# The pre-surgical factors that determine the decision to proceed to resection in children diagnosed with high-risk neuroblastoma in a resource limited setting

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**ABSTRACT**

Surgical control has prognostic value in neuroblastoma (NB). Advanced NB is common at diagnosis in South Africa. We investigated the pre-surgery factors that influenced decisions to perform surgical resections. We included 204 patients with high-risk NB from a national retrospective study, who completed induction chemotherapy between 2000 and 2016.

The median age was 32.4 months (IQR 15.1 – 53.5 months). Primary tumor resection was achieved in 76.9% of patients between 0-18 months of age, 51.8% between 18-60 months and 51.7% older than 60 months ($p < 0.001$). Only 43.2% of patients with distant metastatic disease had surgery done ($p < 0.001$). LDH was >750 U/L in 46.8% and ferritin >120 g/

**KEYWORDS**

High-risk; image defined risk factors; neuroblastoma; predicting surgery; remission; South Africa

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dL in 53.1% of those who had surgery ($p = 0.005$). The majority (80.4%), who had achieved post-induction metastatic complete remission (mCR), were operated, while 28.7% without mCR had surgery ($p < 0.001$). The long-term overall survival in patients with mCR and primary tumor resection was 36.5% compared to those with mCR without primary tumor resection (25.4%) and without mCR (≤3.0%)($p < 0.001$). Age ($p < 0.001$), stage ($p < 0.001$), mCR ($p < 0.001$) and treatment setting ($p < 0.001$) were of prognostic significance. The tumor site and MYCN-amplification did not significantly predict resection rates. Post-induction mCR and stage were associated with surgical resection and five-year OS ($p < 0.001$) on multivariate analysis.

Patients with high-risk NB who achieved mCR and had primary tumor resections are curable in limited resourced settings. Stage and post-induction mCR were significant variables that led to surgery. These variables should be included as indications in the management of metastatic NB in resource limited settings.

**TEACHING POINTS**

- High-risk neuroblastoma that achieved post-induction chemotherapy metastatic remission and have undergone resection, is curable, even in limited resource settings.
- Achieving metastatic complete remission was the only factor that significantly predicated if surgery was done.
- The age at diagnosis, stage and hospitals with expertise in neuroblastoma surgery were of prognostic significance in South Africa.
- If a patient with high-risk neuroblastoma achieves metastatic complete remission in a resource limited setting, it should be an indication for resection of the primary tumor.

**Abbreviations:** CI: Confidence intervals; COG: Children's Oncology Group; CT: Computed tomography; HR: High risk; IDRF: Image defined risk factors; INPC: International Neuroblastoma Pathological Classification; INRG: International Neuroblastoma Risk Group; INSS: International Neuroblastoma Staging System; LDH: Lactate dehydrogenase; LMICs: Low- and middle-income countries; mCR: Complete metastatic remission; NB: Neuroblastoma; OS: Overall survival; SA: South Africa; SIOPEN: International Society of Pediatric Oncology European Neuroblastoma group

## Introduction

Neuroblastoma (NB) is a neuro-endocrine tumor which is the second most common solid tumor diagnosed in children,[1,2] and although less common in lower to middle income countries (LMIC), often present with either high risk and/or advanced disease.[3] As with other solid tumors, the primary treatment modality for local control is surgery followed by radiotherapy.[1,2] Excluding a limited number of patients with low-risk disease, who may be observed,[4,5] surgery is a vital component in the curative management in NB independent of risk stratification.[1,2]

According to North American protocols, the primary tumor must be resected as soon as it is possible.[2,6] Although induction chemotherapy may reduce a primary tumor to optimize the possibility of resection, resection may proceed without induction chemotherapy if resection is possible.[2,6] This will occasionally mean excising the primary

tumor when metastatic disease is still present and further metastatic response may be anticipated with additional treatment whilst European protocols require metastatic remission before attempting surgery.[7,8] The degree of resection of primary tumors is proven to have prognostic value, but is unclear in patients with metastatic disease, who are treated with multimodal therapy.[9,10] Image-defined risk factors, namely radiological features seen at the time of NB diagnostic imaging, can predict resectability of a tumor.[11,12] Challenges of surgical resection include extensive disease, encasing crucial major vessels and infiltrating organs such as the liver and the spleen, which complicates surgical interventions.[13]

While low-risk local disease may be surgically less complex for complete resection, in intermediate and high-risk disease evidence-based guidance advocates for a gross-total resection of 50-90% and >90% respectively, whenever possible without risking increased morbidity such as vascular injury or organ loss.[14] The ability to perform surgical interventions is dictated by the surgical expertise in resecting neuroblastoma tumors, the anatomical position of the tumor, response to chemotherapy, size, vascularity, and the status of IDRFs after induction chemotherapy, which may remain unchanged or have progressed.[15] The uneven distribution of surgical skills in unequally resourced settings means that the complex surgeries required in NB are either technically very challenging or not performed at all.[16,17]

In South Africa, there is an uneven distribution of resources to treat NB and patients present at a late stage with advanced tumors.[18] Therefore, most patients are diagnosed with HR-disease and thus have outcomes that are poor.[16,19] Previous studies in South Africa have shown that the clinical presentation as well as lack of access to experienced surgeons in some areas of the country result in many tumors, especially with metastasis at diagnosis, not being resected and patients undergoing palliation by default.[16] Even in settings with adequate resources, high-risk patients do not have their tumors resected, based on poor prognostication alone.[17] Until 2019 there was no standardized national protocol in South Africa to guide surgical management and the decision to continue with surgical resection was based on the recommendations of multidisciplinary team discussions and surgical expertise. This study aimed to evaluate the patient and tumor characteristics, as well as pre-surgery factors during management that influence a decision to perform a surgical resection in a resource limited setting.

## Materials and methods

### *Patient selection of the cohort*

Surgical data collected during the national retrospective NB study for the period 2000 till 2016, was analyzed (Figure 1). NB diagnosis was confirmed with pathology or radiological imaging, as well as bone marrow aspirate combined with confirmatory urine homovanillic acid and vanillylmandelic acid. Patient records were included if there was imaging (x-rays, ultrasound, computed tomography and/or magnetic resonance imaging) of sufficient quality to retrospectively evaluate for image-defining-risk factors (IDRFs) by certified radiologists. There were 271 patients included for analysis with 79 excluded as they had incomplete surgical data, or palliated upfront, had no surgical intervention due to disease progression or death during induction (Figure 1).

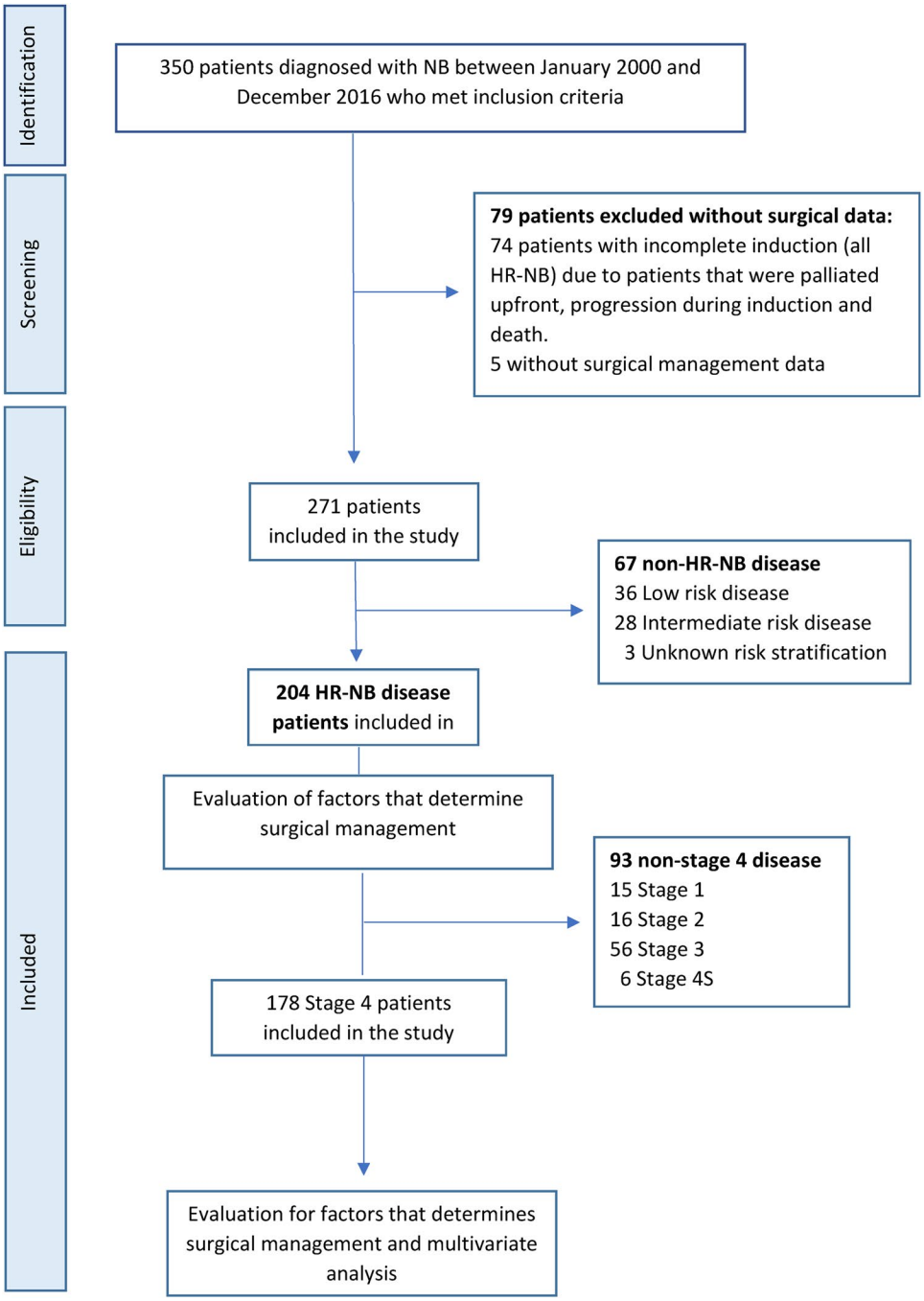


**Figure 1.** PRISMA flow diagram depicting the patient inclusion.

Thus, patients that was never eligible for curative surgery. Data analysis included age at diagnosis, stage, pathology, biology, risk stratification or management-related outcomes as predictors that influenced the decision toward surgical intervention. A smaller HR-NB cohort (n = 204) was evaluated for univariate analysis alone to exclude the

confounding attributed to risk stratification. To evaluate the significance of post-induction metastatic remission rate (mCR), only the metastatic cohort (stage 4 disease), adjusted for age, was analyzed. For the primary objective, decision to perform surgery was the study endpoint, whilst OS and survival time were evaluated as secondary endpoints. The degree of resection was not considered during evaluation, because post-surgical imaging to determine the degree of resection was very rarely done and this was rather based on the surgeon's subjective evaluation.

The stage of disease was defined according to the International Neuroblastoma Staging System (INSS) and was retrospectively staged for the study purpose (Supplemental Table 1); pathology risk stratification was based on the International Neuroblastoma Pathology Classification and IDRFs were defined according to the International Neuroblastoma Risk Group (INRG) staging system.[11,20] The NB treatment setting was defined by SIOP-PODC Adapted Risk Stratification and Treatment Guidelines: Recommendations for Neuroblastoma in Low- and Middle-Income Settings. IDRFs reports were sourced retrospectively.[6] Most of the radiological records were still paper based and images could not be reevaluated retrospectively. Metastatic remission was defined by the 2014 INRG treatment response classification.[21]

## Statistical analysis

IBM SPSS version 25 (IBM Corporation, USA) statistical software was used to evaluate descriptive data. Age at diagnosis was assessed using non-parametric tests. All other factors were assessed with parametric tests including lactate dehydrogenase (LDH) (level of prognostic differentiation of 750 U/L) and ferritin (level of prognostic differentiation of 120 g/dL) based on the findings of Parikh et al.[6] Categorical association between independent variables such as tumor marker, pathology, INSS, INRG staging and IDRF analytical groups, surgical complications, mCR and OS were assessed using the two-sided, Pearson Chi-square ($\chi^2$) test. Calculations in the stage 4 cohort were adjusted for age at diagnosis to eliminate the effect of confounding.

The Fishers exact test was applied with cohorts of less than five. The results were described using Kaplan-Meier curves with differences evaluated using log-rank tests. OS was defined as the time in months from diagnosis to death or date of last clinical follow-up. To estimate the effect of IDRFs and clinical factors on OS, univariate and multivariable Cox regression (for survival time) and log regression (for percentage five-year OS) modeling approaches were employed. Where relevant evaluations were adjusted for age. The proportional hazards assumption was also confirmed for the final multivariable model. A *p*-value less than 0.05 was considered significant.

## Results

Two-hundred and seventy-one patients were included with a male to female ratio of 1:0.96 (males 50.9%; females 49/1%) (Supplemental Table 2). The median age was 32.4 months (IQR 15.1; 53.5 months, range 0.2 – 204.3 months). The most common

primary was in the abdomen (n = 199, 73.4%), followed by thoracic (n = 29; 10.7%), and paraspinal tumors (n = 15, 5.5%). The majority were metastatic disease metastatic (stage 4 INSS and stage M INRG n = 178, 65.7%).

Most of the seventy-one tumors (26.2%) had favorable histology, 94 (34.7%) had unfavorable histology whilst 106 (39.1%) diagnoses were confirmed on bone marrow aspirates and the International Neuroblastoma Pathology Classification (INPC) could not adequately be evaluated.

An elevated LDH above 750 U/L occurred in 127 patients (46.9%) and ferritin was raised (>120 mg/dL) in 69 patients (25.5%). MYCN-amplification was detected in 64 tumors (23.6%), whilst was not amplified in 58 (21.4%). It was unknown in 149 (55.0%) tumors.

The disease was stratified as HR in 204/271 (75.3%) patients, IR in 28/271 (10.3%) and LR in 36/271 (13.3%). Only three (1.1%) patients could not be stratified.

In the total cohort, IDRFs (including ascites and pleural effusions) were present in 106 (39.1%) patients and absent in 165 (60.9%) patients (Supplemental Table 3). There was at least one IDRF in 96 (35.4%) patients and six (6.3%) had more than one IDRF. Eleven (4.1%) patients presented with a pleural effusion or ascites. Only one patient had an IDRF with a pleural effusion.

Most children under 18 months of age (76.9%, n = 78) had surgical resection (Table 1), followed by half of those between 18 – 60 months of age (n = 135, 51.8%) and half of those over 60 months of age (n = 58, 51.7%) ($p < 0.001$). There was no significant difference between males and females who were operated (respectively 58.0% vs. 60.2%; $p = 0.715$). Surgical resection included mostly abdominal tumors (n = 113, 56.8%), followed by nineteen thoracic tumors (65.5%), twelve paraspinal tumors (80%), four abdominal-retroperitoneum-pelvic tumors (40.0%), three pelvic tumors (75.0%), two thoraco-abdominal tumors (66.7%), two cervical tumors (33.3%) and one cervico-thoracic tumor (100%), (not statistically significant $p = 0.591$).

### *Stage, tumor markers, pathology and risk stratification related to surgical resection (Table 1)*

All stage 1 patients had a tumor resection of the primary tumor (n = 15/15, 100%). Operative rates for stage 2 and stage 3 were 93.8% (n = 15/16) and 83.9% (n = 47/56) respectively. Only 50% (n = 3/6) of stage 4S tumors were operated followed by those with stage 4 (n = 80/178, 44.9%) disease ($p < 0.001$). Tumors with favorable histology were operated more frequently (n = 63/71, 88.7%) than those with unfavorable histology (n = 56/94; 59.6%; $p < 0.001$). Operative rates were higher in those patients with an LDH below 750 U/L (n = 87/127, 68.5%) than those with a LDH above 750 U/L (n = 67/127, 52.8%; $p = 0.005$). The same trend followed for patients with ferritin below 120 ng/dl (n = 44/69, 63.8%) and above 120 ng/dl (n = 61/121, 50.4%; $p = 0.030$) and for those who were MYCN non-amplified (n = 39/58, 67.2%) compared to those who were (n = 38/64, 59.4%; $p = 0.316$). LR patients were operated most frequently (n = 31/36, 86.1%), followed by IR patients (n = 22/28, 78.6%), those with unstratified disease (n = 2/3, 66.7%) and finally the HR (n = 105/204, 51.4%) patients ($p < 0.001$).

**Table 1.** The factors that determine access to surgery in children diagnosed with high-risk NB in South Africa between 2000 and 2016.

| | | Surgical status N (%) | | | |
|---|---|---|---|---|---|
| | | Operated | Not operated | Total N (%) | p-value |
| Age | 0–18 months | 27 (67.5) | 13 (57.5) | 40 (19.6) | <0.001 |
| | 18.1–60 months | 56 (48.3) | 60 (51.7) | 116 (56.9) | |
| | >60 months | 22 (45.8) | 26 (54.2) | 48 (23.5) | |
| | Total | 105 (51.5) | 99 (48.5) | 204 | |
| Sex | Male | 54 (50.5) | 52 (49.5) | 106 (52.0) | 0.715 |
| | Female | 51 (52.0) | 47 (48.0) | 98 (48.0) | |
| | Total | 105 (51.5) | 99 (48.5) | 204 | |
| Primary site | Abdomen | 82 (50.9) | 79 (49.1) | 161 (78.9) | 0.591 |
| | Thorax | 7 (50.0) | 7 (50.0) | 14 (6.8) | |
| | Paraspinal | 8 (72.7) | 3 (27.3) | 11 (5.4). | |
| | Neck | 2 (40.0) | 3 (60.0) | 5 (2.5) | |
| | PNF | 2 (40.0) | 3 (60.0) | 5 (2.5) | |
| | Abdominal-retroperitoneum-pelvis | 2 (66.7) | 1 (33.3) | 3 (1.5) | |
| | Pelvis | 1 (50.0) | 1 (50.0) | 2 (2.0) | |
| | Thoraco-abdominal | 0 (0.0) | 1 (100) | 1 (0.5) | |
| | Other | 0 (0.0) | 1 (100) | 1 (0.5) | |
| | Cervico-thoracic | 1 (100) | 0 (0.0) | 1 (0.5) | |
| | Total | 105 (51.5) | 99 (48.5) | 204 | |
| INSS | Stage 2 | 3 (60.0) | 2 (40.0) | 5 (2.5) | <0.001 |
| | Stage 3 | 30 (88.2) | 4 (12.8) | 34 (16.7) | |
| | Stage 4 | 70 (43.2) | 92 (56.8) | 162 (79.4) | |
| | Stage 4S | 1 (33.3) | 2 (66.7) | 3 (1.5) | |
| | Total | 104 (51.0) | 100 (49.0) | 204 | |
| INRG | L1 | 24 (92.3) | 2 (7.7) | 26 (12.7) | <0.001 |
| | L2 | 10 (76.9) | 3 (23.1) | 13 (6.3) | |
| | M | 70 (43.2) | 92 (56.8) | 162 (79.4) | |
| | MS | 1 (33.3) | 2 (66.7) | 3 (1.5) | |
| | Total | 105 (51.5) | 99 (48.5) | 204 | |
| INPC | FH | 24 (85.7) | 4 (14.3) | 28 (13.7) | <0.001 |
| | UH | 43 (55.8) | 34 (44.2) | 77 (37.7) | |
| | Unknown | 37 (37.4) | 62 (62.6) | 99 (48.5) | |
| | Total | 104 (51.0) | 100 (49.9) | 204 | |
| LDH | <750 | 51 (61.4) | 32 (38.6) | 83 (40.7) | 0.005 |
| | >750 | 51 (46.8) | 58 (53.2) | 109 (53.4) | |
| | Unknown | 2 (16.7) | 10 (83.3) | 12 (5.9) | |
| | Total | 104 (51.0%) | 100 (49.9%) | 204 | |
| Ferritin | <120 | – | – | – | 0.030 |
| | >120 | 102 (53.1) | 90 (46.9) | 192 (94.1) | |
| | Unknown | 2 (16.7) | 10 (83.3) | 12 (5.9) | |
| | Total | 104 (51.0) | 100 (49.9) | 204 | |
| MYCN | Non-amplified | 22 (62.9) | 13 (37.1) | 35 (17.2) | 0.316 |
| | Amplified | 29 (52.7) | 26 (47.3) | 55 (27.0) | |
| | Unknown | 53 (46.5) | 61 (53.5) | 114 (55.8) | |
| | Total | 104 (51.0) | 100 (49.9) | 204 | |
| Hospital (care setting)* | Hospital A (3) | 3 (50.0) | 3 (50.0) | 6 (6.2) | 0.001 |
| | Hospital B (2) | 30 (60.0) | 20 (40.0) | 50 (24.5) | |
| | Hospital C (3) | 15 (46.9) | 17 (53.1) | 32 (15.7) | |
| | Hospital D (2) | 11 (50.0) | 11 (50.0) | 22 (10.8) | |
| | Hospital E (1) | 0 (0.0) | 6 (100.0) | 6 (2.9) | |
| | Hospital F (2) | 0 (0.0) | 1 (100.0) | 1 (0.5) | |
| | Hospital G (1) | 0 (0.0) | 1 (100.0) | 1 (0.5) | |
| | Hospital H (3) | 26 (60.0) | 18 (40.0) | 45 (22.1) | |
| | Hospital I (3) | 7 (41.2) | 10 (58.8) | 17 (8.3) | |
| | Hospital J (3) | 11 (45.8) | 13 (54.2) | 24 (11.8) | |
| | Total | 104 (51.5) | 100 (48.5) | 204 (100) | |
| Care setting* | 1 | 0 (0.0) | 7 (100) | 7 (34.3) | 0.449 |
| | 2 | 42 (57.5) | 31 (42.5) | 73 (35.8) | |

(*Continued*)

**Table 1.** (Continued).

| | | Surgical status N (%) | | | |
|---|---|---|---|---|---|
| | | Operated | Not operated | Total N (%) | p-value |
| | 3 | 63 (50.8) | 61 (49.2) | 124 (60.8) | |
| | Total | 105 (51.5) | 99 (48.5) | 204 (100) | |
| mCR | In remission | 45 (80.4) | 11(19.6) | 56 | <0.001 |
| | Not in remission | 35 (28.7) | 87 (71.3) | 122 | |
| | Total | 80 | 98 | 178 | |
| IDRFs | No IDRFs | 74 (49.0) | 77 (51.0) | 151 | 0.322 |
| | One or more IDRFs | 27 (61.4) | 17 (38.6) | 44 | |
| | Pleural effusions or ascites | 4 (44.4) | 5 (55.6) | 9 | |
| | Total | 105 | 99 | 204 | |

*SIOP-PODC setting of neuroblastoma care[6].

The difference between those operated with no IDRFs versus those with IDRFs in HR-NB group were not significant (no IDRFs: 74/151, 49.0% versus with IDRFs: 77/151, 51.0%) ($p = 0.322$). There were more stage 2 (60.0%) and stage 3 (88.2%) tumors operated compared to stage 4 (43.2%) ($p < 0.001$). More stage L1 (92.3%) and L2 (76.9%) tumors were operated than stage M (43.2%) ($p < 0.001$).

### *Metastatic remission rate and surgical resections (Table 2)*

Only a third of patients with metastatic disease obtained mCR 56/178 (31.5%) versus 122/178 (68.5%), who did not achieve mCR ($p < 0.001$). Of those in mCR, 45/56 (80.4%) had their tumors resected ($p < 0.001$). Those that were not resected (n = 9/11, 81.8%) had IDRFs. Of the patients who had not achieved mCR, 35/122 (28.7%) had their tumors resected ($p < 0.001$).

### *SIOP-PODC treatment setting (Table 2)*

More patients were managed in setting 2 (35.8%) and 3 (60.8%) hospitals compared to 34.3% in setting 1 hospitals ($p = 449$). In setting 2 hospitals, 57.5% of tumors are resected compared to 50.8% in setting 3 hospitals and none in setting 1 hospitals ($p = 0.449$).

### *Five-year overall survival rates (Tables 2 and 3)*

The five-year OS for patients in the whole cohort who had a tumor resection of the primary tumor was 30.5% compared to 7.1% in those who did not have a tumor resection ($p < 0.001$) (Figure 2). The five-year OS for patients with no IDRFs was 21.4%, with one IDRF 22.5%, more than one IDRF 0.0% and patients with ascites or a pleural effusion at diagnosis were 11.1% ($p = 0.004$).

High-risk stage 4 patients who achieved post-induction mCR, achieved a five-year OS of 44.6% compared to 1.6% in those with mCR ($p < 0.001$) (Figure 2). High-risk stage 4 patients who had a primary tumor resection had a five-year OS of 30.5% compared to 7.1% in those who did not have a primary tumor resection ($p < 0.001$) (Figure 3). Larger centers of expertise (Hospital A, B, C, H, J) had better OS than

**Table 2.** Univariate analysis of the prognostic value of patient and tumor related factors and management on the overall survival in South African children diagnosed with NB.

| Univariate analysis | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Median 95% CI | | | |
| Factors | | N (%) | Std. error | Lower | Upper | 5-year OS (%) | p-value |
| mCR | In remission | 56 (31.5) | 58.40 | 0.000 | 214.551 | 44.6 | <0.001 |
| | Not in remission | 122 (68.5) | 1.17 | 12.006 | 16.594 | 1.6 | |
| | Total | 178 (100) | 1.65 | 15.863 | 22.337 | 15.2 | |
| IDRFs* | None | 127 (61.9) | 2.365 | 15.964 | 25.236 | 21.4 | 0.004 |
| | One IDRF | 40 (19.5) | 8.222 | 2.385 | 34.615 | 22.5 | |
| | >1 IDRF | 4 (2.0) | 2.150 | 1.916 | 10.344 | 0.0 | |
| | Other IDRFs | 24 (11.7) | 3.858 | 3.338 | 18.462 | 8.3 | |
| | Pleural effusions and ascites | 10 (4.9) | 0.298 | 18.516 | 19.684 | 11.1 | |
| | Total | 205* | 1.651 | 15.863 | 22.337 | 19.2 | |
| INSS | Stage 1, 2, 4S | 8 (3.9) | – | – | – | 41.0 | <0.001 |
| | Stage 3 | 34 (16.7) | 0.626 | 0.569 | 6.616 | 19.8 | |
| | Stage 4 | 162 (79.4) | 0.596 | 1.184 | 12.250 | 13.0 | |
| | Total | 204 | 1.651 | 15.863 | 22.337 | 19.2 | |
| INRG | L1 | 26 (12.7) | 20.588 | 100.341 | 181.046 | 50.0 | <0.001 |
| | L2 | 13 (6.4) | 25.464 | 0.000 | 97.609 | 30.8 | |
| | M | 162 (79.4) | 1.381 | 14.094 | 19.506 | 13.0 | |
| | MS | 3 (1.5) | 32.007 | 124.967 | 250.433 | 33.3 | |
| | Total | 204 | 1.651 | 15.863 | 22.337 | 19.2 | |
| Surgical status | Operated | 106 (52.0) | 5.123 | 15.558 | 35.642 | 30.5 | <0.001 |
| | Not operated | 98 (48.0) | 1.336 | 14.081 | 19.319 | 7.1 | |
| | Total | 204 (100) | 1.651 | 15.863 | 22.337 | 19.2 | |
| Hospital | Hospital A | 6 (2.9) | 20.784 | 0.000 | 77.679 | 16.7 | 0.001 |
| | Hospital B | 50 (24.5) | 11.941 | 57.175 | 103.986 | 24.0 | |
| | Hospital C | 32 (15.7) | 18.611 | 68.551 | 141.506 | 35.5 | |
| | Hospital D | 22 (10.8) | 9.620 | 14.711 | 52.422 | 4.5 | |
| | Hospital E | 6 (2.9) | 8.960 | 9.055 | 44.178 | 0.0 | |
| | Hospital F | 1 (0.5) | 0.000 | 10.900 | 10.900 | 0.0 | |
| | Hospital G | 1 (0.5) | 0.000 | 20.600 | 20.600 | 0.0 | |
| | Hospital H | 45 (22.1) | 12.294 | 31.307 | 79.500 | 17.8 | |
| | Hospital I | 17 (8.3) | 1.937 | 10.976 | 18.568 | 0.0 | |
| | Hospital J | 24 (11.8) | 18.494 | 34.911 | 107.406 | 25.0 | |
| | Total | 204 | 6.172 | 53.107 | 77.301 | 19.2 | |
| Care setting** | 1 | 7 (3.4) | 14.010 | 0.000 | 48.059 | 0.0 | 0.449 |
| | 2 | 73 (35.8) | 3.370 | 15.495 | 28.705 | 32.2 | |
| | 3 | 124 (60.8) | 1.493 | 14.474 | 20.326 | 26.1 | |
| | Total | 204 | 1.651 | 15.863 | 22.337 | 19.2 | |

*One IDRF had a pleural effusion or ascites – which accounts for the percentages adding up to more than 100%.
**IOP-PODC setting of neuroblastoma care[6].

**Table 3.** The bivariate analysis between the surgical status and mCR rate in patients with stage 4 disease.

| Overall survival outcomes | | | | | |
|---|---|---|---|---|---|
| mCR status | Surgical status | N (%) | Five-yr OS (%) | Ten-yr OS (%) | p-value |
| In remission | Resection | 37/47 (78.7) | 49.9 | 36.5 | <0.001 |
| | No resection | 10/47 (21.3) | 51.2 | 25.4 | |
| Not in remission | Resection | 33/114 (28.9) | 3.0 | 3.0 | <0.001 |
| | No resection | 81/114 (71.1) | 3.1 | 1.2 | |

CI, confidence interval; mCR, metastatic complete remission; OS, overall survival.

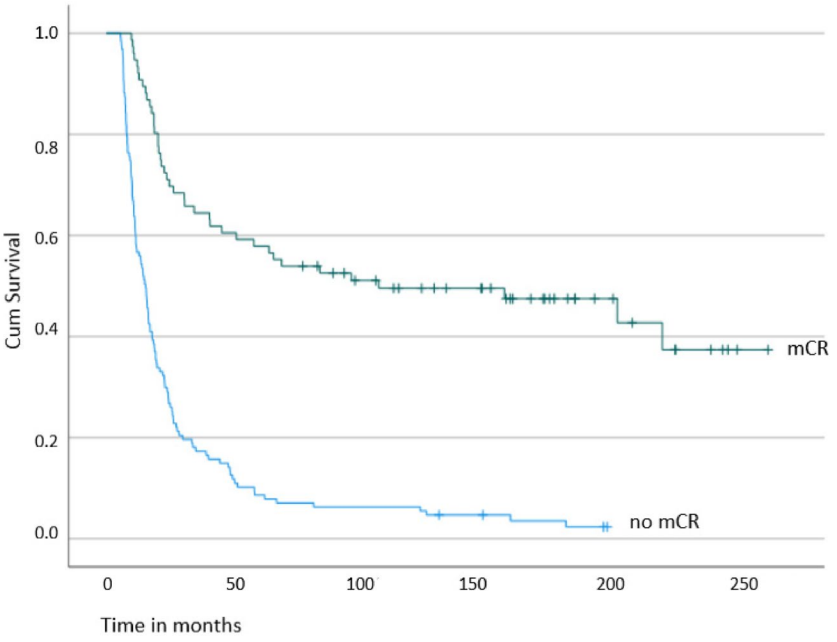


**Figure 2.** A Kaplan-Meier curve of the overall survival based on surgical status.

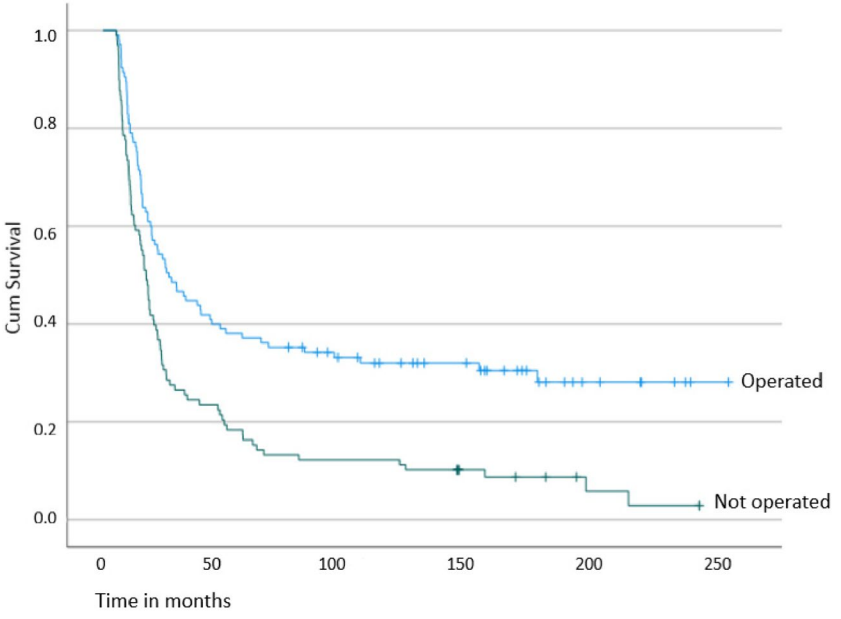


**Figure 3.** A Kaplan-Meier curve of the overall survival based on post-induction chemotherapy metastatic remission rate ($p < 0.001$).

those with less expertise (Hospital D, E, F, G, I) ($p = 0.001$). The SIOP-PODC setting of NB care were not significant ($p = 0.449$). On cross tabulating mCR and surgical status, high-risk stage 4 patients who obtained mCR and unwent primary tumor resection had a five-year OS of 49.9% compared to 51.2% those who did not ($p < 0.001$), but had ten-year OS the outcomes are 36.5% and 25.4% respectively ($p < 0.001$). The five-year OS between patients who didn't obtain mCR and unwent tumor resection compared to those who did obtain mCR and had no tumor resection were 3.0% and 1.2% respectively ($p < 0.001$) (Figure 4).

### *Univariate and multivariate analysis*

On univariate analysis age, stage, pathology classification, risk stratification; mCR status ($p < 0.001$), LDH ($p < 0.005$), ferritin ($p < 0.03$) and treating hospital ($p = 0.001$) determined whether patients were deemed eligible for surgery whilst mCR, surgical status ($p < 0.001$) and IDRFs ($p = 0.004$) determined five-year OS outcomes (Table 2). On multivariate analysis of the HR-NB cohort, achieving mCR ($p < 0.001$), INSS ($p = 0.025$) and INRG stage ($p = 0.005$) were the only significant factors determining whether patients had a tumor resection and determined the OS (Table 4).

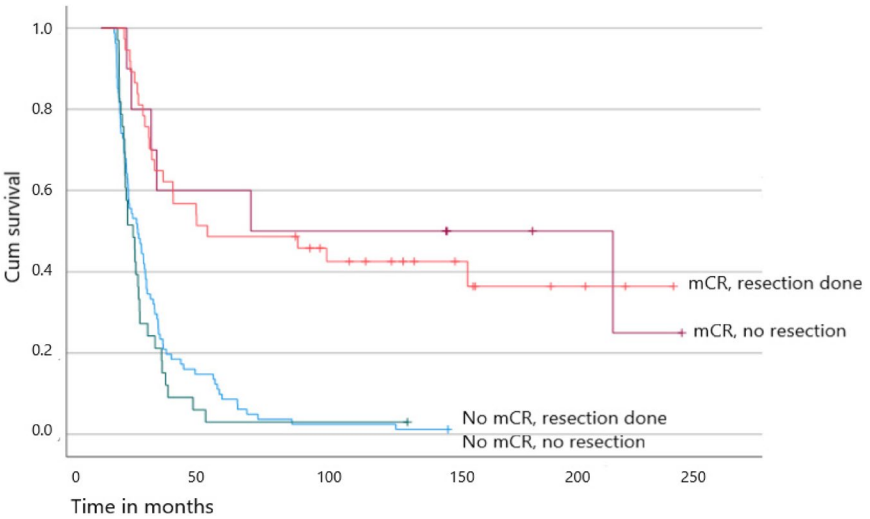


**Figure 4.** Kaplan-Meier curves of the overall survival based on surgical status following metastatic remission status ($p < 0.001$).

**Table 4.** Multivariate analysis of the prognostic factors in South African children diagnosed with NB.

| Multivariate analysis | | | | | | |
|---|---|---|---|---|---|---|
| | | | | 95,0% CI | | |
| Factors | Std. Error | HR | Mean | Lower | Upper | p-value |
| mCR | 0.211 | 0.221 | 0.374 | 0.146 | 0.334 | <0.001 |
| INSS | 0.596 | 3.809 | 0.793 | 1.184 | 12.250 | 0.025 |
| INRG | 0.307 | 2.751 | 0.793 | 1.506 | 5.025 | 0.005 |

## Discussion

In South African patients diagnosed with NB, various management risk factors determined whether a surgical resection of the primary tumor was done and included stage, the hospital resources and if post-induction metastatic remission was obtained. Only post-induction mCR and stage were independently predictive of outcome on multivariate analysis. The contribution of surgery, especially the degree of resection, in the management of high-risk neuroblastoma has been questioned in the context of autologous stem cell transplants and immunotherapy.[9–11] The results of this study not only identify the importance of achieving mCR, but following mCR up by resecting the primary tumor in high-risk disease in the absence of autologous stem cell transplants and immunotherapy.

Globally the approach to surgery in NB has a strong association with disease risk stratification.[22] The Children's Oncology Group (COG) risk stratification is a surgery-based system where upfront resection determines the risk in combination with other factors like age, stage, pathological and biological characteristics.[22] The greatest factor determining HR status in the South African cohort is metastatic disease as resources are limited to determine MYCN status (<55% was determined) or segmental chromosomal aberrations (none were determined). The INRGSS does not rely on surgery for risk stratification but does accommodate upfront surgical interventions when feasible.[16] Yet during univariate analysis the INSS, INRGSS and IDRF were individually significant factors that determined whether primary tumors were resected. On multivariate analysis IDRFs were not significant, yet stage and mCR were. South Africa has a disproportionately high percentage of HR-NB disease (75.3%). Although this is in keeping with other LMICs such as Egypt (68-75.8%) and Kenya (92.3%),[23] it is higher than HICs such as Germany (31.3%).[23] In Turkey and China, two upper-MICs like South Africa, the surgical rate for HR and stage 4 disease was 81% and 63.1%, respectively.[7, 24] In the Turkish study 18% had surgery before induction chemotherapy and 63% received delayed surgery.[24] These percentages did not exclude patients with incomplete induction or death during chemotherapy which means that the percentage of patients eligible for surgery was likely to be higher. In South Africa only 44.9% of patients had tumor resections. Not all patients (80.4%) who completed induction chemotherapy, achieved mCR and therefore eligible for surgery, had surgery as are prescribed by international protocols. INSS, INRG and mCR all have the factor of metastasis in common, therefore we concluded that before resectability, distant metastases had to be in remission before resection was attempted. Based on the multivariate analysis, the factors that did not determine whether a resection was done, are important in informing risk stratification only.

There is no consensus whether pre-induction (primary) surgery or delayed surgery (after several cycles or post-induction) have superior outcomes, nor the degree of resection between GTR or resections greater than 90%.[10] In the Turkish study all patients who achieved mCR and a very good partial response (VGPR) after induction chemotherapy, had a tumor resection.[24] In a cohort where only 29% of HR received autologous bone marrow transplants and no targeted therapies, the five-year OS was 36%.[24] The Chinese study of patients diagnosed with stage 4 (HR) disease with a post-induction primary tumor response rate between 50% to 100% had a three-year

OS of 55.4% in the absence of autologous bone marrow transplants or targeted therapies.[7] The three-year OS rate between a sub-total resection and GTR was 56.8% and 64.2%, respectively.[7]

International studies have varied in their approaches to the timing of surgery in high-risk disease,[25] In comparison, North American approaches determined that surgical intervention should happen when operability has been achieved during induction chemotherapy.[25] Even with metastatic disease still present, surgery was advocated, followed by additional treatment for a further metastatic response.[26] This may be as early as after the four cycles of induction chemotherapy. The Japanese Neuroblastoma Study Group trials from JN-H-11 in 2011 to the current JN-H-15 delayed local control with surgery and irradiation until after high-dose myeloablative chemotherapy to consolidate metastatic control prior to primary tumor control.[2] The multi-national SIOPEN group investigated an extended induction with topotecan-vincristine-doxorubicin during the HR-NBL-1 protocol to access surgery with an optimal metastatic response.[26] The outcomes of all these strategies were comparable.[2, 25,26] There were no standardized indications and guidelines for surgery during the study period in South African patients diagnosed with metastatic NB and HR disease. The result was a lack of continued high-intensity treatment to gain metastatic remission, application of radiotherapy as local therapy or autologous transplant in response to the omission of resection of the primary and limited metastatic disease. The failure to resect the primary tumor may have led to the proliferation of resistant clones and/or ensure continuous mRNA shedding that contributed to distant metastases being reestablished after mCR has been achieved that decreased the survival in the cohort that obtained metastatic complete remission, but where the primary was not resected.[27] We postulate that the lack of significance regarding the setting of care as prognostic factor in South Africa is due to the very low number of autologous transplantations done which delineates between setting 2 and 3 care.[6] This is in contrast to individual hospitals being of prognostic importance due to the multidisciplinary expertise in these hospitals.

In various settings access to consolidation therapies is dependent on the completion of local therapies, thus limiting the optimal management of patients, especially in settings with limited surgical expertise.[16] In the South African setting the evaluation for surgery in HR disease was delayed to the fourth and sixth cycle during induction chemotherapy, because there was no value to evaluate patients for stem cell apheresis if autologous transplants were not available.[16] The reason for not operating on all patients who achieved complete metastatic remission is not clear or whether IDRFs were considered in the decision for surgical interventions. In addition to the fact that some tumors remain irresectable due to their anatomical position encasing vital structures (INSS 3 and INRGSS L2), we postulate that the poor outcomes in the absence of consolidation treatment and desire to safeguard resources such as limited theater time and staff, influenced access to operating theaters in favor of procedures for patients with diseases with better outcomes.[16,17] The significance of the setting of care on univariate analysis points to the possible role of surgical experience and opinion of irresectability where tumors remain unresectable after induction chemotherapy.

In LMICs more clinical and basic investigation guidelines to distinguish between HR-NB and very high risk-NB should be developed to prevent relegation of all HR-NB to palliative treatment purely based on historical outcomes and the extent of resection should be guided by international standards according to risk stratification. These challenges are faced by all LMICs who must carefully balance the optimal use of resources against achieving the best outcomes possible.

South Africa only introduced a standardized treatment protocol in 2019, which excludes the study period and may have contributed to the limitations in this retrospective study. The INRG radiological practice guidelines of 2011 based on IDRFs were not part of the standardized radiological protocol and may have been underreported. Only mCR was used as a post-induction chemotherapy outcome because the data was not robust enough to evaluate the accessibility of surgery for patients who obtained a VGPR metastatic response rate.

Multi-disciplinary teams in South Africa should discuss individual patients to treat and cure where feasible. Surgical teams should broaden the inclusion criteria for surgical interventions in line with international guidelines on the merits of individual patients especially where mCR has been achieved and those patients that achieve a mCR should be referred to a center for surgical resection of residual the tumor. Medical and radio-oncology teams should facilitate continued tumor response and local tumor control post-surgery. Referral pathways for patients diagnosed with NB should include regional transfers to high volume surgical centers with experienced surgeons and peri-operative facilities. This will provide surgical care while the lack of local experience as a limiting factor to surgical access is improved.

## Conclusions

In South Africa stage and post-induction mCR were the only significant predictors whether local surgical control for primary tumor for HR-NB were performed. It should be included in the indications for surgical management of metastatic neuroblastoma and treatment options for increased post-induction metastatic remission rates should be sought. Further prospective studies are needed to define other indications for surgical resection in the South African and other resource limited settings.

## Conflict of interest

There is no conflict of interest.

## Author contributions

JvH and MK authors conceptualized and designed the study. All authors collected data, developed the protocol and critically reviewed and revised the manuscript. TME provided statistical support and critically reviewed and revised the manuscript.

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## Data availability statement

Data is available on reasonable request to the authors.

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