APPLICATION OF THE INTERNATIONAL NEUROBLASTOMA RISK GROUP STAGING SYSTEM 2009 (INRGSS 2009) IN DIAGNOSIS AND PROGNOSIS OF CHILDHOOD NEUROBLASTOMA

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ABSTRACT

Background: Neuroblastoma is the most common extracranial solid tumor of childhood. INRGSS 2009 divides patients into stages L1, L2, M, Ms, from which, in combination with histopathology, molecular biology, each patient will be divided into risk groups from which to guide prognosis and suitable treatment. ***Objectives:*** Describe the clinical and laboratory features of neuroblastoma in children; distribution of pediatric neuroblastoma stages according to the INRGSS 2009 classification and its value in predicting survival outcomes. ***Methods:*** This was a cross-sectional study combined with retrospective and prospective. Patients were diagnosed with neuroblastoma and classified according to INRGSS 2009 at the Pediatric Center, Hue Central Hospital. ***Results:*** The age at the time of diagnosis ranged from 1 day old to 9 years old, with a mean of 35.4 ± 25.5 months. Regarding primary tumor, 73.5% of cases were found in the abdomen, the mediastinum region (22.4%), an undetermined region (4.1%). Systemic symptoms, local symptoms and symptoms caused by metastasis were frequently reported. At the time of diagnosis, 73.5% of the patients had distant metastases (stage M or MS). The EFS of the whole group at 12 and 24 months old were 86.3 % and 64.7% respectively. The OS was 77.9% at 24 months old. Most of these patients had a progressive disease: 6.1% were in stage L1; 20.4% were in stage L2; 69.4% were in stage M; and 4.1% were in stage MS. Estimated mean of event-free survival for L1 was 38.7 ± 3.5 months, L2 was 40.5 ± 4.2 months and M was 28.0 ± 2.5 months ($p < 0.05$). ***Conclusions:*** Most neuroblastoma tumors are abdominal and have distant metastases. LDH and ferritin elevations are prevalent. Neuroblastoma outcomes can be predicted using the INRGSS 2009 classification.

Keywords: *neuroblastoma, children, clinical features, INRGSS 2009*

I. BACKGROUND

Neuroblastoma is the most common extracranial solid tumor of childhood and represents a neoplastic expansion of neural crest cells in the developing sympathetic nervous system. The primary tumor originates anywhere along the sympathetic chain but most frequently arises from the adrenal gland [5].

Therapy guided by risk stratification using combination of clinical features and tumor biology provides us the basis for assessing response and modifying care for children with neuroblastoma. This approach led to significant improvement in treatment strategies and outcomes [4].

The most recent and frequently used was the International Neuroblastoma Staging System (INSS) 1993, used from about 1989–2010, was based, in part, on the extent of surgical resection [6]. This was problematic as it precluded the pretreatment classification

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of stage, making cross-clinical group comparisons, particularly for research purposes, more challenging and less standardized.

In 2009, the INRG Task Force published their recommendations both for new staging and risk group stratification (INRGSS 2009). INRG staging is based on image-defined risk factors (IDRFs) pre-therapy rather than postsurgical. This system divides patients into stages L1, L2, M, Ms, from which, in combination with histopathology, molecular biology, each patient will be divided into risk groups from which to guide prognosis and suitable treatment [8].

The INRGSS 2009 serves as a crucial tool for classifying neuroblastoma patients into risk groups based on prognostic factors. These factors include INRGSS stage, age at diagnosis, histologic category and grade of differentiation, MYCN amplification, 11q aberration, tumor cell ploidy. By considering these factors, the INRGSS assigns patients to four risk groups: very low-risk, low-risk, intermediate-risk, and high-risk. This risk stratification guides treatment decisions, with low-risk patients requiring less aggressive treatment compared to high-risk patients who benefit from intensive multimodal therapy regimens [12].

In Hue Central Hospital, the SIOPEN (Société Internationale d'Oncologie Pédiatrique) protocol is employed for the evaluation and management of neuroblastoma patients. This protocol aligns with international guidelines and incorporates risk-adapted treatment strategies. By utilizing the SIOPEN protocol alongside INRGSS risk stratification, physicians at Hue Central Hospital can ensure evidence-based and personalized treatment approaches for each neuroblastoma patient.

In order to contribute to solving the above problem, we conducted research with 2 goals:

1. Describe the clinical and laboratory features of neuroblastoma in children.

2. Distribution of pediatric neuroblastoma stages according to the INRGSS 2009 classification and its value in predicting survival outcomes.

II. MATERIALS AND METHODS

2.1. Subjects

Neuroblastoma patients are being treated and monitored at the Pediatric Center, Hue Central Hospital from June 2022 to August 2023.

2.2. Eligibility Criteria

The minimum criterion for a diagnosis of neuroblastoma is that diagnosis must be based on one of the following [6]:

+An unequivocal pathologic diagnosis made from tumor tissue by immunohistochemistry.

+The combination of bone marrow aspirate or trephine biopsy containing unequivocal tumor cells and increased levels of serum catecholamines or urinary catecholamine metabolites.

2.3. Exclusion criteria

- The patient has received specific treatment before.
- Insufficient clinical and laboratory data to evaluate the study
- Patients and family members do not agree to participate in the study

2.4. Method

Study design: Cross-sectional descriptive study combined with retrospective and prospective.

Data collection: pre-designed questionnaires and research records were collected from the medical records at the department.

Research process:

Record the initial clinical and laboratory information of pediatric patients with suspected neuroblastoma.

All patients received whole-body computed tomography, bilateral bone marrow biopsy and necessary tests for evaluation and classification.

Application International Neuroblastoma Risk Group Staging System 2009 to classify patients [8].

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

All patients enrolled in this study received treatment according to the SIOPEN protocol and were followed throughout the study period for the assessment of survival outcomes.

2.5. Statistical Analysis

The data was inputted, processed, and examined using SPSS Statistics 27 and Excel 2019. This study employed the Chi-square test and the t-test, revealing a statistically significant difference at a significance level of $p < 0.05$. This investigation employed the Kaplan-Meier estimator and the log-rank test to analyze survival outcomes in neuroblastoma patients.

III. RESULTS

3.1. Epidemiological features

Table 1. ***Epidemiological features of patients with neuroblastoma***

Features		Number (N =49)	Percentage (%)
Age	Mean	35.4 ± 25.5 months	
	< 12 months	13	26.5
	12 – 18 months	3	6.1
	> 18 months	33	67.3
Sex	Male	27	55.1
	Female	22	44.9
Region	Urban	18	36.7
	Rural	31	63.3

The mean age of the study group was 35.4 ± 25.5, of which the majority were > 18 months, the proportion of men and women was almost equal, mainly patients from rural areas.

3.2. Clinical and laboratory features

Table 2. ***Clinical features of childhood neuroblastoma***

Features		Number (N =49)	Percentage (%)
Primary tumor	Thorax	11	22.4
	Abdomen	36	73.5
	Without primary tumor	2	4.1
Symptom	Abdominal pain	19	38.8
	Abdominal distention	18	36.7
	Fever	13	26.5
	Loss of appetite	9	18.4
	Pain	8	16.3
	Palor	8	16.3
	Weight loss	7	14.3
	Accidental	3	6.1
Metastasis		36	73.5
Metastasis sites	Bone marrow	23	46.9
	Skeletal system	17	34.7
	Lympho nodule	14	28. 6
	Lung	5	10.2
	Liver	4	8.2
	Skin	3	6.1
	Brain	3	6.1

The majority of primary tumors (74.9%) were abdominal, and 4.1% of patients had no primary tumor. The most common symptoms in neuroblastoma patients were abdominal pain and distention, followed by fever, loss of appetite, paleness, and pain. At initial diagnosis, 73.5% of patients in the study group had metastases, most commonly to the bone marrow, skeletal system, and lymph nodes.

Table 3. ***Laboratory features in childhood ITP***

Features	Number (N =49)	Percentage (%)
Neutropenia	10	20.4
Anemia	35	71.4
Thrombocytopenia	8	16.3
Elevated liver enzymes	13	26.5
Kidney failure	0	0.0
Increase LDH	32	65.3
Increase Ferritin	35	71.4

The most common laboratory changes in study patients were anemia, increased lactate dehydrogenase (LDH), and increased ferritin, each occurring in over 70% of cases. Neutropenia, thrombocytopenia, and elevated liver enzymes were also observed in nearly 20% of cases.

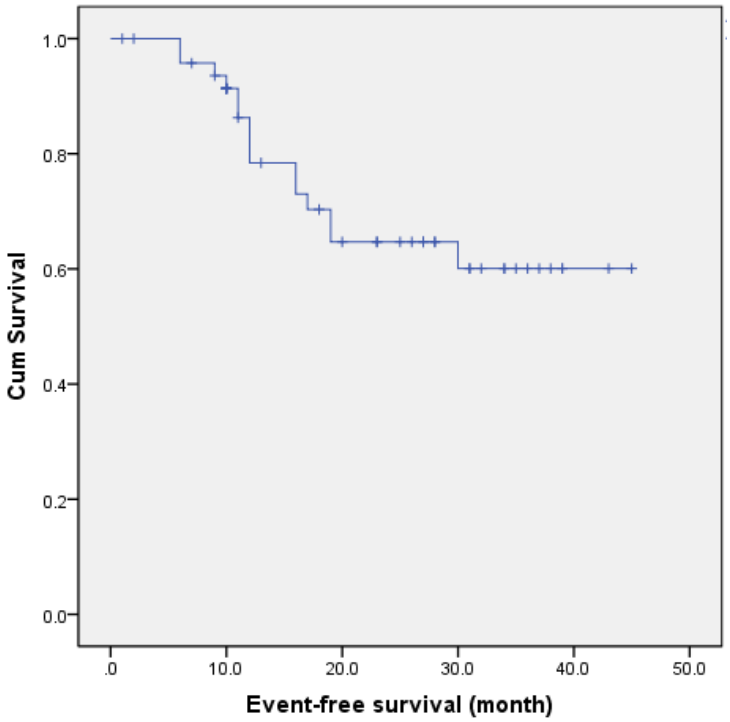

Figure 1. ***Event-free survival (EFS) in neuroblastoma patients***

Estimated event-free survival at 24 and 36 months were 64.7 ± 7.7% and 60.1 ± 8.4%, respectively.

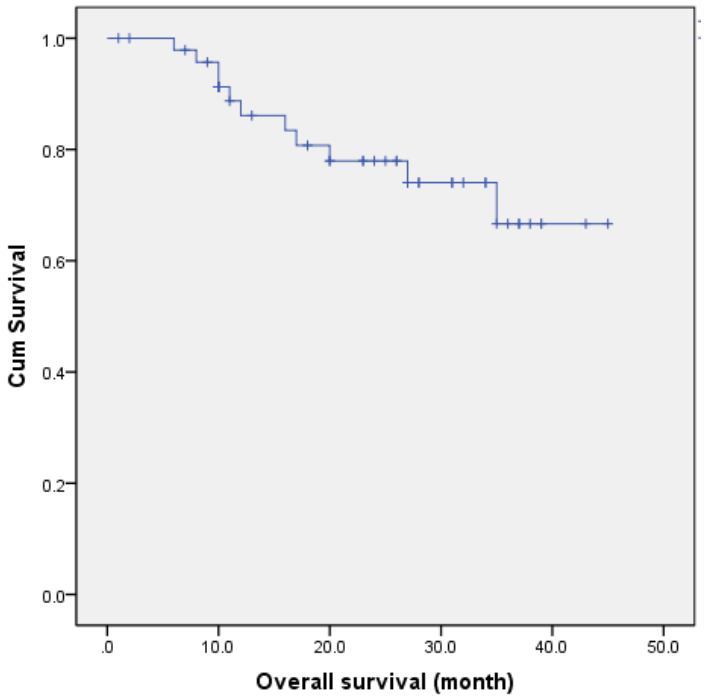

Figure 2. ***Overall survival (OS) in neuroblastoma patients***

Estimated overall survival at 24 and 36 months were 77.9 ± 6.6% and 74.0 ± 7.3%, respectively.

3.3. Distribution of pediatric neuroblastoma stages according to the INRGSS 2009 classification and its value in predicting survival outcomes.

Table 4. ***Stages classification by INRGSS 2009***

Stages classification by INRGSS 2009	Number	Percentage (%)
L1	3	6.1
L2	10	20.4
M	34	69.4
MS	2	4.1
Total	49	100.0

The majority of patients in the study group were classified as stage M according to the INRGSS 2009 staging system.

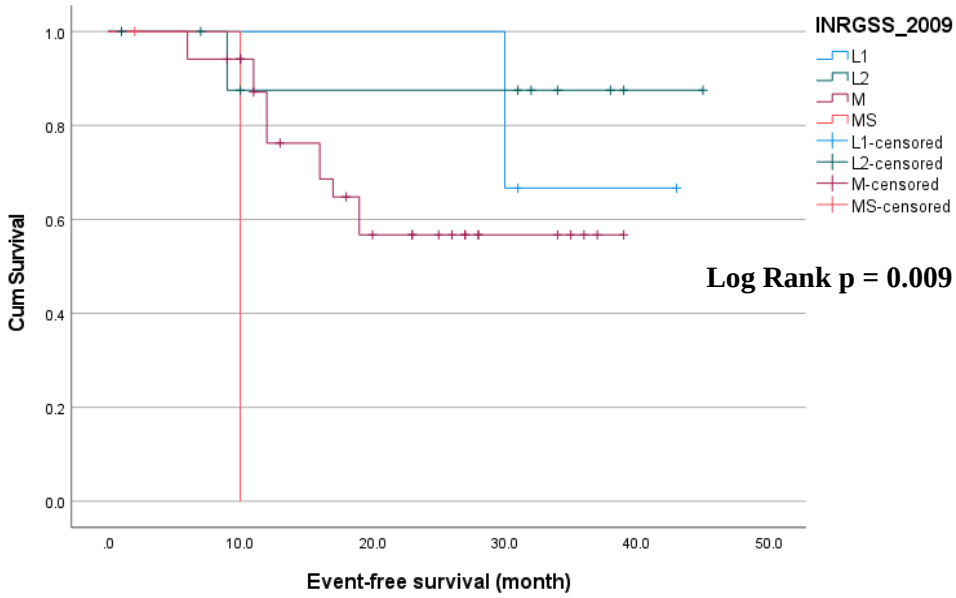

Figure 3. ***Comparison Event-free survival (EFS) between INRGSS 2009 stages Estimated mean of event-free survival for L1 was 38.7 ± 3.5 months, L2 was 40.5 ± 4.2 months and M was 28.0 ± 2.5 months.***

IV. DISCUSSION

4.1. Epidemiological features

The age of the 49 patients with neuroblastoma at diagnosis ranged from 1 day to 9 years, with a mean of 35.4 ± 25.5 months. Children older than 18 months constituted the largest group (67.3%), followed by children younger than 12 months (26.5%) and children aged 12-18 months (6.1%). The average age of children with neuroblastoma at diagnosis is reported to be 23 months. A review of 3,666 children with neuroblastoma in cooperative groups in the United States between 1986 and 2001 reported a mean age of 19 months [2]. The higher average age in our study may reflect the delayed diagnosis in most of the patients studied. Notably, 26.5% of patients were younger than 1 year old, confirming the high incidence of the tumor in this age group.

Of the patients, 27 (55.1%) were male and 22 (44.9%) were female, with a male predominance and a ratio of 1.23:1. This

male:female ratio is similar to that reported in other studies [13].

4.2. Clinical and laboratory features

The primary tumor was located in the abdomen in 36 cases (73.5%), the mediastinum in 11 cases (22.4%), and an unknown location in 2 cases (4.1%). Lucena et al. reported that nearly 75% of primary tumors in neuroblastoma are abdominal, and 4.1% of patients have no primary tumor. The most common symptoms in neuroblastoma patients are abdominal pain and distention, with other possible symptoms including fever, loss of appetite, paleness, and pain. At initial presentation, 73.5% of patients in the study group had metastases, most commonly to the bone marrow, bone, and lymph nodes [13].

The children with NB had an extremely varied diagnostic clinical picture, which is similar to what has been described in the literature [1]. In our study, non-specific, systemic signs, such as fever (26.5%), loss of appetite (18.4%) and weight loss (14.3%), were frequently reported. These signs and symptoms were also prevalent in the study performed by Collaço et al., who analyzed 50 cases of NB in a reference hospital in Curitiba, Paraná [1].

In addition to systemic signs, patients presented specific symptoms based on the tumor location. In 73.5% of cases in our study, neuroblastoma occurred in the abdomen. In these cases, the most common symptoms were distention (36.7%) and pain (38.8%). According to the literature, on physical examination, the tumor is typically hard, fixed, and difficult to demarcate, located in the kidneys and extending into the hypochondrium and flank, and may cross the midline of the abdomen [2].

At diagnosis, 73.5% of patients had distant metastases (stage M or MS), most commonly to the bone marrow and skeletal system. Patients often present with symptoms due to metastases, such as bone pain, anemia, neutropenia, thrombocytopenia, and elevated liver enzymes.

In our study, 65.3% of patients had elevated lactate dehydrogenase (LDH) and 71.4% had elevated serum ferritin. LDH and serum ferritin are downstream clinical manifestations of the upstream genomic aberrations and environmental influences that lead to tumorigenesis and drive aggressive disease progression. LDH and ferritin are strong prognostic factors with high reproducibility and are simple to obtain [9].

The event-free survival (EFS) of the entire group was 64.7 ± 7.7% and 60.1 ± 8.4% at 24 and 36 months, respectively (Figure 1). The overall survival (OS) was 74.0 ± 7.3% at 36 months (Figure 2). In a study by Ali Aykan Ozguven, the EFS at 60 and 108 months was 84.7 ± 7.7% and 72.6 ± 7.7%, respectively, and the OS was 91.7 ± 8% at 108 months [11]. In another study, the 5-year OS and EFS were 62% and 52%, respectively, and the 10-year OS and EFS were 53% and 47%, respectively [13]. We will continue to follow up for long-term research.

4.3. Distribution of pediatric neuroblastoma stages according to the INRGSS 2009 classification and its value in predicting survival outcomes.

According to the INRGSS 2009 staging system, the majority of patients in our study had progressive disease: 6.1% were in stage L1, 20.4% were in stage L2, 69.4% were in stage M, and 4.1% were in stage MS. In Arlene Naranjo's study, the distribution of patients across INRGSS 2009 stages was as follows: 31% stage L1, 17% stage L2, 40% stage M, and 7% stage MS [10].

According to the INSS staging system, 6.1% of patients in our study had stage 1 disease, 14.4% had stage 2 disease, 6.1% had stage 3 disease, 69.4% had stage 4 disease, and 4.1% had stage 4S disease. In Januária

Nunes Lucena's study, the majority of patients had localized disease (stage 1, 2, or 3): 46% were in stage 1, 6% were in stage 2, 27% were in stage 3, 12% were in stage 4, and 9% were in stage 4S [13].

The number of patients with stage M neuroblastoma (according to the INRGSS 2009 staging system) or stage 4 neuroblastoma (according to the INSS 1993 staging system) has increased significantly at Hue Central Hospital, as it is one of only three hospitals in Vietnam that performs hematopoietic stem cell transplantation for high-risk neuroblastoma patients. As a result, most high-risk neuroblastoma patients are transferred to our hospital from other hospitals.

INRGSS 2009 system would allow for pretreatment staging rather than postsurgical staging (INSS 1993). This is important in patients with localized disease who do not require surgical resection such as those with perinatally diagnosed disease. These patients could not be properly staged with INSS as surgical resection is required to define stage 1 or 2 disease. European groups had already adopted image-defined risk factors to eliminate surgical style or skill from the evaluation of risk. In addition to the use of radiographic features in place of surgical resection, several other changes were included in the INRG system including elimination of lymph node assessment and midline nature of tumors and use of 18 months instead of 12 months to define MS disease [3].

Our study found that the INRGSS 2009 classification was significant in predicting event-free survival (EFS) with a p-value of less than 0.05 in the Log Rank test. We were unable to perform a comparison of overall survival (OS) due to insufficient mortality data. These results suggest that the INRGSS 2009 is valuable in predicting outcomes in patients with neuroblastoma. A large report from COG of 4,832 eligible patients found that the 5-year event-free survival rates were 90.3 ±1.0% for stage L1, 83.9 ± 1.7% for stage L2, and 51.8 ± 1.4% for stage M [7]. These results are similar to those of our study.

V. CONCLUSION

Neuroblastoma is a heterogeneous disease with a diverse range of clinical presentations, including systemic symptoms, local symptoms, and symptoms caused by metastases. The majority of neuroblastoma tumors arise in the abdomen and have distant metastases at diagnosis. Elevated lactate dehydrogenase (LDH) and ferritin levels are also common findings. The INRGSS 2009 classification is valuable in predicting outcomes in children with neuroblastoma.

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ETHICAL CONSIDERATION

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards. This study was approved by the Ethics Committee of Hue University of Medicine and Pharmacy. The personal information of the patient (name, phone number, address) was not collected. Other data was anonymized and maintained with confidentiality.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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