The importance of local control management in high-risk neuroblastoma in South Africa

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Abstract

Purpose: To investigate the impact of local therapies on high-risk neuroblastoma (HR-NB) outcomes in South Africa.

Methods: Data from 295 patients with HR-NB from nine pediatric oncology units between 2000 and 2014 were analysed. All patients received chemotherapy. Five-year overall (OS) and event free survival (EFS) were determined for patients who had received local therapy, either surgery or radiotherapy or both.

Results: Surgery was performed in only 35.9% (n = 106/295) patients. Surgical excision was done for 34.8% (n = 85/244) of abdominal primaries, 50.0% (n = 11/22) of thoracic primaries; 22.2% (n = 2/9) neck primaries and 66.7% (n = 8/12) of the paraspinal primaries. Only 15.9% (n = 47/295) of all patients received radiotherapy. Children, who had surgery, had an improved five-year OS of 32.1% versus 5.9% without surgery ($p < 0.001$). Completely resected disease had a five-year OS of 30.5%, incomplete resections 31.4% versus no surgery 6.0% ($p < 0.001$). Radiated patients had a five-year OS of 21.3% versus 14.2% without radiotherapy ($p < 0.001$). Patients who received radiotherapy without surgical interventions, had a marginally better five-year OS of 12.5% as opposed to 5.4% ($p < 0.001$). Patients who underwent surgery had a longer mean overall survival of 60.9 months, while patients, who were irradiated, had a longer mean overall survival of 7.9 months ($p < 0.001$). On multivariate analysis, complete metastatic remission ($p < 0.001$), surgical status ($p = 0.027$), and radiotherapy status ($p = 0.040$) were significant predictive factors in abdominal primaries.

Conclusion: Surgery and radiotherapy significantly improve outcomes regardless of the primary tumor site, emphasizing the importance of local control in neuroblastoma.

Keywords Neuroblastoma · Surgery · Radiotherapy · South Africa · Local therapies · High-risk · Intermediate-risk

Abbreviations

COG: Children's Oncology Group

EFS: Event-free survival

FH: Favorable histology

GTR: Gross total resection

HIC: High-income countries

HR: High risk

IDRF: Image define risk factors

INSS: International Neuroblastoma Staging System

LMIC: Low- and middle-income countries

NA: Not amplified

NB: Neuroblastoma

nGTR: Near gross total resection

OS: Overall survival

PFS: Progression-free survival

PTR: Primary tumor site relapse

POUs: Pediatric oncology units

RT: Radiotherapy

STR: Subtotal resection

UH: Unfavorable histology

Introduction

Neuroblastoma is a solid tumor of the sympathetic nervous system and contributes to 7–10% of all childhood cancer deaths [1]. Outcomes are poor in the absence of local therapies, such as surgery and radiotherapy, especially in low and middle income countries [1, 2]. The

tumor is chemotherapy and radiotherapy sensitive [1], but can develop significant treatment resistance without local treatment interventions [1]. Cure in high-risk (HR) neuroblastoma is determined by the stage, tumor biology, chemotherapy response, and local treatment [1, 2]. Therefore, in HR disease (metastatic disease, unfavorable histology, raised tumor markers, MYCN amplification and adverse genetics), surgery and radiotherapy are mandatory for cure as components of multimodal management [1, 2]. Local therapies have increased importance in resource limited settings, where access to autologous transplant and molecular targeted therapies as part of standard of care, are limited [2].

Resection of the tumor is not always a feasible therapeutic modality due to the macroscopic encasing of vital structures, such as significant blood vessels, including the aorta and inferior vena cava [3]. With encasement, surgery becomes challenging, with a high surgical morbidity and mortality. Encasement of the abdominal arteries is the single worst prognostic indicator during surgery [3]. IDRF are a set of anatomical site-specific signs that confer a poorer prognosis and assists in surgical decisions toward resection in NB [4]. Before the standardization of image defined risk factors (IDRF) to assess operability post-induction chemotherapy, decisions regarding surgery were made by multi-disciplinary teams (MDTs).

Radiotherapy is used for local control, focal metastatic spread, and symptom control in curative and palliative settings [2]. In HR metastatic disease, the role of radiotherapy for local control and survival in the era of supplementary multimodal therapies remains unclear. Yet complementary radiotherapy, when used as a component of trimodal therapy alongside chemotherapy and surgery, has survival advantages [5]. By utilizing radiotherapy, the same response rates can be achieved in the primary tumor bed, as well as at metastatic sites, for both large and minimal residual tumors [5].

In HR disease, where autologous transplant and molecular targeted therapies are not available, the extent of resection has an impact on the overall (OS) and event-free survival (EFS) [3]. In high-income countries (HIC), a favorable surgical outcome is mandatory for autologous transplant, radiotherapy and targeted therapy, securing an overall survival of up to 60% [2]. Historically, in HIC, chemotherapy, surgery and radiotherapy obtained an OS of approximately 20%, compared to less than 20% in resource-limited settings [2]. In combination with curative care options, local therapies contribute to the prolongation of progression free survival (PFS) and quality of life [6, 7].

A retrospective review was done to determine the value of local therapies on the outcomes of children diagnosed with HR-NB in South Africa, where autologous bone marrow transplants and molecular targeted therapies are readily not available. The objective was to develop standardized national treatment protocols for local therapies, including identifying limitations in the current management of NB in South Africa.

Materials and methods

A total of 295 children with HR-NB were diagnosed in nine dedicated pediatric oncology units (POUs) in South Africa from January 2000 to December 2014 (see Supplementary Figure 1). Diagnosis was confirmed through either a biopsy, bone marrow investigations, or raised urinary catecholamines if biopsy was not possible.

Patients were clinically and radiologically staged according to the International Neuroblastoma Staging System (INSS), using ultrasonography, computed tomography or magnetic resonance imaging of the neck, chest and abdomen, as well as bone marrow aspirate and trephine biopsy. Depending upon the available facilities, staging, and skeletal screening were done by ^{123}I-MIBG scan and/or bone scan. Where available, staging with ^{129}fluorodeoxyglucose-positron emission tomography was done in patients with ^{123}I-MIBG scan non-avid tumors. Risk classification was based on the International Neuroblastoma Risk Groups (INRG) classification system (see Appendix), to identify patients with HR disease [1].

Univariate and multivariate analysis for five-year OS were only calculated for abdominal primaries due to insignificant results in the small cohorts of other primary sites.

Guidelines for local therapies

Data was not robust enough to retrospectively restage patients post induction chemotherapy (pre-operatively) according to IDRF. Most patient records and imaging were stored in non-electronic formats, with incomplete or lost IDRF information. The indication for surgery and external beam radiotherapy treatment was based on risk-based treatment protocols according to the Children's Oncology Group (COG) [8, 9] or the International Society of Paediatric Oncology European Neuroblastoma group (SIOPEN) approaches [10]. In South Africa, the choice of protocol was according to institutional preference and the application decided by MDTs and guided by institutional expertise. Emergency surgery was performed for the alleviation of neurological or obstructive symptoms. It was not standard practice in South Africa to perform post resection imaging to assess the completeness of resections.

Definitions

Metastatic remission was defined as complete remission according to the International Neuroblastoma Response Criteria (INRC), revised in 1993 and 2012 [11, 12]. Complete resection was defined as greater than 90% resection as reported by surgeons. Incomplete resection was defined as resection less than 90%, or surgical reports stating an incomplete resection. No surgery was defined as the absence of any surgical excision of the primary tumor, and/or if only a biopsy was done. Radiotherapy treatment was defined as any radiotherapy to the local tumor bed or to metastatic sites for curative or palliative indications.

The overall survival (OS) time was defined as the period from diagnosis to death or date last seen, and event-free survival (EFS) was calculated from the date of diagnosis until disease progression on chemotherapy, or relapse, or treatment abandonment, death or date last seen. Progression-free survival (PFS) was calculated from the date of diagnosis until disease progression on chemotherapy, or relapse or death. Lost to follow-up was defined as any patient who did not return for follow-up appointments for one year and was unreachable despite efforts to contact the family.

Ethical approval was obtained from The Faculty of Health Sciences Research Ethics Committee of Stellenbosch University and the National Department of Health.

Statistical analysis

Data were analyzed using IBM SPSS version 25 (IBM Corporation, USA) statistical software [13]. Medians were used to determine estimations using Student's *t* test. Where estimations could not be determined by median values, the mean values were used. In cohorts of fewer than five observations, Fisher's exact test was applied. The Pearson chi-square test (χ^2) was employed to assess the categorical associations among covariates. Two-year and five-year overall survival (OS), event-free (EFS) survival, and progression-free survival (PFS), with associated 95% confidence intervals, were calculated using Kaplan–Meier curves. Multiple Cox regression modelling was employed to assess the statistical significance of various prognostic factors. The proportional hazards assumption was also confirmed for the final multivariable model. A *p* value of less than 0.05 was considered significant for all calculations. Some cohorts were too small (less than five) for meaningful calculations and were not included in the final tables.

Results

The majority of patients were diagnosed with abdominal primaries (adrenal and extra-adrenal) (82.7%; *n* = 244/295) followed by thoracic primaries (7.5%; *n* = 22/295), paraspinal (4.0%; *n* = 12/295), neck (3.0%; *n* = 9/295); primary not found (2.0%; *n* = /295); bone only (0.4%; *n* = 1/295) and one in the soft tissue of the cheek (0.4%) (see Table 1, Supplementary Figure 1).

Table 1 Surgical and radiological interventions according to primary site

Local therapies according to anatomical site of primary				
Primary site	Both local therapies *n* (%)	Surgery only *n* (%)	Radiotherapy only *n* (%)	No therapy *n* (%)
Abdominal	28 (11.5%)	60 (24.6%)	15 (6.1%)	141 (57.8%)
Thoracic	2 (9.0%)	10 (45.5%)	0 (0%)	10 (45.5%)
Neck	1 (11.1%)	1 (11.1%)	0 (0%)	7 (77.8%)
Paraspinal	0 (0%)	8 (66.7%)	0 (0%)	4 (33.3%)
Other	0 (0%)	0 (0%)	1 (12.5%)	7 (87.5%)
Total	31 (10.5%)	79 (26.8%)	16 (5.4%)	169 (57.3%)
Surgical intervention according to anatomical site of primary				
Primary site	Operated *n* (%)	Not operated *n* (%)	Total	
Abdominal	85 (34.8%)	159 (65.2%)	244	
Thoracic	11 (50.0%)	11 (50.0%)	22	
Neck	2 (22.2%)	7 (77.8%)	9	
Paraspinal	8 (66.7%)	4 (33.3%)	12	
Other	0 (0.0%)	8 (100.0%)	8	
Total	106 (35.9%)	189 (64.1%)	295	
Radiotherapy according to anatomical site of primary				
Primary site	Radiated *n* (%)	Not radiated *n* (%)	Total	
Abdominal	43 (17.6%)	201 (82.4%)	244	
Thoracic	2 (9.1%)	20 (90.9%)	22	
Neck	1 (11.1%)	8 (88.9%)	9	
Paraspinal	0 (0%)	12 (100.0%)	12	
Other	1 (12.5%)	7 (87.5%)	8	
Total	47 (15.9%)	248 (84.1%)	295	

The majority of patients were not operated (64.1%; *n* = 189/295). Surgery excision was done for 34.8% (*n* = 85/244) of the abdominal primaries, 50.0% (*n* = 11/22) of thoracic primaries; 22.2% (*n* = 2/9) of neck primaries and 66.7% (*n* = 8/12) of the paraspinal primaries. The majority of patients did not receive radiotherapy (84.1%; *n* = 248/295). Irradiation to the tumour bed was done for only 17.6% (*n* = 43/244) of the abdominal primaries, 9.1% (*n* = 11/22) of thoracic primaries; 11.1% (*n* = 1/9) of neck primaries and none of the paraspinal primaries. Eleven patients (3.8%) received an autologous bone marrow transplant after induction chemotherapy, surgery, and radiotherapy.

The main reasons why patients were not operated were the failure to achieve metastatic remission after induction chemotherapy (49.2%; *n* = 93/189), local progression of disease (26.5%; *n* = 50/189); metastatic progression of disease (6.3%; 12/189) or death during induction chemotherapy (4.2%; *n* = 8/189) (see Supplementary table 1). Nine (4.7%) patients were palliated from diagnosis and five (2.6%) abandoned induction chemotherapy.

Patients, who underwent surgery, had a better five-year OS of 32.1% and EFS of 30.2%, compared to patients not operated with a five-year OS of 5.9% and a five-year EFS of 5.3% ($p < 0.001$) (see Table 2). There was also a significant improved five-year OS per anatomical site for patients operated versus patients not operated: abdominal primary 28.2% compared to 5.7% ($p < 0.001$) (see Fig. 1); thoracic primary 63.6% compared to 9.1% ($p = 0.001$) and paraspinal 25.0% compared to 0.0% ($p < 0.001$). The significant five-year EFS per anatomical site for patients that could be operated and patients not operated were: abdominal primary 25.9% compared to 5.1% ($p < 0.001$); thoracic primary 63.6% compared to 9.1% ($p = 0.003$); neck 50.0% compared to 0.0% ($p = 0.03$) and paraspinal 25.0% compared to 0.0% ($p = 0.001$).

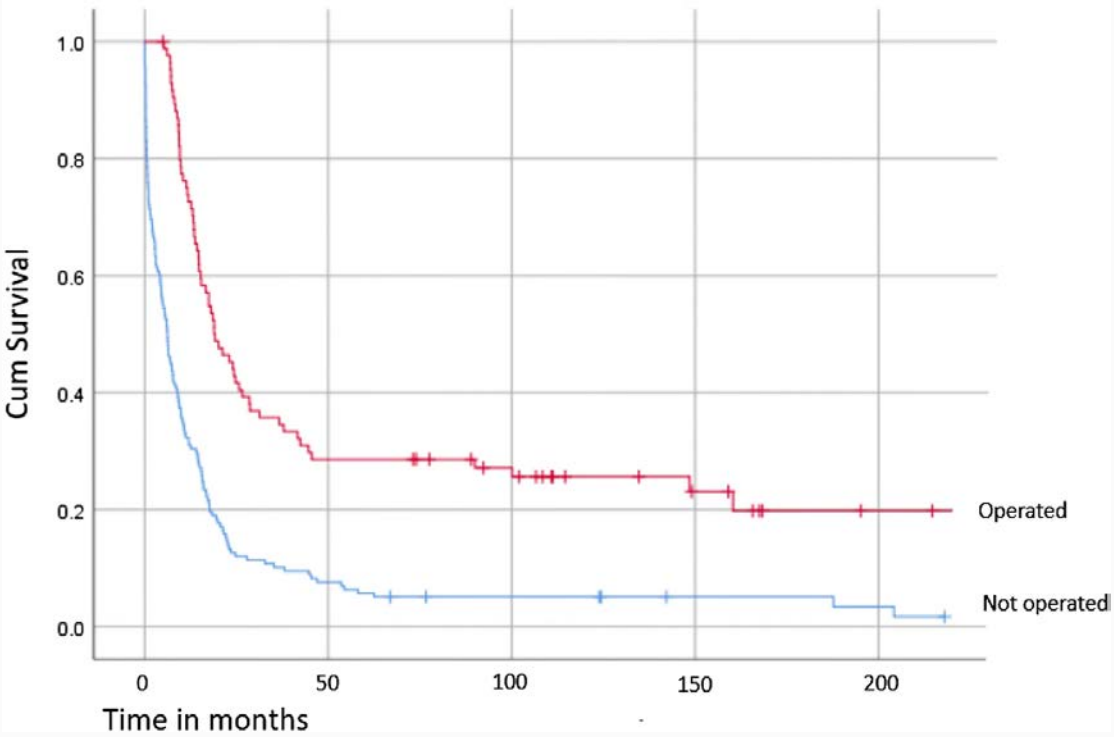

Fig. 1. Kaplan–Meier curve for OS of surgical status in HR-NB with abdominal primaries ($p < 0.001$)

Table 2 Surgical outcomes

Outcomes for surgical intervention according to site of primary tumour						
Primary site	5 years OS			5 years EFS		
	Operated	Not operated	*p* value	Operated	Not operated	*p* value
Abdominal	28.2%	5.7%	< 0.001	25.9%	5.1%	<0.001
Thoracic	63.6%	9.1%	0.001	63.6%	9.1%	0.003
Neck	50.0%	0.0%	0.225	50.0%	0.0%	0.030
Paraspinal	25.0%	0.0%	< 0.001	25.0%	0.0%	0.001
Other	12.5%	12.5%	NS	12.5%	12.5%	NS
Total	32.1%	5.9%	< 0.001	30.2%	5.3%	<0.001

Outcomes for the extent of surgical resection according to site of primary tumour				
Primary site	5 years OS			
	Complete resection	Incomplete resection	No resection	*p* values
Abdominal	28.6%	25.6%	5.8%	<0.001
Thoracic	57.1%	60.0%	10.0%	0.017
Neck	0.0%	100.0%	0.0%	0.271
Paraspinal	0.0%	33.3%	0.0%	<0.001
Other	–	–	12.5%	NS
Total	30.5%	31.4%	6.0%	<0.001
Primary site	5 years EFS			
	Complete resection	Incomplete resection	No resection	*p* values
Abdominal	26.5%	23.1%	5.2%	<0.001
Thoracic	57.1%	60.0%	10.0%	0.030
Neck	100.0%	0.0%	0.0%	0.095
Paraspinal	0.0%	33.3%	0.0%	0.003
Other	–	–	12.5%	NS
Total	30.5%	27.5%	5.5%	0.001

OS overall survival, *EFS* event free survival

The five-year OS was significantly improved for patients regardless of primary site with either complete resection or incomplete resection, at 30.5% and 31.4% respectively, compared to 6.0% in patients who did not receive any surgery ($p < 0.001$) (see Table 3). Only two operated patients (1.9%) died from surgical complications due to post-operative bleeding (Fig. 2).

Table 3 Radiotherapy outcomes

Outcomes for radiotherapy according to site of primary tumour						
Primary site	5 years OS			5 years EFS		
	Irradiated	Not irradiated	*p* value	Irradiated	Not irradiated	*p* value
Abdominal	18.6%	12.5%	0.008	16.3%	11.5%	0.035
Thoracic	0.0%	40.0%	0.518	0.0%	40.0%	0.518
Neck	100.0%	0.0%	0.107	0.0%	12.5%	0.192
Paraspinal	16.7%	16.7%	NS	16.7%	16.7%	0.126
Other	100.0%	0.0%	0.110	100.0%	0.0%	NS
Total	21.3%	14.2%	< 0.001	17.0%	13.8%	0.076
Outcomes for radiotherapy without prior surgery						
Primary site	5 years OS			5 years EFS		
	Radiotherapy only	No therapy	*p* value	Radiotherapy only	No therapy	*p* value
Abdominal	6.7%	5.8%	< 0.001	6.7%	5.0%	< 0.001
Thoracic	–	10.0%	0.007	–	10.0%	0.013
Neck	–	0.0%	0.271	–	0.0%	0.095
Paraspinal	–	–	NS	–	0.0%	0.001
Other	100.0%	0.0%	0.110	100.0%	0.0%	0.126
Total	12.5%	5.4%	< 0.001	12.5%	4.8%	0.001

OS overall survival, *EFS* event free survival

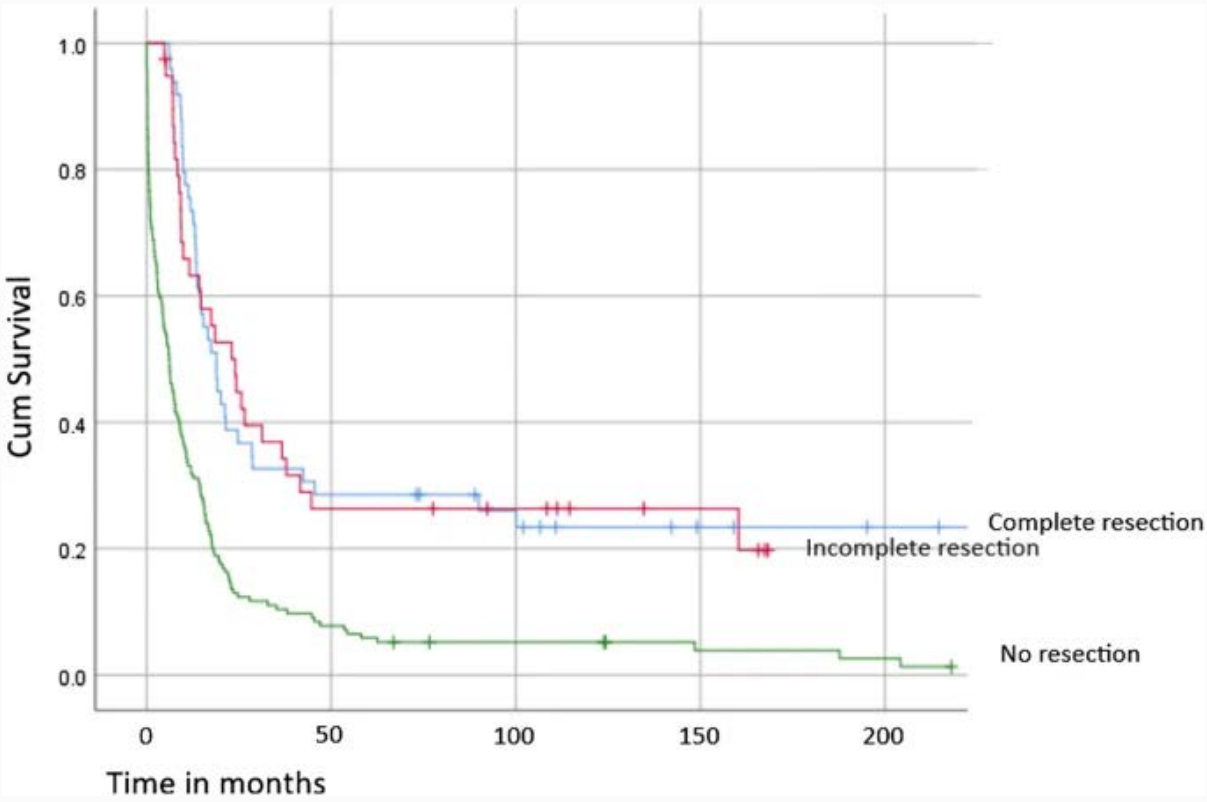

Fig. 2. The Kaplan–Meier curve for OS of the extent of resection in HR-NB with abdominal primaries ($p < 0.001$)

Patients, who were irradiated, had a better five-year OS of 21.3% and EFS of 14.2% compared to patients that were not irradiated with a 5-year OS of 17.0% ($p < 0.001$) and 5-year EFS of 13.8% ($p = 0.076$) (see Table 3). The five-year OS for patients with irradiated abdominal primaries was 18.6% compared to 12.5% in patients that were not irradiated ($p = 0.008$) (see Fig. 3). The five-year EFS for patients with irradiated abdominal primaries

was 16.3% compared to 11.5% in patients who were not irradiated ($p = 0.035$).Patients who received only radiotherapy in combination with chemotherapy had a better five-year OS of 12.5%, compared to 5.4% in those who received chemotherapy alone ($p < 0.001$), with similar findings for EFS (12.5% with radiotherapy versus 4.8% without radiotherapy) ($p < 0.001$). (see Table 3).

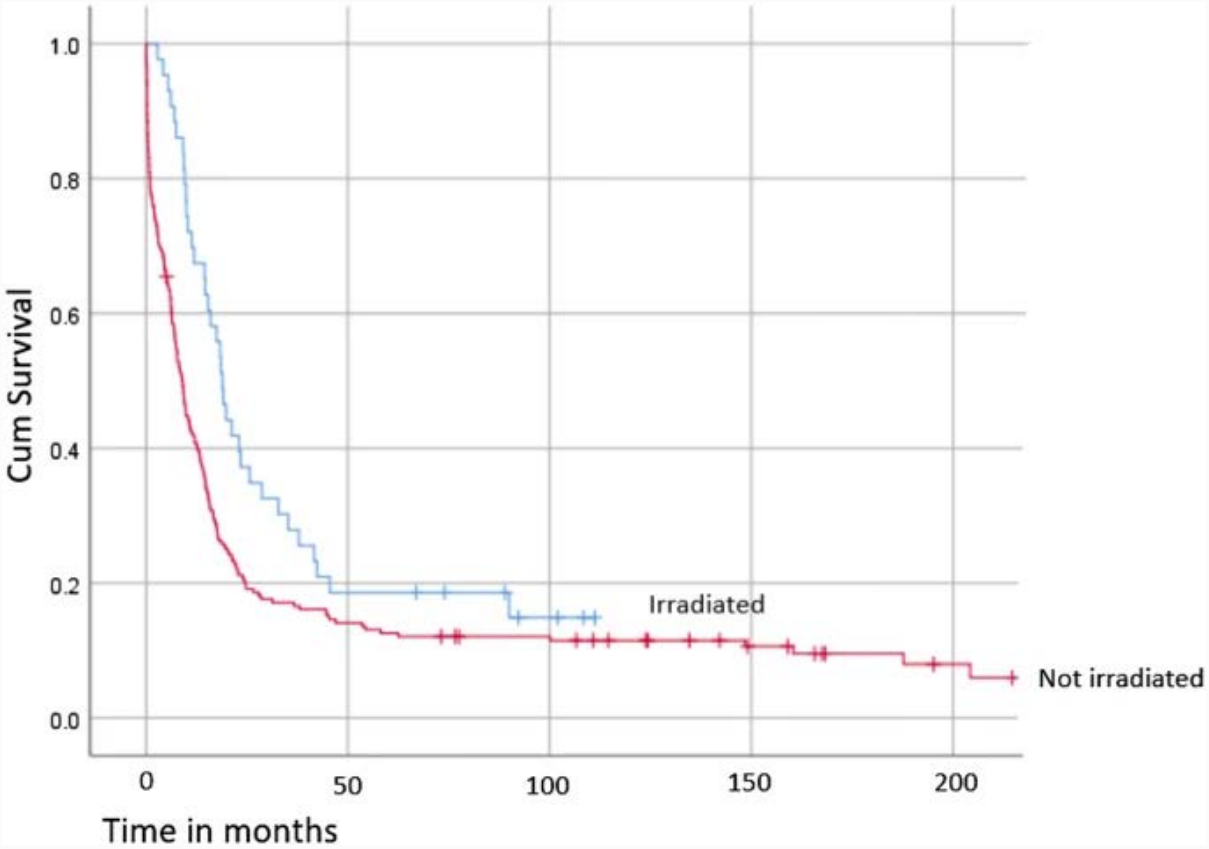

Fig. 3. Kaplan–Meier curve of OS of radiotherapy status for HR-NB with abdominal primaries ($p = 0.008$)

Operated patients had a longer mean OS of 60.9 months (80.6 months versus 19.7 months) (median 12.8 months) compared to those, who did not receive any surgery ($p < 0.001$) (see Table 4). In patients who were irradiated, the mean OS was an average of 7.9 months longer (46.2 months versus 38.3 months)(median 9.7 months) compared to those who did not receive any radiotherapy ($p < 0.001$) (see Table 4).

Table 4 Overall survival advantage for surgical, radiotherapy, and transplant interventions

Overall survival advantage HR abdominal NB according to surgery treatment					
Surgery total (mean)	Estimate (months)	Std. error	95% confidence interval		
			Lower limit	Upper limit	*p* value
Not operated	19.747	3.304	13.271	26.222	< 0.001
Operated	80.613	9.366	62.256	98.971	
Abdominal (mean)					
Not operated	19.455	3.530	12.536	26.374	< 0.001
Operated	69.664	9.751	50.552	88.776	
Thoracic (mean)					
Not operated	23.015	12.102	0.000	46.735	0.001
Operated	160.233	26.001	109.272	211.195	
Neck (mean)					
Not operated	10.981	3.696	3.736	18.226	0.225
Operated	49.567	25.244	0.089	99.044	
Paraspinal (mean)					
Not operated	3.958	1.741	0.547	7.370	< 0.001
Operated	62.896	24.042	15.773	110.019	
Overall survival advantage HR abdominal NB according to extent of resection					
Surgery (mean)	Estimate (months)	Std. error	95% confidence interval		
			Lower limit	Upper limit	*p* value
Complete	77.896	12.540	53.318	102.473	< 0.001
Incomplete	77.680	12.598	52.988	102.372	
None	19.466	3.250	13.096	25.836	
Overall survival advantage HR abdominal NB according to radiotherapy treatment					
Radiotherapy total (mean)	Estimate (months)	Std. error	95% confidence interval		
			Lower limit	Upper limit	*p* value
Irradiated	46.229	8.102	30.349	62.110	0.007
Not irradiated	38.350	4.578	29.377	47.324	
Abdominal (median)					
Irradiated	18.900	1.552	15.859	21.941	0.008
Not irradiated	8.967	0.859	7.283	10.651	
Thoracic (mean)					
Irradiated	29.350	18.383	0.000	65.381	0.518
Not irradiated	10.367	1.066	8.277	12.456	
Overall survival in high risk according to autologous hemopoietic stem cell transplant (HSCT)					
HSCT (mean)	5 years OS	Estimate (months)	Std. error	95% Confidence interval	
				Lower limit	Upper limit	*p* value
With	40%	37.867	10.115	18.042	57.691	0.268
Without	19%	17.433	2.741	12.062	22.805	

OS overall survival, *HSCT* hemopoietic stem cell transplant

On univariate analysis only thoracic primaries were of prognostic value compared to abdominal primaries ($p = 0.006$) in determining OS (see Table 5). The significant prognostic factors on multivariate analysis were age less than 18 months ($p < 0.001$), LDH < 750 U/L ($p < 0.001$) and favourable histology ($p = 0.042$). For abdominal primaries, metastatic remission status after induction chemotherapy ($p < 0.001$), surgical status ($p = 0.027$), and radiotherapy status ($p = 0.040$) were of prognostic importance for OS (see Table 6).

Table 5 Univariate analysis of prognostic factors in HR-NB

Univariate analysis of the primary site as prognostic factor in HR-NB				
	Hazard ratio	95% CI for HR		*p* value
		Lower limit	Upper limit	
Primary site (abdominal comparator)				0.053
Thoracic vs abdominal primary	0.456	0.260	0.800	0.006
Neck vs abdominal primary	1.020	0.503	2.067	0.956
Paraspinal vs abdominal primary	0.765	0.406	1.443	0.408
Other sites vs abdominal primary	1.479	0.696	3.146	0.309
Univariate analysis of prognostic factors in HR abdominal NB				
Surgical status (operated comparator)	Hazard ratio	95% CI for HR		*p* value
		Lower limit	Upper limit	
Not operated vs operated	2.647	1.968	3.560	< 0.001
Resection status (complete surgery comparator)				< 0.001
Incomplete vs compete surgery	1.019	0.626	1.658	0.939
No surgery vs compete surgery	2.604	1.811	3.744	< 0.001
Radiotherapy status (irradiated comparator)				
Not irradiated vs radiated	1.615	1.128	2.314	0.009
Age group (< 18 months comparator)				< 0.001
18–60 months	2.626	1.732	3.980	< 0.001
> 60 months	1.975	1.226	3.181	0.005
Stage (Stage 1, 2 and 4s comparator)				0.001
Stage 3	1.852	0.630	5.440	0.263
Stage 4	3.609	1.329	9.800	0.012
LDH (< 750 U/L comparator)				< 0.001
> 750 U/L vs < 750 U/L	1.729	1.254	2.386	0.001
Unknown vs < 750 U/L	3.115	2.043	4.750	< 0.001
Ferritin (< 120 g/dl comparator)				0.006
> 120 g/dl vs < 120 g/dl	1.713	1.200	2.445	0.003
Unknown vs < 120 g/dl	1.699	1.180	2.447	0.004
Pathology (FH comparator)				0.019
UH vs FH	1.953	1.206	3.161	0.006
Unknown vs FH	1.880	1.177	3.002	0.008
MYCN status (NA comparator)				0.047
Amplified vs NA	0.871	0.537	1.412	0.575
Unknown vs NA	1.292	0.844	1.977	0.239
Post-induction metastatic remission status (in remission comparator)				< 0.001
Not in remission vs in remission	5.153	3.435	7.729	< 0.001
Unknown status vs in remission	8.903	3.619	21.901	< 0.001

Table 6 Multivariate analysis of prognostic factors in HR abdominal NB

Multivariate analysis of prognostic factors in HR abdominal NB at diagnosis				
	Hazard ratio	95% CI for HR		*p* value
		Lower limit	Upper limit	
Age group (< 18 months comparator)				<0.001
18–60 months	2.331	1.529	3.554	<0.001
> 60 months	1.806	1.106	2.948	0.018
LDH (< 750 U/L comparator)				<0.001
> 750 U/L vs < 750 U/L	1.698	1.215	2.372	0.002
Unknown vs < 750 U/L	2.922	1.910	4.470	<0.001
Pathology (FH comparator)				0.042
UH vs FH	1.808	1.109	2.948	0.018
Unknown vs FH	1.796	1.116	2.889	0.016
Multivariate analysis of prognostic factors in HR abdominal NB during management				
	Hazard ratio	95% CI for HR		*p* value
		Lower limit	Upper limit	
Age group (< 18 months comparator)				0.017
18–60 months	1.842	1.172	2.895	0.008
> 60 months	1.425	0.848	2.396	0.182
LDH (< 750 U/L comparator)				0.004
> 750 U/L vs < 750 U/L	1.602	1.149	2.233	0.005
Unknown vs < 750 U/L	2.016	1.276	3.186	0.003
Post-induction metastatic remission status (in remission comparator)				<0.001
Not in remission vs in remission	3.732	2.405	5.792	<0.001
Unknown status vs in remission	4.130	1.543	11.057	0.005
Surgical status (operated comparator)				
Not operated vs operated	1.541	1.052	2.258	0.027
Radiotherapy status (irradiated comparator)				
Not irradiated vs radiated	1.416	1.016	1.973	0.040

CI confidence interval, *HR* high-risk, *NB* neuroblastoma, *FH* favorable histology, *UH* unfavorable histology

Operated patients relapsed with metastatic disease (24.5%; *n* = 26/106), which was similar for irradiated patients with metastatic relapse (10.6%; *n* = 5) and metastatic progression (42.6%; *n* = 20) (see Supplementary Table 2).

Discussion

Surgery is the most fundamental treatment modality in the multi-modality treatment of neuroblastoma with curative intent to ensure loco-regional control of the disease, regardless of metastasis [2, 14]. In stage III patients, complete resection affords better survival, especially in those with unfavorable tumor biology [15, 16]. In stage IV tumors, either complete resection or gross total resection (GTR) of 95% was recommended when possible. The COG A3973 study concluded that even a near GTR of greater than 90% obtained superior OS [17]. After surgery, age and tumor biology are the most powerful determinants of outcome in patients with neuroblastoma. In this study, only age below 18 months was significant as a prognostic factor. Surgical skill and experience may influence the subjective evaluation of resectability by the surgeon [18]. Improvements in EFS and OS in resected tumors may thus be a reflection of a more favorable biological profile and those who could not be resected had an adverse prognosis at diagnosis.

During the HR-NBL1/SIOPEN trial between 2002 and 2015, 98% of patients underwent surgery compared to only 35.9% of the patients with HR disease reported in this South

African study, while only 15.9% of HR disease tumors received radiotherapy compared to 88% in the HR-NBL1/SIOPEN trial [19]. This may have been due to a combination of factors including inequitable access to paediatric surgical expertise, shortage of operating slots, availability of radiotherapy facilities, and a chemotherapy-only strategy for metastatic patients [20].

The evidence of the prognostic significance and ideal extent of resection is conflicting. Multiple changes in systemic treatment, such as the quality and quantity of autologous transplants and molecular targeted therapies, as well as revisions of risk classification systems have complicated evaluations [21, 22]. Retrospective studies at Memorial Sloan Kettering (MSK) have proven superior survival outcomes for children with complete surgical resections (CSR) versus partial surgical resections (PSR), especially in metastatic disease [23, 24]. The MSK two-year survival rates of CSR compared to PSR were 80% versus 38%. On the basis of this, it is possible to conclude that CSR was superior to PSR, even for stage IV patients with bone marrow involvement [24,25,26]. This could not be validated in other reports [23]. The difference in survival outcomes for MYCN amplified tumours compared to non-amplified tumours were proportional to surgical outcomes for PSR compared to CSR [27]. This study demonstrated significant survival advantage if patients had tumor resection, regardless of extent if more than 50%. On multivariate analysis, the extent of resection did not reach significance, with metastatic remission being the most significant prognostic factor.

In the HR-NBL1/SIOPEN Trial, complete resection had a better five-year OS compared to incomplete resection (39% vs 30%) [19]. A meta-analysis of 19 studies in patients with HR-NB concluded that GTR did confer an OS advantage above subtotal resection (STR) at both three years and five years. However, this was only true for STR over biopsy only at three years [21]. Only in asymptomatic stage II patients with LR disease did less than 50% resection confer excellent outcomes with surgery alone [28]. Chemotherapy was restricted to patients with progression of symptomatic disease or less than 50% resection [28]. In South Africa, a survival advantage was demonstrated across all risk classifications at 2 years and 5 years with complete or incomplete resections.

The role of radiotherapy has been investigated in emergency presentations, palliation and local and metastatic disease in relation to chemotherapy and surgery, as has the role of in the transplant setting [4, 5]. Radiotherapy plays a significant role in high-risk disease, regardless of resection or nodal involvement [29, 30]. In Egypt, patients who received radiotherapy to primary sites had a superior three-year OS of 57.6% compared to 23.4% in patients who were not irradiated ($p = 0.007$) [31]. Similarly this was reflected in the three-year EFS rate, with 42.5% for irradiated patients compared to 19.5% in patients not receiving radiotherapy ($p = 0.032$) [31].

Reports estimate that 40% of HR patients will relapse [32]. Local relapses at the primary tumor and metastatic sites play a major role in mortality, especially in high-risk patients [30, 31]. The NB97 radiotherapy approach focused on residual tissue of the primary tumor site to compensate for the outcome disadvantage of incomplete response to induction therapy [32]. It was concluded that the administration of radiotherapy could compensate

for the residual tumor [32]. Patients who were irradiated at metastatic sites had better OS than patients who did not receive radiation to metastatic sites [33]. Metastatic recurrence was less likely in previously irradiated sites than in unirradiated sites [34]. In this study, patients who could undergo surgery relapsed mainly at metastatic sites (24.5%) as compared to the primary tumor bed (6.6%). The reason could be that less than 16% of patients were irradiated (*see* Supplementary Figure 1). Metastatic progression was the main event in both patients that were not irradiated (57.7%) as well as irradiated patients (42.6%).

In keeping with expert opinion in the SIOP-PODC guidelines, in the absence of a surgical resection, radiotherapy to the primary tumor, with or without metastatic sites, had a short-term benefit in patients, with a superior two-year OS in unresected patients receiving radiotherapy versus patients not receiving radiotherapy [2].

It is not clear to what extent local therapies influence outcomes in HR-NB in therapies that include single or tandem autologous transplants, molecular targeted therapy and maturation therapy [20]. Yet, in variable resource settings where chemotherapy, radiotherapy and surgery are the only treatment options, the impact of surgery with or without radiotherapy on survival has been advantageous. The benefit is amplified with a combination of both. In settings where autologous transplants and targeted therapies are not available, other treatment modalities are paramount in metastatic sites, especially if there were isolated or limited number of metastatic sites [2].

Limitations

The study was retrospective with non-randomized cohorts and treatment protocols between POUs were not standardized. The determination of risk stratification was limited by the absence of genetic information on the tumors. Documentation of the extent of resection was not standardized. Certain cohort samples were too small to determine significant results.

Conclusion

Where possible, resections should be attempted, regardless if a resection is a complete total resection, near gross total resection or incomplete resection, provided that resections are not mutilating or increase the risk for mortality. Radiotherapy as standard of care should be part of standard management and metastatic control with autologous bone marrow transplants should be considered, if possible, in LMICs. A national treatment protocol should be introduced to standardize assessment and management of HR neuroblastoma with the aim of improving outcomes.

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Contributions

JvH conceptualized and designed the study, collected data, performed the data analysis and wrote the manuscript. MK assisted with concept development, as well as design of the study, supervised data analysis, critically reviewed and revised the manuscript. TE performed the statistical analysis. GPH, as expert pediatric surgeon, supervised the surgical content and contributed patient-related data. All other authors collected data in their respective pediatric oncology units and contributed significantly to the manuscript.