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SPECIAL ARTICLE

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The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report

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ABSTRACT

Purpose

Because current approaches to risk classification and treatment stratification for children with neuroblastoma (NB) vary greatly throughout the world, it is difficult to directly compare risk-based clinical trials. The International Neuroblastoma Risk Group (INRG) classification system was developed to establish a consensus approach for pretreatment risk stratification.

Patients and Methods

The statistical and clinical significance of 13 potential prognostic factors were analyzed in a cohort of 8,800 children diagnosed with NB between 1990 and 2002 from North America and Australia (Children's Oncology Group), Europe (International Society of Pediatric Oncology Europe Neuroblastoma Group and German Pediatric Oncology and Hematology Group), and Japan. Survival tree regression analyses using event-free survival (EFS) as the primary end point were performed to test the prognostic significance of the 13 factors.

Results

Stage, age, histologic category, grade of tumor differentiation, the status of the *MYCN* oncogene, chromosome 11q status, and DNA ploidy were the most highly statistically significant and clinically relevant factors. A new staging system (INRG Staging System) based on clinical criteria and tumor imaging was developed for the INRG Classification System. The optimal age cutoff was determined to be between 15 and 19 months, and 18 months was selected for the classification system. Sixteen pretreatment groups were defined on the basis of clinical criteria and statistically significantly different EFS of the cohort stratified by the INRG criteria. Patients with 5-year EFS more than 85%, more than 75% to ≤ 85%, ≥ 50% to ≤ 75%, or less than 50% were classified as very low risk, low risk, intermediate risk, or high risk, respectively.

Conclusion

By defining homogenous pretreatment patient cohorts, the INRG classification system will greatly facilitate the comparison of risk-based clinical trials conducted in different regions of the world and the development of international collaborative studies.

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INTRODUCTION

Neuroblastoma (NB) is remarkable for its broad spectrum of clinical behavior, with some tumors regressing or maturing, whereas others progress despite intensive multimodality treatment.[1,2] This diversity in behavior correlates closely with a number of clinical and biologic features,[2] and combinations of prognostic variables are used for risk-group assignment and treatment stratification. However, the factors selected by various cooperative groups to define risk are not uniform. For example, the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) uses age, surgical risk factors defined by imaging, and *MYCN* status for risk-group assignment of locoregional tumors, whereas the Children's Oncology Group (COG) uses age, postsurgical staging, *MYCN* amplification, histology, and DNA ploidy.[3,4] Furthermore, the increasing number of genetic features included in more recently developed clinical trials to guide therapy decisions[5-7] further complicates comparisons.

To facilitate comparison of clinical trials performed throughout the world, the William Guy Forbeck Research Foundation sponsored an international conference more than 20 years ago. The outcome of the conference was published as the International Neuroblastoma Staging System (INSS).[8,9] During the last two decades, there have been major advances in understanding the genetics

of NB. Although the unfavorable prognostic factor *MYCN* amplification[10] is used by all cooperative groups for risk-group stratification and therapeutic decisions, other prognostically significant genetic features[5-7,11] have not been consistently incorporated into risk classification schemas. Furthermore, only some cooperative groups include tumor histology for risk-group assessment.[12,13]

To develop a consensus approach to pretreatment risk stratification, a task force of investigators with expertise in NB from the major pediatric cooperative groups around the world was established in 2004. A new International Neuroblastoma Risk Group (INRG) Staging System (INRGSS) was designed to stratify patients at the time of diagnosis before any treatment, as detailed in the companion article by Monclair et al.[14] In the INRGSS, extent of locoregional disease is determined by the absence or presence of image-defined risk factors (L1 and L2, respectively). Stage M will be used for widely disseminated disease, and MS describes metastatic NB limited to skin, liver, and bone marrow without cortical bone involvement in children age 0 to 18 months with L1 or L2 primary tumors. In addition, the Task Force's recommendations for defined standard operating procedures for molecular diagnostic testing of NB tumor tissue, criteria for the evaluation of bone marrow metastatic disease by immunocytochemistry and RT-PCR and for the assessment of metastatic disease by MIBG will be described in future reports.

PATIENTS AND METHODS

INRG Task Force Members

In 2004, investigators from the major cooperative groups, COG (North America and Australia), the German Pediatric Oncology and Hematology Group (GPOH), the Japanese Advanced Neuroblastoma Study Group (JANB), the Japanese Infantile Neuroblastoma Co-operative Study Group (JINCS), SIOPEN and China with expertise in NB were contacted by ADJP and SLC and invited to participate in an initiative to establish the INRG classification system. The major goal of the Task Force was to develop a consensus approach for pretreatment risk stratification of NB, based on statistical analyses of prognostic factors.

The leaders of the cooperative groups were asked to nominate six individuals with expertise in one or more of the following categories: clinical trials related to NB, chemotherapy, surgery, pathology, biology, radiology, nuclear medicine and statistics. In addition, young investigators were invited, and 52 investigators were identified. Four committees were formed: Surgery, Chair—Tom Monclair; Statistics, Chair—Wendy B. London; Biology, Chair—Peter F. Ambros; and Metastatic Disease, Chair—Katherine K. Matthay. The four chairs of the committees and the co-chairs of the INRG Task Force (A.D.J.P. and S.L.C.) comprised the INRG Executive Committee. Four international conferences were held: June 2004 in Genoa, Italy; September 2005 in Whistler, Vancouver, Canada sponsored by the William Guy Forbeck Research Foundation; May 2006 in Los Angeles, CA; and September 2006 in Geneva, Switzerland.

Table 1. Number of Patients in the International Neuroblastoma Risk Group Analytic Cohort by Country or Cooperative Group of Origin

Country or Cooperative Group	No.	%
COG	4,235	48.1
SIOPEN: Previous European Neuroblastoma Study Group (ENSG)	917	10.4
SIOPEN: Italy	304	3.5
SIOPEN: Spain	410	4.7
SIOPEN: LNESG1 trial	526	6.0
Germany	1,938	22.0
Japan	470	5.3
Total	8,800	100

Abbreviations: COG, Children's Oncology Group; SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group.

Patient Cohort

Data were collected on patients enrolled on COG, GPOH, JANB, JINCS, or SIOPEN trials. Enrollment cutoff of 2002 was chosen to allow at least 2 years of follow-up at the 2004 data freeze. Eligibility for inclusion in the INRG cohort included (1) confirmed diagnosis of NB, ganglioneuroblastoma (GNB), or ganglioneuroma (GN) maturing; (2) age no older than 21 years; (3) diagnosis between 1990 and 2002; and (4) informed consent. In addition to date of diagnosis and follow-up data, information on 35 potential risk factors were requested: age, INSS stage, Evans stage, Shimada classification, Shimada histologic category, Shimada grade, Shimada mitosis-karyorrhexis index (MKI), International Neuroblastoma Pathology Classification (INPC), INPC histologic category, INPC grade of tumor differentiation, INPC MKI, *MYCN* status, DNA ploidy (defined as DNA index ≤ 1.0 v > 1.0), 11q loss of heterozygosity (LOH), 11q aberration, unbalanced 11q LOH, 1p LOH, 1p aberration, 17q gain, serum ferritin, serum lactate dehydrogenase (LDH), six primary tumor sites, and eight metastatic sites. Analyses were performed on 8,800 unique patients.

Statistical Considerations

Objective, inferential criteria formed the initial basis for definition of the risk groups. However, because there were too few patients who had known values for all the factors and challenges of reaching international agreement, the final decision regarding the delineation of pretreatment risk groups was made by consensus on the basis of treatment strategies and overall survival (OS), in addition to event-free survival (EFS) results.

Survival Analyses

The primary analytic end point was EFS. Time to event was defined as time from diagnosis until time of first occurrence of relapse, progression, secondary malignancy, or death, or until time of last contact if none of these occurred. EFS was selected as the primary end point because the majority of patients with non–high-risk disease who have an event successfully achieve treatment salvage, and it is difficult to discriminate subsets using OS because of fewer events (deaths) in the lower-risk cohorts, resulting in lower power. Univariate analyses using a log-rank test, at a 5% significance level and without adjustment for multiple testing, were performed to identify factors statistically significantly predictive of EFS to be carried forward into the survival-tree regression. Kaplan-Meier curves were examined for each factor (data not shown).[15] Cox proportional hazards regression models were used to identify the most highly statistically significant variable to create a given split or "branch" in the survival tree.[16-19] The survival tree methodology, rather than attempting to develop a prognostic index, was used to develop the classification because the consensus of the clinical and scientific participants involved was that the survival tree approach was more intuitive, reflected the customary format for risk-group presentation in this disease, and could be used more easily internationally. The assumption of proportional hazards was tested. For practical reasons, all factors were analyzed as binary variables. All EFS and OS values are reported at the 5-year time point $\pm$ the SE.

Methods to Dichotomize Age, LDH, and Ferritin

Age was dichotomized using methods previously described by London et al (n = 3,666 COG patients from the INRG database).[20] Excluding these 3,666 patients, the analysis to identify an optimal age cutoff was repeated (data not shown). For LDH and ferritin respectively, the median value was used to dichotomize the cohort, and two binary variables were created for the survival-tree analysis.

Justification for Utilizing Underlying Components of Histologic Classification

The INPC and Shimada histology systems use age at diagnosis and histologic features of the tumor to categorize tumors as favorable versus unfavorable. This results in a duplication of the prognostic contribution

("confounding") of age when histology is used in a risk-group schema that includes age. To determine which histologic features were independently associated with outcome, tumor grade (differentiating *v* poorly differentiated or undifferentiated), MKI (low or intermediate *v* high), histologic category (GN-maturing or GNB-intermixed *v* GNB-nodular or NB), and age (< 547 *v* ≥ 547 days) were analyzed with EFS tree regression.[17-19,21]

Methods to Reduce the Number of Prognostic Variables

The 35 potentially prognostic factors were consolidated to 13 for analysis. Only factors where data were available for more than 5% of the 8,800 patients were included. Because Shimada and INPC are similar, histology data were consolidated into a single system. INPC was the default, but Shimada diagnosis, grade of tumor differentiation, or MKI were used if the corresponding INPC value was unknown. INSS was selected as the staging criteria. In situations where INSS and Evans definitions were the same (ie, INSS stage 1 = Evans stage I), Evans stage was used if INSS was unknown. Unbalanced 11q LOH and 11q aberrations data were combined into a single variable: "11q aberration." Similarly, 1p LOH and 1p aberrations were combined into the variable "1p aberration." 17q gain data were available for less than 5% of the patients, so 17q was not further analyzed. Using univariate analyses, six primary tumor sites were consolidated into one binary variable (adrenal *v* nonadrenal), as were eight metastatic sites (presence of metastases *v* no metastases).

The INRG database included a crude categoric variable for initial treatment. However, no statistical adjustment for treatment was performed. Because treatment has been assigned for many years using prognostic factors, treatment group is confounded with the prognostic factors,

Table 2. Clinical Characteristics of the International Neuroblastoma Risk Group Analytic Cohort (N = 8,800)

Factor	EFS		Patients		5-Year EFS (%)			5-Year OS (%)		
	Hazard Ratio	95% CI	No.	%	Rate	SE	Log-Rank *P*	Rate	SE	Log-Rank *P*
Age, days										
< 365	3.6	3.3 to 4.0	3,734	42	84	1		91	1	
≥ 365			5,066	58	49	1	< .0001	55	1	< .0001
Age, days										
< 547	3.7	3.4 to 4.0	4,773	54	82	1		88	1	
≥ 547			4,027	46	42	1	< .0001	49	1	< .0001
Year of enrollment/diagnosis										
≥ 1996	1.4	1.2 to 1.4	4,493	51	69	1		76	1	
< 1996			4,307	49	59	1	< .0001	66	1	< .0001
Initial treatment										
Observation, surgery, or standard chemotherapy	4.1	3.8 to 4.4	4,515	68	79	1		86	1	
Intensive multimodality			2,170	32	34	1	< .0001	41	1	< .0001
INSS stage										
1, 2, 3, 4S	5.2	4.8 to 5.7	5,131	60	83	1		91	1	
4			3,425	40	35	1	< .0001	42	1	< .0001
Evans stage										
I, II, III, IVS	6.6	5.8 to 7.6	2,022	63	86	1		91	1	
IV			1,177	37	31	2	< .0001	36	2	< .0001
Serum ferritin (ng/mL)										
< 92	3.6	3.2 to 4.0	2,170	50	81	1		87	1	
≥ 92			2,175	50	46	1	< .0001	52	1	< .0001
LDH (U/L)										
< 587	2.4	2.2 to 2.7	2,586	50	77	1		85	1	
≥ 587			2,592	50	53	1	< .0001	58	1	< .0001
Histologic classification (INPC, Shimada if INPC missing)										
Favorable	6.6	5.7 to 7.5	2,724	64	89	1		95	1	
Unfavorable			1,536	36	40	2	< .0001	49	2	< .0001
Diagnostic category (INPC, Shimada if INPC missing)										
1 = NB, stroma-poor			3,657	90	64	1		71 ±	1	
2 = GNB, intermixed, stroma-rich			144	3	95	3		96	2	
3 = GNB, well diff., stroma-rich			38	1	80	9	< .0001	79	9	< .0001
4 = GNB, nodular (composite)			232	6	53	5		68	5	
(2 and 3) *v* (1 and 4)	4.7	2.8 to 7.8								
Grade of NB differentiation (INPC, Shimada if INPC missing)										
Differentiating	2.5	2.0 to 3.3	518	16	83	2		89	2	
Undifferentiated			2,759	84	63	1	< .0001	72	1	< .0001
MKI (INPC, Shimada if INPC missing)										
Low, intermediate	3.2	2.8 to 3.8	2,690	87	74	1		82	1	
High			393	13	37	4	< .0001	44	4	< .0001

NOTE. Hazard ratios denote increased risk of an event for the second row within a given category compared with the first row.
Abbreviations: INPC, International Neuroblastoma Pathology Classification; EFS, event-free survival; OS, overall survival; NB, Neuroblastoma; GNB, Ganglioneuroblastoma; MKI, Mitosis Karyorrhexis Index.

resulting in reduced ability to detect the effect of a prognostic factor if adjustment for treatment is made. Therefore, instead of statistically adjusting for treatment, post hoc interpretation and the delineation of pretreatment groups were based on knowledge of how groups of patients had been treated historically.

Methods to Identify Prognostically Distinct Subgroups

The methodologic goal was to identify subgroups that were both statistically and clinically significantly different from one another, such that resulting subgroups of patients would be as homogenous as possible in terms of biology and outcome. The prognostic significance of the 13 factors was tested in the overall cohort, and the one with the highest χ^2 value was retained to create two subgroups or "nodes." The remaining factors were then tested within each node. This process was repeated within each node until the sample size was too small to proceed, or until no further statistically significant variables were found. In some nodes, the number of patients with known values for all factors being tested became too small for multivariate analysis. In this situation, factors were tested in a pairwise fashion in the model. The winner for each comparison was recorded, and the factor with the most "wins" was selected to create the next branch. Although not optimal, this approach was deemed necessary to overcome the problem of missing data.

RESULTS

INRG Cohort

The proportion of patients in the INRG analytic cohort of 8,800 was fairly evenly distributed between North America (48%) and Europe (47%), plus patients from Japan (5%) (Table 1). Tables 2 and 3 and Appendix Table A2 (online only) summarize the clinical and biologic characteristics of the cohort. The overall 5-year EFS and OS rates were 63% ± 1% and 70% ± 1%, respectively, with median follow-up of 5.2 years in 5,819 patients alive without an event. The assumption of proportional hazards was not violated for either EFS or OS except for 17q gain and skin metastases which were of no consequence because they were not among the final 13 risk factors evaluated. Also, at each split of the survival regression tree, the assumption of proportional hazards was upheld for EFS and OS.

Stage

The EFS tree regression analysis was performed on the basis of INSS stage. As described in Monclair et al,[14] an analysis of SIOPEN data (n = 474) found both INSS stage and INRGSS highly prognostic of EFS, and validated the German study.[22] This retrospective analysis supports the translation of EFS tree regression results (in terms of INSS stage) into the INRG Classification system (in terms of INRGSS): INSS 1 → INRGSS L1; INSS 2, 3 → INRGSS L2; INSS 4 → INRGSS M; and INSS 4S → INRGSS MS.

Age

The predictive ability of age was shown to be continuous in nature in the analysis of COG patients (n = 3,666) and within the balance of INRG patients. As recognized by the Task Force, it would be optimal to evaluate age as a continuous variable for risk stratification because outcome gradually worsens with increasing age. However, using two age groups was considered more feasible for these analyses. The analysis of non-COG patients within the INRG cohort confirmed the findings of London et al,[20] with support for an optimal "cutoff" between 15 and 19 months. For practical reasons, the Task Force's consensus was an age cutoff of 18 months (547 days) for the INRG classification system. Although the cutoff could be anywhere in this range, once selected, this age cutoff must be consistently applied as the exact number of days. However, for patients with diploid, stage M, *MYCN* nonamplified tumors, the Task Force elected to use the more conservative age cutoff of 12 months (365 days).

LDH and Ferritin

The median value to dichotomize LDH was 587 U/L, and for ferritin was 92 ng/mL.

Tumor Histology

In the EFS tree analysis testing histologic category, grade of tumor differentiation, MKI, and age, we found evidence of independent prognostic ability of each factor. This was tested in half the patients

Table 3. Genetic Characteristics of the International Neuroblastoma Risk Group Analytic Cohort (N = 8,800)

Factor	EFS		Patients		5-Year EFS (%)			5-Year OS (%)		
	Hazard Ratio	95% CI	No.	%	Rate	SE	Log-Rank *P*	Rate	SE	Log-Rank *P*
MYCN status										
Not amplified	4.1	3.8 to 4.5	5,947	84	74	1		82	1	
Amplified			1,155	16	29	2	< .0001	34	2	< .0001
Ploidy										
> 1 (hyperdiploid)	2.3	2.0 to 2.6	2,611	71	76	1		82	1	
≤ 1 (diploid, hypodiploid)			1,086	29	55	2	< .0001	60	2	< .0001
11q										
Normal	2.3	1.9 to 2.9	844	79	68	3		79	2	
Aberration			220	21	35	5	< .0001	57	5	< .0001
1p										
Normal	3.2	2.8 to 3.8	1,659	77	74	2		83	1	
Aberration			493	23	38	3	< .0001	48	3	< .0001
17q gain										
No gain	1.7	1.3 to 2.3	187	52	63	4		74	4	
Gain			175	48	41	5	.0006	55	5	.0009

NOTE. Hazard ratios denote increased risk of an event for the second row within a given category compared with the first row.
Abbreviations: INPC, International Neuroblastoma Pathology Classification; EFS, event-free survival; OS, overall survival; LOH, loss of heterozygosity.

(randomly selected) and the results confirmed in the other half. Excellent outcome was seen for patients with GN-maturing and GNB-intermixed tumors. For patients with GNB-nodular and NB tumors, age (younger than 18 $v \geq$ 18 months) was the most statistically significant factor. Within patients younger than 18 months with GNB-nodular and NB tumors, high MKI was associated with significantly lower EFS than low/intermediate MKI. Within patients 18 months of age or older with GNB-nodular and NB tumors, undifferentiated or poorly differentiated grade was associated with significantly lower EFS than differentiating grade. To prevent confounding of the effect of age, we analyzed histologic features (histologic category, MKI, and grade of differentiation) in lieu of the INPC.

Primary Site and Metastases

Adrenal primary tumor site had statistically significantly worse EFS than all other primary sites combined. For metastases, the most significant split was the presence versus absence of metastases.

EFS Tree Regression Analyses

The presence of classic metastases was the most significant prognostic factor in the EFS tree regression analysis of the overall cohort. The EFS and OS of INSS non–stage 4 (including 4S) patients were 83% ± 1% and 91% ± 1%, respectively, and 35% ± 1% and 42% ± 1% for children with stage 4 disease (Fig 1A).

Subclassification of Non–Stage 4 Patients

Within the patients with non–stage 4 disease (INSS stage 1, 2, 3, and 4S), histologic category (ie, GN-maturing and GNB-intermixed versus GNB-nodular and NB) was the most powerful prognostic factor (EFS: 97% ± 2% and 83% ±1, respectively). Of the 162 non–stage 4 INSS stage patients with GN-maturing or GNB-intermixed, only two had *MYCN* amplification, and both were alive without event at the time of this analysis. Because these tumors have a distinct clinical nature, the cohort of GN-maturing and GNB-intermixed was regarded as a terminal node. Within non–stage 4 GNB-nodular and NB patients, *MYCN* status was the most powerful prognostic factor (Fig 1A). Patients with *MYCN*-nonamplified tumors had EFS of 87% ± 1% and OS of 95% ± 1%, and 46% ± 4% and 53% ± 4% for patients with *MYCN*-amplified tumors. Within the *MYCN*-nonamplified cohort, patients with stage 1 disease had significantly better outcome than those with stages 2,3,4S (EFS: 93% ± 1% v 82% ± 1%; OS: 98% ± 1% v 92% ± 1%; Fig 1B). EFS for stage 1 patients with normal chromosome 1p was statistically better compared with those with 1p aberration (94% ± 2% v 78% ± 10%). However, OS was excellent regardless of the status of chromosome 1p (normal 1p: 99% ± 1%; 1p aberration: 100%). Therefore, 1p status was not included as a criterion in the INRG classification system and stage 1 was a terminal node.

Although survival rates for patients with stages 2, 3 disease (EFS: 82% ± 1%; OS: 92% ± 1%) and stage 4S patients (EFS: 82% ± 2%; OS: 91% ± 2%) were not statistically significantly different, treatment intensity differed. Because there are different treatment approaches in this group (4S disease is commonly observed whereas treatment for stage 2 and 3 tumors is surgery with or without chemotherapy), stage 2, 3 patients were split from stage 4S patients for further survival tree analyses. Within stage 2, 3 patients, those younger than 18 months old had statistically higher EFS than those 18 months of age or older (88% ± 1% v 69% ± 3%). In *MYCN* nonamplified stage 2, 3 patients younger than 18 months old, 11q aberration was the most highly prognostic of the biomarkers evaluated, with lower EFS (60% ± 20%) and OS (84% ± 14%) than normal 11q (EFS: 83% ± 5%; OS: 98% ± 2%; Fig 1B).

In patients with *MYCN*-nonamplified stage 2, 3 tumors who were 18 months of age or older, 11q aberration was the most statistically significant factor, but grade of tumor differentiation was also highly significant and identified additional poor-prognosis patients without evidence of 11q aberration (Fig 1B). The Task Force therefore decided to combine 11q aberration with grade into a single prognostic factor, categorizing patients who had either 11q aberration and/or undifferentiated (or poorly differentiated) histology (EFS: 61% ± 11%; OS: 73% ± 11%) versus those who did not have either one of the poor-outcome features (EFS: 80% ± 16%; OS: 100%).

Within the patients with *MYCN*-nonamplified stage 4S tumors, 11q aberration was the most highly prognostic factor (11q aberration—EFS: 38% ± 30%, OS: 63% ± 38%; normal 11q—EFS: 87% ± 7%, OS: 97% ± 4%). The number of patients within this cohort is small, and additional evaluation will be needed to further evaluate the impact of 11q aberration in this subset of patients.

MYCN-amplification was detected in only 8% of patients with stage 1 to stage 4S disease (Fig 1C). Although EFS rates for stage 1 patients were not statistically significant different from those of stage 2, 3, and 4S patients, less intensive treatment was administered to patients with *MYCN*-amplified stage 1 tumors. Because of the difference in treatment strategies, further survival tree analyses were performed separately in stage 1 patients versus stage 2, 3, and 4S patients. LDH was most highly prognostic for patients with *MYCN*-amplified stage 1 tumors (< 587 U/L—EFS: 55% ± 15%, OS: 85% ± 10% $v \geq$ 587 U/L—EFS: 40% ± 22%, OS: 58% ± 22%) and within the stage 2, 3, and 4S subset (< 587 U/L—EFS: 67% ± 9%, OS: 72% ± 8% $v \geq$ 587 U/L—EFS: 43% ± 5%, OS: 47% ± 5%). LDH is known to reflect tumor burden, and of the 169 *MYCN*-amplified stage 2, 3, and 4S patients with elevated LDH, 72% were stage 3. In view of the small number of patients in this cohort and the nonspecific nature of LDH, the Task Force decided not to include LDH in the classification system.

Subclassification of Patients With Stage 4 Disease

Age was the most powerful prognostic variable within 3,425 patients with stage 4 disease (Fig 1D). Children younger than 18 months had EFS and OS rates of 63% ± 2% and 68% ± 2%, respectively. Children 18 months of age or older had EFS and OS rates of 23% ± 1% and 31% ± 1%, respectively. Although serum ferritin ($< v \geq$ 92 ng/mL) was shown to be prognostic in the cohort of patients age 18 months and older by the EFS tree regression, outcome was poor in both cohorts, with EFS rates of 43% ± 4% and 20% ± 2%, respectively. Further statistically significant splits for *MYCN* status were identified within both ferritin cohorts ($< v \geq$ 92 ng/mL), but EFS and OS were poor in all of these subsets. Thus, serum ferritin did not add clinically relevant information in this cohort of patients with poor prognosis and was not included in the INRG classification schema. Within patients younger than 18 months with stage 4 disease, *MYCN* status was the most powerful prognostic factor. EFS was 83% ± 2% for children younger than 18 months with stage 4 disease lacking *MYCN* amplification versus 26% ± 4% for those with *MYCN*-amplified tumors. Within *MYCN*-nonamplified patients younger than 18 months with stage 4 disease, ploidy had prognostic significance. Patients with a DNA index greater than 1.0 had EFS of 85% ±

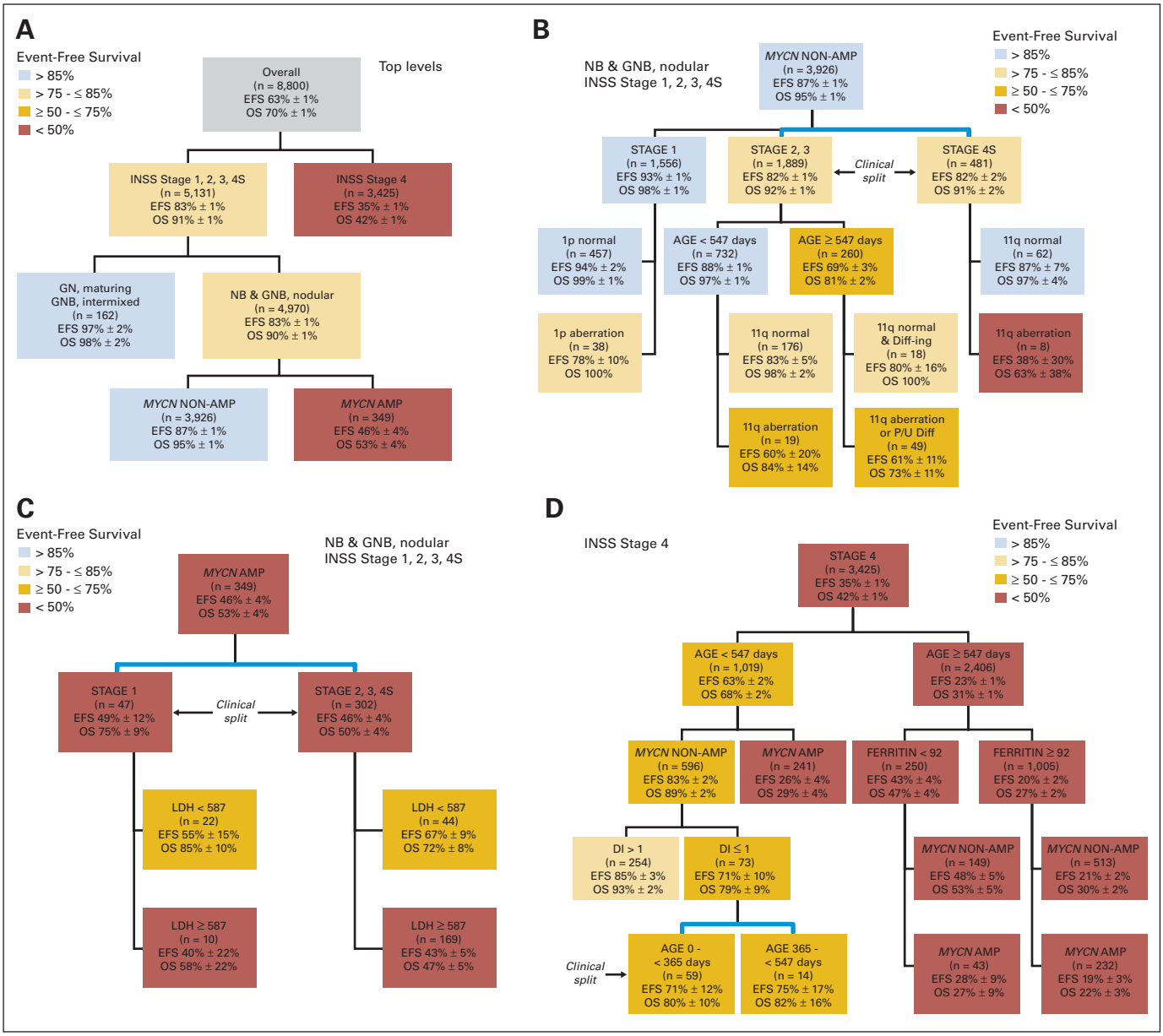

Fig 1. EFS tree regression analysis of INRG analytic cohort. Unless otherwise noted, a split or branch occurs for the most highly statistically significant factor as identified using a Cox proportional hazards regression model. (A) Top levels of the overall tree. (B) Subtree for NB and GNB-nodular, non–stage 4 *MYCN* NON-AMP patients. The split of stage 2, 3 from stage 4S patients was a clinical decision and not the result of statistical significance. (C) Subtree for NB and GNB-nodular, non–stage 4 *MYCN* AMP patients. The split of stage 1 from stage 2, 3, 4S patients was a clinical decision and not the result of statistical significance. (D) Subtree for INSS stage 4 patients. EFS, event-free survival; OS, overall survival; DI, DNA index; AMP, amplified; NON-AMP, nonamplified; INRG, International Neuroblastoma Risk Group; NB, neuroblastoma; GNB, ganglioneuroblastoma; GN, ganglioneuroma; INSS, International Neuroblastoma Staging System; LDH, lactate dehydrogenase.

3%, whereas EFS was 71% ± 10% for DNA index 1.0 or less. Although EFS for patients with stage 4 tumors younger than 12 months were not statistically significantly different from those 12 months or older to younger than 18 months, substantially higher-intensity treatment regimens were administered to patients who were 12 to younger than 18 months of age. On the basis of ploidy data and the excellent outcome of young children with stage 4 disease with favorable biologic features, several cooperative groups have developed clinical trials testing reduction in treatment for this cohort. In patients with diploid, *MYCN*-nonamplified stage 4 tumors, clinical justification was used to split patients younger than 12 months from 12 months and older to younger than 18 months of age, as the international consensus is that the intensity of therapy should not be reduced in this later group.

INRG Classification System

In summary, the consensus INRG classification schema includes the criteria INRG stage, age, histologic category, grade of tumor differentiation, *MYCN* status, presence/absence of 11q aberrations, and tumor cell ploidy. Sixteen statistically and/or clinically different pretreatment groups of patients (lettered A through R) were identified using these criteria (Fig 2). The proportion of patients grouped using EFS cut points for 5-year EFS of more than

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

Fig 2. International Neuroblastoma Risk Group (INRG) Consensus Pretreatment Classification schema. Pretreatment risk group H has two entries. 12 months = 365 days; 18 months = 547 days; blank field = "any"; diploid (DNA index ≤ 1.0); hyperdiploid (DNA index > 1.0 and includes near-triploid and near-tetraploid tumors); very low risk (5-year EFS > 85%); low risk (5-year EFS > 75% to ≤ 85%); intermediate risk (5-year EFS ≥ 50% to ≤ 75%); high risk (5-year EFS < 50%). GN, ganglioneuroma; GNB, ganglioneuroblastoma; Amp, amplified; NA, not amplified; L1, localized tumor confined to one body compartment and with absence of image-defined risk factors (IDRFs); L2, locoregional tumor with presence of one or more IDRFs; M, distant metastatic disease (except stage MS); MS, metastatic disease confined to skin, liver and/or bone marrow in children < 18 months of age (for staging details see text and Monclair et al[14]); EFS, event-free survival.

85%, more than 75% to ≤ 85%, ≥ 50% to ≤ 75%, or less than 50%, were 28.2%, 26.8%, 9.0%, and 36.1%, respectively (Table 4). The categories were designated as very low (A, B, C), low (D, E, F), intermediate (G, H, I, J), or high (K, N, O, P, Q, R) pretreatment risk subsets.

DISCUSSION

In recent years, the need to develop an international consensus for pretreatment risk stratification for children with NB has become increasingly apparent. To achieve this goal, an international task force established the INRG classification system. The prognostic effect of 13 variables in an 8,800-patient cohort was analyzed, with EFS, not OS, as the primary end point for the reasons identified earlier in this article. The INRG classification system includes the seven factors that were highly statistically significant and also considered clinically relevant. Similar to other series, patients with widely disseminated stage 4 disease had significantly worse outcome than those with locoregional disease or stage 4S NB.[9,23] As described in the article by Monclair et al,[14] a new pretreatment staging system was designed for the INRG classification system. In the INRGSS, extent of locoregional disease is determined by the absence or presence of image-defined risk factors (L1 and L2, respectively). Stage M will be used for disseminated disease, analogous to INSS stage 4. Similar to INSS stage 4S tumors, metastases are limited to skin, liver, and bone marrow without cortical bone involvement in INRGSS MS disease. However, the definition of MS has been expanded to include toddlers age 12 to younger than 18 months and large "unresectable" primary tumors (L1 or L2). As discussed in the companion article by Monclair et al,[14] the inclusion of L2 tumors is based on the excellent outcome of all 30 children enrolled on the SIOPEN 99.2 trial who met the criteria for INSS stage 4S disease and, in addition, had midline infiltration of the primary tumor, after treatment with a few cycles of chemotherapy or observation alone (B. De Bernardi, personal communication, February 2008). Although there is some concordance of patients between the INRGSS and the INSS staging systems, the two systems differ in the sense that the INSS staging system contains inherent confounding of surgical treatment versus extent of tumor, whereas INRGSS removes that confounding because it is assigned before surgery. The important similarity of the two systems is that INRGSS retains the prognostic value of staging that has been well documented for INSS staging, with statistically significantly higher EFS for L1 compared with L2. There is statistical justification for use of INRG staging for assigning patients to pretreatment groups, although prospective evaluation of the risk grouping based on the INRGSS staging system will be mandatory.

Table 4. Proportion of Patients When Arbitrary EFS Cut Points Are Applied to Cluster Rows of the International Neuroblastoma Risk Group Consensus Stratification (for illustrative purposes)

Pretreatment Risk Group	%	
	5-Year EFS	Proportion of Patients
Very low	> 85	28.2
Low	> 75 to ≤ 85	26.8
Intermediate	≥ 50 to ≤ 75	9.0
High	< 50	36.1

Abbreviation: EFS, event-free survival.

The analysis of the INRG data confirmed that the predictive ability of age is continuous in nature for NB. By convention, virtually all cooperative groups have used the 12-month cutoff to determine risk.[1] Similar to a previous study of COG patients,[20] our analysis of the INRG cohort indicated that the optimal age cutoff is between 15 and 19 months. Children age 12 to younger than 18 months with hyperdiploid stage 4 disease who lack *MYCN* amplification have excellent outcome when treated with intensive therapy on high-risk clinical trials.[24,25] These results suggest that therapy may be reduced safely in a subset of young children with stage 4 disease, and clinical trials testing this question have recently been developed. An age cutoff of 18 months (547 days) was, therefore, selected for the INRG classification system for all children except those with diploid, stage M tumors

without amplification of *MYCN* for whom the more conservative, 12-month cutoff will be maintained.

Tumor histology is another well established prognostic variable in NB.[12,13] To avoid confounding of age and INPC, we tested histologic category, MKI, grade of tumor differentiation, and age in the EFS tree regression analyses in lieu of INPC. We found that histologic category and tumor differentiation were statistically significantly associated with EFS. Consistent with the inferior prognosis that has been reported in patients with Shimada unfavorable histology INSS stage 3 tumors that lack *MYCN* amplification,[26] we found that outcome was worse for patients age 18 months and older with *MYCN*-nonamplified stage 2, 3 poorly differentiated or undifferentiated tumors compared with those with differentiating tumors.

To accurately stratify patients with locoregional tumors using the INRG classification system, sufficient samples of tumor tissue will be required for genetic/expression studies and for histologic category determination. In addition, there is a need for wide-scale education of pediatric pathologists to ensure that different histopathologic grades are uniformly and reproducibly recognized. The challenges of distinguishing GNB-intermixed from GNB-nodular are significant when the entire tumor is not resected. Surgical biopsy needs to be guided by the radiological appearances of the tumor, with any heterogeneous areas targeted. Adequate tissue samples are mandatory to evaluate histologic grade of differentiation in locoregional NBs that lack *MYCN* amplification in children 18 months of age or older. In most cases, multiple "true-cut" cores will yield sufficient tissue to determine tumor grade of differentiation, but fine-needle aspirates are not likely to provide adequate quantities of tissue for histologic analysis and are not appropriate. In metastatic tumors, fine-needle aspirates may provide adequate information for genetic analysis.

A number of genetic aberrations have been identified in NB tumors that are strongly associated with outcome. Our analysis confirmed the unfavorable prognostic significance of *MYCN* amplification, and in the INRG classification system, *MYCN* status is used to stratify patients into different pretreatment risk groups. We also found that 11q aberration was associated with worse outcome in patients with L2 or MS tumors that lack *MYCN* amplification. Similar to previous studies,[25,27-29] the prognostic value of DNA ploidy was demonstrated in children younger than 18 months of age with stage 4 disease and normal *MYCN* copy number. Recommendations regarding standardized methods for evaluating *MYCN* copy number, tumor cell ploidy, and other genetic aberrations in NB tumors will be reported in a future article.

Recent studies suggest that low-risk tumors may be best defined by the absence of *MYCN* gene amplification and any structural genetic abnormalities, (including either 11q and/or 1p aberrations and/or 17q gain).[30,31] The Task Force agreed that it would be optimal to evaluate genetic aberrations in NB tumors using genome-wide methods. However, because this type of analysis is not routinely performed by the large cooperative groups, incorporation of more global genetic data in the current INRG was not considered feasible at the present time. The immediate challenges are (1) to ensure that adequate tumor material is available for prospective "comprehensive" genetic investigations on every patient and (2) to identify technologies that are not cost prohibitive and will yield rapid and reproducible results. It is anticipated that the future INRG classification system will rely on the genetic profile of NB tumors, rather than the presence or absence of individual genetic abnormalities.

A limitation of this analysis is that there was no statistical adjustment for treatment, and therefore, patients in any of the 16 lettered rows may have received very different therapy. It is intended to extend the INRG database prospectively, and it will be critical to collect data on details of therapy.

In conclusion, the INRG classification system will ensure that children diagnosed with NB in any country are stratified into homogenous pretreatment groups. We strongly recommend that cooperative groups begin using this risk schema now. The very low-, low-, intermediate-, and high-risk categories were defined according to EFS cutoffs. These four categories were included in the classification schema to assist treating physicians in evaluating the prognostic impact of the combination of factors in each of the 16 lettered rows in the INRG classification system. Although these risk categories could have been defined differently, we selected EFS cutoff values that are commonly used for treatment stratification at the present time. For example, at most centers around the world, patients with features that are associated with estimated EFS rates of less than 50% are treated with intensive, multimodality strategies, whereas those predicted to have more than 85% EFS receive minimal therapy. We anticipate that risk group stratification will be further refined as treatment for high-risk disease improves and genome-wide DNA and expression analysis of tumors becomes more routine. It must be emphasized that we are not recommending that treatment be assigned according to these four broad risk-group categories. Rather, the key to reaping the benefits of this system will be the assignment of patients in one of the 16 pretreatment lettered designations in the INRG classification system to a single treatment group without splitting that row in different treatment subgroups. We anticipate that eligibility criteria for treatment protocols will likely include several of the 16 INRG pretreatment designations, and that the combinations of the 16 pretreatment groups that will be included in clinical trials studies conducted by each of the cooperative groups may be different. Therefore, it will be critical to individually report the outcome of patients assigned to each of the 16 pretreatment designations. This approach will greatly facilitate the comparison of risk-based clinical trials conducted in different regions of the world, provide a platform to ask randomized surgical questions, and lead to the development of international collaborative studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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