which failed to properly migrate. Neuroblastoma is commonly found in children under 12 months of age. The survival rate of these patients is still relatively low, both in developed countries and Indonesia.

Objective To determine whether age, sex, primary tumor location, degree of cell differentiation, and patient compliance are associated with the survival of children with neuroblastoma at Dr. Sardjito Hospital.

Methods This retrospective cohort study included pediatric neuroblastoma patients at Dr. Sardjito Hospital, Yogyakarta, Central Java, between January 2012 to September 2020. We collected secondary data from medical records and registration data of pediatric cancer patients in the Pediatric Hematology Oncology Department of Dr. Sardjito Hospital, we matched te data based on medicals records and manual data in the ward and poyclinic olyclinic, which included age at diagnosis, sex, primary tumor location, degree of cell differentiation, and patient adherence to therapy. To confirm weather the information about survived or death, apart from medical record we did tracking by telephone to the parent.

Results Of 54 pediatric neuroblastoma patients, 54% were female. The median length of observation was 13.25 months, with an incidence rate of 62/100 person-years and a median survival of 13 months from the time of diagnosis. The 5-year survival rate in our study was 21.3%. Multivariate analysis revealed that stage IV patients had higher risk of death (HR 10.9; 95%CI 1.47 to 81.01; P=0.02) compared to other stages. Sub-group follow-up analysis revealed no significant difference in stage IV male patients compared to female patients (HR 1.62; 95%CI 0.81 to 3.22; P=0.172). The survivial in group with primary tumor location outside the adrenal medulla and stage IV was not significantly different from patients whose tumor location was unknown (HR 2.45; 95%CI 0.71 to 8.43; P=0.155). The group whose primary tumor location was in the adrenal medulla did not have a significant difference in survival compared to patients whose primary tumor location was unknown (HR 2.09; 95%CI 0.84 to 5.22; P=0.114).

Conclusion The predictor factors studied are not significantly associated with mortality in children with neuroblastoma. **[Paediatr Indones. 2023;63:73-9; DOI: https://doi.org/10.14238/pi63.2.2023.73-9]**.

Keywords: *child; neuroblastoma; cancer; solid tumor; predictor; survival rate*

Neuroblastoma is an extracranial solid tumor originating from neural crest cells that fail to migrate. Neuroblastoma is most common in children. Generally, it occurs at below 12 months of age, with an incidence of 58 per 1,000,000 infants. The United States records 1 case per 7,000 live births annually.[1] In 2010, United States recorded 10.7 cases out of 1,000,000 children.[2] Europe recorded 4 cases of 1,000,000 cases of embryonal cancer (neuroblastoma, nephroblastoma and retinoblastoma) in children every year.[3]

The International Neuroblastoma Risk Group (INRG) *Database* recorded survival rates of 75-85% in the low-risk group, 50-75% in the intermediate-risk group, and <50% in the high-risk group. In Europe, the 5-year survival rate for neuroblastoma was 88-90% for stage I and II, but only 22% for stage IV

From the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Central Java, Indonesia.

Corresponding author: Pudjo Hagung Widjajanto. Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital. Jl. Raya Manisrenggo, Prambanan, Sidodadi, Klaten. 08122787724. Email: pudjo007@yahoo.com.

Submitted January 2, 2022. Accepted April 4, 2023.

disease.[3,4] Mortality due to neuroblastoma in Europe accounted for 13% of all malignancy-related mortality in children.[2] A survival study conducted in pediatric neuroblastoma patients at Dr. Sardjito Hospital, Yogyakarta, showed an overall five-year survival rate of 27%, while in Dr. Cipto Mangunkusumo Hospital, Jakarta, it was 37%.[5,6]

Methods

This observational study had a retrospective cohort design. The subjects were children with neuroblastoma who underwent treatment at the Pediatric Hematology and Oncology Department, Dr. Sardjito Hospital, Yogyakarta, Central Java, and were diagnosed from January 2012 to September 2020. Secondary data was collected using a case report form from medical records and child cancer patient registration data, including age at diagnosis, sex, primary tumor location, degree of cell differentiation, stage, time from diagnosis to time of death, and patient adherence to the given therapy. To confirm weather the information about survived or death, apart from medical record we did tracking by telephone to the parent.

Data were analyzed using the *Statistical Package for Social Science (SPSS) version 22.0* for *Windows*. The study was approved by the Research Ethics Committee of Sardjito General Hospital.

Results

From January 1, 2012 to September 30, 2020, there were 66 pediatric patients aged 0-18 years diagnosed with neuroblastoma at Dr. Sardjito Hospital, Yogyakarta, Central Java. Twelve patients were excluded due to incomplete data (4 patients' medical record data were not accessible and 8 patients were lost to follow-up). Thus, a total of 54 patients were included, of whom 37 (68.5%) died. The basic characteristics of subjects at the time of diagnosis are presented in **Table 1**.

Univariate analysis in **Table 2** showed that children with stage IV neuroblastoma had 3.64 times higher risk of mortality than those with stage IVs. The >12 month age group at the time of diagnosis had 1.86 times higher risk of mortality compared to the <12 month age group, but it was not statistically significant (P=0.023).

Multivariate analysis in **Table 2** revealed that stage IV neuroblastoma had 10.9 times higher risk of

Table 1. Basic characteristics of subjects (N=54)

Characteristics	Survived (n=17)	Died (n=37)	P value
Age, n			
<12 months	4	4	0.23
≥12 months	13	33	
Sex, n			
Female	11	18	0.27
Male	6	19	
Location of primary tumor, n			
Outside adrenal medulla	6	5	0.07
Adrenal medulla	6	25	
Unidentified	5	7	
Stage, n			
IVs	5	3	0.005
I-III	3	1	
IV	9	33	
Cell differentiation, n			
Well differentiated	2	7	0.43
Poorly differentiated	8	12	
No pathological examination	7	18	
Compliance, n			
Good	7	23	0.149
Poor	10	14	

death compared to stage IVs (P=0.02). However, the age at diagnosis of > 12 months showed a protective result, though it was not statistically significant. Other variables such as stage II-III, age, sex, location of primary tumor, cell differentiation, and adherence to therapy were not significantly associated with mortality.

A stage IV subgroup analysis showed no significant difference between males and females (**Table 3**). However, the risk of death was 1.62 times higher in males than in females with stage IV, but it was not significant (P=0.172). Also, there was no significant difference in mortality between the stage IV unknown location of primary tumor group and the outside adrenal medulla location group. However, patients with the primary tumor location outside the adrenal medulla had a 2.45 times higher risk of death than in patients whose primary tumor location was unknown. In addition, there was no significant difference in mortality between the stage IV adrenal medulla primary tumor location group vs. the unknown tumor location group. But patients with adrenal medulla tumor location had 2.09 times higher risk of death.

Figure 1 shows the survival analysis of a child with neuroblastoma. Median monitoring for 13.25 months. The total sample was 54 people, 37 died with an incidence rate of 62/100 person year, with a median survival of this study was 13 months (95% CI 8.18 to 17.8 months) since the patient was diagnosed, with survival at 1 year, 2 years, 3 years and 5 years respectively are 53.7%, 29.8% and 21.3%.

Discussion

The results of the analysis stated that the overall survival for 5 years in our study was 21.3%. The INRG stated that the 5-year survival rate after diagnosis was less than 50%, while in Indonesia, it was reported to be 25%6 and 27%.[5] The low survival rate in Indonesia is likely due to late patient presentation at stage IV, which is often accompanied by distant metastases.[2,5,6,16]

The similarity between our study and the other two Indonesian studies was that most patients were in stage IV at the time of diagnosis (77.4%, 53%,6 and 85%,5 respectively). The INRG stated that 40% of pediatric neuroblastoma patients were in stage IV at the time of diagnosis.[4-6] Cancer cells can spread to form new tumors in organs far from the primary tumor location, which is known as a metastatic process.

Table 2. Univariate and multivariate analyses of mortality and patient characteristics

Variables	Univariate Cox regression			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age						
<12 months						
≥12 months	1.86	0.65 to 5.32	0.24	0.28	0.05 to 1.63	0.16
Sex						
Female						
Male	1.38	0.73 to 2.64	0.32			
Location of primary tumor						
Outside adrenal medulla						
Adrenal medulla	0.72	0.23 to 2.28	0.58			
Unidentified	1.32	0.57 to 3.05	0.52			
Stage						
IVs						
I-III	0.79	0.08 to 7.59	0.84	2.41	0.15 to 39.39	0.54
IV	3.64	1.08 to 12.16	0.04	10.91	1.47 to 81.01	0.02
Cell differentiation						
Well differentiated						
Poorly differentiated	0.60	0.63 to 4.28	0.31			
Adherence to therapy						
Good						
Poor	0.79	0.41 to 1.54	0.50			

Table 3. Subgroup analysis of stadium IV analysis of survival of children with neuroblastoma

Variables	Status		Univariate			Multivariate		
	Survived (n=9)	Event (n=33)	HR	95%CI	P value	HR	95%CI	P value
Age, n			-	-	-			
<12 months	0	0						
≥12 months	9	33						
Gender, n								
Female	6	16	1.62	0.81 to 3.22	0.172	1.58	0.78 to 3.18	0.201
Male	3	17						
Tumor location, n								
Outside adrenal medulla	2	5	2.45	0.71 to 8.43	0.155	2.49	0.72 to 8.64	0.149
Adrenal medulla	2	22						
Unidentified	5	6						
Cell differentiation, n								
Well differentiated	1	7						
Poorly differentiated	5	12	0.671	0.26 to 1.74	0.411			
No pathological examination	3	14						
Compliance, n								
Good	4	33						
Poor	5	11	0.97	0.47 to 2.01	0.934			

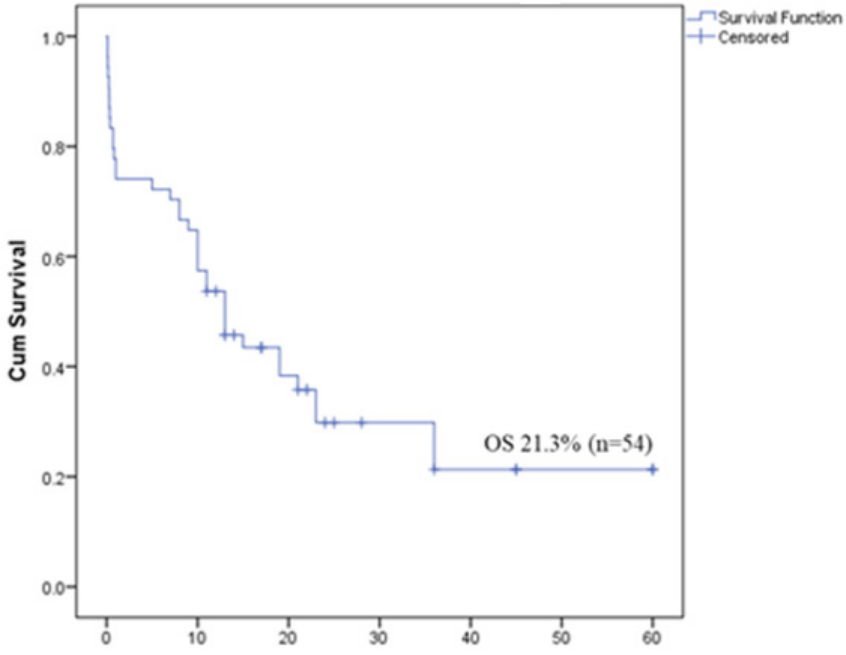

Figure 1. Overall survival

Tumors in stage IV can spread to distant lymph nodes, bones, bone marrow, liver, skin, and/or other organs. Most of our stage IV subjects had distant metastases, based on medical records and registration data that we have although no further analysis was carried out.

Based on the literature, MYCN gene amplification induces tumor cell division, causing distant metastases. Most of our subjects had distant metastases, both with stage IV and IVs. Stage IVs tumors can spontaneously regress, but in our study, 3 patients with stage IVs

died. According to their medical records, the causes of death were abdominal compartment syndrome, hydroureter, DIC, and septic shock.

The age group in this study showed that there were more girls than boys, based on two types of age groups dominated by the girls. There was no significant difference in survival between age groups between < 12 months or >12 months. Most patients in the >12 month age group were in stage IV (42 subjects) compared to the <12 month age group which consisted of mostly patients in stages I-III (4 subjects).

Our subjects were predominantly female, unlike the other two Indonesian studies.[5,6] No significant difference in mortality was noted between sexes, but the analysis may not have been meaningful because there were 22 females and 20 males with stage IV (42; 77.8%), and far fewer with stages I-III (4; 7.4%). Thus, we could not determine if mortality was influenced by sex factors related to androgens that stimulate tumor growth or because of advanced stage disease.

The primary tumor locations were not mentioned in the previous Indonesian studies.[5,6] We found that overall, 57.4% of primary tumors were in the adrenal medulla, and no significant difference in mortality based on the primary tumor location. The higher mortality in the adrenal medulla group was due to the fact that such patients only sought medical treatment in stage IV. The unbalanced proportion of subjects in the primary tumor location groups with stage IV also affected the analysis. The location of the primary tumor in the adrenal medulla has worse prognoses than other locations, but because most of our subjects were in stage IV, the stage of presentation may have had greater influence on mortality than the primary tumor location. The deaths of these patients were either due to the effects of the tumor on the adrenal medulla or due to the stage IV condition or both.

We found that 37% of the biopsy results showed poor differentiation, Unfortunately, histopathological examination was not performed in the other patients. However, the analysis showed no significant difference in mortality between the well-differentiated and poorly differentiated groups. Again, the incomplete pathology data of subjects may render the analysis results meaningless, as 9 (16%) patients with good cell differentiation, 20 (37%) had poor differentiation, and 25 (46%) did not undergo histopathological examination because no biopsy was performed. Twelve (70.6%) deceased patients in the stage IV subgroup had poor cell differentiation.

A limitation of our study was that the potential risk factors of mortality were not further differentiated and analyzed. In addition, we did not analyze for relationships between mortality and nutritional status or sepsis status, or other characteristics. In the subgroup analysis, there was no significant difference in mortality between each group of variables. However, clinically the risk of death was 1.62 times higher in males. In addition, the outside adrenal medulla group had 2.45 times higher risk of mortality, while the adrenal medulla group had 2.09 times higher risk of mortality. The number of patients with stage I-III in our study was small, and there no stage 1 patients. Most of the patients presented at an advanced stage and had distant metastases, so this situation overlapped with other variables that might have also been associated with mortality.

It was difficult to assess whether variables were risk factors, or due to worsening conditions as a result of stage IV and metastases. Another study limitation was that the sample size was less than the minimum required size, due to being a single center study and our small number of cases.

Other conditions recorded in subjects' medical records as causes of death were sepsis, intracranial metastases, pulmonary metastases, abdominal compartment syndrome, poor nutrition, heart failure, respiratory failure, shock or conditions for which the cause of death was unknown because the patient died at home or in another hospital.

Nutritional status was one condition that could not be explained in our study. The supporting data for assessing nutritional status in children with neuroblastoma were incomplete, moreover, the weight, height, and upper arm circumference measurements were not all included in the medical records. Only 8 patients had an assessment of their nutritional status. Upper arm circumference data is useful for assessing the nutritional status of children with tumors and organ enlargement. But incomplete data and/or assessment of nutritional status were limitations of our study.

In conclusion, the 5-year survival rate in our study is 21.3%. None of the variables studied shows significant differences in mortality. Indeed, the most obvious finding was that because most subjects were

diagnosed as stage IV, it was very difficult to distinguish whether death was caused by the stage of disease or other factors. For further study, more complete data is needed to expand the study variables. Government programs, in conjunction with the Indonesian Pediatrics Society, should educate parents, so that neuroblastoma in children can be recognized early for improved prognosis.

Conflict of interest

None declared.

Funding acknowledgment

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Ahmed AA, Zhang L, Reddivalla N, Hetherington M. Neuroblastoma in children: Update on clinicopathologic and genetic prognostic factors. Pediatr Hematol Oncol. 2017;34:165–85. DOI: https://doi.org/10.1080/08880018.2017.1330375.
2. Louis CU, Shohet JM. Neuroblastoma: molecular pathogenesis and therapy. Annu Rev Med. 2015;66:49-63. DOI: https://doi.org/ 10.1146/annurev-med-011514-023121.
3. Gatta G, Ferrari A, Stiller CA, Pastore G, Bisogno G, Trama A, *et al.* Embryonal cancers in Europe. Eur J Cancer. 2012;48:1425-33. DOI: https://doi.org/10.1016/j.ejca.2011.12.027.
4. Cohn SL, Pearson ADJ, London WB, Monclair T, Ambros PF, Brodeur GM, *et al.* The International Neuroblastoma Risk Group (INRG) classification system: an INRG task force report. J Clin Oncol. 2009;27:289-97. DOI: https://doi.org/10.1200/JCO.2008.16.6785.
5. Sutaryo, Kristian SD. 'A five-year review of children with neuroblastoma at Dr. Sardjiro General Hospital,Yogyakarta, Indonesia' Paediatr Indones. 2019;51:207-12. DOI: https://doi.org/10.14238/pi59.3.2019.157-63
6. Garniasih RD, Windiastuti E, Gatot D. Karakteristik dan kesintasan neuroblastoma pada anak di Departemen Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Indonesia Rumah Sakit Cipto Mangunkusumo. Sari Pediatr. 2009;11:39-46. DOI: https:// doi.org/10.14238/sp11.1.2009.39-46.
7. Hallett A, Traunecker H. A review and update on neuroblastoma. Paediatr Child Health (Oxford). 2012;22:103-7. DOI: https://doi.org/10.1016/j.paed.2011.08.005.
8. Sandoval JA, Malkas LH, Hickey RJ. Clinical significance of serum biomarkers in pediatric solid mediastinal and abdominal tumors. Int J Mol Sci 2012;13:1126-53. DOI: https://doi.org/1 0.3390/ijms13011126.
9. El-Sayed MI, Ali AM, Sayed HA, Zaky EM. Treatment results and prognostic factors of pediatric neuroblastoma: a retrospective study. Int Arch Med 2010;3:37. DOI: https://doi.org/ 10.1186/1755-7682-3-37.
10. Hale G, Cula MJ, Blatt J. Impact of gender on the natural history of neuroblastoma. Pediatr Hematol Oncol. 1994;11:91-7. DOI: https://doi.org/10.3109/08880019409141905.
11. Bown N, Cotterill S, Lastowska M, O'Neill S, Pearson AD, Plantaz D, *et al.* Gain of chromosome arm 17q and adverse outcome in patients with neuroblastoma. N Engl J Med. 1999;340:1954-61. DOI: https://doi.org/10.1056/NEJM199906243402504.
12. Komotar RJ, Otten ML, Starke RM, Anderson RCE. Chromosome 1p and 11q deletions and outcome in neuroblastoma - a critical review. Clin Med Oncol. 2008;2:419-20. DOI: https://doi.org/ 10.4137/cmo.s391.
13. Chistison-Lagay ER, La Quaglia MP. Neuroblastoma and other adrenal tumors. In: Carachi R, Grosfedd JL, eds. The surgery of childhood tumors. 2nd edn. Heidelberg: Springer Berlin; 2016. p. 231-56. DOI: https://doi.org/10.1007/978-3-662-48590-3. ISBN: 978-3-662-48590-3.
15. Goldsby RE, Matthay KK. Neuroblastoma: evolving therapies for a disease with many faces. Paediatr Drugs. 2004;6:107-22. [cited YEAR MONTH DATE]. Available from: https://link.gale.com/apps/doc/A199991057/AONE?u=anon~e84d0ab3&sid=googleScholar&xid=89182a78.
16. Taggart DR, London WB, Schmidt M Lou, DuBois SG, Monclair TF, Nakagawara A, *et al.* Prognostic value of the stage 4S metastatic pattern and tumor biology in patients with metastatic neuroblastoma diagnosed between birth and 18 months of age. J Clin Oncol. 2011;29:4358-64. DOI: https://doi.org/ 10.1200/JCO.2011.35.9570.
17. Permono B, Ugrasena I. Neuroblastoma. Jakarta: Ikatan Dokter Anak Indonesia; 2018. p. 315-23.
18. Shay JW, Wright WE. Role of telomeres and telomerase in cancer. Semin Cancer Biol. 2011;21:349-53. DOI: https://doi.org/ 10.1016/j.semcancer.2011.10.001.

19. Sung KW, Yoo KH, Koo HH, Kim JY, Cho EJ, Seo YL, *et al*. Neuroblastoma originating from extra-abdominal sites: association with favorable clinical and biological features. J Korean Med Sci. 2009;24:461-7. DOI: https://doi.org/10.3346/jkms.2009.24.3.461.
20. Sun J, Wang D, Guo L, Fang S, Wang Y, Xing R. Androgen receptor regulates the growth of neuroblastoma cells in vitro and in vivo. Front Neurosci. 2017;11:116. DOI: https://doi.org/ 10.3389/fnins.2017.00116.
21. Roche J. The epithelial-to-mesenchymal transition in cancer. Cancers (Basel). 2018;10:9-12. DOI: https://doi.org/10.3390/cancers10020052.
22. Koen EJ, Coolier AB, Maharaj SK. Particle-in-cell simulations of a beam driven plasm. Physics of Plasmas. 2012;19:1420-28. DOI: https://doi.org/10.1063/1.3695402.
23. Sastry KSR, Karpova Y, Prokopovich S, Smith AJ, Essau B, Gersappe A, *et al.* Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation. J Biol Chem. 2007;282:14094-100. DOI: https://doi.org/10.1074/jbc.M611370200.
24. Ayurini RI. Kepatuhan pengobatan pada pasien kanker. Psikodimensia. 2015;14:83-95. DOI: https://doi.org/10.24167/psiko.v14i2.973.
25. Budiman A, Khambri D, Bachtiar H. Faktor yang mempengaruhi kepatuhan berobat pasien yang diterapi dengan tamoxifen setelah operasi kanker payudara. J Kesehat Andalas. 2013;2:20. DOI: https://doi.org/10.25077/jka.v2i1.60.
26. Ricafort R. Tumor markers in infancy and children. Pediatr Rev. 2011;32:306-8. DOI: https://doi.org/ 10.1542/pir.32-7-306.