The association of clinical characteristics and tumour markers with image-defined risk factors in the management of neuroblastoma in South Africa

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Author contributions

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

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Running title

Associations of IDRFs in NB in South Africa

Features

Tables: 4

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Abbreviations:

AO	Airway obstruction
CI	Confidence intervals
COG	Children's Oncology Group
CT	Computed tomography
HR	High risk
INPC	International Neuroblastoma Pathological Classification
INRG	International Neuroblastoma Risk Group
INSS	International Neuroblastoma Staging System
LDH	Lactate dehydrogenase
LMICs	Low- and middle-income countries

MBC	Multiple body compartments
mCR	Complete metastatic remission
NB	Neuroblastoma
NS	Not significant
OI	Organ infiltration
OS	Overall survival
SE	Spinal extension
SIOPEN	International Society of Paediatric Oncology European Neuroblastoma group
VE	Vascular encasement

ABSTRACT

Background

Image defined risk factors (IDRFs) in neuroblastoma (NB) predict surgical complications and management outcomes. As there is a lack of data regarding the association of IDRFs with clinical and pathological factors, this study evaluates the prognostic value of IDRFs to predict NB survival outcomes.

Methods

This was a retrospective study including 345 patients and reviewed diagnostic imaging for 20 IDRFs, pleural effusions and ascites. The IDRFs were grouped into five "primary IDRFs" cohorts with vascular encasement, involvement of multiple body compartments, organ infiltration, airway obstruction and intraspinal extension. The association between clinical, histopathologic, and biological characteristics of NB and management was evaluated.

Results

More patients without IDRFs were operated compared to patients with IDRFs with a trend towards significance (64.4% vs 35.6%, p=0.082). Patients with multiple compartment tumour involvement ($p = 0.003$) and organ infiltration ($p < 0.001$) had a higher risk of surgical complications. The five-year OS of the group with more than one IDRF was 0.0% and those with pleural effusions or ascites 6.7%, associated with the worst outcome ($p = 0.005$). The total number of IDRFs were not predictive of the metastatic remission rate ($p = 0.585$), nor overall survival (OS) ($p = 0.142$) with no conclusive association found between IDRF groups and clinical or biological markers.

Conclusions

Patients with more than one IDRF had the shortest survival time, while those with pleural effusions and ascites at diagnosis had a poor outcome. Standardised reporting of IDRFs is crucial for predicting prognosis.

[249 words]

INTRODUCTION

Neuroblastoma (NB) is a neuro-ectodermal tumour of the sympathetic system with a diverse clinical, pathological, and biological disease spectrum [1]. Despite the increasing knowledge of molecular and epigenetic characteristics that drives the clinical presentation, translational clinical applications have not been fully evaluated [1]. In low- and middle-income countries (LMICs) staging and risk stratification systems that are contingent on surgical resection or biological features limit the determination of management [2]. The International Neuroblastoma Risk Group Staging System (INRGSS) incorporates clinical factors detected at diagnosis for the disease stratification with image defined risk factors (IDRFs) as an integral part of this system [3].

IDRFs constitute a list of 20 radiologically determined tumour pathologies or risk factors described in 2004 and revised in 2009 by the International Neuroblastoma Risk Group project [4,5]. These factors represent radiological signs of vascular or nerve encasement, the presence of tumour in multiple body compartments, organ invasion, airway obstruction and intraspinal invasion. The revised factors include two additional factors, namely pleural fluid and ascites, that must be documented, but are not part of the main IDRF group [4,5].

Numerous publications discussed individual risk factors in the management of NB and their prognostic implications [1,2,6]. The surgical implications of IDRFs and its prognostic importance gained focus to determine the indications for surgical interventions [7,8]. Post induction chemotherapy IDRFs are valuable in predicting intra-operative risk factors, such as haemorrhage, and the possibility of achieving a complete resection [7]. The SIOPEN-group has determined that the IDRF pattern between diagnosis and after induction chemotherapy was unchanged in 50% of patients. Preoperative vascular encasement of central abdominal blood vessels predicted surgical outcomes and complications, event free survival (EFS) and overall survival (OS) [8]. Yet limited information was available regarding the association of diagnostic prognostic factors, such as age, stage, tumour markers and pathology with IDRFs [9].

The tools for improved risk stratification and optimising the amount of information gained from available investigations in a particular resource setting, are important [2]. This includes evaluating the utility of radiological investigations beyond that of diagnostic, staging and response evaluations. The aim of this study is to evaluate if IDRFs have prognostic implications like validated risk factors in the management of NB and determine possible associations with these risk factors.

Methods

Data collection

Data were collected from clinical, radiological, and pathological reports in patient records from ten paediatric oncology units across South Africa of 463 patients, treated for NB between January 2000 and December 2016 (*Figure 1*). Radiological imaging included x-rays, ultrasound imaging, computed tomography (CT) or magnetic resonance imaging (MRI). Disease stage was defined according to the International Neuroblastoma Staging System (INSS) and prognostic risk of pathology was based on the International Neuroblastoma Pathology Classification (INPC) [2]. The lactate dehydrogenase (LDH) and

Ferritin binary values were 750 U/L and 120 g/dL respectively as described in the SIOP-PODC Adapted Risk Stratification and Treatment Guidelines: Recommendations for Neuroblastoma in Low- and Middle-Income Settings [2]. IDRFs were defined according to the INRG staging system [4]. The IDRFs were divided into analytical groups as defined by Temple *et al.* and labelled as "Primary IDRFs": vascular encasement (VE); multiple body compartments (MBC); organ infiltration (OI); airway obstruction (AO) and intraspinal tumour extension (SE) [9]. Two additional groups, not described by Temple *et al.,* were defined in this study: "Secondary IDRFs" which included encasement of the brachial plexus roots, pelvic tumour crossing the sciatic notch and extension to the base of the skull (*Table 1*) and the second group which comprised conditions not defined as IDRFs (the pleural effusion and ascites group) [9]. Twenty-seven patients without imaging and 91 patients with insufficient clinical data were excluded (absence of tumour markers: n=56; incomplete radiological results: n=30; and five without outcome data). The study investigated three distinct outcomes namely OS, surgical complications, and metastatic complete remission (mCR). Only patients with stage 4 disease (metastatic disease) were evaluated for mCR.

Metastatic remission was defined by the 2009 and revised 2014 INRG treatment response classifications as no evidence of metastatic disease [10,11]. Surgical complications were defined as follows: major intra- or postoperative haemorrhage defined as blood loss greater than 10% of the estimated blood volume based on the patient's weight or blood loss during or after surgery that needed intervention due to a change in vital parameters [12,13]. Renal injury included postoperative development of acute kidney injury (independent from tumour invasion), renal ischemic events or injuries necessitating a nephrectomy [12,13]. Vascular injuries were defined as injuries to large blood vessels where surgical intervention was needed or which led to an obstructive clotting event that was treated with anticoagulants [12,13].

Statistical analysis

Descriptive data were evaluated with IBM SPSS version 25 (IBM Corporation, USA) statistical software and the differences in medians were assessed using the Mann-Whitney U test or Student's t-test. Categorical association between independent variables such as tumour marker, pathology, INSS and IDRF analytical groups, surgical complications, mCR and OS were assessed using the Pearson Chi-square (χ^2) test.

With cohorts of less than five the Fishers exact test was applied. Before performing regression models, the collinearity between IDRFs and the statistical outcomes were performed using Spearman rank correlations [14]. The number of IDRFs was used as predictor to determine the association between outcomes (surgical complications, mCR, OS) and clinical factors. Regression models were done adjusting for age to limit the introduction of confounding factors. OS and associated 95% confidence intervals (CI) were calculated and 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 last clinical follow up. To estimate the effect of IDRFs and clinical factors on OS, univariate and multivariable Cox regression modelling approaches were employed. The proportional hazards assumption was also confirmed for the final multivariable model. For all calculations a *p*-value less than 0.05 was considered significant.

Results

Demographic data

The study included 345 patients diagnosed with NB. The male to female ratio was 1:0.93. The majority (73%, n = 252) were older than 18 months of age with median age 40.3 months (range 18.1 – 204.3 months) and 27% were 18 months or younger (n = 93) with a median age of 8.3 months (range 0.16 – 17.6 months) (*Table 2*).

Patient, tumour and management data

The patient and tumour characteristics cross referenced with one or more IDRFs are summarized in table 2. There were 242 (70.1%) patients with stage 4 or metastatic disease followed by 62 (18.0%) stage 3 disease, 17 (4.9%) with stage 2 disease, 15 (4.3%) with stage 1 disease and 9 (2.6%) with stage 4S disease. Of the total cohort 218/345 (68.15%) tumours were not associated with IDRFs, 110/345 (31.8%) were associated with IDRFs and 17/345 (0.05%) had pleural effusions and ascites (*Figure 1*). Of the 110 IDRFs documented, the primary IDRFs accounted for 81/110 (73.6%) of which 36/81 (44.4%) were intraspinal tumour extension, 17/81 (21.0%) involvement of multiple body compartments, 13/81 with airway compression or obstruction, 9/81 (11.1%) infiltration into adjacent organs and structures and 6/81 (7.4%) were vascular encasement. The secondary IDRFs accounted for 29/110 (26.4%) of which 23/29 (79.3%) were pelvic tumours crossing sciatic notch, 4/29 (13.8%) tumours extending into the skull base and 2/29 (6.9%) encasing the brachial plexus. There were 16 patients with pleural effusions (94.2%) and one with ascites one (5.8%) (*Figure 1 and table 2*).
Nearly half of the patients (46.4%; n=160) had tumour debulking of which 35.6% (n = 57) presented with an IDRFs at diagnosis. Of those not operated, 37.9% (n = 70) presented with an IDRF. Two (1.3%) patients had peri-operative surgical complications of whom one had an IDRF. Only 23.6% (n = 57/242) obtained mCR with a five-year OS for the total cohort of 23.8% (p = 0.005) (*Table 3*). Of those that achieved mCR 31.6% (n = 18/57) had IDRFs and of those who did not achieve mCR, 38.9% (n = 72/185) had IDRFs (p = 0.244)(not significant, NS).

Assessment of collinearity among variables included in the analysis

A Spearman Rank correlation matrix was performed to evaluate collinearity between the patient, tumour characteristics and the total IDRF cohort (*Figure 2*) as well as the individual IDRFs (*Figure 3*). The collinearity between mCR and OS was “strong” (Spearman's ρ = -0.65 and -0.66) (*Figure 2 and 3*). There is a “moderate” inverse linear association between stage and pathological characteristics (Spearman's ρ = -0.47 and -0.4 respectively).The total IDRF cohort had a “very weak” linear association with stage (Spearman's ρ = 0.00), pathological characteristics (Spearman's ρ = 0.1), LDH (Spearman's ρ = 0.03), ferritin (Spearman's ρ = -0.02) and MYCN (Spearman's ρ = 0.04), as did the collinearity between the individual IDRFs and LDH, ferritin and surgical complications were “very weak” (Spearman’s ρ = -0.19 to 0.19) (*Figure 2 and 3*).

Association of IDRF groups with clinical, biological and outcome factors

Only surgical complications were associated with IDRFs when the association between management factors and outcomes with individual IDRFs was evaluated (*Table 5 and 6*). The invasion of organs ($p < 0.001$) and tumour in multiple body compartments ($p = 0.003$) were associated with surgical complications. Patients without IDRFs had a five-year OS of 23.9% compared to 29.3% for patients with IDRFs ($p = 0.142$) (NS). Patients with pleural effusions and ascites had a five-year OS of 6.7% ($p = 0.142$) (NS) . (*Table 4*). Patients without IDRFs had a median survival time of 14.8 months compared to 18 months for patients with IDRFs ($p = 0.142$) (NS). Patients with pleural effusions and ascites had a median survival period of 17.4 months ($p = 0.142$) (NS). (*Table 4*). Patients with only one IDRF had the longest survival time (22.8 months), followed by patients that presented with either a pleural effusion or ascites (17.4 months), and patients without IDRFs (15.6 months) ($p = 0.005$), which was significant. Patients with more than one IDRF had the shortest survival time of 6.1 month ($p = 0.005$), again very significant. Patients, presenting with no or one IDRF at diagnoses, had a five-year OS, respectively 23.9% and 31.9% ($p = 0.005$) (*Figure 4*), which was significant. Patients who presented with pleural effusions and ascites or more than one IDRF had the worst five-year OS with respectively 6.7% and 0% ($p = 0.005$), again significant.

Discussion

The study demonstrated that the absence or presence of IDRFs alone does not predict survival nor if mCR will be achieved, but that the number of IDRFs were associated with OS. The presence of ascites and pleural effusions at diagnosis was an indicator of poor prognosis. No strong linear associations were found between the total IDRF cohort or individual IDRFs with clinical characteristics of NB. While the collinearity of LDH and INPC with mCR and five-year OS was weak, INSS had a moderate linear association. Organ invasion and a tumour across multiple body compartments were the only two clinical characteristics with a significantly higher association with surgical complications.

Temple *et al.* on behalf of the Children's Oncology Group (COG) biology study, and Brisse *et al.* reported MYCN-amplification was associated with the presence of IDRFs [4,9]. This study could neither reproduce the association between MYCN-amplification nor establish an association with LDH and ferritin with IDRFs.
Vascular encasement at diagnosis was previously reported as associated with surgical complications [9] while this study showed that organ invasion ($p < 0.001$) and a primary tumour in multiple compartments ($p = 0.003$) were significantly associated with surgical complications. Vascular encasement could not be assessed adequately as only 33.3% of tumours that encased vascular structures were operated in South Africa and should be verified in similar studies as few surgical complications were documented in the South African cohort.

Although ascites and pleural effusions at diagnosis are not defined as IDRFs, in this study their presence indicated a poor prognosis ($p = 0.005$), which differs with the findings of a St. Jude Children's Research Hospital study that about 10% of patients presenting with pleural effusions [15] were associated with unfavourable biologic features and high-risk disease, but with no significant impact on survival outcomes [15]. In the INRG staging system pleural effusions and ascites remote from the body compartment of the primary tumour, are considered metastatic disease [3]. Overall survival was also poorer in the South African cohort where the 6.7% five-year OS for those patients presenting with pleural effusion and ascites was lower than the reported 17.8% five-year OS for stage 4 (metastatic) disease in South Africa [16]. In our study all the children died without having achieved metastatic

remission compared to the Gupta *et al.* study where only 62.1% died from either progressive disease or recurrent disease. All the sites where disease recurred were adjacent to the pleural effusions at diagnosis [15].

There was no significant survival advantage whether patients presented with or without IDRFs. In our study patients with one IDRF had the longest median survival time (22.8 months) compared to only 6.1 months for patients than one IDRFs. Since patients without IDRFs have a shorter median survival time (15.6 months) than those with one IDRF, no conclusion could be drawn on the relationship of IDRFs and survival time. We concluded that the survival time was influenced by other factors independent from IDRFs such as stage. In our study, patients with pleural effusions and ascites had a shorter survival time than patients with one IDRF which is represented by pleural effusions in remote body compartments [3]. A second more important factor could be the scope of treatment patients received. Patients with IDRFs was less likely to achieve mCR and they were also less likely to be operated. Temple *et al.* found that IDRFs were associated with poor prognostic pathology [9]. Not achieving mCR could indicate more adverse pathology or biology and chemotherapy resistance. Incomplete resections or NB tumours not being operated leads to poorer survival outcomes [17].

Limitations in the study included non-CT related diagnostic imaging in the study in keeping with the resource limitations in centers. The inclusion of ultrasound introduces a report bias as this modality is operator dependent. As paediatric oncology is mainly practiced in academic institutions, it is possible that these operators were still in training.

The INRG established radiological practice guidelines in 2011 and the SACCSG only introduced a national neuroblastoma protocol in 2019 [4]. It is possible that radiological reporting did not include the presence of IDRFs and as such there was under reporting of these. Temple *et al.* reported that most (77.6%) patients presented with an IDRF [9], but in our study only a third (31.9%) of patients presented with an IDRF. The number of operative complications were low. We postulated that this was due to the low number of patients that were operated. The reasons for the low operative rate were not part of this study but does need further investigation. A delayed start of chemotherapy or consolidation treatment after surgical complications has a negative impact on outcomes and surgical interventions should be evaluated for tumour resection at the earliest possible opportunity within the context of tumour biology, IDRFs and disease response [18].

Tumour markers, pathology reporting and biological investigations were not standardised, nor was the reporting. Thus, the study samples varied with some cohorts containing few numbers. This may have limited the interpretation of results.

Conclusion

Some individual IDRFs are predictive of surgical outcomes while the number of IDRFs are inversely proportionate to the survival duration. Based on other studies, IDRFs could potentially provide greater insight into tumour histology and biology without having to utilise advanced genetic or molecular testing that may not be available. In the South African population an association between IDRFs and tumour characteristics could not be proven, possibly due to a false low reporting of IDRFs. Therefore, standardised reporting of IDRFs and clinical characteristics regardless of the resource setting should be advocated in the management of NB. Further studies regarding clinical applications of IDRFs, especially in LMICs, are needed.

Conflict of interest

There is no conflict of interest.

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Data availability statement

Data is available on reasonable request to the authors.

[2636 words]

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Tables and figures

Tables and figures

Figure 1: PRISMA flow diagram for the patient inclusion

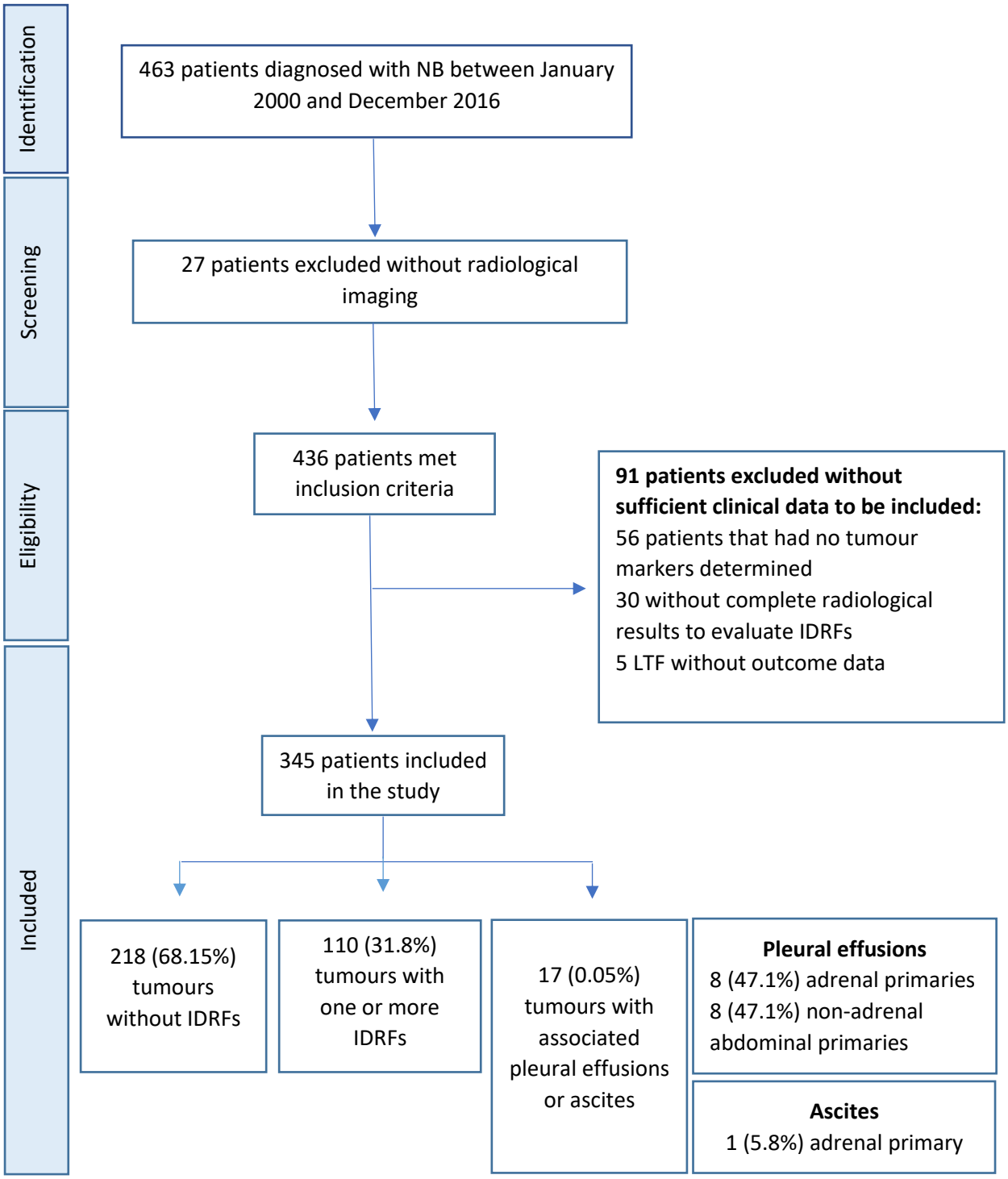


Figure 2. A Spearman Rank correlation matrix between the image defined risk factors cohort and characteristics of neuroblastoma

	IDRFs	INSS	INPC	LDH	Ferritin	MYCN	mCR	OS	Surg com
IDRFs	1.00	0.00	0.1	0.03	-0.02	0.04	-0.03	0.02	0.01
INSS	0.00	1.00	0.38	0.30	0.33	0.24	-0.47	0.47	0.05
INPC	0.1	0.38	1.00	0.26	0.13	-0.02	-0.4	0.45	0.08
LDH	0.03	0.30	0.26	1.00	0.26	0.33	-0.25	0.32	-0.01
Ferritin	-0.02	0.33	0.13	0.26	1.00	0.12	-0.28	0.35	0.05
MYCN	0.04	0.234	-0.02	0.33	0.12	1.00	-0.08	0.03	0.11
mCR	-0.03	-0.47	-0.4	-0.25	-0.28	-0.08	1.00	-0.66	-0.6
OS	0.02	0.47	0.45	0.32	0.35	0.03	-0.66	1.00	0.04
Surg com	0.01	0.05	0.08	-0.01	0.05	0.11	-0.6	0.04	1.00

Abbreviations:
IDRFs – Image defined risk factors; INSS – International neuroblastoma staging system; INPC – International neuroblastoma pathology classification; mCR – metastatic complete remission; OS – overall survival; Surg com – surgical complications

-0.8 to -1.0	-0.6 to - 0.79	-0.4 to -0.59	-0.2 to -0.39	0.00 to -0.19	0.00 to 0.19	0.2 to 0.39	0.4 to 0.59	0.6 to 0.79	0.8 to 1.0

The Spearman correlation coefficient: +1 indicates a perfect association of ranks; zero indicates no association between ranks; -1 indicates a perfect negative association of ranks. **Interpretation:** 0.00-0.19 "very weak"; 0.20-0.39 "weak"; 0.40-0.59 "moderate"; 0.60-0.79 "strong"; 0.80-1.0 "very strong"

Figure 3. A Spearman Rank correlation matrix between individual image defined risk factors and characteristics of neuroblastoma

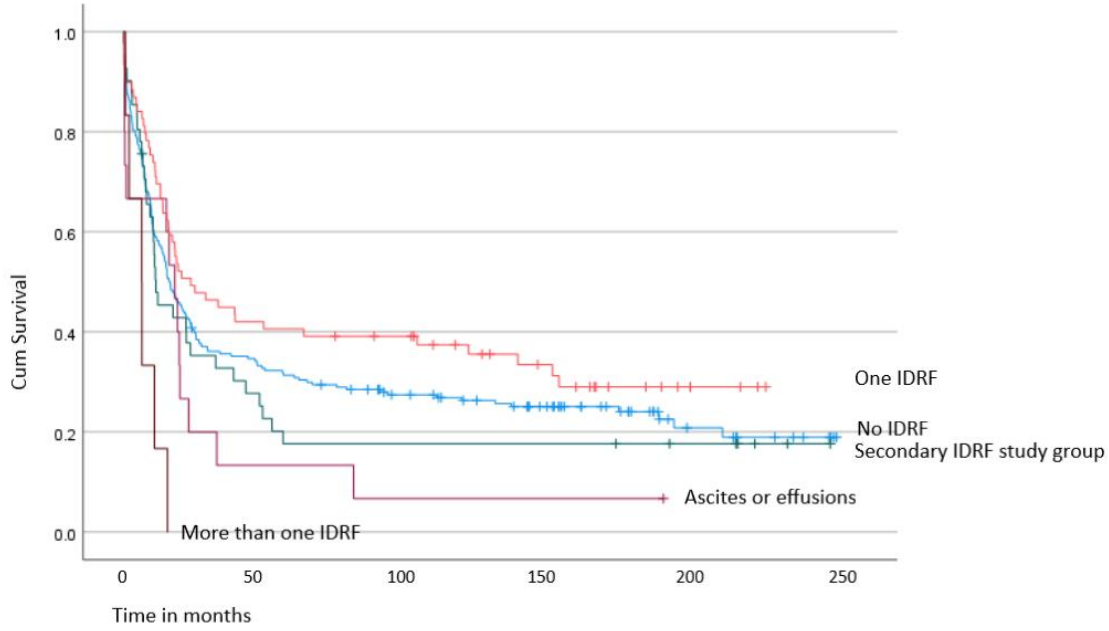
	VE	MBC	OI	AO	SE	INSS	INPC	LDH	Ferritin	MYCN	mCR	OS	Surg com
VE	1.00	-0.03	0.11	-0.02	-0.04	0.00	-0.02	0.00	0.07	0.01	0.01	0.02	0.01
MBC	-0.03	1.00	0.04	0.02	-0.03	-0.01	-0.06	-0.02	0.06	-0.03	0.01	-0.06	-0.15
OI	0.11	0.04	1.00	-0.03	0.00	-0.07	-0.06	0.05	0.03	-0.07	0.01	0.00	-0.22
AO	-0.02	0.02	-0.03	1.00	-0.01	0.04	0.01	0.01	-0.00	-0.08	0.02	0.00	0.01
SE	-0.04	-0.03	0.00	-0.01	1.00	-0.08	-0.00	-0.14	-0.14	0.06	-0.08	-0.03	0.02
INSS	0.00	-0.01	-0.07	0.04	-0.08	1.00	0.34	0.23	0.09	0.02	0.46	0.47	-0.04
INPC	-0.02	-0.06	-0.06	0.01	-0.00	0.34	1.00	0.06	0.01	0.19	0.32	0.32	0.02
LDH	0.00	-0.02	0.05	0.01	-0.14	0.23	0.06	1.00	0.17	0.09	0.25	0.31	0.02
Ferritin	0.07	0.06	0.03	0.00	-0.14	0.09	0.01	0.17	1.00	0.04	0.13	0.13	-0.04
MYCN	0.01	-0.03	-0.07	-0.08	0.06	0.02	0.19	0.09	0.04	1.00	0.13	0.14	0.06
mCR	0.01	0.01	0.01	0.02	-0.08	0.46	0.32	0.25	0.13	0.13	1.00	-0.65	-0.06
OS	0.02	-0.06	0.00	0.00	-0.03	0.47	0.32	0.31	0.13	0.14	-0.65	1.00	-0.04
Surg com	0.01	-0.15	-0.22	0.01	0.02	-0.04	0.02	0.02	-0.04	0.06	-0.06	-0.04	1.00

Abbreviations: VE – vascular encasement; MBC – multiple body compartments; OI – organ infiltration; AO – airway obstruction; SI – intraspinal extention; INSS – International neuroblastoma staging system; INPC – International neuroblastoma pathology classification; mCR – metastatic complete remission; OS – overall survival; Surg com – surgical complications

-0.8 to -1.0	-0.6 to - 0.79	-0.4 to -0.59	-0.2 to -0.39	0.00 to -0.19	0.00 to 0.19	0.2 to 0.39	0.4 to 0.59	0.6 to 0.79	0.8 to 1.0

The Spearman correlation coefficient: +1 indicates a perfect association of ranks; zero indicates no association between ranks; -1 indicates a perfect negative association of ranks. **Interpretation:** 0.00-0.19 "very weak"; 0.20-0.39 "weak"; 0.40-0.59 "moderate"; 0.60-0.79 "strong"; 0.80-1.0 "very strong"

Figure 4. Overall survival analysis for the number of IDRFs (p = 0.005)



Abbreviations: IDRFs – image defined risk factors

Tables:

Table 1: The definition of the image defined risk factor (IDRF) analytical groups

IDRF group	Components of each IDRF group
Primary IDRFs	
Vascular encasement (VE)	*Neck:* Tumour encasing carotid artery, vertebral artery, internal jugular vein, subclavian vessels *Thorax:* Tumour encasing the aorta, major aortic vessels and/or vena cava *Abdomen:* Tumour encasing branches of superior mesenteric artery at mesenteric root, origin of celiac axis and/or origin of superior mesenteric artery *Pelvis:* Tumour encasing iliac vessels
Involvement of multiple body compartments (MBC)	Tumour involvement into two adjacent body compartments: Neck-chest, chest-abdomen, abdomen-pelvis
Infiltration of adjacent organs and/or structures (IO)	Tumour infiltration into the porta hepatis, pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, or mesentery
Airway compression / obstruction (AO)	Tumour compressing the trachea or primary bronchi
Intraspinal tumour extension (SE)	Tumour extension more than one third into the intraspinal space in the axial plane Tumour involvement in leptomeningeal space Abnormal spinal cord signal, or involvement in the sciatic foramen
Secondary IDRFs	
Additional IDRF group	Tumour extending to skull base Tumour encasing brachial plexus roots Pelvic tumour crossing sciatic notch
Pleural effusion and ascites group	
Recorded conditions not defined as IDRFs	Pleural effusion and ascites, with or without malignant cells

Table 2: Patient characteristics in relation to the IDRFs

	Total	**Patients with one or more IDRF**
	N (%)	**N (%)**
Age at diagnosis		
≤18 months	93 (27)	35 (37.6)
> 18 months	252 (73)	97 (38.5)
Sex		
Male	179 (51.0)	73 (40.8)
Female	166 (49.0)	59 (35.5)
Primary site		
Abdomen	253 (73.3)	67 (26.5)
Pelvis	6 (1.7)	3 (50.0)
Thorax	32 (9.3)	18 (56.3)
Neck	8 (2.3)	6 (75.0)
Cervico-thoracic	2 (0.6)	2 (100.0)
Thoraco-abdomenal	4 (1.2)	4 (100.0)
Abdominal-retroperitoneum-pelvis	9 (2.6)	9 (100.0)
Paraspinal	17 (4.9)	17 (100.0)
No primary found	10 (2.9)	5 (50.0)
Other	4 (1.2)	1 (25.0)
Total	345 (100.0)	
International Neuroblastoma Staging System		
Stage 1	15 (4.3)	5 (33.3)
Stage 2	17 (4.9)	5 (29.4)
Stage 3	62 (18.0)	27 (43.5)
Stage 4	242 (70.1)	91 (37.6)
Stage 4S	9 (2.6)	4 (44.4)
Total	345 (100.0)	
Risk classification		
Low Risk	39 (11.3)	15 (38.5)
Intermediate Risk	29 (8.4)	14 (48.3)
High Risk	272 (78.8)	101 (37.1)
Unknown	5 (1.4)	2 (40.0)
Total	345 (100.0)	
International Neuroblastoma Pathology Classification		
Favourable histology	80 (23.2)	28 (35.0)
Unfavourable histology	125 (36.2)	55 (44.0)
Unknown	140 (40.6)	47 (33.6)
Total	345 (100.0)	
LDH		

<750 U/L	138 (40.0)	53 (38.4)
>750 U/L	180 (52.2)	72 (40.0)
Unknown	27 (7.8)	7 (25.9)
Total	345 (100.0)	
Ferritin		
<120 mg/dL	75 (21.7)	32 (42.7)
>120 mg/dL	158 (45.8)	59 (37.3)
Unknown	112 (32.5)	40 (35.7)
Total	345 (100.0)	
MYCN amplification status		
Non-amplification	64 (18.6)	22 (34.4)
Amplification	77 (22.3)	29 (37.7)
Unknown	204 (59.1)	76 (37.3)
Total	345 (100.0)	
IDRFs		
Number of IDRFs per patient	**N (%)**	
No IDRFs With one IDRF More than one IDRFs	218/345 (63.1) 110/345 (31.9) 17/345 (4.9)	
IDRF groups		
Primary IDRFs Vascular encasement Involvement of multiple body compartments Infiltration of adjacent organs and/or structures Airway compression / obstruction Intraspinal tumour extension		**81/127 (63.8)** 6/81 (7.4) 17/81 (21.0) 9/81 (11.1) 13/81 (16.1) 36/81 (44.4)
Secondary IDRFs Tumour extending to skull base Tumour encasing brachial plexus roots Pelvic tumour crossing sciatic notch		**29/127 (22.8)** 4/29 (13.8) 2/29 (6.9) 23/29 (79.3)
Pleural effusions and ascites Pleural effusions Ascites		**17/127 (13.4)** 16/17 (94.2) 1/17 (5.8)
Total		345

Abbreviations: IDRFs – image defined risk factors, LDH – lactate dehydrogenase

Table 3: Management and outcomes

	N (%)	p-value
Metastatic complete remission (mCR)		
mCR	**57/242 (23.6)**	0.244
No IDRFs	39/57 (68.4)	
With one IDRF	14/57 (24.6)	
More than one IDRFs	4/57 (7.0)	
No mCR	**185/242 (76.4)**	
No IDRFs	113/185 (61.1)	
With one IDRF	61/185 (33.0)	
More than one IDRFs	11/185 (5.9)	
Total metastatic disease	242 (100.0)	
Patients operated		
Operated	**160/345 (46.4)**	0.082
With IDRFs	57/160 (35.6)	
Without IDRFs	103/160 (64.4)	
Not operated	**185/345 (53.6)**	
With IDRFs	70/160 (37.9)	
Without IDRFs	115/160 (62.1)	
Total	345 (100.0)	
Surgical complications		
With operative complications	**2/160 (1.3)**	<0.001
With IDRFs	1/2 (50.0)	
Without IDRFs	1/2 (50.0)	
Without complications	**158/160 (98.7)**	
Total operated	160 (100.0)	

Abbreviations: IDRFs – image defined risk factors

Table 4: The association of the number of IDRFs with survival time and overall survival

	N (%)	Survival time (months)				5-yr OS	P-value
		Median Estimate	Std. Error	95% CI			
				Lower	Upper		
Presence of IDRFs							
No IDRFs	213 (61.8%)	14.8	2.107	10.670	18.930	23.9%	0.142
IDRFs	117 (33.9%)	18.0	4.330	9.514	26.486	29.3%	
Pleural effusion or ascites	15 (4.3%)	17.4	2.447	12.603	22.197	6.7%	
Number of IDRFs							
No IDRFs	213 (61.8%)	15.6	2.031	11.620	19.580	23.9%	0.005
One primary IDRF	69 (20.0%)	22.8	8.721	5.707	39.893	31.9%	
> 1 primary IDRF	7 (2.0%)	6.1	2.652	0.903	11.297	0.0%	
Secondary IDRFs	41 (11.9%)	10.9	4.071	2.921	18.879	19.5%	
Pleural effusion or ascites	15 (4.3%)	17.4	2.447	12.603	22.197	6.7%	
OS	345	15.9	1.374	13.207	18.593	23.8%	

Abbreviations: IDRFs – image defined risk factors; CI – confidence interval; OS - overall survival

Table 5: The association of clinical variables and outcomes with IDRFs (adjusted for age)

	Predictor	HR	95% CI		P-value
			Lower	Upper	
Outcomes					
OS	Total IDRF groups	0.816	0.479	1.392	0.456
mCR		1.140	0.713	1.824	0.585
Surgical complication		6.798	0.982	47.083	0.052
Clinical variables					
INSS	Total IDRF groups	0.687	0.421	1.123	0.135
INPC		1.020	0.565	1.840	0.948
MYCN		0.876	0.447	1.715	0.699
LDH		0.929	0.584	1.479	0.757
Ferritin		0.597	0.333	1.071	0.083

Abbreviations: HR – Hazard ratio; IDRFs – image defined risk factors; CI – confidence interval; OS - overall survival; mCR – metastatic complete remission; INSS – International Neuroblastoma Staging System; INPC – International Neuroblastoma Pathology Classification; LDH – lactate dehydrogenase

Table 6: The association of IDRFs with surgical complications

IDRF		Surgical comp	N (%)	P - value
MBC	Absent	Yes	1 (0.3%)	0.003
		No	327 (99.7%)	
	Present	Yes	1 (5.9%)	
		No	16 (94.1%)	
	Total	Yes	2 (0.6%)	
		No	343 (99.4%)	
IO	Absent	Yes	1 (0.3%)	<0.001
		No	335 (99.7%)	
	Present	Yes	1 (11.1%)	
		No	8 (88.9%)	
	Total	Yes	2 (0.6%)	
		No	343 (99.4%)	

Abbreviations: IDRFs – image defined risk factors, MC – multiple body compartments, IO – organ invasion