WHAT IS NEUROBLASTOMA?

Part 3: Risk Assignment

A combination of clinical features and tumor characteristics are used to group children with NB into low-, intermediate, or high-risk categories based on the predicted behavior of the tumor. Treatment is stratified according to risk group assignment with more aggressive treatments used for high-risk patients and less therapy for low- and intermediate-risk patients. This section discusses how risk groups are assigned. For more specific information describing the treatment plans for each risk group, *see* "**Understanding the Basics of Frontline Treatments."**

NBs tumors can display a wide range of behavior, from tumors that grow smaller or disappear on their own without treatment (usually in infants), to widespread disease that is difficult to cure in preschoolers and older children and that requires aggressive treatment. The risk assignment systems were developed to group together the children with similar prognoses. The previous sections "**Description, Diagnosis and Staging**" and "**Tumor Pathology and Genetics**" cover staging and tumor characteristics. These factors (age, stage, pathology, and genetics) are evaluated to determine the risk assignment (low, intermediate, or high risk), and risk group determines the treatment plan and reflects the patient's prognosis.

It is important to note that various study groups have assigned risk differently (as well as having devised different treatment protocols). In 2009, an international task force established the "International Neuroblastoma Risk Group" or INRG Classification System using a staging system that is based on imaging, the INRGSS and other established prognostic markers. *See* more on this revision in the "**Appendix**" to this section as well as the current 2007 COG risk schema.

The discussion here utilizes the Children's Oncology Group risk assignment schema (COG: US, Canada, Australia, New Zealand, Netherlands, Switzerland). This schema refers to stage, age, MYCN status, Shimada Classification (i.e., favorable or unfavorable histology), and DNA ploidy (or DNA index) used by COG to assign risk.[1]

Of all NB cases diagnosed:

- 37% of all NBs are low risk (good prognosis, minimal treatment);
- 18% of all NBs are intermediate risk (good prognosis, moderate treatment); and
- 45% of all NBs are high-risk (poor prognosis, intensive treatment).[2]

This means that in the U.S. every year approximately 260 low-risk cases are diagnosed, 130 intermediate-risk, and 315 high-risk cases (with about 700 total for all groups). A brief overview of each NB risk group follows, with prognosis and treatment intensity compared. (Terms used in the criteria below are discussed in the prior section, "**Tumor Pathology and Genetics**.")

COG Low Risk (2007 revision)

INSS Stage	Age	MYCN amp > 10 copies	DNA ploidy (DNA index)	Histology (Shimada)	Other
1	any	any	any	any	
2A or 2B	any	no	any	any	> 50% resection
4S	<12	no	hyperdiploidy	favorable	asymptomatic

	months		DNA index >1		

Prognosis and treatment for Low Risk Patients. About 37 percent of all NBs are classified as "low risk." Many of these tumors are discovered by chance and treatment requires only surgery. Occasionally a "wait and see" approach is recommended because some types of low-risk NB are known to go away on their own. Emergency treatment (surgery, chemotherapy, or radiation) is very individualized if critical symptoms are caused by the tumor, such as compromised breathing or spinal compression. ***See* "Overview of Treatment for Low and Intermediate Risk NB."** Children diagnosed with low-risk NB have a survival rate as high as 95 percent.

COG Intermediate Risk (2007 revision)

INSS Stage	Age	MYCN amp > 10 copies	DNA ploidy (DNA index)	Histology (Shimada)	Other
2A or 2B	any	no	any	any	< 50% resection
2A or 2B	any	no	any	any	bone marrow biopsy only
3	<12 mo	no	any	any	
3	≥ 12 mo	no	any	favorable	
4	<12 mo	no	any	any	
4	12-18 mo	no	hyperdiploidy DNA index >1	favorable	
4S	<12 mo	no	diploidy DNA index = 1		
4S	<12 mo	missing	missing	missing	
4S	<12 mo	no			Symptomatic
4S	<12 mo	no	any	unfavorable	

Prognosis and treatment for Intermediate Risk Patients. About 18 percent of all NB cases are deemed "intermediate risk." Children with intermediate-risk disease generally require surgery and four to eight rounds of moderate-dose outpatient chemotherapy, but have a very good prognosis, with overall 90 percent of children surviving.[3] ***See* "Overview of Treatment for Low and Intermediate Risk NB."**

COG High Risk (2007 revision)

INSS Stage	Age	MYCN amp > 10 copies	DNA ploidy (DNA index)	Histology (Shimada)	Other
2A or 2B	any	yes	any	any	
3	any	yes	any	any	
3	≥ 18 mo	no	any	unfavorable	
4	any	yes	any	any	
4	12-18 mo	no	diploidy DNA index = 1	any	
4	12-18 mo	no	any	unfavorable	
4	>18 mo	any	any	any	
4S	<12 mo	yes	any	any	

Prognosis and treatment for High Risk Patients. The remaining 45 percent of NB cases are considered "high risk." Current stand of care treatment for children with high-risk disease includes

high-dose induction chemotherapy, surgery, consolidative therapy with 2 cycles of high-dose chemotherapy and stem cell transplant, and post-consolidation therapy with anti-GD2 antibody therapy, the cytokine GM-CSF, and isotretinoin. Although the percent of children surviving has increased with this aggressive treatment, relapse remains a significant hurdle. With this treatment approach, approximately 60% of patient are alive without relapse 3 years from diagnosis (Reference Park JR et al., JAMA 2019).[4,5] ***See* "Overview of Treatment for High Risk NB."**

Summary

This and the previous two sections of **"What is Neuroblastoma?**" describe the general features, diagnosis, staging, tumor pathology and genetics, and risk group assignment for NB. This description has been prepared by laymen and is intended only as a brief general introduction of these matters for parents. More detailed information can be found in the sources listed at the end of Part 1 and in the various footnotes. Another valuable source of the most up-to-date research findings are the respective lists provided by major cancer centers of publications by the NB doctors and researchers affiliated with them.

However, as emphasized above, NB exhibits widely disparate characteristics and seems unique in every child. The specific nature of your child's NB disease and his or her treatment must always be determined by an experienced pediatric oncologist. Although many parents find that the information in secondary sources and research papers about NB increases their understanding of their child's illness, there is no substitute for an informed discussion of these matters with your child's oncologist.

Addendum on Revised Staging and Risk Assignment

NB Staging and Risk Classification Revisions

Until recently, there has been no international agreement on criteria for risk assignment, so study groups in addition to COG, such as those in Japan, Germany (GPOH), and Europe (SIOP) have developed their own risk classification systems. This lack of agreement makes it difficult to compare results of treatments used in international studies.

The INRG Risk Classification was established in 2009 in an effort to develop uniform risk group definitions internationally (Ref Cohn SL et al., J. Clin. Oncol 2009). A new staging system was developed (INRGSS—International Neuroblastoma Risk Group Staging System) for this classification system which takes in account "image-defined risk factors" (IDRFs) at diagnosis, distinguishing between tumors that can be safely removed and those that cannot be surgically removed at diagnosis. In Europe surgical risk factors (determined by imaging) have long been used as a criteria included in risk assignment.[6]

The INRGSS staging system can be summarized as follows:
Stage L1 – localized tumor (without image-defined risk factors);
Stage L2 – locoregional tumor (with image-defined risk factors);
Stage M – metastatic disease, except for MS;
Stage MS – metastatic disease under 18 months with spread to only skin, liver, under 10% of bone marrow, or same as 4S.[7]

The prognostic factors used in the INRG risk classification system include INRGSS (stage L1, L2, M, MS), age (under or over 18 months), tumor grade, presence or absence of *MYCN* amplification, unbalanced 11q aberration, and DNA ploidy. Based on these markers, patients are assigned to *four* risk groups: very-low, low, intermediate, and high. This system is now more than 10 years old, and

efforts are ongoing to revise the INRG Risk Classification System to include additional genomic factors including ALK mutations and segmental chromosomal abberations.

The current COG Neuroblastoma Risk Classification System includes the following criteria, INSS stage, age, MYCN status, ploidy, and histology. Based on the work of the INRG Task Force, efforts to revise the COG Risk Classification System to include INRGSS instead of INSS are ongoing.

COG Neuroblastoma Risk Groups (2007)

Stage	Age	MYCN	Ploidy	Histology	Other	Risk Group
1						Low
2A/2B		NA			> 50% resect.	Low
		NA			<50% resect.	Inter.
		NA			Bx only	Inter.
		Amp				High
3	< 547 d	NA				Inter.
	≥ 547 d	NA		FH		Inter.
		Amp				High
	≥ 547	NA		UH		High
4	<365 d	Amp				High
	< 365 d	NA				Inter.
	365-<547 d	Amp				High
	365-<547 d		DI=1			High
	365-<547 d			UH		High
	365-<547 d	NA	DI>1	FH		Inter.
	≥547 d					High
4S	<365 d	NA	DI> 1	FH	Asymptomatic	Low
	<365 d	NA	DI=1			Inter.
	<365 d	Missing	Missing	Missing		Inter.
	<365 d	NA			Symptomatic	Inter.
	<365 d	NA		UH		Inter.
	<365 d	Amp				High

Recent Changes to COG Risk Assignment Schema

Please contact info@cncfhope.org with any comments

Field Code Changed

[1] Children's Oncology Group Neuroblastoma Risk Grouping, National Cancer Institute (last modified 11/2007)
[2] Maris, John. Translating Neuroblastoma Genomics to the Clinic, ASCO 2007 Education Session, ASCO Annual Meeting presentation
[3] Baker, DL et al A phase III trial of biologically-based therapy reduction for intermediate risk neuroblastoma, *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 9504.
[4] Cheung, NK "Reducing Therapy for Low-risk and Advancing Immunotherapy for High-risk Neuroblastoma" Embryonal Cancers I: Neuroblastoma---Recent Advances in Biology and Therapy, Education Session, 2007 Educational Book, 2007 ASCO Annual Meeting presentation
[5] George RE, Li S, Medeiros-Nancarrow C, *et al* (June 2006). "High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update". *J. Clin. Oncol.* 24 (18): 2891–6. PMID 16782928.
[6] Monclair, T "The new international neuroblastoma risk group

staging system – implications for surgeons" SIOP Education Book 2006, International Society of Paediatric Oncology, p.64

[7] Maris, J et al. "Neuroblastoma." *The Lancet*, Volume 369, Issue 9579, pages 2106-2120 (June 2007)