The management and outcomes of neuroblastoma in South African children

PhD thesis presented on 5 January 2021 at Stellenbosch University, Faculty of Medicine and Health Sciences, Cape Town, South Africa

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Keywords

Neuroblastoma, South Africa, middle-income country, limited resources, adapted management protocol

Introduction

After brain tumours, neuroblastoma is the most diagnosed childhood solid tumour in high-income countries (1). Yet the incidence of this metabolically active sympathetic system malignancy has not accurately been described in low- and middle-income countries (2). One reason is the heterogeneous clinical picture and spectrum of patho-physiology that lends itself to misdiagnosis and underdiagnosis (3,4). This contributes to children with neuroblastoma often presenting in advanced stages of the disease with poor outcomes (2). Other contributing factors are the limited treatment modalities, and poorly understood biology of neuroblastoma in children living in low- and middle-income countries (2,3,4).

In the South African context national research into the epidemiological and clinical characteristics as well as management outcomes have not been conducted. Paired with the initiative of the South African Children's Cancer Study Group to develop prospective cancer-based protocols, we investigated neuroblastoma in South Africa with the aim to improve overall survival.

Our retrospective study showed that South Africa has a higher-than-average number of patients with high-risk (HR) tumours (75.6%), mainly because of advanced disease (70%) and a 54% *MYCN*-amplification of tumours (5). These findings were higher than high-income countries (HIC), but comparable to other low- and middle-income countries (LMICs) such as India and Brazil (4,6). Belgium, part of the SIOPEN (International Society of Paediatric Oncology European Neuroblastoma) group, about 53% of neuroblastoma (NB) tumours are stratified as HR, with 20% *MYCN*-amplification (7). Between 2000 and 2016 the incidence for neuroblastoma in South Africa was estimated to be 1.74-2.6 cases/million children (8). This is much lower than the 10.4 cases per million children reported in HICs and the 12.6 cases/ million children in Belgium (9). Very low risk disease had a 2-year overall survival (OS) of 94.1%, low risk (LR) disease 81.6%, intermediate risk (IR) disease 66.7% and HR disease 27.6% ($p<0.001$, 95% CI) (5). This contrasts to the higher five-year OS of 84.6% observed for all risk stratifications, and a two-year OS of 70% for high-risk disease for Belgian patients (10). We hypothesised that the poorer outcomes in the IR cohort was due to inclusion of patients with HR disease in this cohort. A limited number of tumours were tested for *MYCN* (38.4%) and an inability to determine neuroblastoma related genetic characteristics made risk stratification more difficult.

In the limited cohort of patients with LR disease (n = 30; 7.7%), we concluded that there was no prognostic advantage to high intensity chemotherapy. Therefore, we recommended a surgical approach in LR disease with chemotherapy in specific indications (11). In IR disease a doxorubicin-based chemotherapy regimen was recommended, with surgery and radiotherapy according to the degree of surgical tumour resection (11). During the study evaluating induction chemotherapy for HR disease, the OPEC/OJEC (carboplatin, cisplatin, etoposide, cyclophosphamide and vincristine) regimen proved the most advantages with regards to toxicity and metastatic remission rates (12). In the absence of autologous stem cell transplants, both surgery and radiotherapy had prognostic significance during management (11). Patients with HR disease who could be operated with a complete resection of 90% or incomplete resection of between 50% to 90% had an improved five-year OS of 32.1% versus 5.9% without surgery ($p<0.001$) (11). Patients who had been irradiated without surgery had a marginally better five-year OS of 12.5% as opposed to 5.4% ($p<0.001$) (11).

Our research confirmed the value of non-specific tumour marker lactate dehydrogenase (LDH) and ferritin in the risk stratification of neuroblastoma and predicting outcomes such as metastatic complete remission (mCR) rate and OS (13). Our study reproduced the prognostic cut-point values recommendations of 750 U/L for LDH and 120ng/dl for ferritin proposed by the International Society for Paediatric Oncology's Committee for Developing Countries (SIOP-PODC) (2,13). Ferritin proved to have predictive value, comparable to modified Curie scores, in determining mCR (13). LDH was comparable to modified Curie scores when predicting 2-yr OS. Age at diagnosis remained a significant prognostic factor, as recommended in HICs, even with a delayed age at diagnosis in LMICs (14).

Our findings could serve as a roadmap for other low- and middle-income countries to develop their own resource-based neuroblastoma management initiative. In South Africa, with our findings, policy makers and medical systems can justify initiatives to optimise resources in the country and encourage multi-disciplinary collaborations to ensure that patients diagnosed with neuroblastoma have access to all treatment options. With the implementation of a national neuroblastoma protocol, South Africa continues the target of decreasing the mortality of childhood malignancies according to the World Health Organisation's 2030 goals and supports the SIOP-PODC motto of "every child deserves a chance".

The thesis consisted of nine chapters that have been published as individual articles.

"The management of neuroblastoma in limited-resource settings" (15)

Neuroblastoma is the most common solid tumour in HICs, but in LMICs, limited knowledge is available about NB beyond data published in abstracts and reports by single institutions. The last report on NB in South Africa was published by Hesseling et al in the 1990s (16). From these few reports, patients in LMICs present at a later mean age at diagnosis, more advanced disease and with more high-risk prognostic indicators. The resource-poor settings limit the scope of management, resulting in treatment approaches not being standardised. This narrative review provided an extensive overview of the regional approaches of LMICs towards NB, summarised the presenting symptoms, disease characteristics at diagnosis and the prognostic factors. Due to the non-standardised reporting of outcomes between LMICs and HICs the comparison was not feasible, and an overview of reported results was analysed. Finally, the review reflected on the barriers to the implementation of evidence-based treatment protocols and socioeconomic variables that influenced the diagnosis, management and follow-up of patients with NB.

"Reporting incidences of neuroblastoma in various resource settings" (8)

NB contributes to approximately 7% of all childhood malignancies that are diagnosed yearly worldwide. For various reasons accurate incidences of paediatric malignancies in sub-Saharan countries, have not been documented including inaccurate recording in tumour registries. In South Africa, underreporting of up to 50% has been reported compared to HIC statistics. The heterogeneous spectrum of NB disease poses a diagnostic challenge and the subsequent inclusion into tumour registries in limited-resourced settings. This study evaluated the context of NB in LMIC if HIC reporting standards were applied and the expected incidences were calculated. South Africa has two tumour registries that include childhood malignancies. We evaluated the NB data of patients diagnosed between 2000 and 2016, which included clinical file data from ten paediatric oncology units (POUs) and NB patients in South Africa who were included in the two registries. The same methodology was applied for the age at diagnosis and sex in patients diagnosed with NB.

"Overall survival for neuroblastoma in South Africa between 2000 and 2014" (5)

For the development of a standardised prospective national management protocol for NB in South Africa, it was necessary to evaluate the local OS against international data to formulate management recommendations. The hypothesis was that the various NB treatment strategies had varying outcomes in South Africa. A national multicentre chart review of newly diagnosed NB patients between 2000 and 2014 in nine POUs of South Africa was done. The data that were sourced retrospectively were the known risk factors of NB including age, stage, non-specific and specific tumour markers, pathology and biological disease characteristics. Numerous treatment modalities that were applied during management were evaluated. The outcomes, mCR, EFS (event free survival) and OS were determined for all patients registered with the SACTR (South African Children's Tumour Registry) during the 14-year period. This information was used to evaluate the various treatment protocols used in South Africa and to facilitate the development of the prospective management protocol aligned with both international guidelines and local resources.

"Age at diagnosis as a prognostic factor in South African children with neuroblastoma" (14)

Age at diagnosis has consistently remained an important prognostic factor in determining treatment risk classifications of NB despite the advances in treatment options. LMICs had reported older median ages at diagnosis compared to HICs (*Figure 1*). During the retrospective study the same delay in the age at diagnosis was reported in South Africa. Internationally, children under the age of 12 months have a favourable prognosis regardless of tumour biology and patients older than five years have poor outcomes. The research hypothesis is that the delayed age of presentation in South Africa would have prognostic implications for the risk stratification and therefore for the management. In keeping with international findings, the study team determined that the 18-month cut-point value was of prognostic significance in South African children diagnosed with NB as well.

"The correlation of tumour markers and 123I-mIBG-studies in South African children with neuroblastoma" (13)

An mIBG scan is part of the gold standard in the diagnosis and evaluation of NB treatment response, but is not freely available in LMICs. Furthermore, the production of radioisotopes is not reliable. In NB, it is important to administer chemotherapy at the indicated intervals and therefore it is important to be able to perform tests at the correct point of evaluation. Blood-based tests are part of the standard of care, are cheaper and need limited technology to perform. Non-specific tumour markers lactate dehydrogenase (LDH) and ferritin have extensively been validated in the prediction of treatment response and OS. The *MYCN*-gene is a NB specific tumour marker and has been validated in predicting treatment response and outcomes as well. *MYCN*-amplification can be determined on both tissue from the NB tumour as well as the NB-cells in bone marrow aspirates yet requires lab-based technology that is often centralised in countries and more expensive than LDH and ferritin. In our study both LDH and ferritin predicted two-year OS, where the modified Curie scores did not. We concluded that LDH and ferritin may serve as surrogate tumour markers to the gold standard of mIBG-scans to assist in the management of NB in LMICs with limited resources.

"Induction chemotherapy for high-risk neuroblastoma in South African children" (12)

Seventy-eight percent of patients diagnosed in South Africa between 2000 and 2016 with NB, had high-risk tumours. As metastatic remission after induction therapy in high-risk neuroblastoma (HR-NB) was of prognostic importance, this study investigated mCR after induction chemotherapy during the three standard induction protocols for NB in the South African setting. The objective was to identify an induction regimen for HR-NB based on remission rate, toxicity and OS that could be administered in al POUs in South Africa. There was no significant difference in the mCR and OS between the three induction regimens but OPEC/OJEC had the most favourable toxicity profile for the South African setting. The same outcomes were drawn between the Rapid COJEC (SIOPEN protocol) and N5-MSKCC (St Jude's Hospital, North American protocol) with the N5-MSKCC induction protocol causing greater toxicity (10).

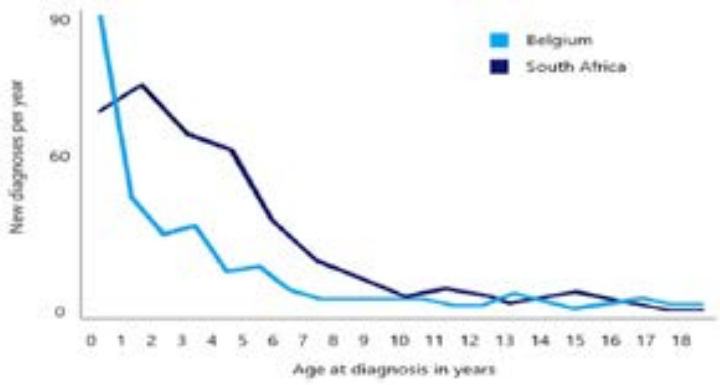
"The importance of local control management in neuroblastoma in South Africa" (11)

Surgery and radiotherapy are important in the local tumour management of NB. In patients with low-risk tumours, surgery is curative, whilst in patients with intermediate-risk tumours, surgery, chemotherapy and, in cases of residual tumours, radiotherapy are curative. HR-NB trimodal therapy (chemotherapy, surgery and radiotherapy) only has an OS of up to 20-25% (*Figure 2*). In higher-resourced settings, autologous stem cell transplants, molecular targeted therapies and maturation therapy have increased the outcomes up to 60-65% OS but made the significance of local therapies unclear. The role of surgery in NB in South Africa, especially the degree of resection, has never been evaluated. The relevance of radiotherapy in curative and palliative management in the absence of surgery has not been explored in the South African paradigm. The study concluded that a surgical resection between 90% to 100% had better outcomes than no surgery and that radiotherapy in the absence of surgery increased the progression-free survival.

"The implementation of a national paediatric oncology protocol for neuroblastoma in South Africa" (17)

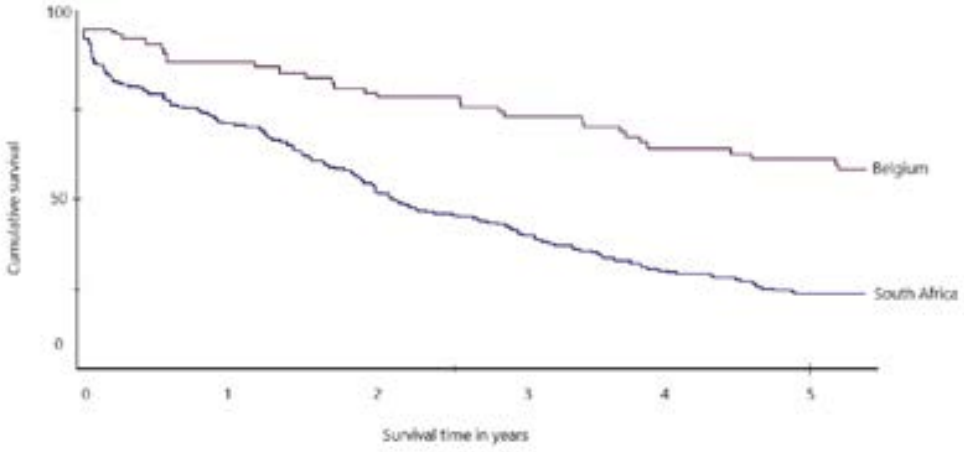
Collaborative guidelines are important in establishing a standard of paediatric oncology care in South Africa. The South African Children's Cancer Study Group (SACCSG) has embarked on developing national management protocols for individual childhood malignancies. The evaluation of the development process of the neuroblastoma protocol by the NB-working group of South Africa, valuable resources and methodologies for future protocol development were documented. The SACCSG NB-2017 protocol was an example where multiple international guidelines were incorporated for the local setting as an adapted management protocol. The implementation research of this article may provide insight into the development and implementation of similar treatment guidelines in other LMICs.

Figure 1: *A comparison of the age at diagnosis for neuroblastoma in a high-income country (Belgium) compared to a resource limited country (South Africa)*



Graph: Created by J van Heerden and M Kruger. **Sources:** The Belgian graph is based on data from the Belgian Cancer Registry. The South Africa graph is based data from the retrospective study in this thesis.

Figure 2: *The Kaplan Meier curve representing the five-year overall survival for high-risk neuroblastoma in South Africa compared to Belgium*



Graph: Created by J van Heerden and M Kruger.

"Inequality in paediatric oncology in South Africa – the neuroblastoma case study" (18)

South Africa adopted its first democratic Constitution in 1996. The Bill of Rights included a section protecting children's rights beyond the constitutional right to life and equality. With the guarantee of access to health services enshrined in the Constitution, lifesaving treatment for neuroblastoma should be included in the right to life-saving medical treatment. With a more equitable population-based distribution of the country's budget and various administrative reforms, the national health services should after 20 years have established equal health care access to children with cancers. Based on the data from our retrospective NB study between 2000 and 2014, we evaluated the equity of the human resources, the level of paediatric oncology services and the access to these services based on distance and travel duration. We concluded that inequity to access these resources for children with cancer in South Africa, was still a large problem.

"An interim assessment of the prospective national neuroblastoma protocol (SACCSG NB-2017) in South Africa".

The running of a successful trial and recruitment of patients depends on many contributing factors. The interim analysis of the SACCSG NB-2017 clinical trial and the sub-optimal inclusion of patients were evidence to this. The factors that contribute to investigator trial participation are institutional, national and/ or individual to single investigators. Although many factors can be mitigated, others are not and flexibility towards the research should be adopted with a greater emphasis on co-operative participation. South African universities have no standardised or shared ethics application procedure. Neither are reciprocal ethics approvals between universities in place for more efficient cooperation. This leads to excessive, burdensome administration in a system where research is already challenging. The personal experience of co-investigators led to the exclusion of study eligible patients because participating POUs have felt the psycho-emotional situation such as pre-terminal presentations, not conducive for including patients on the palliative aspect of the study. The interest in the subject matter, number of staff to oversee the clinical workload and a resistance to work in a research study group added many degrees of complexity in executing the study. The responsibility of co-investigators familiarising themselves with a new national treatment protocol in combination with the infrequent diagnosis of a rare disease, such as NB, in a single POU contributed to low retention of the study protocol. Since the outbreak of the COVID-19 pandemic an already overburdened South African medical system, increased pressures arose.

This relegated academic and administrative responsibilities secondary to the pandemic's management responsibilities.

The value of neuroblastoma research done in LMICs for HICs

With increasing evidence of genetic and epigenetic variations in NB, questions regarding the population-based genetic profiles in NB are still unanswered. One conclusion in our thesis is that South Africa might truly have a lower incidence of NB, independent from the resource and delayed health seeking behaviour limitations. With the limited to no genetic and molecular data available from LMICs, conclusions cannot be made regarding local profiles.

Fundamental clinical research, including translational research, is possible in LMICs because of the higher need for clinical applications of advanced tests to improve outcomes, but at a lower cost. The value of resource allocation is acutely present in LMICs compared to HICs, yet the experienced gained regarding resource management is valuable to HICs as well.

Most HICs collaborate in study groups who utilise trial protocols based on standard of care and interventions with clear indications. In LMICs the possibilities are greater for treatments with favourable evidence to be studied outside the study group trials. This opens avenues for developing more strategies to treat NB with locally available resources which can be used in HICs.

Conclusion

This thesis highlights the landscape of NB in LMICs through the lens of the South African experience. NB is often underdiagnosed and under reported, which leaves basic epidemiological questions on NB in limited resource settings unanswered. The high burden of advanced and high-risk disease not only represents the unique pathology in limited resource settings, poses significant challenges in the management of NB, often with poor outcomes. Achieving early diagnosis remains a challenge in LMICs which includes South Africa. Therefore, advocacy to improve public awareness should increase and include the early warning signs of childhood cancer in the integrated management of childhood illnesses (IMCI) to assist all level of health care workers to recognize childhood cancer with an immediate referral (19). The methodical development of a national protocol indicated the possibility of managing NB, but with the conclusion that the use of local therapies, such as surgery and radiotherapy, should be optimised for improved outcomes. Both the COVID-19 pandemic and reluctance to recruit advanced stage patients limited the recruitment of patients into the national NB clinical trial. Of great importance is to encourage initiatives towards bio-banking in South Africa to study the genetic profiles of diseases unique to the region. With the diversity of the genetic landscape in South Africa and the ever-increasing research into genetic and epigenetic targets in NB, biological knowledge could contribute to a greater understanding in the outcome variations as well as research into the pharmacokinetics and dynamics in the treatment of NB (20).

By promoting collaborative research efforts and relevant research questions, rare diseases such as neuroblastoma in South Africa could be managed in national management protocols, with the goal of improving the survival rates and eventually being able to cure high-risk disease.

Conflict of interest

There is no conflict of interest to disclose.

Acknowledgements

The data for survival analysis were provided by the South African Children's Cancer Study Group Neuroblastoma Workgroup: Dr Jaques van Heerden, Prof Mariana Kruger, Prof Marc Hendricks, Dr Anel van Zyl, Dr Jan du Plessis, Dr Ané Büchner, Prof Janet Poole, Dr Ele Madzhia, Dr Vhutshilo Netshituni, Prof Gita Naidu, Dr Barry van Emmenes, Dr Johani Vermeulen, Dr Liezl du Plessis and Tonya Esterhuizen.

Funding

The work of this PhD was funded by the vzw Kinderkankerfonds, Belgium.

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