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Management outcomes of South African children diagnosed with neuroblastoma in adolescence

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ABSTRACT

Background: Neuroblastoma (NB) is an indolent disease in adolescents. Only 5 % of neuroblastoma diagnoses are made in adolescents and adults. Limited data exists on Africans of older age groups.
Objectives: We aimed to compare the characteristics and outcomes of South African children ≥10 years diagnosed with NB with international reports.
Patients and methods: Multicentric, retrospective data of South African patients (0–15 y) with NB diagnosed between January 2000 and December 2016 were analyzed. Clinical profiles and outcomes of adolescents (≥10 years) with NB were compared to those of the younger patients in our cohort. The outcomes of adolescents (≥10 years) with NB were compared with those reported in the global literature.
Results: Thirty adolescents with a male-to-female ratio of 1:0.6 were diagnosed with NB, constituting 6.5 % of all patients with NB. Metastatic disease at diagnosis was present in 24 (75 %), including lung metastases in 2 (6 %). Half of the patients presented with a raised lactate dehydrogenase (LDH) and/or ferritin and unfavorable pathology.
Post-induction remission rates were higher in the adolescent group (33 %) compared to the 18–59 months (24.8 %) and 5–9.9 years (29.7 %) cohorts but less than the <18 months (47.2 %) cohort ($p < 0.001$). The adolescent group had the poorest five-year overall survival (20.9 %) compared to the children <18 months (39.0 %), 18–59 months (44.1 %), or 5–9.9 years old (63.5 %) ($p < 0.001$).
Conclusions: Despite a favorable response rate to induction chemotherapy, the five-year overall survival of adolescents with NB is dismal in South Africa.

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Abbreviations:

COG	Children's Oncology Group
CR	Complete resection
EFS	Event-free survival
HR	High-risk
ICR	Incomplete resection
IR	Intermediate-risk
INPC	International Neuroblastoma Pathological Classification
INRG	International Neuroblastoma Risk Group
INSS	International Neuroblastoma Staging System
IQR	Interquartile range
LDH	Lactate dehydrogenase
LMIC	Low- and middle-income countries
LTFU	Lost-to-follow-up
LR	Low-risk
mCR	Complete metastatic remission
MYCN	N-myc gene amplification
NB	Neuroblastoma
OS	Overall survival
PODC	Paediatric Oncology for Developing Countries
POUs	Paediatric oncology units
SIOP	Society for Paediatric Oncology
VLR	Very low-risk

1. Introduction

Neuroblastoma (NB) has a broad spectrum of clinical manifestations. It is predominantly a disease of young children (<5 years) but also presents in adolescents and adults [1]. Fewer than 5 % of cases are diagnosed in patients ten years and older [1]. The heterogeneous clinical behavior ranges from spontaneous regression of lesions in infants and rapidly progressing disseminated disease in younger children to slow progression in older patients [1]. Age at presentation is a significant factor in the International Neuroblastoma Pathological Classification (INPC) as well as risk-stratification, as recommended by various Childhood Cancer Consortia, such as the Children's Oncology Group (COG), the International Neuroblastoma Risk Group (INRG), and the International Society of Pediatric Oncology-Pediatric Oncology in Developing Country (SIOP-PODC) guidelines for the treatment of NB in low- and middle-income countries (LMIC) [2].

Studies from high-income countries (HIC) suggest that NB in older ages has a more indolent course and is associated with specific genetic mutations. However, outcomes are poorer than for younger patients who have more aggressive pathology [1,3]. Data on older children and adolescents in LMICs are limited. A single institution study from Brazil reported a neuroblastoma prevalence of 2.9 % in adolescents and young adults. Authors reported a more indolent disease course and outcomes similar to those in HICs, with a five-year overall survival (OS) of 14 % [4]. Data on NB amongst the South African adolescents and adults are limited to a case series of three adult patients with extra-adrenal and abdominal primaries [5].

The primary objective of this study was to describe the clinicopathological characteristics and outcomes of South African children ≥10 years diagnosed with NB and to contrast that to the younger age groups. The secondary objective was to correlate the data with the international literature.

2. Methodology

2.1. Patient population (Fig. 1)

We conducted a retrospective chart review of children with NB treated at 11 pediatric oncology units (POU) in South Africa between January 2000 and December 2016. The diagnosis was based on histopathology of tumor tissue or infiltrated bone marrow specimens or typical radiological features with raised urine catecholamine levels.

The entire cohort was divided into four age categories: <18 months, 18–59 months, 5–9.9 years, and 10–15 years. The South African public health service defines children as up to the age of 15 years. Patients between 0 and 18 months with stage 4S/MS were excluded because of the unique pathophysiology of these tumors [2].

2.2. Staging and risk-stratification

Definitions for staging and risk classifications were based on the International Neuroblastoma Staging System (INSS) and the INRG staging system [2]. Pathology classification was done according to the INPC [6] and risk stratification to the COG classification system [1,2]. LDH and ferritin cut points were based on the recommendations of the SIOP-PODC management guidelines for neuroblastoma [2]. Remission was defined by the International Neuroblastoma Treatment Response criteria based on computed tomography (CT) or magnetic resonance imaging (MRI) in combination with bilateral bone marrow aspirates and trephines, including mIBG (metaiodobenzylguanidine)-imaging, where available [7].

2.3. Chemotherapy

The chemotherapy regimens included rapid COJEC, OJEC/OPEC, and the doxorubicin-containing St Jude Children's Research Hospital-based protocol for high-risk patients, CADO for intermediate-risk patients and CE for low-risk patients [8]. These treatment protocols guided surgical and radiotherapy interventions. A few treating centers had access to autologous stem cell transplants, and immunotherapy was unavailable.

2.4. Literature review

A literature search was performed using Pubmed, Scielo, and Google Scholar. The search terms included, but were not limited to, “neuroblastoma,” “adolescents,” “young adults,” adults” and “outcomes.” The aims were to identify published case series of 1) ≥5 adolescents (≥10 years), specifically from LMIC, or 2) adults (≥18 years) with NB. We compared the data on clinical profiles and outcomes of South African adolescents with NB with those reported in the international literature.

2.5. Data collection and statistical analysis

Data were analyzed using Stata 15.0, represented as means with standard deviation or median with interquartile range (IQR) for continuous variables and as frequencies or proportions for categorical variables. Kaplan-Meier survival curves were generated to obtain the OS rate and median survival time. Cox regression analysis was used to identify the predictors of OS. The five-year OS was defined as the period from diagnosis to death or the date last seen. Patients were categorized as "lost-to-follow-up" (LTFU) if they did not return for follow-up appointments for two years and were unreachable despite all efforts. Due to the poor global outcomes and aggressive nature of neuroblastoma, patients lost to follow-up were censored as dead during survival analysis. A p-value of less than 0.05 was considered significant.

The Stellenbosch University Medical Research Ethics Committee approved the study (Ref: N17/04/037), and reciprocal ethics approval was received from all participating universities. The study was conducted according to the Declaration of Helsinki.

3. Results

Age distribution of the patients was as follows: 126 (27.3 %) patients <18 months, 150 (32.4 %) in the 18–59 months group, 142 (30.7 %) in the 5–9.9 years group and 30 (6.5 %) in the adolescent group.

Patient and tumor characteristics of the adolescent cohort is summarized in Table 1:

Eighteen (60 %) were male and 12 (40 %) female. Half presented with adrenal primaries followed by extra-adrenal abdominal tumors in 10 (33 %) and thoracic primaries in 3 (10 %). There was one patient, each with pelvic and an unidentified primary (3 % each).

Most (n = 24; 80 %) had stage 4 disease at diagnosis with metastases to multiple sites. The sites of metastases were as follows: bone and bone marrow metastases (n = 19/24; 79 %), followed by lung metastases (n = 2/24; 8 %), distant lymph nodes (n = 2/24; 8 %) and one (4 %)had liver metastases. Six had localized disease: 2 (7 %), 3 (10 %), and 1 (3 %) had stage 3, 2, or 1 disease, respectively. According to the INRG staging, 24 (80 %) patients presented with stage M disease, five (17 %) with L2, and one (3 %) with stage L1 disease.

Half of the tumors had unfavorable histology. Fifteen (50 %) and 13 (43 %) presented with an elevated LDH (>750 IU/L) or serum ferritin (>120 ng/ml). Nine (30 %) had a documented *MYCN* gene amplification (*MYCN*) status, of which five (56 %) were non-amplified and four (44 %) were amplified. All *MYCN*-amplified tumors had distant metastasis to the bone and bone marrow. Most

Table 1
Clinical, laboratory profile, and outcomes of South African patients ≥10 years diagnosed with neuroblastoma between 2000 and 2016.

S No.	Sex	Age (mo)	Primary	INSS stage	INRGSS stage	Distant metastases	LDH (IU/L)	Ferritin (ng/ml)	INPC	MYCN	Risk	Remission	Survival (mo)	Outcome
1	F	121	Adrenal	4	M	Lungs	563	243	NA	NA	HR	No	99	Dead
2	M	125	Adrenal	4	M	Liver, lymph nodes	1359	NA	NA	NA	HR	No	56	Dead
3	F	126	Abdominal (Extra-adrenal)	4	M	Lungs	2518	NA	NA	NA	HR	No	58	Dead
4	M	126	Adrenal	4	M	BM, lymph nodes	1958	NA	NA	NA	HR	No	56	Dead
5	M	126	Abdominal (Extra-adrenal)	3	L2	None	280	102	NA	NA	IR	Yes	60	Dead
6	F	132	Adrenal	1	L1	None	NA	NA	NA	NA	LR	Yes	107	Alive
7	M	133	Adrenal	4	M	Bone, BM	3592	1455	NA	Amp	HR	No	129	Dead
8	F	134	Adrenal	4	M	Bone, BM	11520	539	UH	NA	HR	No	191	Dead
9	M	134	Adrenal	2	L2	None	1129	NA	UH	NA	LR	Yes	116	Dead
10	M	140	Adrenal	4	M	Bone, BM	1452	482	UH	NA	HR	Yes	120	Dead
11	M	140	Abdominal (Extra-adrenal)	4	M	Bone, BM	1167	1584	NA	NA	HR	No	18	Dead
12	M	141	Abdominal (Extra-adrenal)	4	M	Bone, BM	4066	NA	UH	NA	HR	No	92	Alive
13	M	142	Abdominal (Extra-adrenal)	4	M	Bone, BM	1225	NA	NA	NA	HR	No	44	Dead
14	F	142	Abdominal (Extra-adrenal)	4	M	Bone, BM	709	1486	UH	NA	HR	No	128	Dead
15	M	143	Adrenal	2	L2	None	NA	24	FH	NA	LR	Yes	17	Alive
16	M	145	Abdominal (Extra-adrenal)	3	L2	None	538	86	UH	NA	IR	Yes	156	Dead
17	F	150	Abdominal (Extra-adrenal)	4	M	Bone, BM	314	NA	NA	NA	HR	No	213	Dead
18	F	150	Adrenal	4	M	Bone, BM	1489	490	UH	NA	HR	No	236	Dead
19	M	150	Chest	4	M	Bone, BM	2769	1276	UH	Amp	HR	No	90	Dead
20	M	151	Chest	4	M	Bone, BM	1397	1447	NA	NA	HR	No	73	Dead
21	M	167	Adrenal	4	M	Bone, BM	444	750	NA	NA	HR	No	100	Dead
22	F	167	Pelvic	4	M	Bone, BM	2649	64	UH	NA	HR	Yes	171	Alive
23	M	175	Adrenal	4	M	Bone, BM	356	202	NA	NA	HR	No	196	Dead
24	M	188	Adrenal	4	M	Bone, BM	335	NA	NA	NA	HR	No	135	Dead
25	M	196	Adrenal	4	M	Bone, BM	585	194	UH	Amp	HR	Yes	126	Dead
26	M	204	Abdominal (Extra-adrenal)	4	M	Bone, BM	NA	NA	UH	NA	HR	No	33	Dead
27	F	124	Thorax	2	L2	None	310	NA	UH	NA	LR	Yes	51	Dead
28	F	124	Adrenal	4	M	Bone, BM	1201	1031	UH	NA	HR	Yes	1	Dead
29	M	124	Primary not found	4	M	Bone, BM	NA	NA	UH	NA	HR	No	1	Dead
30	F	124	Abdominal (Extra-adrenal)	4	M	Bone, BM	314	101	UH	Amp	HR	No	10	Dead

INSS: International Neuroblastoma Staging System; INRG: International Neuroblastoma Risk Group; INPC: International Neuroblastoma Pathology Classification; BM: bone marrow; UH: Unfavorable histology; FH: Favorable histology; NA: Not available; Amp: Amplified; LR: low-risk; IR: intermediate-risk; HR: high-risk.

patients had high-risk disease (n = 24; 80 %), four (13 %) had low-risk and two (7 %) intermediate-risk disease, respectively. All low or intermediate-risk NB obtained complete remission status after neoadjuvant chemotherapy and/or surgical resection. After induction chemotherapy, four (17 %) of the 24 high-risk NB (HR-NB) achieved complete metastatic remission, and no tumors were operated on. None of the HR-NB tumors were irradiated, nor did any patients with HR-NB receive maintenance therapy with anti-GD2 immunotherapy. The median follow-up period was 92 (IQR 44–135) months.

3.1. Bivariate analysis between age group cohorts and disease characteristics

Metastatic disease at presentation was noted in 70 % of adolescent patients, 80 % in patients 5–9.9 years, 80 % in patients 18–59 months, and 51 % in patients <18 months (p < 0.001).

Based on the INRG staging system, the adolescent cohort presented with a comparable percentage (16.7 %) of stage L2 disease [18–59 months old (15.9 %) and 5–9.9 years old (17.2 %)] but was less than in the <18 months old cohort (23.6 %) (p < 0.001). The <18 months old cohort also presented with a significantly higher percentage (14 %) of stage L1 disease compared to the adolescent cohort (3.3 %) (p < 0.001). The adolescent group presented with more non-bone and bone marrow metastases (lungs 6 %, liver 3 %, and distant lymph nodes 6 %) than the other age groups (p = 0.048).

The adolescents were also more likely to present with unfavorable histology (94 %) compared to younger patients [<18 months (43 %), 18–59 months old (70 %) and 5–9.9 years old (74 %)] (p < 0.001). Patients <18 months at presentation were more likely to present with favorable histology (47 %), in contrast with the 18–59 months (50 %), 5–10 years (57 %), or the adolescents (3.3 %) (p < 0.001).

The median LDH value for the adolescent group was 1184 U/L (IQR 444–1958) compared to 688 U/L (IQR 398–1602) in <18 months, 1229 U/L (IQR 562–2967) in 18–59 months, and 723 U/L (IQR 392–2114) in the 5–9.9 years (p = 0.003). LDH >750 U/L was recorded in 15/26 (58 %) adolescent patients, 27/54 (50 %) of the 18–59 months, and 48/102 (47 %) patients <18 months (p = 0.017).

The median ferritin value for the adolescent group was 489 ng/ml (IQR 102–1276) compared to 126 ng/ml (IQR 53–288) in <18 months, 249 ng/ml (IQR 113–539) in 18–59 months old and 253 ng/ml (IQR 235–661) in the 5–9.9 years old (p < 0.001). Most of the adolescent group (n = 13/18; 72 %) presented with ferritin levels >120 ng/ml, comparable to the 18–59 months.

(n = 108/150; 72 %), lower than the 5–9.9 years (n = 34/40; 85 %) but higher than the <18 months old (n = 34/71; 47.9 %) (p = 0.018). The relative proportion of high-risk disease was 80 % in the adolescents in comparison to 89 % in the 18–59 months old group and 86 % in the 5–10 years old group (p < 0.001).

The INPC classification was known in 246 (53.1 %) of patients. Unfavorable histology was seen in 24.4 % (n = 30/123) patients <18 months, 38.6 % (n = 95/246) in 18–59 months old, 31.3 % (n = 20/64) in the 5–9.9 years old and 50 % (n = 15/30) adolescents (p < 0.001).

In the 182 patients where *MYCN* amplification was known, there was amplification in 41.7 % (n = 20/48) patients <18 months, 65 % (n = 67/103) in 18–59 months old, 50 % (n = 11/22) in the 5–9.9 years old and 55.6 % (n = 5/9) adolescents (p = 0.05).

The risk stratification could not be determined in 22 (4.7 %) patients. Low-risk disease was seen in 22.8 % (n = 28/123) patients <18 months, 4.9 % (n = 67/246) in 18–59 months old, 6.3 % (n = 4/64) in the 5–9.9 years old and 13.3 % (n = 4/30) adolescents (p < 0.001). Intermediate-risk disease was seen in 17.1 % (n = 21/123) patients <18 months, 4.0 % (n = 10/246) in 18–59 months old, 4.7 % (n = 3/64) in the 5–9.9 years old and 6.7 % (n = 2/30) adolescents (p < 0.001). High-risk disease was seen in 48.0 % (n = 59/123) patients <18 months, 89.0 % (n = 219/246) in 18–59 months old, 85.9 % (n = 55/64) in the 5–9.9 years old and 80.0 % (n = 24/30) adolescents (p < 0.001).

Complete remission after induction chemotherapy was achieved in 33 % (n = 10) of the adolescent group, which was higher than the 18–59 months old (n = 108, 25 %) and 5–9.9 years old (n = 12, 30 %) cohorts, but less than the <18 months old (n = 60, 47 %) cohort (p < 0.001).

There was no statistical significance in the distribution of sex (p = 0.47) or location of the primary tumor (p = 0.23) between the four cohorts.

3.2. Five-year overall survival outcomes

The significant factors for five-year OS were age (p < 0.001), LDH level >750 IU/L (p = 0.011), and whether complete tumor remission was achieved after induction chemotherapy (p = 0.006). The adolescent group had the poorest five-year OS of 20.9 % compared to the <18 months old cohort (39 %), 18–59 months old (44 %) and 5–9.9 years old (63.5 %) (p < 0.001) (Fig. 2). Those patients who presented with an LDH level <750 IU/L had a five-year OS of 56 % compared to 45.5 % if the level was above 750 IU/L (p = 0.011). Patients who achieved complete remission after induction chemotherapy had a five-year OS of 56.8 % compared to 43.2 % who failed to achieve complete remission (p = 0.006). Event-free survival cannot be reported due to incomplete data.

Poor prognostic factors for five-year OS included age ≥10 years, LDH >750 U/L, and incomplete remission after induction chemotherapy. Factors that did not predict survival included sex, stage (INSS or INRGSS), type of metastases, histology, ferritin, MYCN amplification status, and risk stratification.

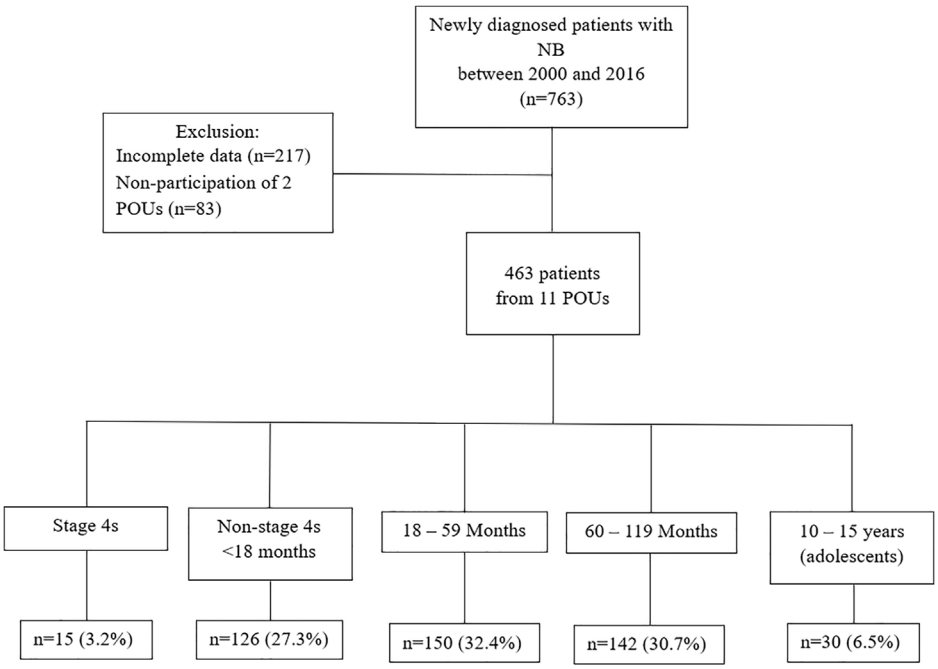
Literature review [1,4,9–16].

The authors identified thirty-four articles, abstracts, and documents on NB in populations aged 10 years and older. Ten studies described cohorts of patients from North America, Europe, China, and Brazil. Of these, three (30 %) were national studies, and seven (70 %) were single-center studies. Only two (20 %) were from an LMIC setting. Twelve (35.3 %) articles were case reports or case series of adult patients. Fourteen (41.2 %) articles described the clinical characteristics and pathophysiology in older groups of patients diagnosed with NB.

The total number of adolescent and adult patients diagnosed with NB between 1968 and 2018 was 195 (Table 2), with a male-to-female ratio of 1:0.9. The mean age was 14 years (range 10–86 years). Adolescents constituted 70.3 % of the cohort. The NB incidence decreased with older age, with the adult cohort contributing 29.7 %. Males presented more often with metastatic disease. The long-term survival for the entire cohort was 39.5 %, but 40.9 % and 36.2 % for the adolescent and adult cohorts, respectively. The outcome for the non-stage 4 patients was 62 % compared to 26.6 % for the cohort with distant metastatic spread.

4. Discussion

Children diagnosed with NB at an older age are reported to have a more indolent course but poorer survival outcomes than those diagnosed at younger ages [3]. The South African cohort had a more pronounced male predominance than reported in international cohorts. We found unfavorable long-term outcomes and dismal rates of post-induction complete remission for high-risk disease, reminiscent of what is reported in the literature. Despite the higher levels of LDH and ferritin and a higher prevalence of unfavorable histology, the adolescent patients had similar outcomes to the



NB – neuroblastoma; SACTR – South African Children's Tumour Registry; POUs – Pediatric Oncology Units

Fig. 1. FLOW diagram**:** Study cohorts.

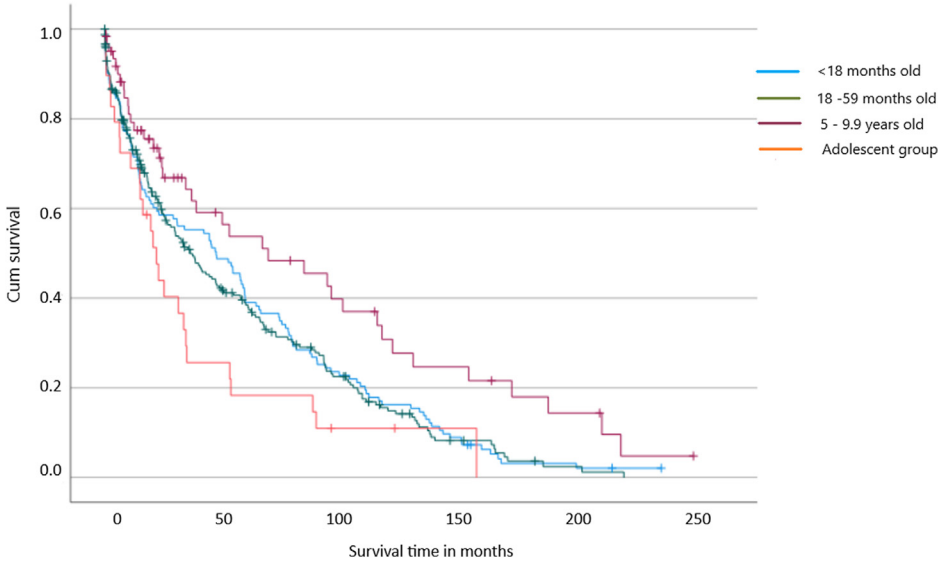


Fig. 2. The five-year overall survival outcomes based on age groups ($p < 0.001$)**.**

other age groups in our cohort [8]. This corresponds with higher levels of LDH and ferritin and a greater percentage of unfavorable histology usually observed in NB with unfavorable molecular profiles.

The proportion of patients who present at >10 y of age ranges from 2.3 % to 4.8 % [1,4,9–16]. We report a percentage of 6.5 %, but the numbers are too small to draw robust conclusions. Different POUs have different age cut-offs in South Africa, with some POUs being allowed to accept patients up to 18 years and others only up to 12 years. Published cohorts included adolescents up to 18 years of age for analysis. Although cases older than 15 years contribute a small percentage of the global prevalence of NB [17], we may argue that the South African percentage is high compared to other groups because fewer infant cases of NB are diagnosed in South Africa [18], a group that globally contributes the highest number of cases. The percentage of adolescent NB cases may be falsely over-represented because the percentage of children less than 18 months old in South Africa is underdiagnosed [19].

Tumor characteristics in children ten years or older may include bilateral adrenal primaries and/or larger tumor volumes at presentation, rare morphologic features, and novel mutations on multiple DNA microarray results [20]. The French group reported

Table 2
Summary of literature on adolescent and adult neuroblastoma [1,4,9–16].

Case series	Period	N (%)	Male: Female ratio	Median age (years)	Range (years)	Outcome survival N (%)	Median duration of follow-up (months)	Range (months)
Brazil **(Casteleti et al.)** [4]								
Total	1991–2012	7	3:4	11.5	10.4–30.1	1/7 (14.2)	3.32	2.06–11.37
Adolescents		5 (71.4)	2:3	10.9	10.4–16.6	1/5 (20.0)	4.15	2.06–11.37
Adults		2 (28.6)	1:1	24.7	19.4–30.1	0/2 (0.0)	3.23	3.15–3.32
Non-Stage 4		1 (14.3)	0:1	16.6	–	0/1 (0.0)	4.15	–
Stage 4		6 (85.7)	3:3	10.8	10.4–30.1	1/6 (16.7)	3.15	2.06–11.37
China (Jin et al.) [9]								
Total	2017–2020	5	3:2	20.0	15.0–25.0	4/5 (80.0)	15.0	2.0–28.0
Adolescents		3 (60.0)	2:1	15.0	15.0	3/3 (100.0)	8.0	2.0–15.0
Adults		2 (40.0)	1:1	22.5	20.0–25.0	½ (50.0)	13.5	19.0–28.0
Non-Stage 4		2 (40.0)	1:1	20.0	15.0–25.0	2/2 (100.0)	10.0	2.0–19.0
Stage 4		3 (60.0)	1:2	15.0	15.0–20.0	2/3 (66.7)	15.0	8.0–28.0
French (Gaspar et al.) [10]								
Adolescents	1987–1999	22	13:9	13.7	10.3–16.0	10/22 (45.5)	32	8–148
Non-Stage 4		9 (40.9)	5:4	12.6	10.9–16.0	8/9 (88.9)	77	22–148
Stage 4		13 (59.1)	8:5	13.8	10.3–17.8	2/13 (15.4)	24	8–82
Italy (Conte et al.) [11]								
Adolescents	1979–2002	53	24:29	12.0	10.0–18.0	20/53 (37.7)	33	2–192
Non-Stage 4		22 (41.5)	5:17	12.0	10.3–16.1	12/22 (54.5)	38	14–192
Stage 4		31 (58.5)	19:12	12.6	10.0–18.0	8/31 (25.8)	21	2–120
Italy (Podda et al.) [12]								
Total	1982–2001	27	16:11	17.0	12.0–69.0	5/27 (18.5)	40	9–307
Adolescents		14 (51.9)	9:5	14.0	12.0–17.0	3/14 (21.4)	39	9–307
Adults		13 (48.1)	7:6	21.0	18.0–69.0	2/13 (15.4)	40	15–258
Non-Stage 4		11 (40.7)	7:4	17.0	12.0–69.0	5/11 (45.5)	97	12–307
Stage 4		16 (59.3)	9:7	17.0	12.0–25.0	0/16 (0.0)	33	9–125
International Neuroblastoma Risk Group (INRG) database (Mossé et al.) [1]								
Total	1990–2002	200	–	–	10.0–21.0	46 ± 5 % 5yr OS	–	–
Adolescents		–	–	–	10.0–17.0	–	–	–
Adults		–	–	–	18.0–21.0	–	–	–
Non-Stage 4		86 (42.0)	–	–	10.0–17.0	66–91 % 5yr OS	–	–
Stage 4		114 (58.0)	–	–	18.0–21.0	22 ± 5 % 5yr OS	–	–
Spain (Castel et al.) [13]								
Total	1992–2007	22	12:10	13.33	10.18–24.69	13/22 (59.1)	26	4–116
Adolescents		19 (86.4)	10:9	11.91	10.18–16.98	11/19 (57.9)	28	6–116
Adults		3 (13.6)	2:1	19.21	18.59–24.69	2/3 (66.7)	16	4–36
Non-Stage 4		10 (45.5)	4:6	11.27	10.18–19.21	8/10 (80.0)	16	6–116
Stage 4		12 (54.5)	8:4	13.33	10.93–24.69	5/12 (41.7)	28	4–106
USA (Franks et al.) [14]								
Total	1968–1995	16	9:7	20.0	13.0–36.0	4/16 (25.0)	41	2–258
Adolescents		6 (37.5)	4:2	15.0	13.0–17.0	1/6 (16.7)	22	2–258
Adults		10 (62.5)	5:5	28.0	18.0–36.0	3/10 (30.0)	42	15–197
Non-Stage 4		7 (43.8)	4:3	32.0	13.0–33.0	2/7 (28.6)	62	24–258
Stage 4		9 (56.2)	5:4	17.0	15.0–32.0	2/9 (22.2)	33	2–132
USA (Kushner et al.) [15]*								
Total	1985–2001	30	16:14	19.0	12.0–41.0	13/30 (43.3)	34.0	9.0–181.0
Adolescents		15 (50.0)	9:6	14.0	12.0–18.0	7/15 (46.7)	39.0	9.0–181.0
Adults		15 (50.0)	7:8	24.0	19.0–41.0	6/15 (40.0)	34.0	11.0–117.0
Non-Stage 4		3 (10.0)	2:1	20.0	18.0–27.0	2/3 (66.7)	117	13.0–130.0
Stage 4		27 (90.0)	14:13	18.0	12.0–41.0	11/27 (40.7)	34.0	9.0–181.0
Total (from the entire literature)								
Total	1968–2020	182	96:86	14	10–69	70/182 (38.5)		
Adolescents		137 (75.3)	73:64	13	10–17.8	56/137 (40.9)		
Adults		45 (24.7)	23:22	26	18–86	21/58 (36.2)		
Non-Stage 4		65 (35.7)	28:37	23	10.18–69	39/65 (60.0)		
Stage 4		117 (64.3)	68:49	14.2	10–41.0	31/117 (26.5)		

*All case series included children from 10 years of age and above except Kushner et al. (USA), who included children 12 years and older.

an almost equal number of localized and metastatic diseases [10], whereas 70 % of the South African adolescent group presented with metastases. This is in keeping with the percentage of South African patients presenting with metastatic disease across all age groups [21]. Furthermore, the South African cohort exhibited more lung metastases, which is not the most common site of seeding in NB. A literature review of 137 concluded that adolescents and adults diagnosed with NB frequently presented with heterogeneous clinical factors, genetic factors, and tolerance to treatment [9].

In our study, the *MYCN* status was known in less than a quarter of tumors, which makes interpretation unreliable. Yet 44.4 % of tumors in the South African adolescent cohort were *MYCN*-amplified. In the younger age groups, up to 50 % were *MYCN*-amplified. NB is indolent in older children, and *MYCN* amplification was infrequently identified [1]. Suzuki et al. reported combined *MYCN*-amplification rates of 9 % in adolescents and adults, while Mossé et al. reported rates of 11–13 % [1,16]. Yet a loss of heterozygosity at 11q and 3p chromosomal segments and identification of *ATRX* mutations predominantly in older patients with NB further supports biological differences in older age groups. An Italian study identified that 17q gain and *ALK* mutations were associated with advanced age at diagnosis and poor prognosis [22]. This was confirmed by a Spanish study that concluded that adolescents with advanced disease fared poorer than younger patients with advanced NB [13].

Compared to resource-limited settings, data from the Survival, Epidemiology, and End Results (SEER) review reported superior five-year OS of 46.2 % and 36.3 % in adolescents and adults, respectively [23]. In a Brazilian study, children ≥9 years had an inferior OS than reported cohorts of children (20 % and 62 %, respectively). European studies reported similar findings [22]. The five-year OS for the older ages in the South African cohort followed the same trend, with poorer outcomes than for the younger age groups. We postulate that, in the absence of advanced treatment options such as autologous transplant and targeted therapies, the more aggressive nature of tumors in younger age groups and the high prevalence of advanced disease at presentation account for the higher mortality. The five-year OS of the South African adolescent group is comparable to the United States of America (25 %), better than the Brazilian cohort (14.2 %) but far worse than Spanish, France, and Italian cohort (37.7–59.1 %) [13]. Suzuki et al. further described an indolent clinical course in adolescents with longer post-relapse survival compared to adults, who had rapid progression after relapse with a five-year progression-free survival of only 9.7 % [16]. Those patients alive after five years died in the following five years. The ten-year OS was only 19.0 % [16]. The reason was the different salvage therapies administered in the two cohorts [16]. In our study, the survival of adolescents decreased significantly after five years compared to the adult cohort in the Memorial Sloan Kettering Cancer Centre's experience. The reason was the absence of autologous bone marrow transplants, immunotherapy, or other salvage options.

Despite these poor outcomes, reports indicate that adolescents and adults tolerate autologous transplants and immunotherapy with anti-GD2 well, alike young children [1,16]. These therapies may provide additional survival benefits, which remain untested in the South African cohort [1,16]. However, the adolescent group in South Africa had superior survival rates to those <18 months group. We postulate that in the <18-months group, only children with symptomatic or advanced disease are diagnosed, and patients in whom the tumor spontaneously regresses rarely get clinical attention [18]. This may result in false low survival in this age group.

Complete molecular profiles of South African children diagnosed with NB, including those in adolescence, have not been reported. The only tumor marker of prognostic significance was LDH. The adolescent cohort had lower mean LDH values but poorer five-year OS. This finding does not align with general validated results that lower LDH values are associated with better OS [2]. A relationship between LDH levels and slow-growing NB tumors has not been established. It would be valuable to perform microarrays on tumors of South African patients to ascertain homologies between the stage 2, 3, and 4 disease cohorts, given the number of patients with stage 4 who achieved remission.

Data on post-induction remission rates in older patients are limited. A French study reported an excellent partial response rate but a low complete post-induction remission rate of 10 % and 0 %, respectively [10]. This contrasts with the 33 % reported for older age groups in our South African study, which is comparable to younger age groups.

This study is limited by its historical nature and the limited molecular information available on South African cohorts. Our small cohort of patients with NB in adolescence limits more advanced statistical evaluation, interpretation of tumor characteristics and poor prognostic factors. We decided to censor patients lost to follow-up as “dead”. In the absence of autologous transplant and immunotherapy, it is unlikely that these patients survived, and we aimed to prevent reporting a false high OS outcome.

5. Conclusion

The clinical spectrum of South African children diagnosed with NB is varied and displays some characteristics divergent from international reports. While international reports indicated poorer outcomes for older age groups, the South African cohort indicated that the indolent nature of the disease in the advanced age group may provide some treatment response advantage, albeit not a survival advantage. With optimal advanced treatment options, survival can be improved to approach that of European cohorts.

Contributors’ statement

JvH and MK conceptualised and designed the study. JvH analyzed data and wrote the manuscript. JvH and TME performed the statistical analysis. All authors collected and contributed data, critically reviewed, edited and revised the manuscript. The manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and that each author confirms that the manuscript follows ethical and good academic practice guidelines.

Data availability statement

Data is available on reasonable request and guidelines as determined by ethical committees.

Ethical statement

The Stellenbosch University Medical Research Ethics Committee approved the study (Ref: N17/04/037) with reciprocal ethics approval received from all participating universities. The Patient consent was waivered because data was sourced retrospectively. The study was conducted according to the principles of the Declaration of Helsinki.

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Conflict of interest

There is no conflict of interest to disclose.

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References

[1] Mossé YP, Deyell RJ, Berthold F, Nagakawara A, Ambros PF, Monclair T, et al. Neuroblastoma in older children, adolescents, and young adults: a report from the International Neuroblastoma Risk Group project. Pediatr Blood Cancer 2014;61(4):627–35.
[2] Parikh N, Howard S, Chantada G, Israels T, et al. SIOP-PODC adapted risk stratification and treatment guidelines: recommendations for neuroblastoma in low- and middle-income settings. Pediatr Blood Cancer 2015;62(8):1305–16.
[3] Mazzocco K, Defferrari R, Sementa AR, Garaventa A, Longo L, De Mariano M, et al. Genetic abnormalities in adolescents and young adults with neuroblastoma: a report from the Italian Neuroblastoma Group. Pediatr Blood Cancer 2015;62(10):1725–32.
[4] Casteleti P, Senerchia AA, Caran E. Neuroblastoma in patients over 10 Years old: a 21-year experience at a single institution. Austin Pediatr 2017;4(1):1052.
[5] Behr A, Uijs RRJ, Phillips JI. Neuroblastoma in adults. S Afr Med J 1989;75(4):333–5.
[6] Shimada H, Umehara S, Monobe Y, Hachitanda Y, Nakagawa A, Goto S, et al. International neuroblastoma pathology classification for prognostic evaluation of patients with peripheral neuroblastic tumors: a report from the Children's Cancer Group. Cancer 2001;92:2451–61.
[7] Park JR, Bagatell R, Cohn SL, Pearson AD, Villablanca JG, Berthold F, et al. Revisions to the international neuroblastoma response criteria: a consensus statement from the national cancer institute clinical trials planning meeting. J Clin Oncol 2017;35(22):2580–7.
[8] Van Heerden J, Geel J, Hendricks M, Wouters K, Büchner A, et al. The evaluation of induction chemotherapy regimens for high-risk neuroblastoma in South African children. Pediatr Hematol Oncol 2020;37(4):300–13.
[9] Jin QY, Du SB, Yuan XJ. Exploring the prognosis of neuroblastoma in adolescents and adults: a case series and literature review. Neoplasma 2022;69(2):464–73.
[10] Gaspar N, Hartmann O, Munzer C, Bergeron C, Millot F, Cousin-Lafay L, et al. Neuroblastoma in adolescents. Cancer 2003;98(2):349–55.
[11] Conte M, Parodi S, De Bernardi B, Milanaccio C, Mazzocco K, Angelini P, et al. Neuroblastoma in adolescents: the Italian experience. Cancer 2006;106(6):1409–17.
[12] Podda MG, Luksch R, Polastri D, Gandola L, Piva L, Collini P, et al. Neuroblastoma in patients over 12 years old: a 20-year experience at the istituto nazionale tumori of milan. Tumori 2010;96(5):684–9.
[13] Castel V, Villamón E, Cañete A, Navarro S, Ruiz A, Melero C, et al. Neuroblastoma in adolescents: genetic and clinical characterization. Clin Transl Oncol 2010;12(1):49–54.
[14] Franks LM, Bollen A, Seeger RC, Stram DO, Matthay KK. Neuroblastoma in adults and adolescents: an indolent course with poor survival. Cancer 1997;79(10):2028–35.
[15] Kushner BH, Kramer K, LaQuaglia MP, Modak S, Cheung NK. Neuroblastoma in adolescents and adults: the Memorial Sloan-Kettering experience. Med Pediatr Oncol 2003;41(6):508–15.
[16] Suzuki M, Kushner BH, Kramer K, Basu EM, Roberts SS, Hammond WJ, et al. Treatment and outcome of adult-onset neuroblastoma. Int J Cancer 2018;143(5):1249–58.
[17] Okawa Sumiyo, Saika Kumiko. International variations in neuroblastoma incidence in children and adolescents. Jpn J Clin Oncol 2022;52(6):656–8.
[18] Van Heerden J, Esterhuizen TM, Hendricks M, Poole J, Büchner A, Naidu G, et al. Age at diagnosis as a prognostic factor in South African children with neuroblastoma. Pediatr Blood Cancer 2021;68(4):e28878.
[19] Van Heerden J, Esterhuizen TM, Hendricks M, et al. Age at diagnosis as a prognostic factor in South African children with neuroblastoma. Pediatr Blood Cancer 2021;68:e28878.
[20] McCarthy LC, Chastain K, Flatt TG, Taboada E, Garola R, Herriges J, et al. Neuroblastoma in adolescents and children older than 10 Years: unusual clinicopathologic and biologic features. J Pediatr Hematol Oncol 2019;41(8):586–95.
[21] Van Heerden J, Hendricks M, Geel J, et al. Overall survival for neuroblastoma in South Africa between 2000 and 2014. Pediatr Blood Cancer 2019;66:e27944.
[22] Lucena J, Alves M, Abib S, Souza G, Neves R, Caran E. Clinical and epidemiological characteristics and survival outcomes of children with neuroblastoma: 21 Years of experience at the instituto de oncologia pediátrica, in são paulo, Brazil. Rev Paul Pediatr 2018;36(3):254–60.
[23] Esiashvili N, Goodman M, Ward K, Marcus Jr RB, Johnstone PA. Neuroblastoma in adults: incidence and survival analysis based on SEER data. Pediatr Blood Cancer 2007;49:41–6.