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Inequity in paediatric oncology in South Africa – The neuroblastoma case study

Authors:
Jaques van Heerden[1,2]
Tonya Esterhuizen[3]
Mariana Kruger[1]

Affiliations:
[1]Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

[2]Department of Peadiatrics, Antwerp University Hospital, Antwerp, Belgium

[3]Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Corresponding author:
Jaques van Heerden,
jaques.vanheerden@uza.be

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Background: The South African Constitution affords everyone the right to access healthcare services, but in children the care must ensure survival.

Aim: This study aimed to determine whether there was access to equitable paediatric oncology services for the management of neuroblastoma in South Africa.

Setting: Paediatric oncology services in South Africa between 2000 to 2014.

Methods: A literature review was carried out, focussing on access to healthcare in South Africa for children with neuroblastoma. Services were classified in accordance with the International Society of Paediatric Oncology resource settings for neuroblastoma diagnosis. Supplementary data from a retrospective study of the management of neuroblastoma in South Africa were evaluated.

Results: The neuroblastoma care services in South Africa were not uniformly resourced and accessible across the provinces. Two provinces (2/9 provinces) had excellent healthcare services that included access to transplant facilities, whilst three (3/9 provinces) had no services. Traveling distances to healthcare services pose major challenges, whilst number of medical staff providing oncology care were unequally distributed. The Constitution did not define basic healthcare for children, nor did the National Cancer Control plan acknowledge childhood cancer as a defined entity without provision until 2022.

Conclusion: Children diagnosed with neuroblastoma do not have equitable access to healthcare as stated in the South African Constitution. The case of neuroblastoma highlights the inequitable access to childhood care as a whole in South Africa. As the health of children is a national priority, it is therefore necessary to sensitise policymakers to the needs of children with cancer.

Keywords: paediatric oncology; equality; South Africa; neuroblastoma; patient advocacy.

Introduction

When the Republic of South Africa ratified the United Nations (UN) Convention on the Rights of the Child in 1995 and subsequently enshrined children's rights to health care in 1996 in its Constitution, the country committed to provide children with equitable health care.[1] Section 27 of the South African Constitution affords children access to health care as citizens of South Africa, and they have the right to basic healthcare services under section 28.[2] These two rights in the Bill of Rights *facilitate* the access to health care.[1] Children may lodge a claim against the state for the provision of healthcare services when their parents are unable to afford healthcare services.[1]

The South African Constitution states that the state should also take *reasonable* action to comply with the provision of health care.[2,3] It does not fully define the nature of the healthcare services beyond emergency medical care and basic health services, which may be interpreted as primary health care or preventative health care.[4] Section 28 of the Bill of Rights stipulates that children have a right to basic nutrition, shelter, basic healthcare services and social services.[2] The Constitution protects the right to life, and as oncological diseases are life-threatening, oncological health care should be defined as an essential healthcare service.[2] The government should provide health care in accordance with its available resources but may not allocate a disproportionate share of the budget to one sector of health care, and thereby create shortages for other healthcare services.[4] To be able to prioritise healthcare services, major public health needs should be identified for state funding.[3]

Childhood cancer is one of the leading causes of mortality in high-income countries.[5] Yet, 90% of the world's paediatric population lives in low- and middle-income countries (LMICs), where 84% of the global childhood cancer burden occurs.[6] This is the estimate, taking into account that there may be a 10%–45% underestimation of childhood cancer incidences, partially because of the lack of cancer registries and poor access to oncological health care.[6] In South Africa, the number of underdiagnosed patients is estimated to be in the same region as in other LMICs.[7] As section 37 of the Constitution states that emergency health care is a right, children with cancer should have the right to life-saving treatment regardless of where in South Africa they live.

According to the World Health Organization (WHO), the definition of access to medical care pertains to physical access, economic access and information about health care.[8] Physical access is defined as that 'health facilities, goods and services must be within safe physical reach for all sections of the population, especially vulnerable or marginalised groups'. Economic accessibility is defined as:

> [*A*] measure of people's ability to pay for services without financial hardship. It takes into account not only the price of the health services but also indirect and opportunity costs (e.g. the costs of transportation to and from facilities and of taking time away from work).[8]

Access consists of *services* that can provide the needed care, *timeliness* of receiving the care when it is recognised, a *workforce* that can provide the care and *coverage* or the means to access health care.[9,10]

We aimed to evaluate access to equitable paediatric oncology services for the treatment of neuroblastoma (NB), a childhood malignancy, in line with the stipulations of the South African Constitution. The three issues for evaluation were equal access to NB care, equal paediatric oncology services and other equal resources needed for childhood cancer diagnosis and treatment. Furthermore, we wished to determine whether the state had taken reasonable action for NB health care towards achieving the aim of the WHO International Society for Paediatric Oncology (SIOP) to improve childhood cancer survival in LMICs to 60% by 2030.[11]

Materials and methods

Electronic literature reviews were conducted on the constitutional, legal and ethical issues pertaining to equality of medical care and access to medical care in the South African setting. Searches were conducted on PubMed, Google Scholar, WorldCat and JSTOR with search terms 'access to medical care', 'rights to medical care', 'equal medical care', 'cancer', 'children' and 'South Africa'. The reference lists of publications were screened to supplement the search results.

Setting

South Africa consists of nine provinces, subdivided into nearly 300 districts.[12,13] The health care in the country is administrated by three systems: The national, provincial and the district health systems.[12,13] The National Department of Health (DoH) coordinates with the public and private healthcare services at national, provincial and district levels, whilst administrative, financial and supportive services are regulated at the provincial and district levels.[14] In 2012, South Africa's DoH initiated a National Health Insurance (NHI) plan as an efficient, equitable and sustainable health system.[15] This social health insurance plan was developed to make health care more accessible and affordable for citizens who have no other way of funding such care individually, but it has not yet been implemented because of the funding still being sourced.[15]

Data

Based on the South African Children's Cancer study group's retrospective study of the management and outcomes of NB between 2000 and 2014, we evaluated the burden of three prognostic factors, age at diagnosis, stage and risk stratification, associated with NB in each province of South Africa. Furthermore, we evaluated the human resources and paediatric oncology services during this period by comparing the provincial paediatric oncology services that manage children diagnosed with NB. Paediatric oncology services were evaluated according to the SIOP resource settings for NB diagnosis, staging and risk stratification (Appendix 1).[16] A multi-disciplinary team including sub-specialist doctors, nurses and laboratory staff was involved in managing childhood malignancies.[16] We surveyed only former and current paediatric oncologists and paediatric surgeons attached to paediatric oncology services to establish the number of physicians working in paediatric oncology associated with individual paediatric oncology units (POUs), where possible, annual departmental hospital reports were cross-referenced for confirmation. To evaluate access to POUs, three random furthest points with a named settlement in each province were chosen. The distance and travel duration between the settlement and the nearest paediatric POU were determined with Google Maps®.[17]

Statistical analysis

Data from a retrospective study on the management and outcomes of South African children diagnosed with NB between 2000 and 2014 were used to determine the overall survival (OS) and associated 95% confidence intervals (CI) for each province. These data were described using Kaplan Meier curves with differences evaluated using log rank tests. The Kaplan Meier curves were assessed using IBM SPSS Version 25 (IBM Corporation, USA) statistical software.[18] For all calculations, a p-value less than 0.05 was considered significant.

Ethical considerations

HREC/UREC Reference #: S18/07/138 (PhD).

Results

Geographic characteristics

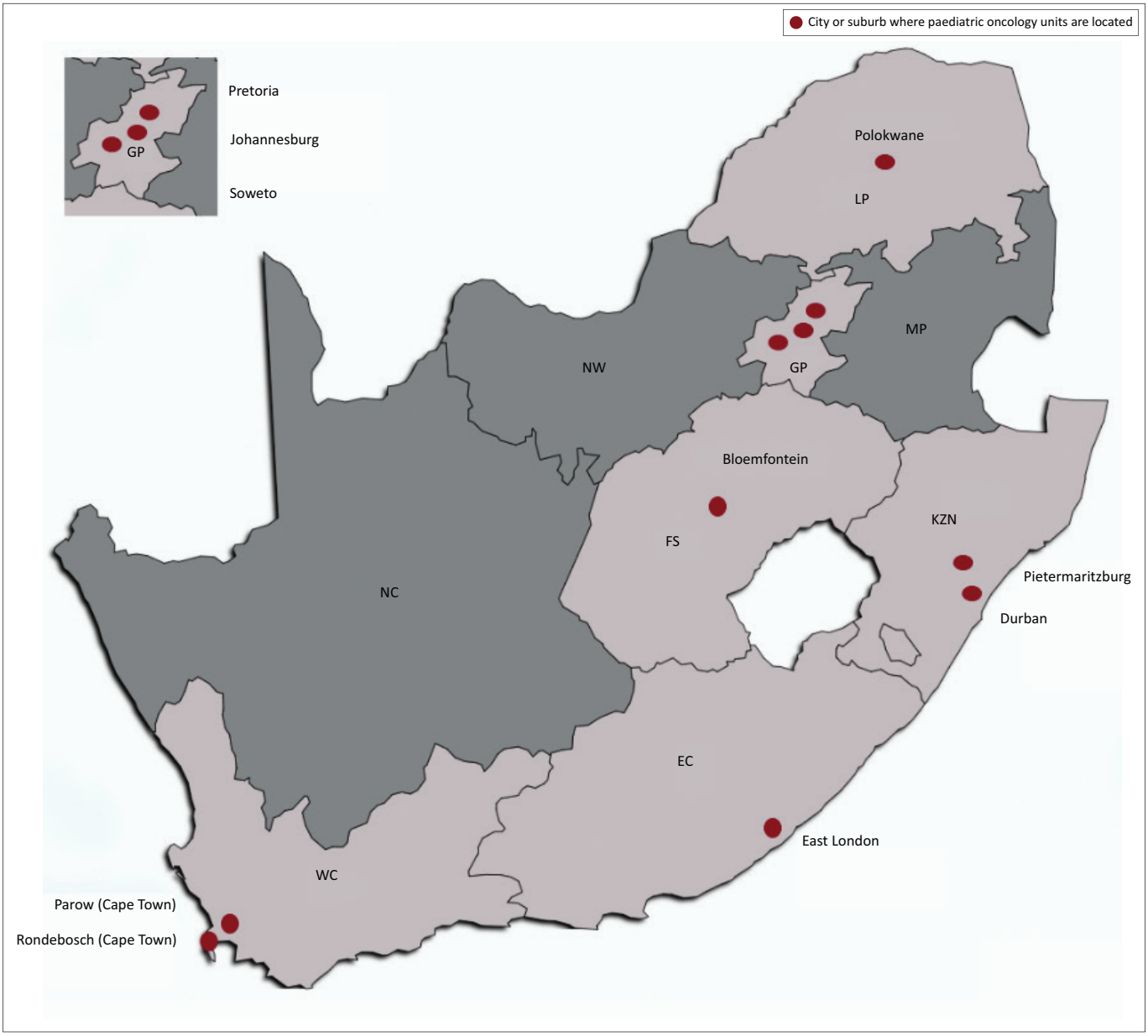
Nearly a third (n = 124, 32.2%) of the 385 children diagnosed with NB in South Africa between 2000 and 2014 (Figure 1) were treated in the Western Cape (WC), 114 (29.6%) were treated in Gauteng (GP) and 62 (16.1%) in the Free State (FS), followed by KwaZulu-Natal (KZN) (n = 55, 14.3%) and the Eastern Cape (EC) (n = 30, 7.8%). Data from Limpopo (LP) were not included in this study because permission to access data could not be obtained.

Age at diagnosis

The median age at diagnosis for the total cohort was 39.9 months (interquartile range [IQR], 15.4–49.6 months) (Table 1). The median age at diagnosis of patients from EC was 34.3 months (IQR, 19.1–48.2 months), 36.6 months (IQR, 12.2–81.9 months) for patients from FS, 36.8 months (IQR, 16.6–51.4 months) for patients from GP, 26.5 months (IQR, 13.5–41.4 months) for patients from WC and 21.3 months (IQR, 13.5–48.0 months) for patients from KZN. In all the provinces, the largest age group was of the 19- to 60-month-old children. GP (JHB, PTA and SWT) had the highest percentage (47%) of children older than 5 years. In all POUs, the predominant age group was of the 19- to 60-month-old children (Table 2). Johannesburg was the POU with the highest percentage (32.3%) of children over 5 years.

Tumour staging at diagnosis

Stage 4 or metastatic disease was the most prevalent (n = 273, 70.9%) (Table 3). All provinces predominantly



EC, Eastern Cape; FS, Free State; GP, Gauteng; KZN, KwaZulu-Natal; LP, Limpopo; MP, Mpumalanga; NC, Northern Cape; NW, North West; WC, Western Cape.

FIGURE 1: The provinces and cities of South Africa with paediatric oncology units from 2000 to 2014.

TABLE 1: Neuroblastoma age groups at diagnosis from 2000 to 2014 per province in South Africa.

Province	EC		FS		GP		KZN		WC		Total	
Median in months (IQR)	34.3 (19.1–48.2)		36.6 (12.2–81.9)		36.8 (16.6–51.4)		21.3 (13.5–48.0)		26.5 (13.5–41.4)		39.9 (15.4–49.6)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age												
0–18 months	5	16.7	16	25.8	32	28.1	17	30.9	39	31.5	109	28.3
19–60 months	22	73.3	26	41.9	60	52.6	27	49.1	67	54.0	202	52.5
> 60 months	3	10.0	20	32.3	22	19.3	11	20.0	18	14.5	74	19.2
Total	**30**	-	**62**	-	**114**	-	**55**	-	**124**	-	**385**	-

EC, Eastern Cape; FS, Free State; GP, Gauteng; KZN, KwaZulu-Natal; WC, Western Cape.

TABLE 2: Neuroblastoma age groups at diagnosis from 2000 to 2014 in South Africa.

Province		EC	FS	GP			KZN		WC		Total
City		EL	BLN	JHB	PTA	SWT	DBN	PMB	PRW	RBH	
Age											
0–18 months	*n*	5	7	16	18	7	16	1	10	29	109
	%	16.7	17.9	25.8	35.3	29.2	32.7	16.7	30.3	31.9	28.3
19–60 months	*n*	22	22	26	23	15	23	4	16	51	202
	%	73.3	56.4	41.9	45.1	62.5	46.9	66.7	48.5	56.0	52.5
> 60 months	*n*	3	10	20	10	2	10	1	7	11	74
	%	10.0	25.6	32.3	19.6	8.3	20.4	16.7	21.2	12.1	19.2
Total		**30**	**62**	**39**	**51**	**24**	**49**	**6**	**33**	**91**	**385**

EC, Eastern Cape; EL, East London; FS, Free State; BLN, Bloemfontein; GP, Gauteng; JHB, Johannesburg; PTA, Pretoria; SWT, Soweto; KZN, KwaZulu-Natal; DBN, Durban; PMB, Pietermaritzburg; WC, Western Cape; PRW, Parow (Cape Town); RBH, Rondebosch (Cape Town).

TABLE 3: Neuroblastoma staging at diagnosis from 2000 to 2014 per province in South Africa.

Province	EC		FS		GP		KZN		WC		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
INSS												
Stage 1	0	0.0	2	3.2	3	2.6	1	1.8	10	8.1	16	4.2
Stage 2	1	3.3	1	1.6	9	7.9	0	0.0	5	4.0	16	4.2
Stage 3	3	10.0	16	25.8	20	17.5	5	9.1	22	17.7	66	17.1
Stage 4	25	83.3	41	66.1	78	68.4	44	80.0	85	68.5	273	70.9
Stage 4s	1	3.3	2	3.2	4	3.5	5	9.1	2	1.6	14	3.6
Total	**30**	-	**62**	-	**114**	-	**55**	-	**124**	-	**385**	-

INSS, International Neuroblastoma Staging System; EC, Eastern Cape; FS, Free State; GP, Gauteng; KZN, KwaZulu-Natal; WC, Western Cape.

TABLE 4: Neuroblastoma staging at diagnosis from 2000 to 2014 in South Africa.

Province		EC	FS	GP			KZN		WC		Total
City		EL	BLN	JHB	PTA	SWT	DBN	PMB	PRW	RBH	
INSS											
Stage 1	*n*	0	2	3	0	0	1	0	1	9	16
	%	0.0	3.2	5.9	0.0	0.0	2.0	0.0	3.0	9.9	4.2
Stage 2	*n*	1	1	5	3	1	0	0	1	4	16
	%	3.3	1.6	9.8	7.7	4.2	0.0	0.0	3.0	4.4	4.2
Stage 3	*n*	3	16	9	4	7	5	0	6	16	66
	%	10.0	25.8	17.6	10.3	29.2	10.4	0.0	18.2	17.6	17.1
Stage 4	*n*	25	41	31	32	15	38	6	24	61	273
	%	83.3	66.1	60.8	82.1	62.5	77.6	100	72.7	67.0	70.9
Stage 4s	*n*	1	2	3	0	1	5	0	1	1	14
	%	3.3	3.2	5.9	0.0	4.2	10.2	0.0	3.0	1.1	3.6
Total		**30**	**62**	**51**	**39**	**24**	**49**	**6**	**33**	**91**	**385**

EC, Eastern Cape; EL, East London; FS, Free State; BLN, Bloemfontein; GP, Gauteng; JHB, Johannesburg; PTA, Pretoria; SWT, Soweto; KZN, KwaZulu-Natal; DBN, Durban; PMB, Pietermaritzburg; WC, Western Cape; PRW, Parow (Cape Town); RBH, Rondebosch (Cape Town).

had Stage 4 disease, but EC (83.3%) and KZN (80.0%) had the highest percentages compared to 68.5%, 68.4% and 66.1% in WC, GP and FS, respectively. WC had the highest percentage Stage 1 or localised disease (n = 10, 8.1%).

The POUs (Table 4) with the highest percentages of patients with Stage 4 or metastatic disease were Pietermaritzburg (KZN), East London (EP) and Pretoria (GP), with 100%, 83.3% and 82.1%, respectively. Rondebosch in Cape Town (WP) (n = 9, 9.9%) and Johannesburg (GP) (n = 3, 5.9%) had the highest percentage of Stage 1 or localised disease.

Risk stratification at diagnosis

High-risk (HR) disease was the most prevalent (n = 294, 76.4%) (Table 5). All provinces predominantly had HR

TABLE 5: Neuroblastoma risk stratification at diagnosis from 2000 to 2014 per province in South Africa.

Province	EC		FS		GP		KZN		WC		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Risk												
LR	1	3.3	2	3.2	11	9.7	2	3.6	26	21.0	42	10.9
IR	1	3.3	1	1.6	10	8.8	3	5.5	14	11.3	29	7.5
HR	27	90.0	59	95.2	93	81.6	34	61.8	81	65.3	294	76.4
Unknown	1	3.3	0	0.0	0	0.0	16	29.1	3	2.4	20	5.2
Total	**30**	-	**62**	-	**114**	-	-	**55**	**124**	-	**385**	-

INSS, International Neuroblastoma Staging System; EC, Eastern Cape; FS, Free State; GP, Gauteng; KZN, KwaZulu-Natal; WC, Western Cape; LR, low-risk; IR, intermediate risk; HR, high-risk.

TABLE 6: Neuroblastoma risk stratification at diagnosis from 2000 to 2014 in South Africa.

Province		EC	FS	GP			KZN		WC		Total
City		**EL**	**BLN**	**JHB**	**PTA**	**SWT**	**DBN**	**PMB**	**PRW**	**RBH**	
Age											
LR	***n***	1	2	7	3	1	2	0	4	22	42
	%	3.3	3.2	13.7	7.7	4.2	4.1	0.0	12.1	24.4	10.9
IR	***n***	1	1	2	0	8	3	0	2	12	29
	%	3.3	1.6	3.9	0.0	33.3	6.1	0.0	6.1	13.2	7.5
HR	***n***	27	59	42	36	15	28	6	27	54	294
	%	90.0	95.2	82.4	92.3	62.5	57.1	100	81.8	59.3	76.4
Unknown	***n***	1	0	0	0	0	16	0	0	3	20
	%	3.3	0.0	0.0	0.0	0.0	32.7	0.0	0.0	3.3	5.2
Total		**30**	**62**	**51**	**39**	**24**	**49**	**6**	**33**	**91**	**385**

EC, Eastern Cape; EL, East London; FS, Free State; BLN, Bloemfontein; GP, Gauteng; JHB, Johannesburg; PTA, Pretoria; SWT, Soweto; KZN, KwaZulu-Natal; DBN, Durban; PMB, Pietermaritzburg; WC, Western Cape; PRW, Parow (Cape Town); RBH, Rondebosch (Cape Town); LR- low-risk; IR, intermediate risk; HR, high-risk.

disease, but EC (90.0%) and FS (95.2%) had the highest percentages compared to 81.6%, 65.3% and 61.8% in GP, WC and KZN, respectively. The percentage of HR disease must be seen in the context of 29.1% of KZN patients not being able to be risk stratified. WC had the highest percentage of low-risk (LR) disease (*n* = 26, 21.0%). The four POUs (Table 6) with the highest percentages of patients diagnosed with HR disease were Pietermaritzburg (KZN), Bloemfontein (FS), Pretoria (GP) and East London (EP), with 100%, 95.2%, 92.3% and 90%, respectively, followed by Johannesburg (GP) (82.4%), Parow in Cape Town (WP) (81.8%), Soweto (GP) (62.5%), Rondebosch in Cape Town (WP) (59.3%) and Durban (KZN) (57.1%). Rondebosch in Cape Town (WP) (*n* = 22, 24.4%), Johannesburg (GP) (*n* = 7, 13.7%) and Parow in Cape Town (WP) (*n* = 4, 12.1%) had the highest percentage of LR disease followed by Pretoria (GP), Soweto (GP), Durban (KZN), East London (EL) and Bloemfontein (FS) with 7.7%, 4.2%, 4.1%, 3.3% and 3.2%, respectively. Pietermaritzburg (KZN) had no patients with LR disease.

Evaluation of access to paediatric oncology services in South Africa (Table 7)

GP was the province with the smallest surface area (18 176 km^2), with the shortest travelling distances to services (83.5–119.0 km) and with the shortest travel duration (59 min – 1 h 34 min). NC was the province with the largest surface area (372 889 km^2), with the furthest travelling distances to services (283.7 km – 1105.5 km) and the longest travel duration (2 h 55 min – 16 h 32 min). WC, with established paediatric oncology services, had comparable distances (427.4 km – 595.8 km) and travel durations (4 h 22 min – 6 h 45 min), with MP (141.1 km – 435.1 km; 1 h 48 min – 4 h 56 min) and NW (336.1 km – 641.8 km; 3 h 40 min – 6 h 46 min) that had no paediatric oncology services.

TABLE 7: Provincial distances and traveling times to the nearest paediatric oncology unit during 2000 to 2014.

Destination to nearest POU	Distance	Travel time
Eastern Cape (168 966 km^2)		
Elyolo to Port Elizabeth	338.8 km	3 h 45 min
Aliwal North to East London	357.8 km	3 h 53 min
Pamlaville to East London	490.3 km	6 h 29 min
Free State (129 825 km^2)		
Memel to Bloemfontein	453.9 km	4 h 37 min
Maseru (border with Lesotho) to Bloemfontein	143.9 km	1 h 47 min
Orania to Bloemfontein	222.9 km	2 h 23 min
Gauteng (18 176 km^2)		
Klipdrif to Soweto	90.8 km	1 h 8 min
Loding to Pretoria	119.0 km	1 h 34 min
Devon to Johannesburg	83.5 km	59 min
KwaZulu-Natal (94 361 km^2)		
Manguzi to Durban	422.0 km	5 h 3 min
Port Edward to Durban	163.7 km	1 h 35 min
Bonjanjeni to Pietermaritzburg	202.1 km	2 h 22 min
Limpopo (125 754 km^2)		
Musina to Polokwane	196.4 km	2 h 19 min
Dwaalboom to Polokwane	362.0 km	3 h 54 min
Hoedspruit to Polokwane	216.8 km	2 h 32 min
Mpumalanga (76 495 km^2)		
Mbuzini to Pretoria	453.1 km	4 h 56 min
Delfkom to Pretoria	391.4 km	4 h 21 min
Lefiso to Pretoria	141.1 km	1 h 48 min
North West (104 882 km^2)		
Vorstershoop to Bloemfontein	544.6 km	5 h 46 min
Vorstershoop to Pretoria	641.8 km	6 h 46 min
Supingstad to Pretoria	336.1 km	3 h 40 min
Northen Cape (372 889 km^2)		
Mier to Cape Town	1105.5 km	8 h 43 min
Mier to Bloemfontein	874.9 km	16 h 32 min
Alexander Bay to Cape Town	786.7 km	7 h 36 min
Noupoort to Bloemfontein	283.7 km	2 h 55 min
Western Cape (129 462 km^2)		
Tsitsikamma to Cape Town	585.6 km	6 h 45 min
Kliprand to Cape Town	595.8 km	4 h 22 min
Murraysburg to Cape Town	427.4 km	6 h 43 min

POU, paediatric oncology unit.

TABLE 8: The number of paediatric oncologists/haematologists in each province between 2000 and 2014.

Location	2000		Location	2014	
	Paediatric oncologist	Paediatric haematologist		Paediatric oncologist	Paediatric haematologist
Eastern Cape					
East London	1	0	East London	0	0
Port Elizabeth	0	0	Port Elizabeth	0	0
Sub-total	1	0	**Sub-total**	0	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
2 928 000	1–2.9 mil	0	2 570 000	0	0
Free State					
Bloemfontein	1	0	Bloemfontein	3	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
1 000 000	1–1 mil	0	980 000	1–326 666	0
Gauteng					
Pretoria	2	0	Pretoria	2	0
Soweto	1	0	Soweto	3	0
Johannesburg	1	0	Johannesburg	3	0
Sub-total	4	0	**Sub-total**	8	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
2 939 000	1–734 750	0	3 743 000	1–467 875	0
KwaZulu-Natal					
Durban	0	2	Durban	0	3
Pietermaritzburg	0	0	Pietermaritzburg	1	1
Sub-total	0	2	**Sub-total**	1	4
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
4 149 000	0	1–2 074 500	4 062 000	1–4 062 000	1–1 037 250
Limpopo					
Polokwane	0	0	Polokwane	0	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
2 421 000	0	0	2 310 000	0	0
Mpumalanga					
Mbombela (Nelspruit)	0	0	Mbombela (Nelspruit)	0	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
1 520 000	0	0	1 564 000	0	0
Northern Cape					
Kimberley	0	0	Kimberley	0	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
398 000	0	0	408 000	0	0
North West					
GaRankuwa	0	0	GaRankuwa	0	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
1 165 000	0	0	1 293 000	0	0
Western Cape					
Rondebosch	3	1	Rondebosch	3	0
Parow	2	0	Parow	3	0
Sub-total	5	1	**Sub-total**	6	0
Provincial totals	**Doctors**		**Provincial totals**	**Doctors**	
1 609 000	1–321 800	1–1 609 000	1 866 000	1–311 000	0
South Africa					
Total	12	3	**Total**	17	4
18 129 000	1–1 510 750	1–6 043 000	18 795 000	1–1 105 588	1–4 698 750

National access to neuroblastoma care

Based on geographical distances in South Africa (Figure 1), road access and travelling time to cover the distances as well as transport options for patients – *timeliness* (Table 7) of access to care were not equal. The Constitution guarantees the *facilitation of gaining* access to health care.[2] Both the 2009 public inquiry into access to healthcare services and the 2017 Foundation for Human Rights paper on monitoring the right of access to health care in South Africa documented ongoing limited resources and access to both patient transport services and emergency transport.[19,20] The greatest burden fell on children and patients from rural areas who needed inter-provincial transfers.[21,22] Not only did patients in MP, NC and NW not have NB medical services in their own provinces, but there was also limited transport for them to access NB care in other provinces.

Anti-neoplastic agents are important for the treatment of NB.[21] Until 2016, approximately 20 basic and essential anti-neoplastic agents listed in the WHO essential anti-cancer medications had not been listed on the South African Essential Drugs list.[23] Subsequent Essential Medicines Formularies for Tertiary and Quaternary Care did also not include anti-neoplastic agents as needed for childhood malignancies.[24,25]

A multi-disciplinary team is crucial for the management of NB. The disciplines should include paediatric oncologists, paediatric surgeons, radio-oncologists, radiologists, pathologists, nuclear physicians, bone marrow transplant specialists and supportive care services (blood transfusion services, pharmacy services and dieticians), but of special importance is the nursing staff.[16] If the provinces without paediatric oncology services are not taken into account, GP and WC that had the smallest percentage of children under the age of 15 years (respectively, 24.5% and 26.7%),[26] had the best access to health care between 2000 and 2014, with more paediatric oncologists and paediatric surgeons than any of the other provinces (Tables 8 and 9). Even in the context of this disproportionate distribution of human resources, both the 2009 public inquiry and the 2017 Foundation for Human Rights working paper concluded that there was a shortage of skilled healthcare workers, especially nursing staff, in the public sector and that their numbers were still decreasing.[20,27]

Equality of the paediatric oncology services delivering neuroblastoma care

The management of NB includes chemotherapy, surgery and radiotherapy.[28,29] In localised NB, trimodal therapy is curative, but in metastatic NB or NB with adverse biology, trimodal therapy leads to a survival of only 20%.[16,28,29] An autologous bone marrow transplant preceded by ablative bone marrow therapy, immunotherapy and maturation therapy with *cis*-retinoic acid is vital, but was not available in South Africa during this time.[28,29]

Between 2000 and 2014, the POUs in South Africa delivered different levels of neuroblastoma management based on the available healthcare resources in each hospital (Table 10). Important in the management of high-risk NB was autologous bone marrow transplant. Pietermaritzburg (KZN) and Polokwane (LP) were Setting 1 POUs with access only to basic levels of health care (Appendix 1). Bloemfontein (FS), Durban (KZN) and East London (EC) were Setting 2 POUs with access to the full range of healthcare management needed, excluding access to bone marrow transplant facilities for children. Rondebosch and Parow (Cape Town, WC), Johannesburg, Pretoria and Soweto (GP), with autologous transplant capabilities, were Setting 3 POUs with an access to the full range of healthcare management facilities, including bone marrow transplant. None of the POUs were classified as Setting 4 POUs, because South Africa does not provide immunotherapy for the treatment of NB.

The existence of a facility does not, however, guarantee access to it, or that access to it would be gained.[30] In South Africa, when a paediatric surgeon was not available, a general surgeon performed surgical interventions when diagnosing NB with the aid of a biopsy or operated on the primary tumour. Radiotherapy services did not routinely reserve time for paediatric NB patients who needed irradiation. Moreover, in both these situations, children had to compete not only for resources, but also with the adult population to gain access to life-saving services.[31] High-risk NB had poor outcomes, high relapse rates and a high need for resources.[16] When the justice principle is applied for access to limited surgical, radiotherapy and transplantation services, these characteristics might work against patients with NB because of competition for resources rather allocated to burden of disease of adult non-communicable diseases. This situation was compounded when paediatric oncology services competed with adult services.[31]

TABLE 9: The number of paediatric surgeons in each province between 2000 and 2014.

Location	2000	Location	2014
	Paediatric surgeons		Paediatric surgeons
Eastern Cape			
East London	3	East London	3
Port Elizabeth	1	Port Elizabeth	1
Sub-total	4	**Sub-total**	4
Provincial total		**Provincial total**	
2 928 000	1–732 000	2 570 000	1–642 500
Free State			
Bloemfontein	1	Bloemfontein	1
Provincial total		**Provincial total**	
1 000 000	1–1 000 000	980 000	1–980 000
Gauteng			
Soweto		Soweto	3
Johannesburg	4	Johannesburg	4
Johannesburg (Private)	2	Johannesburg (Private)	3 2
Pretoria	2	Pretoria	4
Pretoria (Private)	8	Pretoria (Private)	16
Sub-total		**Sub-total**	
Provincial total	**Doctors**	**Provincial total**	**Doctors**
2 939 000	1–367 375	3 743 000	1–233 937
KwaZulu-Natal			
Durban	3	Durban	3
PMB	1	PMB	2
Sub-total	4	**Sub-total**	5
Provincial total	**Doctors**	**Provincial total**	**Doctors**
4 149 000	1–1 037 250	4 062 000	1–812 400
Limpopo			
Polokwane	0	Polokwane	1
Provincial totals	**Doctors**	**Provincial totals**	**Doctors**
2 421 000	0	2 310 000	1–2 310 000
Mpumalanga			
Mbombela (Nelspruit)	0	Mbombela (Nelspruit)	0
Provincial totals	**Doctors**	**Provincial totals**	**Doctors**
1 520 000	0	1 564 000	0
Northern Cape			
Kimberley	0	Kimberley	0
Provincial totals	**Doctors**	**Provincial totals**	**Doctors**
398 000	0	408 000	0
North West			
GaRankuwa	1	GaRankuwa	2
Provincial totals	**Doctors**	**Provincial totals**	**Doctors**
1 165 000	1–1 165 000	1 293 000	1–646 500
Western Cape			
Rondebosch	3	Rondebosch	4
Parow	2	Parow	2
Sub-total	5	**Sub-total**	6
Provincial totals	**Doctors**	**Provincial totals**	**Doctors**
1 609 000	1–321 800	1 866 000	1–311 000
South Africa			
Total	23	**Total**	35
18 129 000	1–788 217	18 795 000	1–537 000

TABLE 10: Evaluation of paediatric oncology units according to the International Society for Paediatric Oncology-Paediatric Oncology of Developing Countries resource settings for neuroblastoma diagnosis, staging and risk stratification.

Location	Basic bloods	LDH and ferritin	X-ray	U/S	CT/MRI	BMT	mIBG	MYCN	Chemotherapy	Surgery	Radiotherapy	ASCT	Level Setting
Eastern Cape													
East London	On site	On site	On site	On site	On site	On site	Off-site	Off-site	On site	On site	On site	No	2
Free State													
Bloemfontein	On site	On site	On site	On site	On site	On site	On site	Off-site	On site	On site	On site	No	2
Gauteng													
Johannesburg	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	Yes	3
Pretoria	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	Yes	3
Soweto	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	Yes	3
KwaZulu-Natal													
Durban	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	No	2
Pietermaritzburg	On site	On site	On site	On site	On site	On site	Off-site	Off-site	On site	On site	On site	No	1
Limpopo													
Polokwane	On site	On site	On site	On site	On site	On site	Off-site	Off-site	On site	On site	Off-site	No	1
Mpumalanga, Northern Cape and North West													
No POUs	None	None	None	None	None	None	None	None	None	None	None	None	None
Western Cape													
Rondebosch	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	Yes	3
Parow	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	On site	Yes	3

U/S, ultrasonography; LDH, lactic dehydrogenase; CT, computed tomography; MRI, magnetic resonance imaging; BMT, bone marrow aspirate and trephine; mIBG, meta-iodobenzylguanidine; ASCT, autologous stem cell transplant; POU,paediatric oncology unit.

'On site' refers to services in the same hospital or same hospital complex in the same city. 'Off-site' refers to services in another hospital complex, another city or province.

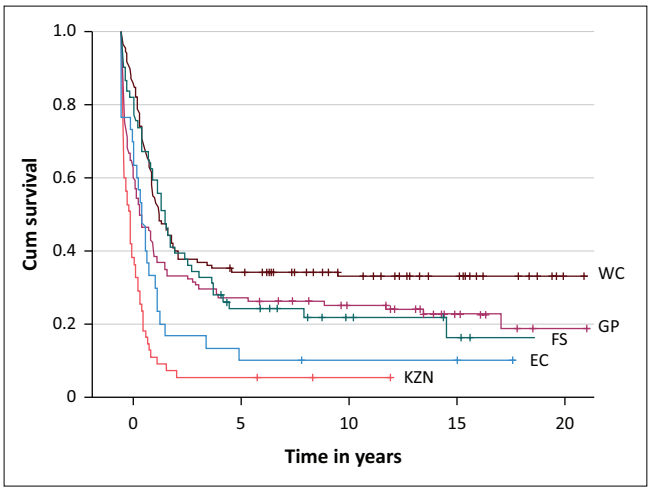
TABLE 11: Provincial and paediatric oncology unit overall survival outcomes.

Location	*n*	%	10-year OS (%)	Std. Error	Median 95% CI		*p*-value
					Lower Bound	Upper Bound	
Provinces							
Eastern Cape	30	7.8	10.0	2.214	5.528	14.206	< 0.001
Free State	62	16.1	21.0	3.001	15.419	27.181	-
Gauteng	75	19.5	22.8	3.129	3.001	15.266	-
KwaZulu-Natal	55	14.3	5.5	1.271	1.709	6.691	-
Western Cape	124	32.2	33.9	3.191	12.313	24.820	-
Total	**385**	-	**22.6**	**1.238**	**10.807**	**15.660**	-
Paediatric Oncology Units							
Bloemfontein	62	16.1	21.0	3.001	15.419	27.181	< 0.001
Durban	49	12.7	4.1	1.960	0.000	6.441	-
East London	30	7.8	10.0	2.214	5.528	14.206	-
Johannesburg	51	13.2	39.2	42.383	0.000	130.070	-
Pietermaritzburg	6	1.6	16.7†	1.225	3.000	7.800	-
Pretoria	39	10.1	5.1	2.809	0.000	11.006	-
Rondebosch	91	23.6	39.6	5.357	12.368	33.366	-
Soweto	24	6.2	16.7	3.715	0.000	14.182	-
Parow	33	8.6	18.2	1.589	11.253	17.480	-
Total	**385**	-	**22.6**	**1.238**	**10.807**	**15.660**	-

†, Although the survival curve for Pietermaritzburg had already reached its plato, the value reflects a 5-year OS (as opposed to a 10-year OS for the other cities).

The right to life – A right to be treated for neuroblastoma and treatment-related complications

Worldwide localised NB without adverse biology (low- and intermediate-risk disease) had 5-year OS rates of upwards from 80%.[16,28,29] In metastatic NB or NB with adverse biology (high-risk disease) with multi-modal therapy, including autologous stem cell transplant (ASCT) and immunotherapy, the 5-year OS rates were 60%.[15,27,28] In South Africa, with limited access to ASCT and no immunotherapy, the 5-year OS was approximately 20%.[32] The inequitable distribution of NB management-related resources had an impact on the survival, as the two provinces GP and WC, with a full range of healthcare services, had survival rates above the national average of 22.6% (Table 11). KZN did not have a paediatric oncologist to complement the multi-disciplinary team until 2013 (the end of the study period) and had the lowest survival rate of 5.5% (Figure 2). The effect of inequitable access to NB care could be demonstrated by comparing Pretoria and Soweto with Johannesburg. All are Setting 3 paediatric oncology services, but during the study period, Johannesburg received referrals from Southern GP (roughly 9088 km^2) and Soweto received referrals from Southern GP and NW (113 970 km^2), whilst Pretoria received referrals from Northern GP, MP and LP (until a POU was opened in Ga-Rankuwa) (roughly 211 337 km^2), which were significantly further away from the child's residence. This potentially may have led to late diagnoses and delays in referrals to central hospitals, contributing to a poorer 10-year



EC,Eastern Cape; FS, Free State; GP, Gauteng Province; KZN, KwaZulu-Natal; WC, Western Cape.

FIGURE 2: Kaplan Meier curves overall survival outcomes for patients diagnosed with neuroblastoma between 2000 and 2014 in each province ($p < 0.001$).

OS for Pretoria (5.1%) and Soweto (16.7%), compared to 39.2% in Johannesburg.[17]

Chronic care or long-term life-saving health care

Since 2009, non-communicable diseases in South Africa, including cancer, have contributed the greatest percentage to the burden of disease in the country.[20] It is estimated that one in every five children up to late adolescence in South Africa was in need of long-term life-saving health care or chronic health care because of a previously life-limiting condition, such as with cancer and palliative care.[33] Yet, when the right to life-saving health care on the basis of a chronic condition was challenged in the constitutional court in the Soobramoney case: Soobramoney vs Minister of Health (KwaZulu-Natal) 1998 (1) SA 765 (CC), the court decided that emergency medical treatment did not include chronic treatment.[34] Therefore, ASCT, which contributes a 15%–20% increase in survival in high-risk NB,[16] is not guaranteed as a right to life under the determination of the constitutional court and neither is any part of paediatric oncology care apart from *acute* life-threatening emergencies such as acute emergencies at diagnosis which include spinal cord compression symptoms and respiratory distress or neutropaenic fever, heart failure caused by chemotherapy-induced anaemia, bleeding because of thrombocytopaenia.[16]

Discussion

Neuroblastoma is a childhood malignancy of the neuro-endocrine system, contributing 15% of the total deaths in the paediatric oncology population and only 20% of cases survive for longer than 5 years because of late diagnosis and advanced disease in LMICs.[16,35] The 5-year OS rate in South Africa is 27%, whilst the country has a youthful population, with 34.3% of the population being under the age of 15 years.[21,32] Since the start of democracy in 1994, the DoH has developed beneficial programmes for children, which include the national integrated nutrition programme, the programme for the prevention of maternal HIV to child transmission and the early childhood development and basic education programmes.[32] Free basic child healthcare services for children under the age of 5 years are included in these programmes. A bias in favour of younger children and preventative medicine is evident in all these programmes, with the health needs of children with chronic diseases, older children and adolescents being neglected.[36] Provincial health departments have directed resources towards paediatric oncology care with initiatives such as the Essentials for Palliative Care and the KwaZulu-Natal paediatric outreach programmes,[33] but paediatric oncology resources through South Africa remain unequal. Gauteng had the second highest number of children under the age of 15 years, and the Western Cape only the fifth highest with, respectively, 21.4% and 10.0% of all children under the age of 15 years in SA.[26] Yet both provinces had the most resources to manage NB. Mpumalanga, with 8.1% of the children under 15 years, and Limpopo with 11.6%, were the two provinces with the least resources and had a fifth of the children in the country.[26] In 2020, Mpumalanga still had no paediatric oncology services and referred children with NB to Pretoria.

The WHO-SIOP joint goal is to achieve a 60% childhood cancer cure rate worldwide.[11,36] The South African government lacked the stewardship to implement National Core Standards, including programmes related to cancer care, in the country.[37] Most cancer-related programmes were adult-centred.[38] The Ministerial Advisory Committee on the Prevention and Control of Cancer (MACC) was established in 2013 and the Strategic Plan for the Prevention and Control of Non-Communicable Diseases ran from 2013 to 2017, but childhood cancer was not a priority, as the focus was again on prevention rather than cure, which is not applicable in childhood cancer.[38] In the 2017–2022 National Cancer Strategic Framework for South Africa, the commitment to paediatric cancers was not stated beyond a paragraph on childhood cancer epidemiology.[39] Therefore, although NB has a peak incidence of cancer in children between the ages of 2 years and 5 years,[16] the paediatric programmes' bias in favour of younger children does not include non-communicable disease management. Access to treatment in the private healthcare setting for childhood cancers, thus for NB, is better than in the public setting. The two-tiered health system benefits the financially independent population or those who can afford private health insurance.[15]

Although NB is classified as a rare disease,[40,41] optimising its management in South Africa is important from the principle of justice as part of setting a basic standard of health care for rare diseases.[42] The international age-standardised rate of NB in countries with standardised cancer registries is 10.5 cases per million.[43] In South Africa, with at least a 50% under-diagnosis of childhood malignancies,[7] the incidence is far less, at 2.7 cases per million.[7] Therefore, improving the quality of awareness of neuroblastoma, as with all childhood cancers, improving diagnostic capabilities and bringing

about increased access to paediatric oncology care are basic, life-saving healthcare services to which children have a right under the Constitution.

The absence of a definition in the Bill of Rights for 'basic health care services' as they pertain to children may be because of the relatively young Constitution or a means for the government not to commit to defined services. As a signatory of the UN Convention on the Rights of the Child, the South African government must prioritise the needs of children as the most vulnerable members of the South African society.[31] Section 7(2) of the Constitution requires the state to 'respect, protect, promote and fulfil the rights in the Bill of Rights'. Concerning the right of access to healthcare services, *respect* determines that the state not unreasonably limits people's access to healthcare services, whether in the public or private sector.[34] Thus, a *reasonable* measure to ensure that children, including children with malignancies, not only survive, but also thrive and reach their full capabilities according to the UN Convention, is to address discriminatory policies and practices[34]: defining basic health care for children and acknowledge the need for chronic healthcare services for children in South Africa. After 25 years of democracy, the scope of paediatric oncology should be acknowledged and a separate national cancer control plan for children should be formulated to address the paediatric epidemiology, pathophysiology and management needs of children with cancer.

Conclusion

In the case study of children diagnosed with neuroblastoma, it was determined that the patients were not afforded equitable access to care, were not afforded the same level of care based on resources and were not afforded the right to life by means of access to medical services as laid down by the South African Constitution. This case of neuroblastoma illustrates the measure of access to care for all paediatric malignancies in South Africa, which is currently a low priority in national cancer control because of the paucity of initiatives by policymakers for children with oncological diseases.

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Authors' contributions

J.v.H. and M.K. conceptualised and designed the study, collected data, performed the data analysis and wrote the manuscript. T.E. was the statistician for data analysis and reviewed the manuscript.

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Data availability

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Appendix 1

International Society of Paediatric Oncology resource settings for neuroblastoma diagnosis, staging and risk stratification.

	Setting 1	Setting 2	Setting 3	Setting 4
Diagnosis	History, Physical examination, Histology of small round blue cell tumour or bone marrow metastases Urinary catecholamines (if available)	-	-	-
Staging	CXR and skeletal survey, Abdominal ultrasound, Bilateral BM aspirate & biopsy	CT neck/ chest/ abdomen/ pelvis 99mTc-bone Scan Bilateral BM aspirate & biopsy	CT neck/ chest/ abdomen/ pelvis 123I- MIBG or 18FDG-PET MRI head or spine if involved Bilateral BM aspirate & biopsy	CT scan neck/ chest/ abdomen/ pelvis 123I- MIBG or 18FDG-PET MRI head or spine if involved Bilateral BM & biopsy
Laboratory	CBC, liver enzymes, LDH, ferritin, creatinine, urinalysis	CBC, liver enzymes, LDH, ferritin, creatinine, urinalysis Urine HVA/ VMA	CBC, liver enzymes, LDH, ferritin, creatinine, urinalysis Urine HVA/ VMA Tumour lysis labs if INSS 4 (electrolytes, Ca Mg PO4, uric acid)	CBC, liver enzymes, LDH, ferritin, creatinine, urinalysis Urine HVA/VMA Tumour lysis labs if INSS 4 (electrolytes, Ca Mg PO4, uric acid)
Pathology	H&E stain	H&E stain IHC	H&E stain, IHC INPC classification (if available) (differentiation grade, MKI) MYCN	H&E stain, IHC INPC classification MYCN, DNA Ploidy segmental chromosome abnormalities
Infrastructure	Nursing, Inpatient Hospital Access to RBC or whole blood	Nursing, Inpatient hospital Access to RBC & Platelets Paediatric Surgeon Family Housing Intensive Monitoring Capabilities	Nursing, Inpatient Hospital Rapid Access to all Blood Products Paediatric Surgeon Family Housing Paediatric ICU Isolation and Transplant Facility	Nursing, Inpatient Hospital Rapid Access to all Blood Products Paediatric Surgeon Family Housing Paediatric ICU Isolation and Transplant Facility
Therapeutics	Antibiotics Standard Chemotherapy	Antibiotics Standard Chemotherapy Radiation Therapy	Antibiotics Standard Chemotherapy Radiation Therapy Transplant Conditioning Agents Isotretinoin	Antibiotics Standard Chemotherapy Radiation Therapy Transplant Conditioning Agents Isotretinoin Anti-GD2 antibody

Source: Parikh N, Howard S, Chantada G, 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):1305–1316. https://doi.org/10.1002/pbc.25501

BM, bone marrow; CT, computerised tomography; CBC, complete blood count; CXR, chest X-ray; FDG-PET, fluorodeoxyglucose positron emission tomography; GD2, disialoganglioside; H&E, hematoxylin and eosin stain; HVA, homovanillic acid; ICU, intensive care unit; IHC, immunohistochemistry; INPC, International neuroblastoma pathology classification; INSS, International neuroblastoma staging system; LDH, lactic dehydrogenase; 123I- MIBG, *meta*-iodobenzylguanidine; MKI, *mitosis-karyorrhexis index*; MRI, magnetic resonance imaging; RBC, red blood cell; VMA, vannillylmandelic acid.