neuroblastoma and are not used for conventional chemotherapy prior to HDC [4, 14, 15]. This HDC regimen consisted of 2 cycles of administration of thiotepa and melphalan with a 1-week interval: this interval facilitated combination therapy at the maximum tolerated dose of a single agent without severe complications. The major adverse effect of this regimen is gastrointestinal mucositis and narcotic drugs are frequently required. However, life-threatening complications such as veno-occlusive disease and renal insufficiency are not observed.

In this case series, the effect of chemotherapy was pathologically validated in primary tumors. No residual tumor cells were observed except in one patient. Scattered viable tumor cells were detected in other resected tumor specimens, though the number of these cells was small and they were embedded in the connective tissue. Similar findings were observed in regional lymph nodes. These scattered cells are tightly embedded in fibrous tissue and might possibly proliferate, contributing to relapse. Thus, it was shown that even HDC rarely totally eradicates tumor cells of the primary tumors.

Concerning local therapy, gross total resection was eventually performed after completion of all systemic chemotherapies. No conclusion has been drawn concerning the role of gross total resection. With our treatment strategy, systemic disease seemed to be controlled sufficiently, and under such conditions the significance of the local therapy may increase. Radiation therapy was not performed in this case series and local recurrence was observed in 2 patients without recurrence in other sites. This might suggest that radiotherapy is beneficial to selected patients who undergo gross total resection. To identify these patients, histopathological evaluation of chemotherapy outcome may provide useful information, in addition to the extent of local disease at initial diagnosis and the extent of surgery. Although the relationship between histopathological findings and clinical outcome was unclear in this series, recruitment of additional patients may assist in drawing some conclusions.

This novel treatment strategy consisting of the postponement of local surgery until the end of chemotherapy combined with intensive induction and consolidation chemotherapy seems feasible. A multicenter phase II study is being planned in Japan to confirm the utility of this strategy.

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SPECIAL ARTICLE

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

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A B S T R A C T

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

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.

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.

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

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("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 Hazard Ratio	EFS 95% CI	Patients No.	Patients %	5-Year EFS (%) Rate	5-Year EFS (%) SE	5-Year EFS (%) Log-Rank P	5-Year OS (%) Rate	5-Year OS (%) SE	5-Year OS (%) 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 Hazard Ratio	EFS 95% CI	Patients No.	Patients %	5-Year EFS (%) Rate	5-Year EFS (%) SE	5-Year EFS (%) Log-Rank P	5-Year OS (%) Rate	5-Year OS (%) SE	5-Year OS (%) 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% $\pm$ 1% and 91% $\pm$ 1%, respectively, and 35% $\pm$ 1% and 42% $\pm$ 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% $\pm$ 2% and 83% $\pm$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% $\pm$ 1% and OS of 95% $\pm$ 1%, and 46% $\pm$ 4% and 53% $\pm$ 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% $\pm$ 1% v 82% $\pm$ 1%; OS: 98% $\pm$ 1% v 92% $\pm$ 1%; Fig 1B). EFS for stage 1 patients with normal chromosome 1p was statistically better compared with those with 1p aberration (94% $\pm$ 2% v 78% $\pm$ 10%). However, OS was excellent regardless of the status of chromosome 1p (normal 1p: 99% $\pm$ 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% $\pm$ 1%; OS: 92% $\pm$ 1%) and stage 4S patients (EFS: 82% $\pm$ 2%; OS: 91% $\pm$ 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% $\pm$ 1% v 69% $\pm$ 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% $\pm$ 20%) and OS (84% $\pm$ 14%) than normal 11q (EFS: 83% $\pm$ 5%; OS: 98% $\pm$ 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% $\pm$ 11%; OS: 73% $\pm$ 11%) versus those who did not have either one of the poor-outcome features (EFS: 80% $\pm$ 16%; OS: 100%).

Within the patients with MYCN-nonamplified stage 4S tumors, 11q aberration was the most highly prognostic factor (11q aberration—EFS: 38% $\pm$ 30%, OS: 63% $\pm$ 38%; normal 11q—EFS: 87% $\pm$ 7%, OS: 97% $\pm$ 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% $\pm$ 15%, OS: 85% $\pm$ 10% $v \geq$ 587 U/L—EFS: 40% $\pm$ 22%, OS: 58% $\pm$ 22%) and within the stage 2, 3, and 4S subset ($<$ 587 U/L—EFS: 67% $\pm$ 9%, OS: 72% $\pm$ 8% $v \geq$ 587 U/L—EFS: 43% $\pm$ 5%, OS: 47% $\pm$ 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% $\pm$ 2% and 68% $\pm$ 2%, respectively. Children 18 months of age or older had EFS and OS rates of 23% $\pm$ 1% and 31% $\pm$ 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% $\pm$ 4% and 20% $\pm$ 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% $\pm$ 2% for children younger than 18 months with stage 4 disease lacking MYCN amplification versus 26% $\pm$ 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% $\pm$
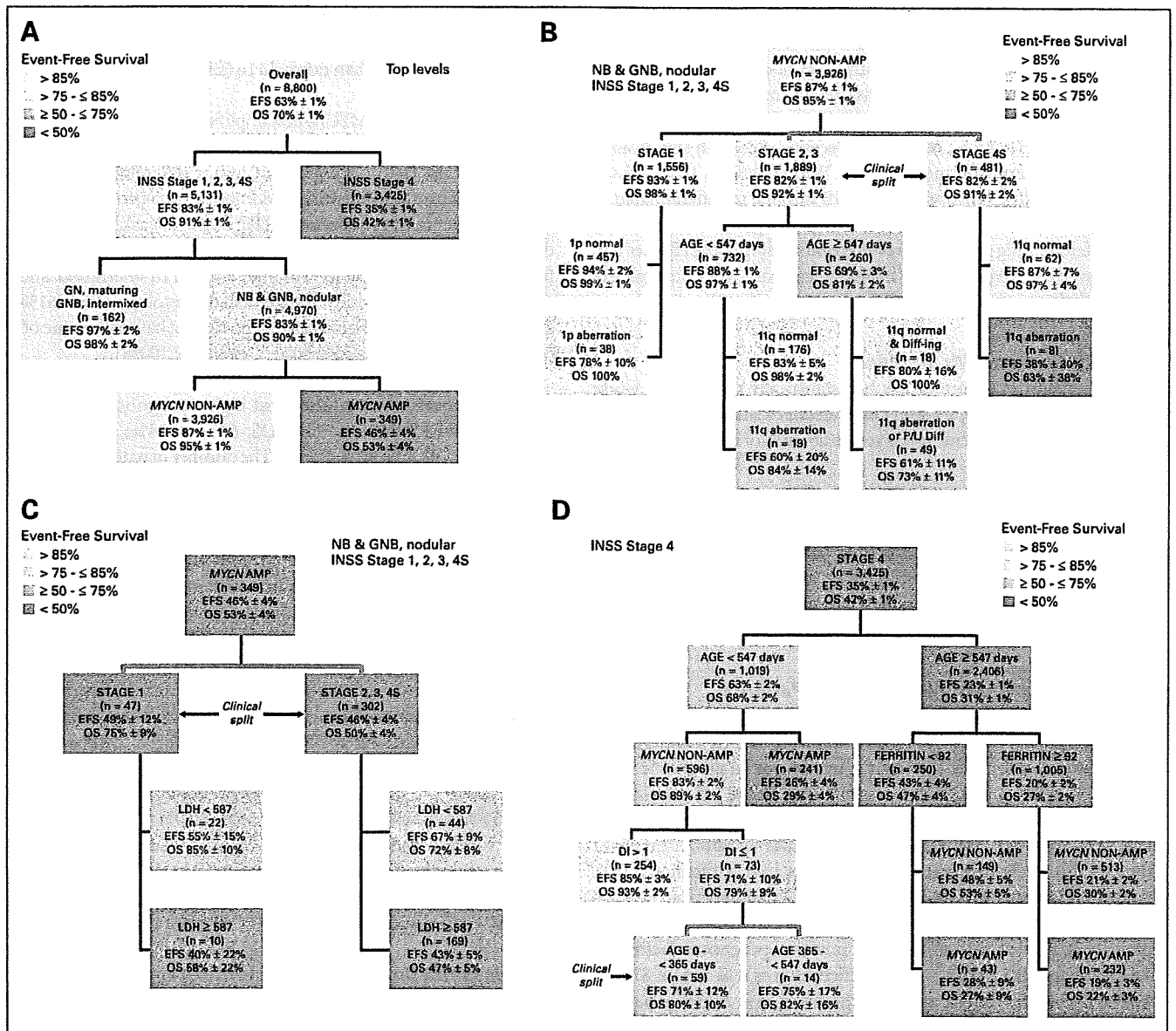
Fig 1. EFS tree regression analysis of INRG analytic cohort. Unless otherwise noted, a split or branch occurs for the most highly statistically significant factor as identified using a Cox proportional hazards regression model. (A) Top levels of the overall tree. (B) Subtree for NB and GNB-nodular, non–stage 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

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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
				NA	Yes		G Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
				NA	Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			H Intermediate
				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
				NA	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 dis-

ease, 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.

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

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.

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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.

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S P E C I A L A R T I C L E

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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

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A B S T R A C T

Purpose
The International Neuroblastoma Risk Group (INRG) classification system was developed to establish a consensus approach for pretreatment risk stratification. Because the International Neuroblastoma Staging System (INSS) is a postsurgical staging system, a new clinical staging system was required for the INRG pretreatment risk classification system.

Methods
To stage patients before any treatment, the INRG Task Force, consisting of neuroblastoma experts from Australia/New Zealand, China, Europe, Japan, and North America, developed a new INRG staging system (INRGSS) based on clinical criteria and image-defined risk factors (IDRFs). To investigate the impact of IDRFs on outcome, survival analyses were performed on 661 European patients with INSS stages 1, 2, or 3 disease for whom IDRFs were known.

Results
In the INGRSS, locoregional tumors are staged L1 or L2 based on the absence or presence of one or more of 20 IDRFs, respectively. Metastatic tumors are defined as stage M, except for stage MS, in which metastases are confined to the skin, liver, and/or bone marrow in children younger than 18 months of age. Within the 661-patient cohort, IDRFs were present (ie, stage L2) in 21% of patients with stage 1, 45% of patients with stage 2, and 94% of patients with stage 3 disease. Patients with INRGSS stage L2 disease had significantly lower 5-year event-free survival than those with INRGSS stage L1 disease (78% ± 4% v 90% ± 3%; P = .0010).

Conclusion
Use of the new staging (INRGSS) and risk classification (INRG) of neuroblastoma will greatly facilitate the comparison of risk-based clinical trials conducted in different regions of the world.

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INTRODUCTION

The International Neuroblastoma Risk Group (INRG) classification system was developed to facilitate the comparison of risk-based clinical trials conducted in different regions of the world by defining homogenous pretreatment patient cohorts. As described in the companion article by Cohn and Pearson et al,[1] the INRG classification system was based on survival tree regression analyses of data collected on 8,800 patients. Because the International Neuroblastoma Staging System (INSS) stage of locoregional tumors is based on the degree of surgical resection, this staging system is not suitable for the INRG pretreatment risk classification system. Therefore, the INRG Task Force[1] (see Appendix, online only, for participants) developed a new staging system

based on tumor imaging rather than extent of surgical resection.

The INSS was developed in 1986 after a meeting that was held to establish international consensus for a common staging system and response to therapy.[2,3] Although many countries around the world adopted the INSS, difficulties have been encountered. For example, according to the INSS, the same tumor can be either stage 1 or 3 depending on the extent of surgical excision, making direct comparison of clinical trials based on INSS stages difficult.[4] Furthermore, patients with localized disease who are observed because tumor regression is anticipated cannot be properly staged using INSS criteria.[5] An additional limitation of the INSS is that assessment of lymph node involvement is necessary for proper staging. However, lymph node sampling is subject to the

thoroughness of the individual surgeon, and the assessment of extra-regional lymph node involvement is difficult to apply uniformly.[2-4]

Image-Defined Risk Factors

Since 1994, the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) has classified locoregional tumors as resectable or unresectable dependent on the absence or presence of "surgical risk factors," but independent of INSS stage.[6] Surgical risk factors are features detected on imaging that make safe, total tumor excision impracticable at the time of diagnosis.[6,7] The SIOPEN principle for stratifying patients with locoregional tumors by imaging features was adopted by the INRG Task Force at a conference in Whistler, Canada, in 2005, and used in the design of the INRG Staging System (INRGSS). However, to avoid confusion with the INSS, the terms resectable and unresectable are not used in the INRG system.

The premise is that a staging system based on preoperative, diagnostic images will be more robust and reproducible than one based on operative findings and approach. Furthermore, because digital radiographs can be reviewed centrally, the images can be evaluated uniformly. As the surgical risk factors are based on radiographic images, it was decided to use the term "image-defined risk factors" (IDRFs), and consensus was reached for the IDRFs listed in Table 1. The IDRFs and the INRGSS are designed for use at the time of diagnosis, but they may also be used at reassessments during treatment. Although not needed for staging patients with disseminated disease, it is recommended that the IDRF status of the primary tumor be recorded in all patients (including patients with metastatic disease), so that the impact of IDRFs on surgical resection, surgical complications, and outcome can be prospectively evaluated in all patients.

Staging Investigations

Diagnosis. In the INRG classification system, the diagnosis of neuroblastoma will be made using INSS criteria.[3] A tissue diagnosis of neuroblastoma can be made by conventional histology (with or without immunohistology and increased urine or serum catecholamine or metabolites). A diagnosis can also be made if unequivocal tumor cells are seen in bone marrow samples and increased urine or serum catecholamines or metabolites are present.

Involvement of bone marrow. Bone marrow involvement should be assessed by two aspirates and two biopsies from bilateral sites according to the recommendations of the INSS.[3] Biopsy is not required for infants younger than 6 months of age. Bone marrow disease is determined by morphology on smears and biopsies. Biopsies should be complemented by immunohistochemical techniques. Immunocytologic and/or molecular techniques are also recommended to evaluate the presence of tumor cells in the bone marrow at the time of diagnosis, although the results of these assays are not used for staging (Beiske et al, manuscript in preparation on behalf of the INRG Task Force).

Required imaging studies. Computed tomography (CT) and/or magnetic resonance imaging (MRI) with three-dimensional measurements and of sufficient quality to address IDRFs is mandatory for imaging the primary tumor. The presence or absence of each individual IDRF should be evaluated and recorded (Table 1). When possible, metastatic sites should also be measured by CT and/or MRI, as this information may be needed to evaluate treatment response.

Iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy is mandatory, and it is recommended that the study is performed before tumor excision and according to the Standard Operating Procedure previously described.[8] One unequivocal MIBG-positive lesion at a distant site is sufficient to define metastatic disease. A single equivocal lesion on MIBG requires confirmation by another imaging modality (plain radiographs, and if negative, MRI) and/or biopsy.

Technetium-99 bone scintigraphy is required only exceptionally, but in all age groups, if MIBG positivity of the primary tumor cannot be confirmed (ie, the primary tumor is removed or is not MIBG-avid). An isolated bone uptake should be confirmed by another imaging modality and/or biopsy.

Staging Definitions

The short-version definitions of the four INRGSS stages are listed in Table 2.

Table 1. Image-Defined Risk Factors in Neuroblastic Tumors

Ipsilateral tumor extension within two body compartments
  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 of 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
Intraspinal 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, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but *not* considered IDRFs
  Multifocal primary tumors
  Pleural effusion, with or without malignant cells
  Ascites, with or without malignant cells

Abbreviation: IDRFs, image-defined risk factors.

Table 2. International Neuroblastoma Risk Group Staging System

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

NOTE. See text for detailed criteria. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.

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Stage L1 tumors are localized tumors that do not involve vital structures as defined by the list of IDRFs (Table 1). The tumor must be confined within one body compartment, neck, chest, abdomen, or pelvis. The isolated finding of intraspinal tumor extension that does not fulfill the criteria for an IDRF (Table 1) is consistent with stage L1.

Stage L2 tumors are locoregional tumors with one or more IDRFs. The tumor may be ipsilaterally continuous within body compartments (ie, a left-sided abdominal tumor with left-sided chest involvement should be considered stage L2). However, a clearly left-sided abdominal tumor with right-sided chest (or vice versa) involvement is defined as metastatic disease.

Stage M is defined as distant metastatic disease (ie, not contiguous with the primary tumor) except as defined for MS. Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumor with enlarged lower mediastinal nodes or a pelvic tumor with inguinal lymph node involvement is considered locoregional disease. Ascites and a pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumor.

Stage MS is metastatic disease in patients younger than 18 months (547 days) with metastases confined to skin, liver, and/or bone marrow. Bone marrow involvement should be limited to less than 10% of total nucleated cells on smears or biopsy. MIBG scintigraphy must be negative in bone and bone marrow. Provided there is MIBG uptake in the primary tumor, bone scans are not required. The primary tumor can be L1 or L2 and there is no restriction regarding crossing or infiltration of the midline.

Special Conditions

In addition to the IDRFs, and independent of the patient's INRGSS stage, three special conditions should be recorded: multifocal primary tumors, pleural effusion, and ascites (Table 1). Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined above (ie, stage L1, L2, M, or MS).

Relationship of INSS and INRG Stage

The INSS system is not in keeping with the INRG goal of a pretreatment classification system because the INSS assessment is made after the completion of the initial surgical procedure, and the INSS assessment is strongly dependent on the approach of the individual surgeon. To address these limitations, the INRGSS was developed. However, the survival tree regression analysis that forms the basis for the INRG classification system[1] could not be performed in terms of INRGSS because the sample size of patients with known surgical risk factors (analogous to the IDRFs that define INRGSS) in the INRG database[1] (< 850) was too small relative to patients with known INSS stage (> 8,500). Posthoc statistical analyses were therefore performed to determine whether it was reasonable to assign staging in terms of IDRFs of INRGSS instead of INSS, and if the prognostic ability of clinical stage was preserved if INRGSS was used. The analyses were restricted to patients with INSS stages 1, 2, or 3 disease because by definition, INSS stage 4 is equivalent to INRGSS M, and INSS stage 4S is very similar to INRGSS MS. Simon et al[9] have previously demonstrated the prognostic value of using IDRFs to define stage in a retrospective review of German neuroblastoma studies. The only other available data that can be used to validate the clinical significance of IDRFs and the INRGSS are those from SIOPEN in the INRG database.[1] The posthoc analysis of the SIOPEN data was performed in an attempt to validate the findings of the German study.

Statistical Considerations

Cross-tabulation of INRGSS and INSS was performed. The primary analytic end point for the predictive ability of INRGSS was event-free survival (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. Univariate analyses were performed to assess the prognostic ability of INRGSS. Kaplan-Meier curves were generated, and curves were compared using log-rank test, with P values less than .05 considered statistically significant.[10] EFS and overall survival (OS) values were reported at the 5-year time point ± SE (per Peto).[11] It was not the goal of this analysis to compare outcome for INRGSS versus INSS (as was done in the study of Simon et al[9]).

Table 3. Distribution of SIOPEN Patients by INRGSS Versus INSS

| INSS Stage	INRGSS L1		INRGSS L2		Total No.
	No.	%	No.	%	
1	239	79	64	21	303
2	81	55	66	45	147
3	12	6	199	94	211
Total	332	50	329	50	661

Abbreviations: SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group; INRGSS, International Neuroblastoma Risk Group Staging System; INSS, International Neuroblastoma Staging System.

RESULTS

A total of 661 patients with INSS stage 1, 2, and 3 disease from SIOPEN met INRG eligibility criteria and had known data for IDRFs. Twenty-one percent of patients with INSS stage 1, 45% of patients with INSS stage 2, and 94% of patients with INSS stage 3 disease had IDRFs (ie, in total, 50% of all localized tumors were INRGSS stage L2; Table 3). The remainder of patients who had no IDRFs were classified as having INRGSS stage L1 disease. Of the 661 SIOPEN patients, 474 patients had available outcome data. Both INSS and INRGSS were found to be highly prognostic. The EFS for patients with INRGSS stage L1 disease (90% ± 3%, n = 213) was statistically significantly higher than for stage L2 (78% ± 4%, n = 261; P = .0010; Fig 1). The OS for patients with INRGSS stage L1 disease (96% ± 2%) was also significantly higher than for patients with INRGSS stage L2 disease (89% ± 3%; P = .0068; Fig 2). The EFS for patients with INSS stage 1 disease (92% ± 3%, n = 209) was statistically significantly higher than for patients with INSS stage 2 (78% ± 6%, n = 103; P = .0005) and INSS stage 3 disease (75% ± 5%, n = 162; P < .0001), whereas patients with INSS stage 2 and 3 disease had similar EFS (P = .6611). The OS rates for patients with INSS stage 1, 2, and 3 disease were respectively 98% ± 2%, 95% ± 3%, and 84% ± 4%.
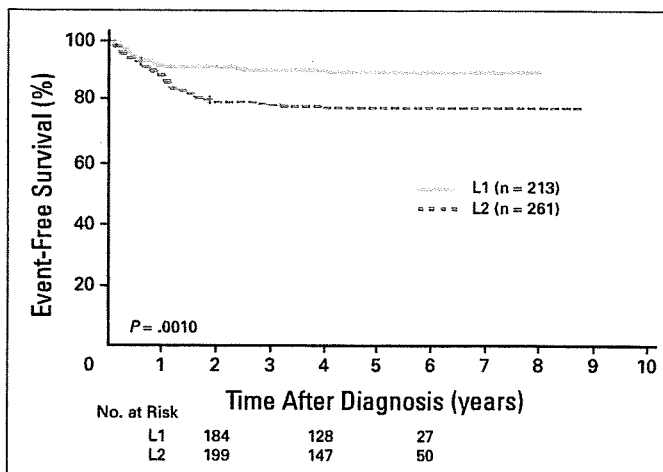
Fig 1. Event-free survival curves for International Society of Pediatric Oncology Europe Neuroblastoma Group patients by International Neuroblastoma Risk Group Staging System stage L1 versus L2 (P = .0010; n = 474). The number of patients at risk for an event are shown along the curves at years 2, 4, and 6.

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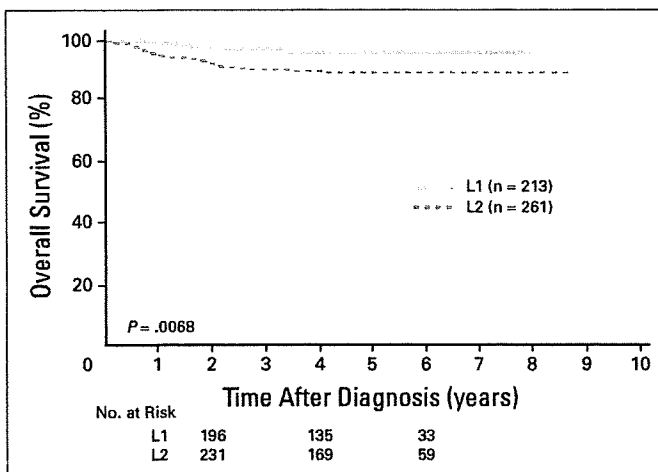
Fig 2. Overall survival curves for International Society of Pediatric Oncology Europe Neuroblastoma Group patients by International Neuroblastoma Risk Group Staging System stage L1 versus L2 (*P* = .0068; n = 474). The number of patients at risk for death are shown along the curves at years 2, 4, and 6.

DISCUSSION

Because excision of the primary tumor is a prerequisite for assigning patients to INSS stages 1 and 2, and because it is possible to downstage patients by surgical treatment at diagnosis,[4] the INSS is not suitable for pretreatment staging and risk assessment. A new clinical staging system (INRGSS) was, therefore, designed specifically to constitute one of seven prognostic factors in the INRG pretreatment classification system.[1] In the INRGSS, locoregional disease is stratified into two stages instead of three (as in INSS). This decision was based on recognition of the increasing importance of biologic prognostic factors and the excellent OS rate for patients with non-metastatic neuroblastomas.[1,12-16] Although the INRGSS can be used as a separate and independent clinical staging system, its primary function is as a component of the INRG. The INRGSS is not intended to substitute for the INSS, and it is anticipated that most cooperative groups will continue to use INSS in parallel with INRGSS.

Data from European studies show that absence or presence of IDRFs at diagnosis has prognostic significance. Our posthoc analysis of SIOPEN data[6] confirmed the results of Simon et al.[9] In both studies, EFS was lower for patients with INRGSS stage L2 compared with L1 tumors, and the differences were highly statistically significant. These observations support the translation of EFS tree regression results (in terms of INSS stages) into the INRG classification system (in terms of INRGSS): INSS 1 → INRGSS L1; INSS 2 and 3 → INRGSS L2; INSS 4 → INRGSS M; and INSS 4S → INRGSS MS.[1]

Because the treatment effect of tumor excision is an inherent part of the INSS, the prognostic value of specific stages within INRGSS and INSS cannot be directly compared. For example, most readers would agree that a comparison between patients with INRGSS stage L1 and INSS stage 1 is actually a comparison between an untreated group of patients and a cohort in whom nearly all patients have already been cured. However, even if INRGSS is not intended to substitute for the INSS, the distribution of patients between the two systems is of interest. In the retrospective study of Simon et al,[9] 84% of 160 patients with INSS stage 1 disease met the criteria for INRGSS stage L1 (ie, no

IDRFs), whereas only 16% of 139 patients with IDRFs (stage L2) had INSS stage 1 disease. Similarly, our posthoc statistical analyses of 661 SIOPEN patients, in whom the clinical impact of surgical risk factors (= IDRFs) was examined prospectively, confirm the results of Simon et al.[9] In the data from SIOPEN (Table 3), 79% of patients with INSS stage 1 disease met the criteria for INRGSS stage L1, whereas 21% of patients with IDRFs (stage L2) had INSS stage 1 disease. In the SIOPEN LNESG1 study, 99% of 367 patients who met the criteria for INRGSS stage L1 underwent primary tumor excision (with one surgery-related death caused by renal failure). Among the 363 patients who underwent surgery, 75% had INSS stage 1 disease, 22% had INSS stage 2 disease, and 3% had INSS stage 3 disease. In 56% of 352 patients who had presence of one or more surgical risk factors (INRGSS stage L2), the initial surgical approach was limited to a biopsy; no attempt at primary tumor excision was made.[6] Furthermore, both studies referred to above demonstrated that primary operations in patients with IDRFs were associated with significantly lower complete excision rates and greater risks of surgery-related complications.[6,9]

Recommendations on treatment are not part of the INRGSS, nor of the INRG. Treatment policies must be decided by the individual cooperative groups. However, a new staging and risk classification system cannot exclude possible treatment alternatives, as is the case with INSS and the treatment option of observation without surgery. Today, OS in localized neuroblastoma is more than 90%,[1,12-16] and it can be assumed that a certain number of survivors have been over-treated. A main challenge in the years to come will be to maintain survival with reduced treatment. The INRGSS has been designed to permit uniform staging of all patients independent of the treatment alternatives contemplated.

The INRGSS differs from INSS in four important ways. First, it is based on preoperative imaging and IDRFs, not surgicopathologic findings. Second, the midline is not included in the staging criteria of the INRGSS. Third, lymph node status is not included in the staging of localized disease. Fourth, whereas INSS stage 4S has an upper age limit of 12 months, the Task Force decided to extend the age group for stage MS to patients younger than 18 months. The statistical basis for selecting a cutoff age of 18 months in INRG stages L2, M, and MS is presented and discussed in the companion article by Cohn and Pearson et al.[1] In one German study, the 5-year EFS was 100% in eight patients aged 12 to 18 months with *MYCN* nonamplified tumors who, apart from age, had classical INSS stage 4S disease.[17] The number of patients with "stage 4S disease aged 12 to 18 months" is small, but because the outcome in this patient cohort remains unclear, it is anticipated that the individual cooperative groups will give these patients special attention in prospective studies where careful stopping rules are included. Unlike INSS stage 4S, stage MS includes patients with primary tumors infiltrating the midline (INSS stage 3). The inclusion of all patients with stage L2 primaries is supported by the results of the SIOPEN 99.2 trial (B. De Bernardi, personal communication, February 2008). In this study, all 30 infants with INSS stage 4 disease having primary tumors corresponding to INSS stage 3 disease because of midline infiltration, and with stage 4S metastatic pattern, survived. Eight patients received no chemotherapy, and the remainder received only one or a few courses of chemotherapy to control symptoms. Only five of the patients had their primary tumor excised.

The effects of treatment on IDRFs are not known, although preliminary data from the SIOPEN Infant Neuroblastoma Study suggests that preoperative chemotherapy (or time) can decrease the incidence of IDRFs by 35% to 40%.[18] It also remains unclear whether the risks of surgical complications are reduced by preoperative chemotherapy when delayed operations are performed in patients who have persistent IDRFs. The impact of individual IDRFs on outcome is currently not known, and the clinical significance of individual IDRFs will need to be analyzed in a larger series of patients to address these questions.

Although surgery is not required for INRGSS staging, the biologic characteristics of the tumor must be known to stratify patients according to the INRG pretreatment classification system.[1] Image-guided core-needle biopsies are acceptable provided adequate material for the histologic and genetic studies are obtained. However, in many cases, complete or partial tumor excision may be a more rational way to obtain tissue for histologic categorization and genetic studies. In the latter case, it must be emphasized that the magnitude of the residual tumor does not influence the INRG stage. Even if completely excised at diagnosis, a localized tumor with (preoperative) one or more IDRFs will still be classified as an INRGSS stage L2.

The Task Force considered using a specific nomenclature to identify subgroups of patients with neuroblastoma with special features like multifocal primary tumors (because of the potential genetic implications of this diagnosis[19,20]). The experience with the INSS does not support a practice of subclassification within a staging system. Although the stage of patients with multifocal primary tumors in the INSS should be given a subscript letter M (stage 1_M, stage $2A_M$, and so on),[3] this subscript has not been widely accepted and only rarely used in published series. The Task Force, therefore, decided not to use subscripts in the INRGSS. This decision implies that patients with important special features not defined by the INRGSS have to be identified by other measures. It is recommended that data regarding the conditions listed in the last portion of Table 1 be collected.

Isolated pleural effusion and ascites are not considered IDRFs in the INRGSS. Although pleural disease is associated with reduced survival rates in patients with metastatic neuroblastoma,[21,22] isolated pleural effusion or ascites is rare in patients with locoregional disease, and its impact on outcome is not clear. In a recent study of 31 patients with neuroblastoma having pleural effusion, none had INSS stage 1 disease and only one had stage 2 disease.[23] It is assumed that the vast majority of patients with ascites also have either metastatic disease or the presence of IDRFs.

The extent of intraspinal tumor extension can range from a small tumor component bulging through one intervertebral foramen to a tumor occupying the majority of the spinal canal. In the SIOPEN studies, intraspinal tumor extension is considered a surgical risk factor if neurologic signs of spinal cord compression are present. However, because clinical signs are not image defined, in INRGSS, it was decided to consider intraspinal tumor extension an IDRF, provided one or more of the imaging criteria listed in Table 1 are present.

In conclusion, the INRGSS is a preoperative staging system that has been developed specifically for the INRG classification system. The extent of disease is determined by the presence or absence of IDRFs and/or metastatic tumor at the time of diagnosis, before any treatment. Use of this pretreatment staging system and the INRG classification system will facilitate the ability to compare results of risk-based clinical trials conducted in different regions of the world, and thereby, provide insight into optimal treatment strategies for patients with neuroblastic tumors.

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Acknowledgment

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総　　説

第 24 回日本小児がん学会教育セッション
神経芽腫に対する集学的治療法：化学療法を中心に

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I　概　　念[1]

神経芽腫 (neuroblastoma) の概念は, Pepper, Hutchinson, Wright の 3 人の先駆者により確立した[2]. 1901 年に Pepper らは肝臓と副腎の先天性肉腫 6 例の報告を行った. 続いて 1907 年に Hutchinson らが副腎腫瘍の眼窩転移例 7 例を報告した. そして 1910 年に Wright らが初めて neuroblastoma の用語を使用し神経芽腫の概念が確立している.

「神経芽腫」とは通常広義に用いられ, それは組織学的な分類として, 狭義の神経芽腫 (neuroblastoma) と神経節芽腫 (ganglioneuroblastoma) 及び神経節腫 (ganglioneuroma) の 3 種類を総称するものである. 最近では広義の神経芽腫を, 脳腫瘍である中枢性神経芽腫と区別するために, 末梢性神経芽腫群腫瘍 (pNTs; peripheral Neuroblastic Tumors) と呼称するようになった[1,3].

神経芽腫は, 胎生期の神経堤 (あるいは神経冠) (neural crest) を起源とする神経芽細胞が成熟分化せずに腫瘍化したものと考えられ, 副腎髄質および交感神経系組織に発生する胎児性腫瘍である[1,3].

発生頻度は小児悪性固形腫瘍の中で脳腫瘍についで多く, 日本の小児がんの中の 10〜20％ を占める. アメリカでは 7,000 人出生に対し 1 人の割合で発生し, 年間約 600〜650 人の発生がある[1]. 日本では出生数あたりの発生頻度は把握されてい

ないが, 日本神経芽腫研究グループ (Japan Neuroblastoma Study Group/JNBSG) の種々のアンケート調査などからの推計では年間に 90〜130 例, そのうち高リスク神経芽腫は年間 50〜70 例程度と考えられる[4]. アメリカ Children's Oncology Group (COG) の統計では年齢のピークは出生時であり, 1 歳未満は 36％, 5 歳未満で 89％, 10 歳未満で 98％ を占める[1].

II　病態生理

神経芽腫の好発部位は副腎で 65％ を占め, その他は頚部, 後縦隔, 後腹膜, 骨盤腔などの交感神経節である. 左右差は 3：2 の割合で左に多い. 転移は骨, 骨髄, 肝, リンパ節, 皮膚, 眼窩等に認められる. 硬膜, 脳実質あるいは肺転移の報告もある[1].

ほとんどの神経芽腫は血清カテコラミン (ドパミン, アドレナリン, ノルアドレナリン) を産生し, その尿中代謝産物であるバニルマンデル酸 (VMA) とホモバニリン酸 (HVA) などが上昇するため, これを腫瘍マーカーとして利用できる. また血中の神経特異エノラーゼ (neuron-specific enolase：NSE) が高値となることも多い[1].

組織学的に狭義の神経芽腫は, クロマチンに富む核と乏しい細胞質からなる小円形の神経芽細胞とわずかな神経線維からなり, その間に間質細胞が存在する. 神経節芽腫は, 未分化な神経芽細胞と分化した神経節細胞が混在するものである. 神経節腫は, 主として神経節細胞からなるものである. 日本病理学会小児腫瘍組織分類委員会分類では, 神経芽腫 (花冠－細線維型・円形細胞型),

日本大学医学部小児科学系小児科学分野

神経節芽腫（分化型・混成型・低分化型），神経節腫に分類している[3]．

Beckwith らの研究から胎生期には多数の *in situ* neuroblastoma が存在し，その大多数は自然に成熟または消退し，残りのごく一部が神経芽腫になるものと推定されている．日本で行われたマススクリーニング症例の検討からも，マススクリーニングで発見された神経芽腫のうちあるものは自然退縮や分化成熟することが判明した[3,5]．しかし1歳半（あるいは1歳）以上で診断される症例はそのほとんどの病期は進行しており，また生物学的予後因子も不良なことが多く，治療抵抗性であることが多い．

1970年代に開始され連綿と継続されている研究から，現在では，予後と密接に関連している因子には，年齢，stage，病理組織学的分類，*MYCN*，DNA ploidy，染色体異常（1p－，11q－，17q＋）等が考えられている[1,3,6]．

Brodeur らの検討では，*MYCN* が増幅している頻度と3年生存率は，良性の神経節腫ではそれぞれ 0/64・100%，低リスク群病期1と2では 31/772・90%，4S では 15/190・80%，進行例では 612/1974・40% である．Shimada らの検討では Favorable Histology（FH）329例では *MYCN* 非増幅325例・増幅4例であるが，Unfavorable Histology（UH）では243例中 *MYCN* 非増幅164例・増幅79例であった．*MYCN* 増幅はすなわち予後不良であるが，非増幅は必ずしも予後良好ではない．UH の中では *MYCN* 増幅腫瘍は非増幅腫瘍より早期に発症する傾向にあり，分化傾向が見られず，high MKI を呈する特徴がある[1]．

DNA ploidy が3倍体の腫瘍は2倍体・4倍体に比し DNA が不安定であるため，細胞の生存及び分裂増殖に不利であり，治療に対する反応性が良いと言われている．Flow cytometry により DNA 量を検討する．DNA index（DI）＝1は diploid を反映し予後不良であるが，FH では schwann 細胞が2倍体のため DI＝1になる[1,3,6]．

Ⅲ 臨床症状

臨床症状には原発部位の腫瘍による症状と転移による症状があり，年齢と原発部位・病期により様々である．

乳児期早期の症例は多くが限局例であり症状を認めない．乳児期のマススクリーニング発見例は一般的に無症状であった．4S 期では，瀰漫性肝転移による腹部膨満症状とそれによる胸部圧迫のための呼吸器症状を認めることがある．進行例には，腹部膨満，食欲不振，発熱などの他に，遠隔転移の症状としての顔面蒼白，貧血，眼球突出，眼瞼出血，骨痛，関節痛，跛行などが認められるが，発熱のみの場合や偶然の腹部腫瘤触知による発見まで無症状のこともある．特殊な症状として，Horner 症候群や opsomyoclonus，小脳性運動失調あるいは脊椎管内への腫瘍進展による神経麻痺，腫瘍から産生されるカテコラミンによる異常な発汗や高血圧，血管作動性腸ペプチド産生による水様性下痢などが見られることがある[1]．

Ⅳ 診 断

診断は原発腫瘍または転移巣の開創生検を行い光学顕微鏡検査により病理組織学的に確定診断する．あるいは，骨髄検査で腫瘍細胞の転移が確認され，かつ尿中 VMA や HVA が明らかに高値である場合は，原発腫瘍の組織学的検討を行わずに神経芽腫と診断してよい．しかしながら原則としては，診断を確定し，治療方針を決定するために必要な腫瘍の生物学的予後因子を検討するために，原発腫瘍（あるいは転移巣）の開創生検を行うべきである．針生検による病理診断は正確な診断に至ることが困難な場合があり，また生物学的予後因子の検索ができないことが多く，神経芽腫以外の固形腫瘍の場合も含め薦められない[1,3]．

MYCN コピー数や DNA ploidy などの分子生物学的予後因子の検索を行うことが，リスク分類による治療方針の決定には必要である[1,3]．

病理組織学的分類は International Neuroblastoma Pathology Classification（INPC）が国際的に標準的である．これは，神経芽腫細胞の形態に，診断時年齢，Schwann 細胞の発達（stroma），神経細胞の分化程度（differentiation），核崩壊程度（Mitosis-karyorrhexis index）（MKI）を加味し，

組織型としては Neuroblastoma/Ganglioneuroblastoma, intermixed/ Ganglioneuroma/ Ganglioneuroblastoma, nodular の4型に分類し，さらに予後のグループとして Favorable Histology Group (FH) と Unfavorable Histology Group(UH)に分類するものである[1,3].

V　病期分類

これまで病期分類は日本小児外科学会悪性腫瘍分類，Evans system, St. Jude Children's Research Hospital and POG classification などが使用されてきたが，現在は神経芽細胞腫国際病期分類（International Neuroblastoma Staging System/INSS）（表1）が使用される[7]. 病期分類には初診時での原発腫瘍の広がり，リンパ節転移，肝転移，あるいは神経芽腫の好発部位である交感神経の経路に沿った部位への転移の把握が必要であり，これには全身の X 線 CT や MRI が必要である．さらに骨及び骨髄転移の検索が必須で，I -123 metaiodo-benzylguanidine（MIBG）シンチグラフィー及び Tc-99 m 骨シンチグラフィーが必要である．骨髄転移の検索には，治療効果の判定として International Neuroblastoma Response Criteria (INRC)（表2）を用いる場合には左右2箇所の腸骨での骨髄穿刺吸引検査と左右2箇所の骨髄生検が必要とされている[7].

VI　リスク分類

神経芽腫は，年齢，病期，病理学的特徴，分子生物学的特徴などにより著しく予後が異なる．このため治療選択の基準として，病期分類にさらにいくつかの予後因子を組み合わせたリスク分類の必要性が提唱されている．リスクは予後との関連により低リスク群，中間リスク群，高リスク群に分類することが一般的である．これまでは日米欧で独自のリスク分類が提案されてきたが，現在は国際的な統一分類の開発（The International Neuroblastoma Risk Classification (INRG)）が企画され討議されている[8,9]. さらに今後は分子生物学的予後因子を組み込んだリスク分類が創案されることと考えられる．代表的なリスク分類である COG のリスク分類では，年齢と INSS 病期分類，INPC 組織分類，*MYCN* 増幅の有無及び DNA index により表3のように分類している[1,10].

VII　鑑別診断

HE 染色による形態判断では鑑別が困難な腫瘍群を小円形細胞腫瘍と呼び，悪性リンパ腫，ユーイング肉腫ファミリー腫瘍，横紋筋肉腫と神経芽腫が含まれる．これらの鑑別には生検あるいは摘出組織を利用して免疫染色や電子顕微鏡検査ある

表1　神経芽細胞腫国際病期分類 （International Neuroblastoma Staging System/INSS）

病期	定義
1	限局性腫瘍で，肉眼的に完全切除．組織学的な腫瘍残存は不問．同側のリンパ節に組織学的な転移を認めない．（原発腫瘍に接し，一緒に切除されたリンパ節転移はあってもよい）
2A	限局性腫瘍で，肉眼的に不完全切除．原発腫瘍に接しない同側リンパ節に組織学的に転移を認めない．
2B	限局性腫瘍で，肉眼的に完全または不完全切除．原発腫瘍に接しない同側リンパ節に組織学的に転移を認める．対側のリンパ節に転移を認めない．
3	切除不能の片側性腫瘍で，正中線（対側椎体縁）を越えて浸潤．同側の局所リンパ節の転移は不問．または，片側発生の限局性腫瘍で対側リンパ節転移を認める．または，正中発生の腫瘍で椎体縁を越えた両側浸潤（切除不能）か，両側リンパ節転移を認める．
4	いかなる原発腫瘍であるかに関わらず，遠隔リンパ節，及び／または，骨，骨髄，肝，皮膚，他の臓器に播種している．（4S は除く）
4S	限局性腫瘍（病期1，2A，2B）で，播種は皮膚，及び／または，肝，骨髄に限られる（1歳未満の患者のみ）．骨髄中の腫瘍細胞は有核細胞の 10％未満で，それ以上は病期4である．MIBG シンチが行われるならば骨髄への集積は陰性．

Brodeur GM, et al: J Clin Oncol 11(8)：1466-77, 1993. より引用