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BRIEF RESEARCH ARTICLE

Neuroblastoma: validation of the INRG classification system in a small series

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Abstract

Purpose In 2009, the *International Neuroblastoma Risk Group* (INRG) published a new classification system of the childhood neuroblastic tumors. In this work, we present the results of the application of this new classification system in our patients.

Methods/patients We conducted a retrospective analysis of the patients diagnosed with a neuroblastic tumor in our center in the last 20 years. We classified them according to the new classification and performed a survival analysis based on the Kaplan–Meier method and Mantel–Cox test.

Results The five-year event-free survival (5-year EFS) was 95.8, 80.8, 50 and 45.9% for the very low, low, intermediate and high-risk groups. Mantel–Cox test showed statistically significant differences between these risk groups ($p = 0.002$).

Conclusion The 5-year EFS for the different risk groups was similar to the expected by the INRG. Therefore, this classification allows us to predict the evolution of this tumor and apply the correct intensity of treatment.

Keywords Neuroblastoma · Classification · Tumor staging · Prognosis

Purpose

Neuroblastic tumors (NT) are the most frequent extracranial solid tumors in children and represent the type of neoplasm more frequently diagnosed in infants. They comprise more than 7% of all malignancies diagnosed in patients < 15 years old and contribute to 15% of all childhood cancer-related deaths [1]. NT derive from the primitive neuroectodermal cells of the neural crest which are the origin of the sympathetic nervous system (SNS). Therefore, they can emerge all around the SNS, being the abdomen the most common localization with 65% of cases [1].

One prominent feature of NT is their clinical heterogeneity. Some regress spontaneously while others develop a refractory disseminated disease leading to patient's death despite the application of combined treatment protocols with chemotherapy (including high-dose), surgery, radiotherapy, differentiating therapy and immunotherapy. This clinical variability stems from biological features of tumor cells [1, 2]. According to Brodeaur, two different groups of tumors can be recognized in base to their biological profile. The first one is characterized by a mitotic alteration leading to hyperdiploidy, and high levels of the tropomyosin receptor kinase A, which results in the tumor maturation or regression owing to the presence or absence of the nerve growth factor (NGF). A second group of tumors, with more unstable genetic profile, presents a near-diploid or near-tetraploid karyotype with segmental chromosome alterations like 17p gain. Within this second type of NT, two additional subgroups can be distinguished: one is characterized by 11q or 14q deletions, while the second one often presents with 1p loss of heterozygosity with or without *MYCN* amplification. Tumors with *MYCN* amplification frequently express high levels of tropomyosin receptor kinase B and brain-derived neurotrophic factor, which represents an autocrine survival pathway that drives to an uncontrolled cell proliferation [2].

During the last decades, improvement of treatment results has largely relied upon precise risk stratification, allowing the intensification of treatment and addition of novel agents for high-risk, while decreasing treatment intensity for lower risk patients [3]. Consequently, different national and international study groups have developed diverse classification systems based in combinations of clinical and

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biological prognostic markers, but criteria applied by each group to define the risk has been variable, making it difficult to compare treatment results across different trials [4]. In 1986, an international group of experts representing almost every pediatric oncology group and organization in USA, Europe and Japan developed an international classification system called the *International Neuroblastoma Staging System* (INSS). This post-surgical classification was based on the presence or absence of metastasis and on the grade of surgical resection of the primary tumor [5]. This system was revised in 1993 including substantial changes such a redefinition of the midline and restrictions on age and bone marrow involvement for stage 4S [6]. In 2004, the *International Neuroblastoma Risk Group* (INRG) Task Force was established with representations from the major pediatric cooperative groups around the world. The aim was to develop an international algorithm for the classification of NT in different risk groups according to homogeneous criteria, thus allowing the comparison of results from clinical trials developed by different groups [7]. In 2008, the INRG defined a new classification system which included clinical features such as patient's age and INRG stage, and biological features such as *MYCN* amplification, ploidy and 11q alterations [7]. They retrospectively analyzed the 5-year event-free survival (EFS) associated to each one of these variables in more than 8800 patients diagnosed between 1990 and 2002 in North America, Europe, Japan and Australia and developed a tree regression analysis to combine them. The resulting system combines 7 prognostic factors to define 16 risk groups. According to 5-year EFS, these 16 groups were then simplified to yield only 4 definite risk-groups: very low, low, intermediate and high-risk groups, with 5-year EFS of > 85%, 75–85%, 50–75%, and < 50%, respectively (Fig. 1a).

Here, we present the results of the application of this classifications system to all patients diagnosed with a NT at our institution.

Methods/patients

Clinical data from all patients diagnosed with a NT in our institution between January 1997 and December 2017 were reviewed. The following data were collected: presence or absence of image defined risk factors (IDRF, Fig. 1b), age at diagnosis, histologic category, grade of tumor differentiation, *MYCN* amplification, 11q aberration, ploidy, date of diagnosis, date of relapse, progression or death, and date of last contact. The INRG classification criteria were retrospectively applied to those cases diagnosed before their publication, and prospectively to patients diagnosed thereafter. For those cases where determinant information was not available, we chose to assign them to the corresponding immediately lower risk group (e.g. a patient with an L2 stage, age less than 18 months, non-amplified *MYCN* status, and 11q aberration unknown, was classified as risk-group "D" instead of "G") [7].

The 5-year EFS (time from diagnosis to progression, relapse or death from any cause) from each different risk group were estimated using the Kaplan–Meier method and were compared according to the Mantel–Cox method. In agreement with the INRG original report, we chose the EFS instead of the overall survival as the main end point because the scarce number of deaths in the very low and low-risk groups would diminish the power of the statistical analysis [7].

Results

We included 60 patients, 41.7% belonged to the very low, 18.3% to the low, 3.3% to the intermediate, and 36.7% to the high-risk group (Table 1).

Table 2 shows the distribution of patients according to prognostic factors. Although information regarding certain prognostic factors was not always available, except for 11q aberration, missing data did not preclude the appropriate stratification of most patients within each of the four risk levels established by the INRG classification system as shown in Table 1.

Five-year EFS for patients in the very low, low, intermediate and high-risk groups were 95.8, 80.8, 50, and 45.9%, respectively. These differences were statistically significant among risk groups ($p = 0.002$) (Fig. 2).

Discussion

We found a distribution of patients that is quite similar to that reported by the INRG Task Force [7]. It is noteworthy that, even in such a small sample, and with a considerable amount of missing information, we were able to stratify patients within the main four risk levels established by the INRG system. Most missing data were related to grade of tumor differentiation, ploidy status and 11q aberrations (Table 2). Ploidy and 11q aberrations were not routinely studied in all patients with neuroblastic tumors until recent years. Nevertheless, excluding patients with ganglioneuroma and ganglioneuroblastoma, ploidy status only affects younger patients with *MYCN* non-amplified disseminated disease, while information regarding 11q aberrations is only needed for the classification of patients with localized unresectable tumors, aged less than 18 months and aged more than 18 months with differentiating tumors, and for patients with an MS stage and *MYCN* non-amplified disease. In contrast, *MYCN* amplification status information is

A

Pretreatment Risk Group	Stage, age, histological category, grade of tumor differentiation, MYCN, 11q aberration and ploidy.
A Very Low	Stage L1/L2, GN maturing /GNB intermixed.
B Very Low	Stage L1, any histology except GN maturing /GNB intermixed, MYCN not amplified.
C Very Low	Stage MS, MYCN not amplified, no 11q aberration.
D Low	Stage L2, < 18 months, any histology except GN maturing /GNB intermixed, MYCN not amplified, no 11q aberration.
E Low	Stage L2, ≥18 months, GNB nodular/neuroblastoma, differentiating, MYCN not amplified, no 11q aberration.
F Low	Stage M, <18 months, MYCN not amplified, hyperdiploid.
G Intermediate	Stage L2, < 18 months, any histology except GN maturing /GNB intermixed, MYCN not amplified, 11q aberration.
H Intermediate	Stage L2, ≥18 months, GNB nodular/neuroblastoma, differentiating, MYCN not amplified, 11q aberration **or** poorly differentiated or undifferentiated, MYCN not amplified.
I Intermediate	Stage M, <12 months, MYCN not amplified, diploid.
J Intermediate	Stage M, 12-18 months, MYCN not amplified, diploid.
K High	Stage L1, any histology except GN maturing /GNB intermixed, MYCN amplified.
N High	Stage L2, ≥18 months, MYCN amplified.
O High	Stage M, <18 months, MYCN amplified.
P High	Stage M, ≥18 months.
Q High	Stage MS, <18 months, MYCN not amplified, 11q aberration.
R High	Stage MS, <18 months, MYCN amplified.

B

Ipsilateral tumor extension within two body compartiments Neck-chest, chest-abdomen, abdomen-pelvis.
Neck Tumor encasing carotid and/or vertebral artery and/or internal jugular vein Tumor extending to base of skull Tumor compressing the trachea
Cervico-thoracic junction Tumor encasing brachial plexus roots Tumor encasing subclavian vessels and/or vertebral and/or carotid artery Tumor compressing the trachea
Thorax Tumor encasing the aorta and/or major branches Tumor compressing the trachea and/or principal bronchi Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal Tumor encasing the aorta and/or vena cava
Abdomen/pelvis Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament Tumor encasing branches of the superior mesenteric artery at the mesenteric root Tumor encasing the origin of the coeliac axis, and/or the superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing the aorta and/or vena cava Tumor encasing the iliac vessels Pelvic tumor crossing the sciatic notch
Intraespinal tumor extension whatever the location provided that: More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures Pericardium, diaprhragm, kidney, liver, duodeno-pancreatic block and mesentery

Fig. 1 **A** International Neuroblastoma Risk Group (INRG) Classification System. *GN* ganglioneuroma, *GNB* ganglioneuroblastoma. Source: Cohn et al. [7]. **b** Image-defined risk factors in neuroblastic tumors. Source: Monclair et al. [8]

Table 1 Distribution of patients in different risk-groups according to the INRG criteria, and 5-year event-free survival (compared with Cohn et al. [7])

Risk group	Proportion of patients (%)		5-year EFS (%)	
	Present study	Cohn et al.	Present study	Cohn et al. (%)
Very low	41.7	28.2	95.8	> 85
Low	18.3	26.8	80.8	75–85
Intermediate	3.3	9	50	50–75
High	36.7	36.1	45.9	< 50

Table 2 Distribution of patients according to prognostic factors

Prognostic factor	*n*
Stage	
L1	19
L2	16
M	21
MS	4
Age (months)	
< 18	31
≥ 18	29
Histologic category	
GNB	9
GN	4
NBL	47
Grade of tumor differentiation	
Differentiating	1
Poorly differentiated	32
Undifferentiated	9
Not available	18
MYCN	
Amplified	11
Non-amplified	42
Not available	7
11q aberration	
Deleted	9
Non-deleted	26
Not available	25
Ploidy	
Diploid	8
Hyperdiploid	16
Not available	36

GN ganglioneuroma, *GNB* ganglioneuroblastoma, *NBL* neuroblastoma

the most relevant biological risk factor for an adequate risk assignment and is particularly relevant for those patients with localized resectable (L1) tumors, those with localized unresectable (L2) tumors, and for younger patients with disseminated disease (both M and MS). However, for patients with disseminated disease, age ≥ 18 months is sufficient to include them in the high-risk group. These patients represent at least one-third of all patients and the most challenging situations on the management of NT. Still, lack of any biological information does not preclude the correct stratification of these patients, thus, allowing an appropriate treatment approach. This is of utmost importance in situations with limited resources, affecting many patients from low and middle-income countries.

Comparing our results with that presented by the INRG, [7] we found a slightly higher proportion of patients in the very low risk group, and lower in the low and intermediate risk group. These differences might be explained by the small sample size, but also by the fact that, in the absence of critical information, we opted to down-stage some patients. Lack of information about 11q aberration might partially explain the low proportion of patients within the intermediate risk group in our series. In fact, only 2 patients were finally allocated to the intermediate risk group, one of them progressed after first-line treatment and eventually dead, rendering a 5-year EFS rate as low as 50%. These results will probably improve after the systematic application of biological discriminating factors such as 11q aberration and ploidy status, as well as additional information from genomic profile. However, our treatment results in terms of EFS for each risk group of patients did not differ from those reported by Cohn et al. [7] which, from our point of view, represents an important evidence of the relevance and applicability of this classification system.

Conclusion

In summary, treatment of pediatric NT must be adapted in each case to a specific risk level defined by the presence or absence of certain clinical and biological factors. The INRG classification system provides a quite simple, easy and adequate method to stratify most patients and predict clinical outcomes. Its systematic application would allow the comparison of treatment results across different treatment approaches.

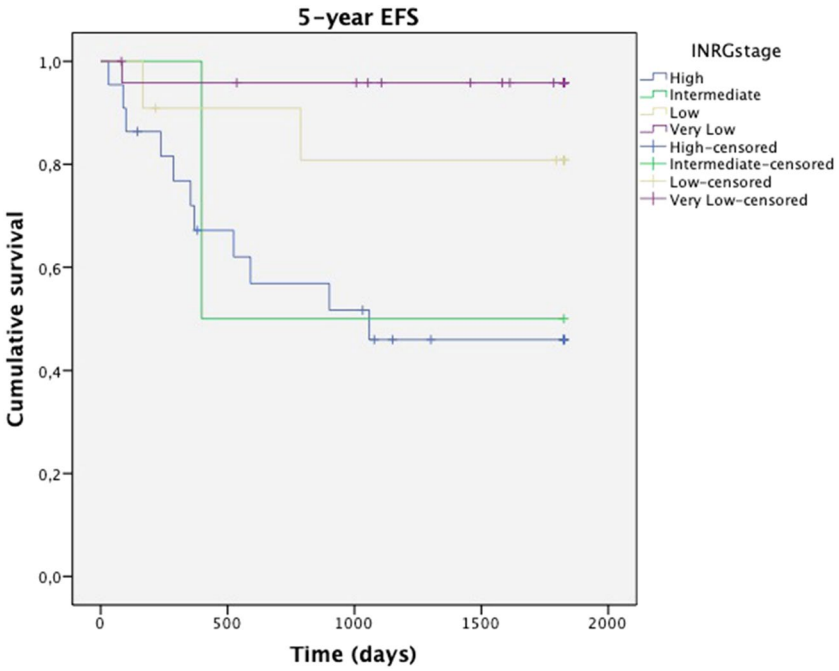

Fig. 2 Five-year event-free survival according to risk-group (95.5, 90.9, 50, and 43% for very low, low, intermediate and high-risk groups, respectively; $p = 0.002$)

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants 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 comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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