WHAT IS NEUROBLASTOMA?

Part 3: Risk Assignment

"Risk assignment" groups children with NB into "good" and "poor" prognostic categories; this is crucial information because different treatment plans are used for each risk group. 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 range significantly in 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) taken together determine the risk assignment (low, intermediate, or high risk), and this ultimately dictates the prognosis and treatment plan.

It is important to note that various study groups have assigned risk differently (as well as having devised different treatment protocols). Currently an international task force is working on a revision to the international staging system (INSS) and devising a new risk assignment system, the "International Neuroblastoma Risk Group" or INRG. *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 months	no	hyperdiploidy DNA index >1	favorable	asymptomatic

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." Children with high-risk disease receive aggressive multi-modal treatment that includes high-dose induction chemotherapy, surgery, radiation, consolidative therapy (single or double stem cell transplant and/or antibody therapy), and differentiation therapy with retinoids in

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an effort to eradicate minimal residual disease. Although the percent of children surviving has increased with this aggressive treatment, relapse remains a significant hurdle. The high number of relapses contributes to a poor long-term survival rate in past years of only about 35 percent for children diagnosed with high-risk disease, although recent studies by some institutions indicate an increasing survival rate of 50% or more for high-risk disease.[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

Revision to INSS Staging and Risk Assignment (INRG)

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 stage and risk assignment system discussed above is under revision by an international task force with the goal of developing a standardized international risk group classification called International Neuroblastoma Risk Group (INRG), and will include a new staging system as well (INRGSS—International Neuroblastoma Risk Group Staging System). The INRGSS proposed will take 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 proposed 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]

To standardize risk assignment worldwide, the INRG task force has proposed a new schema. The proposed system will determine INRG risk according to the 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, which will assign all NB cases into *four* risk groups: very-low, low,

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intermediate, and high.

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

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[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)

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