Scientific Research Publishing

Open Journal of Pathology, 2026, 16(2), 117-128
https://www.scirp.org/journal/ojpathology
ISSN Online: 2164-6783
ISSN Print: 2164-6775

Neuroblastoma in Senegal: Epidemiological, Morphological and Prognostic Study of 35 Cases Diagnosed from 2017 to 2023

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How to cite this paper: Dia, A.N., Gueye, M.V., Diop, N., Ndiade, A., Dansokho, K., Gaye, A.M., Ibondou, R.K., Sy, M. and Dial, C.M.M. (2026) Neuroblastoma in Senegal: Epidemiological, Morphological and Prognostic Study of 35 Cases Diagnosed from 2017 to 2023. *Open Journal of Pathology*, **16**, 117-128.
https://doi.org/10.4236/ojpathology.2026.162013

Received: February 9, 2026
Accepted: March 21, 2026
Published: March 24, 2026

Abstract

Neuroblastoma is classified as peripheral neuroblastic tumors. It is an embryonic malignant neoplasm that impacts the normal development of the sympathetic nervous system. **Objective**: The aim of this study is to delineate the epidemiological, morphological, and histo-prognostic features of neuroblastoma in Senegal. **Methodology:** This study employed a retrospective and descriptive design, during the period from January 2017 to December 2023. The analysis focused on all cases of neuroblastoma that were histologically confirmed and had undergone immunohistochemical evaluation within the Anatomic and Pathological Cytology laboratories of the Idrissa Pouye General Hospital (HOGIP) and Cheikh Anta Diop University (UCAD) of Dakar. **Results:** A total of 35 cases were collected, accounting for 5.27% of all pediatric solid cancers in both study sites (n = 664). The mean age of patients was 5.42 years, with a standard deviation of 4.33. The sex ratio was 0.94. The primary tumor site was singular in 88.57% of cases, with adrenal gland involvement observed in 22.86%. Metastatic neuroblastoma was present at the time of diagnosis in 25.71% of cases. The most commonly observed macroscopic characteristic was a well-circumscribed tumor with firm consistency and a multinodular surface, exhibiting areas of necrosis and hemorrhage. Morphological assessment led to the suspicion of neuroblastoma in 32 cases (91.42%). Histological analysis revealed a predominance of the "poorly differentiated" subtype (57.14%). Based on the International Neuroblastoma Staging System (INSS) classification, 74.29% of pa-

tients were diagnosed in Stage 2B, and 25.71% in Stage 4, often associated with an unfavorable prognosis. **Conclusion:** The observed low incidence of neuroblastoma among Senegalese children may potentially be attributed to diagnostic challenges or spontaneous regression. Our study indicated a predominance of the poorly differentiated subtype. No upward trend in incidence was noted; the majority of cases were diagnosed at advanced stages.

Keywords

Embryonic Tumor, Neuroblastoma, Immunohistochemistry, Sympathetic Nervous System

1. Introduction

Neuroblastoma is an embryonic malignant tumor that affects the normal development of the sympathetic nervous system. It represents the third leading cause of cancer in children under 15 years of age (after high-risk leukemias and central nervous system tumors) and is responsible for 15% of cancer deaths [1] [2].

Its high incidence in developed countries (7% - 10%) is due to the over-exploration of cancers detected by non-invasive imaging and screening tests [3]. In contrast, in African and Asian populations, the incidence rates are lower. This may be explained by a higher prevalence of other childhood cancers within these populations [4] [5].

A morphological study is often sufficient, as neuroblastoma is the typical example of a "small round blue cell" tumor, interspersed with a neurofibrillary matrix. However, the use of a panel of immunohistochemical markers is recommended in some cases.

Neuroblastoma is a very complex and heterogeneous disease. This heterogeneity is associated with numerous factors such as age at diagnosis, stage of the disease, biological and histological characteristics of the tumor, and numerous genetic alterations such as MYC-N amplification and ploidy [6]. All these factors influence the prognosis and treatment options.

The objective of this work was to determine the epidemiological profile, and to describe the histopathological, immunohistochemical, and prognostic aspects of neuroblastoma in the Anatomy and Pathological Cytology (APC) laboratories of Dakar.

2. Materials and Methods

We conducted a cross-sectional, retrospective, multicenter study in two (2) Anatomy and Pathological Cytology (APC) laboratories in the Dakar region (Senegal): Hôpital Général Idrissa POUYE (HOGIP) and Cheikh Anta Diop University (UCAD). This study was based on archived neuroblastoma pathology reports from these two (2) APC laboratories.

Epidemiological data: Frequency, age, sex were reported,

Anatomopathological data:

Inclusion Criteria:

All histopathological examination reports concluding neuroblastoma and confirmed by immunohistochemical analysis were included.

Exclusion Criteria:

All histopathological examination reports for which the blocks were not found or for which immunohistochemical analysis did not confirm neuroblastoma were excluded.

Anatomopathological data such as lesion location, topography, macroscopic and microscopic features, immunohistochemical profile, and histoprognostic stage, obtained for each patient, were archived in a computerized database using Excel software. A descriptive analysis was performed for each variable.

The processing of samples follows the standard procedures in anatomical pathology. Upon receipt, a registration number is assigned and recorded in the department's log. Simultaneously, the following are verified:

- The correct completion of the anatomical pathology examination request form,
- The type of organ sampled,
- The date of sampling,
- And the presence or absence of a fixative (formalin).

We retrieved from the archive's paraffin blocks of selected samples (for immunohistochemical analysis) and slides (stained with H&E) of all samples selected for our study (for review).

Immunohistochimy:

Immunohistochemical confirmation was performed in Morocco for samples from the first five years (2017-2021) and in Dakar for 2022 and 2023. All slides stained with H&E (Hematoxylin-Eosin) and confirmed by immunohistochemistry were reviewed.

Neuroblastomas characteristically show positive staining for synaptophysin, chromogranin, and CD56.

S-100 protein staining was used to identify cytodifferentiated cells such as Schwann cells.

However, they do not show immunoreactivity for EMA, cytokeratin, vimentin, or CD45.

The following antibodies were tested: CD45, CD56, Synaptophisin, Ki67.

3. Results

Epidemiological and Clinical Data:

During the study period, 35 cases of neuroblastoma were identified, representing 5.27% of all pediatric tumors (n = 664). The distribution of cases per year is shown in **Table 1(A)**.

The mean age of the patients was 5.42 years [3 months-17 years] (**Table 1(B)**), with a male-to-female sex ratio of 0.94 (**Table 1(C)**). The majority of patients (51.42%) were diagnosed before the age of 5.

Table 1. Epidemiological characteristics of patients.

Epidemiological characteristics	Number	Percentage
Year of diagnostic (A)		
2017	02	5.71%
2018	03	8.57%
2019	02	5.71%
2020	03	8.57%
2021	04	11.43%
2022	10	28.57%
2023	11	31.43%
Age (years) (B)		
0 - 4 years	18	51.42%
5 - 9 years	07	20 %
10 - 14 years	09	25.71%
15 - 19 years	01	2.86 %
Gender (C)		
Girl	18	51.43%
Boy	17	48.57%

Localization:

In our series, 33 patients (94.29%) presented with a single primary neuroblastoma, while 2 patients (5.71%) presented with a dual primary lesion at two different sites. The localization was not specified for one patient (2.86%), and 9 patients (25.71%) had metastatic disease at diagnosis (Table 2).

Table 2. Distribution of neuroblastoma according to topography.

	Localization	Number	Percentage
Single primitive localization	Adrenal gland	8	22.86%
	Head and neck	12	34.29%
	Abdomino-pelvic	9	25.71%
	Others	2	5.71%
Dual primitive localization	Abdomen + thorax	1	2.86%
	Maxilary + eye	1	2.86%
Secondary localization	Lymph node metastases	06	17.14%
	Bone marrow metastases	01	2.86 %
	Bone metastases	02	5.71%

Anatomopathological Data:

We received 19 biopsy samples (54.28%) and 16 surgical specimens (45.71%). The most frequently observed macroscopic appearance was that of a firm tumor with a multinodular surface, with tissue sections exhibiting necrotic and hemorrhagic changes (Figure 1).

Figure 1. Macroscopic examination: White-gray multinodular tumor displacing the kidney. ACP HOGIP/UCAD Laboratory, Dakar.

A histopathological appearance of differentiated neuroblastoma (small, round, sometimes elongated cells with finely dispersed chromatin in a "salt and pepper" pattern and a small amount of cytoplasm with indistinct cytoplasmic borders) was found in 30 cases (85.71%). A small round cell tumor was suspected in the remaining 5 cases (14.29%) (Figures 2-4).

Immunohistochemical analysis was performed on all patients in the series. The neuroblastomas characteristically showed positive staining for synaptophysin, chromogranin, CD56, and neuronal-specific enolase. S-100 protein staining was used to identify cytodifferentiated cells such as Schwann cells (Figures 5-8).

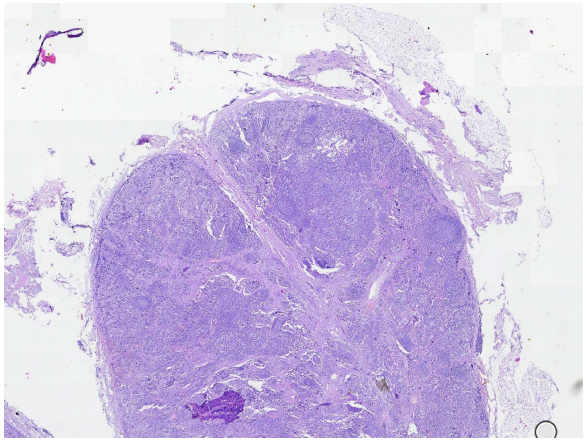

Figure 2. Microscopy: Lymph node infiltrated by a neuroblastoma, Hematoxylin and eosin stain ×100. ACP HOGIP/UCAD Lab. Dakar.

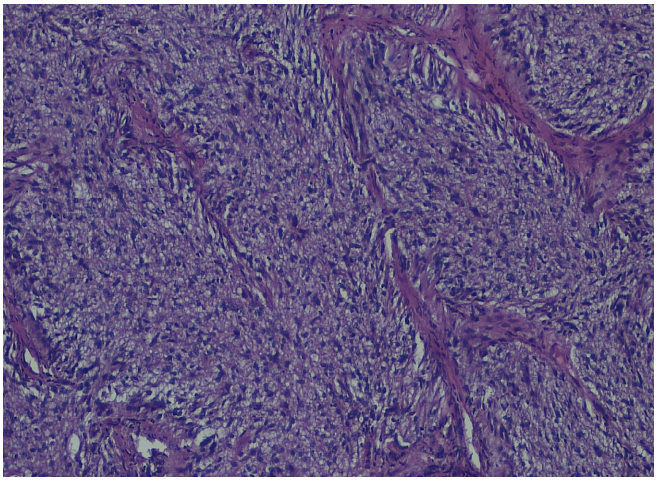

Figure 3. Neuroblasts grouped in discose masses and trabeculae with loose fibrillar foci of neuropil. Hematoxylin and eosin ×100. ACP HOGIP/UCAD Lab. Dakar.

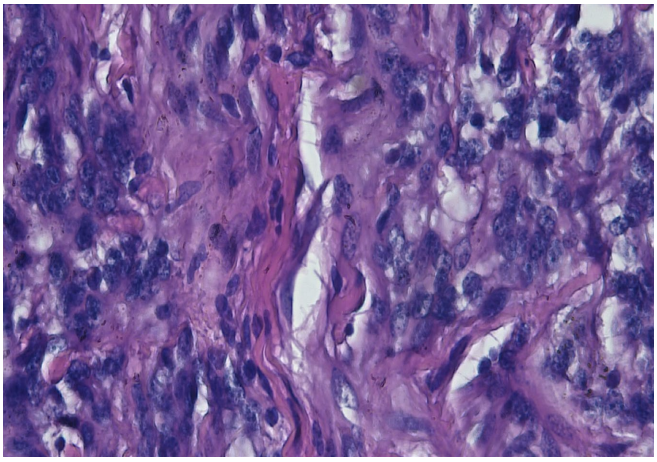

Figure 4. Small, round, sometimes elongated cells with finely dispersed chromatin in a "salt and pepper" pattern and a small amount of cytoplasm with indistinct cytoplasmic borders. (HE ×40) ACP Lab HOGIP/UCADDakar.

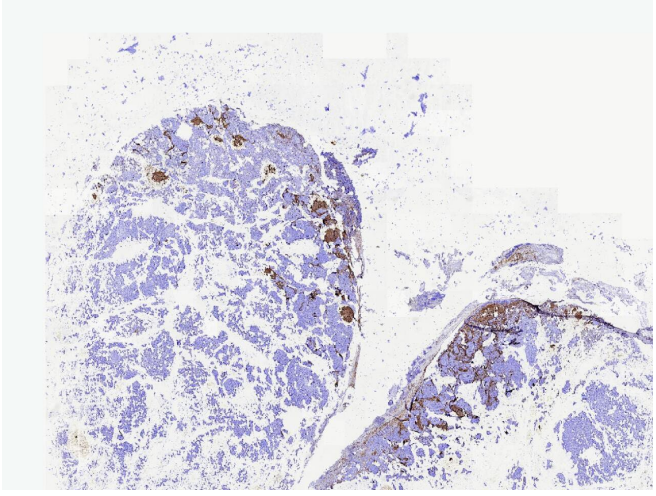

Figure 5. CD45 positive in residual lymphoid tissue. ACP HOGIP/UCAD Lab. Dakar.

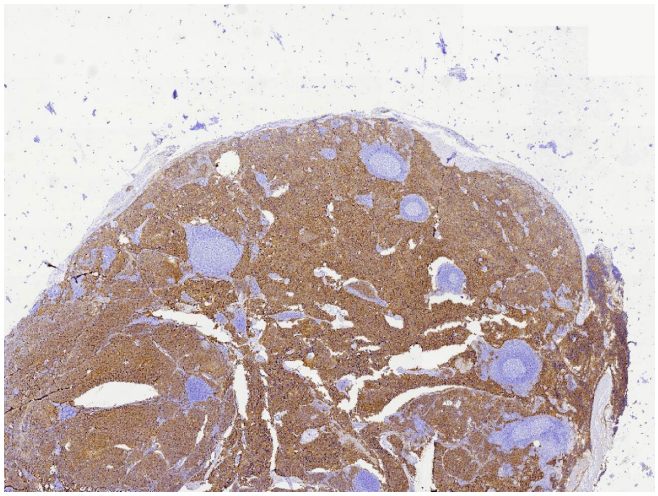

Figure 6. Positive diffuse synaptophysin. ACP HOGIP Lab/UCAD, Dakar.

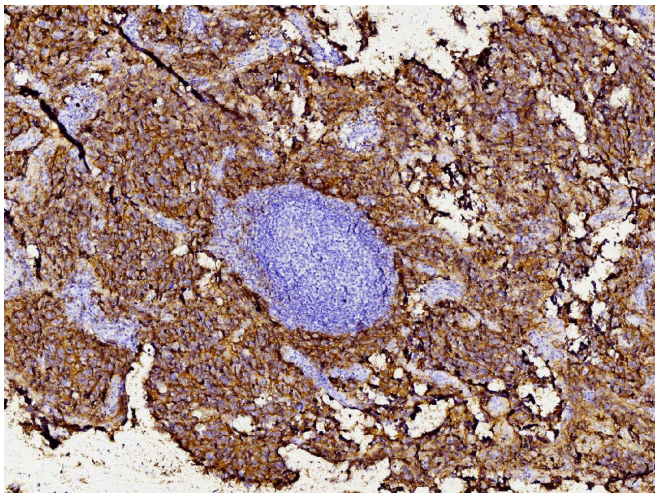

Figure 7. Diffuse and homogeneous membrane labeling with CD56 (×40). ACP Lab HOGIP/UCAD. Dakar.

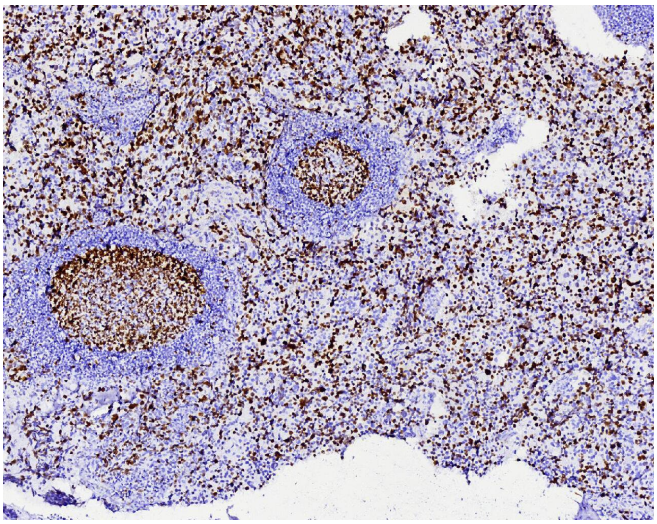

Figure 8. KI67 60% nuclear labeling. ACP HOGIP/UCAD Lab, Dakar.

Histopathological and Prognostic data:

An age > 1 year and abdominal location are associated with a poor prognosis. In our study, among the 35 neuroblastoma cases, 33 were older than one year, representing 92.85% of cases. Abdominal location was described in 8 patients, representing 22.86% of cases. Cervical and pelvic locations were associated with a good prognosis and represented 8.57% and 11.43%, respectively.

According to the INSS (International Neuroblastoma Staging System) classification, 74.29% of patients were at Stage 2B and 25.71% at Stage 4. According to the INPC (International Classification of Neuroblastoma Pathologies - Shimada System) classification, 30 patients had unfavorable histology, representing 85.71%, and 5 had favorable histology, representing 14.29% (Table 3).

Table 3. Distribution of patients according to primary sites, INSS classification and Shimada histological classification.

	Age (year)	
	<1	>1
Primary location		
Adrenal gland	0	8 (22.86%)
Abdomen	2 (5.71%)	6 (17.14%)
Pelvis	1 (2.86%)	2 (5.71%)
Head and neck	0	12 (34.29%)
INSS classification		
Stade 2B	3 (8.57%)	23 (65.71%)
Stade 4	0	9 (25.71%)
Shimada classification		
Favorable	2 (5.71%)	3 (8.57%)
Unfavorable	0	30 (85.71%)

4. Discussion

Neuroblastoma (NB) is an embryonic cancer arising from neural crest stem cells. This cancer is the most common malignancy in infants and the most common extracranial solid tumor in children [7] [8].

The incidence of neuroblastoma in Senegalese children is low compared to that reported in developed countries. In Senegal, neuroblastoma ranks fifth after nephroblastoma, retinoblastoma, lymphoma, and sarcomas. It represents nearly 4% of the activity of the Pediatric Hematology-Oncology Unit in Dakar [9]. In our study, this incidence was 5.27 cases per 1,000,000 children per year. A previous study conducted by the Franco-African Pediatric Oncology Group obtained an incidence of 4 cases per 1,000,000 children per year [10]. The incidence reported

here is similar to that of several Asian, African, and Latin-American countries.

It is likely that the incidence of neuroblastoma in developing countries is actually lower than that reported in developed countries. However, this variation should be interpreted with caution, as data from developing countries are primarily hospital-based and rely on time-limited surveys, which do not allow for valid epidemiological conclusions [10]-[12].

Limited information beyond single-institution experiences regarding neuroblastoma outcomes in Low and Middle Income Countries (LMIC) are available [13]. LMICs often lack functioning cancer registries, and existing ones fail to collect comprehensive data on paediatric cancers [14].

Despite the progressive though slow advances in neuro-oncology care, research, and diagnostics in sub-Saharan Africa (SSA), the epidemiological landscape of pediatric brain tumors (PBTs) remains underestimated [15].

The valuation of neuroblastoma research heterogeneity at African country level is unspecified [16].

Senegal does not have screening programs, such as those used in several developed countries, which have demonstrated that patients can experience spontaneous regression in more than 50% of cases [17] [18].

In our study, the mean age of patients at diagnosis was 5.42 years. It was 24 months in the United States, 19 months in the United Kingdom, 32 months in Morocco, 27 months in Mexico and Denmark, 30 months in Egypt, 36 months in Algeria, and 43 months in Türkiye [10] [12] [19]-[21]. The majority of patients are between 1 and 5 years old at diagnosis. This can be attributed to the spontaneous regression of neuroblastoma in the younger age group (<1 year), the lack of diagnosis in primary healthcare centers, and the nonspecificity of symptoms, which can lead to delayed diagnosis.

Several studies have reported a male predominance of neuroblastoma (sex ratio ranging from 1.1 to 1.5) [3], while in Morocco, a marginal female predominance has been identified (sex ratio: 0.8) [22]. In our study, we noted a female predominance with a sex ratio of 0.94.

Only histology confirms the diagnosis of neuroblastoma, and it is often performed after surgical examination. The histopathological examination revealed in all our patients a diffuse proliferation of small, round, sometimes elongated cells with salt-and-pepper chromatin, little cytoplasm, and indistinct cytoplasmic borders.

The classification of infantile NB proposed by Shimada and colleagues incorporates several aspects, as well as the proportion of differentiating elements (i.e., ganglion cells), the mitosis-karyorrhexis index (MKI), defined as the number of cells undergoing mitosis and karyorrhexis (the denominator is 5,000 neuroblastic cells), and the patient's age. Patient age, in itself, is a powerful prognostic factor in children with NB. Tumors are classified as histologically favorable or unfavorable based on stromal content (rich or poor Schwannian stroma), degree of neuroblastic differentiation, MKI, and age at diagnosis. The entry point into this classi-

fication system is the assessment of the stromal "character". The International Classification of Neuroblastoma Pathologies (INPC) has been used to predict prognosis. This classification is similar to that of Shimada and colleagues, being age-related and based on differentiation, the presence or absence of Schwannian stroma, and MKI.

The International Neuroblastoma Staging System (INSS) classification subdivides neuroblastoma into five stages numbered 1 to 4, in addition to stage 4S. The detection of distant metastases is a major criterion in the classification of neuroblastoma. Indeed, as soon as a distant metastasis is discovered, the tumor is classified as stage 4, except for metastases confined to the skin, liver, and bone marrow before the age of 1 year, which are classified as 4S "special".

Regarding the diagnostic stage and Shimada histological differentiation, as in the literature, we found no association between favorable histology and localized stages (I and II), or between unfavorable histological ratio and advanced stages (III and IV) [23] [24]. Nevertheless, histological evaluation will be necessary in all cases we study in the future to assess this correlation more precisely.

It has been emphasized that neuroblastoma occurs sporadically and that only 2% or fewer patients have a family history of neuroblastoma; however, there are a large number of cases of distinct cancers in family members of patients with neuroblastoma [25]. In our study, no cases of familial neuroblastoma were observed. Based on these data, we believe there may be a non-specific genetic susceptibility to neuroblastoma.

5. Conclusions

Neuroblastoma is the most common extracranial solid tumor in children. Its incidence in Senegal remains low, and diagnosis is often delayed. The most frequently observed macroscopic appearance was that of a firm tumor with a multinodular surface. The diagnosis is histological, and in our study, the poorly differentiated subtype was predominant. Immunohistochemistry allowed us to confirm this diagnosis using various specific neuronal markers such as synaptophysin, chromogranin, CD56, and enolase.

Limits: the relatively small sample size, due to the rarity of neuroblastoma and the two-center recruitment, limits statistical power and the possibility of conducting in-depth comparative analyses. The retrospective nature of the study also exposes the patient to information bias, due to clinical and histopathological records that were sometimes incomplete or heterogeneous. Furthermore, limited access to complementary techniques such as cytogenetic or molecular analyses (particularly the evaluation of MYCN amplification and associated chromosomal abnormalities) prevented optimal prognostic stratification according to international standards.

Ethical statement: all procedures were conducted in accordance with the Declaration of Helsinki and adhered to national and institutional ethical guidelines.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Heck, J.E., Ritz, B., Hung, R.J., Hashibe, M. and Boffetta, P. (2009) The Epidemiology of Neuroblastoma: A Review. *Paediatric and Perinatal Epidemiology*, **23**, 125-143. https://doi.org/10.1111/j.1365-3016.2008.00983.x

[2] Ward, E., DeSantis, C., Robbins, A., Kohler, B. and Jemal, A. (2014) Childhood and Adolescent Cancer Statistics, 2014. *CA*: *A Cancer Journal for Clinicians*, **64**, 83-103. https://doi.org/10.3322/caac.21219

[3] Steliarova-Foucher, D.E., *et al.* (2017) International Incidence of Childhood Cancer, 2001-10: A Population-Based Registry Study. *The Lancet Oncology*, **18**, 719-731. https://www.thelancet.com/oncology

[4] Benaicha, N., Msefer Alaoui, F., Mazouz, A., Amaadour, A., El Fakir, S., Nejjari, C., *et al.* (2015) Devenir des enfants traités et guéris d'un cancer au Maroc. *Revue d'Épidémiologie et de Santé Publique*, **63**, S88. https://doi.org/10.1016/j.respe.2015.03.118

[5] Hadley, L.G.P., Rouma, B.S. and Saad-Eldin, Y. (2012) Challenge of Pediatric Oncology in Africa. *Seminars in Pediatric Surgery*, **21**, 136-141. https://doi.org/10.1053/j.sempedsurg.2012.01.006

[6] Aygun, N. (2018) Biological and Genetic Features of Neuroblastoma and Their Clinical Importance. *Current Pediatric Reviews*, **14**, 73-90. https://doi.org/10.2174/1573396314666180129101627

[7] Maris, J.M. and Matthay, K.K. (1999) Molecular Biology of Neuroblastoma. *Journal of Clinical Oncology*, **17**, 2264-2264. https://doi.org/10.1200/jco.1999.17.7.2264

[8] Newman, E.A., Abdessalam, S., Aldrink, J.H., Austin, M., Heaton, T.E., Bruny, J., *et al.* (2019) Update on neuroblastoma. *Journal of Pediatric Surgery*, **54**, 383-389. https://doi.org/10.1016/j.jpedsurg.2018.09.004

[9] Dial, C., et al (2021) Profil épidémiologique des tumeurs solides pédiatriques durant la première année de mise en place du Centre de Reference pour le Diagnostic des Cancers de l'Enfant (CRDCE). Cancer Control Francophone, 51-53.

[10] Traoré, F., Eshun, F., Togo, B., Yao, J.J.A. and Lukamba, M.R. (2016) Neuroblastoma in Africa: A Survey by the Franco-African Pediatric Oncology Group. *Journal of Global Oncology*, **2**, 169-173. https://doi.org/10.1200/jgo.2015.001214

[11] Boumeddane, A., Moueden, M., et al. (2017) Prise en charge des enfants atteints de neuroblastome au niveau du centre émir Abdel Kader D'Oran 2017. *Journal Marocain des Sciences Médicales*, **21**. https://revues.imist.ma/index.php/JMSM/article/view/12958

[12] Juárez-Ocaña, S., Palma-Padilla, V., González-Miranda, G., Siordia-Reyes, A.G., López-Aguilar, E., Aguilar-Martínez, M., *et al.* (2009) Epidemiological and Some Clinical Characteristics of Neuroblastoma in Mexican Children (1996-2005). *BMC Cancer*, **9**, Article No. 266. https://doi.org/10.1186/1471-2407-9-266

[13] Heerden, J.V. and Kruger, M. (2020) Management of Neuroblastoma in Limited-Resource Settings. *World Journal of Clinical Oncology*, **11**, 629-643. https://doi.org/10.5306/wjco.v11.i8.629

[14] Mallo, B. (2024) Childhood Cancer Epidemiology in the Sub-Saharan French Speaking African Population. Thèse de doctorat, Université Paris Cité.

[15] Nyalundja, A.D., Kanmounye, U.S., Karekezi, C., Laeke, T., Thango, N. and Balogun, J.A. (2024) Pediatric Brain Tumors in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. *Journal of Neurosurgery: Pediatrics*, **33**, 524-535. https://doi.org/10.3171/2024.1.peds23282

[16] Motshudi, M.C., Naidoo, C.M. and Mkolo, N.M. (2024) The Race against Time for the Enhancement of African National Strategic Plans in the Neuroblastoma Research Heterogeneity. *Publications*, **12**, Article 45. https://doi.org/10.3390/publications12040045

[17] Qiu, B. and Matthay, K.K. (2022) Advancing Therapy for Neuroblastoma. *Nature Reviews Clinical Oncology*, **19**, 515-533. https://doi.org/10.1038/s41571-022-00643-z

[18] Okawa, S. and Saika, K. (2022) International Variations in Neuroblastoma Incidence in Children and Adolescents. *Japanese Journal of Clinical Oncology*, **52**, 656-658. https://doi.org/10.1093/jjco/hyac079

[19] Spix, C., Pastore, G., Sankila, R., Stiller, C.A. and Steliarova-Foucher, E. (2006) Neuroblastoma Incidence and Survival in European Children (1978-1997): Report from the Automated Childhood Cancer Information System Project. *European Journal of Cancer*, **42**, 2081-2091. https://doi.org/10.1016/j.ejca.2006.05.008

[20] Aydn, G.B., Kutluk, M.T., Yalçn, B., Büyükpamukçu, M., Kale, G., Varan, A., *et al.* (2009) Neuroblastoma in Turkish Children. *Journal of Pediatric Hematology/Oncology*, **31**, 471-480. https://doi.org/10.1097/mph.0b013e3181a6dea4

[21] Schroeder, H., Wacher, J., Larsson, H., Rosthoej, S., Rechnitzer, C., Pedersen, B.L., *et al.* (2009) Unchanged Incidence and Increased Survival in Children with Neuroblastoma in Denmark 1981-2000: A Population-Based Study. *British Journal of Cancer*, **100**, 853-857. https://doi.org/10.1038/sj.bjc.6604922

[22] Asmae, R., *et al.* (2016) Le profil épidemio-clinique, radiologique, histologique et évolutif du neuroblastome chez l'enfant (Experience de l'unité d'oncologie pédiatrique du CHU HASSAN II de Fès (à propos de 58 cas). https://toubkal.imist.ma/bitstream/handle/123456789/23606/214-16.pdf?sequence=1

[23] Peuchmaur, M., d'Amore, E.S.G., Joshi, V.V., Hata, J., Roald, B., Dehner, L.P., *et al.* (2003) Revision of the International Neuroblastoma Pathology Classification. *Cancer*, **98**, 2274-2281. https://doi.org/10.1002/cncr.11773

[24] Peuchmaur, M. (2004) Les tumeurs neuroblastiques périphériques, classification anatomo-pathologique. *Annales de Pathologie*, **24**, 556-567. https://doi.org/10.1016/s0242-6498(04)94018-7

[25] Maris, J.M. (2010) Recent Advances in Neuroblastoma. *New England Journal of Medicine*, **362**, 2202-2211. https://doi.org/10.1056/nejmra0804577