

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

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### ABSTRACT

#### 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 INRGSS, 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 ( $78\% \pm 4\%$  v  $90\% \pm 3\%$ ;  $P = .0010$ ).

#### 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,<sup>1</sup> 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<sup>1</sup> (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.<sup>2,3</sup> 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.<sup>4</sup> Furthermore, patients with localized disease who are observed because tumor regression is anticipated cannot be properly staged using INSS criteria.<sup>5</sup> 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

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thoroughness of the individual surgeon, and the assessment of extra-regional lymph node involvement is difficult to apply uniformly.<sup>2-4</sup>

## METHODS

### 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.<sup>6</sup> Surgical risk factors are features detected on imaging that make safe, total tumor excision impracticable at the time of diagnosis.<sup>6,7</sup> 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.<sup>3</sup> 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.<sup>3</sup> 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.<sup>8</sup> 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.

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 <i>not</i> considered IDRFs Multifocal primary tumors Pleural effusion, with or without malignant cells Ascites, with or without malignant cells
Abbreviation: IDRFs, image-defined risk factors.

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.

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<sup>1</sup> 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<sup>1</sup> (< 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<sup>9</sup> 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.<sup>1</sup> 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.<sup>10</sup> EFS and overall survival (OS) values were reported at the 5-year time point ± SE (per Peto).<sup>11</sup> 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<sup>9</sup>).

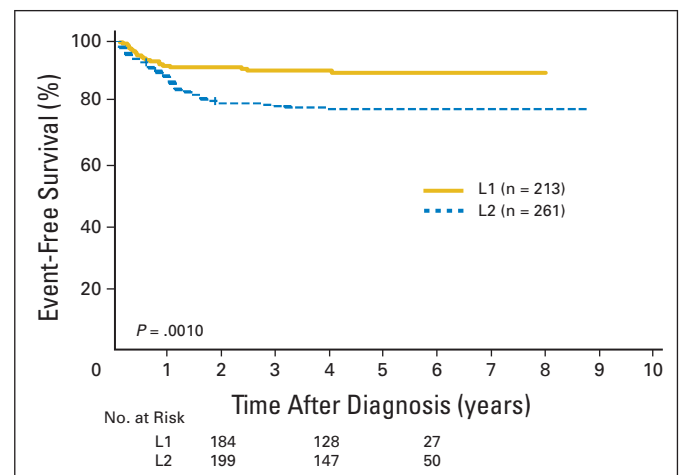
**Table 3.** Distribution of SIOPEN Patients by INRGSS Versus INSS

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

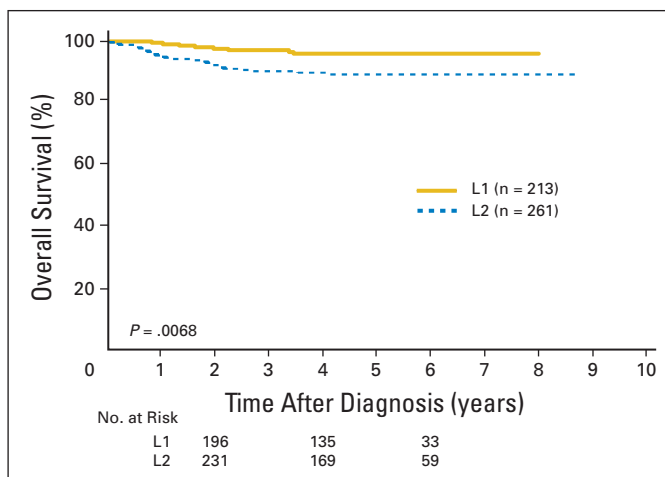
Abbreviations: SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group; INRGSS, International Neuroblastoma Risk Group Staging System; INSS, International Neuroblastoma Staging System.

**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.



**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,<sup>4</sup> 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.<sup>1</sup> 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.<sup>1,12-16</sup> 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 SIOOPEN data<sup>6</sup> confirmed the results of Simon et al.<sup>9</sup> 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.<sup>1</sup>

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,<sup>9</sup> 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 SIOOPEN patients, in whom the clinical impact of surgical risk factors (= IDRFs) was examined prospectively, confirm the results of Simon et al.<sup>9</sup> In the data from SIOOPEN (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 SIOOPEN 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.<sup>6</sup> 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.<sup>6,9</sup>

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%,<sup>1,12-16</sup> and it can be assumed that a certain number of survivors have been overtreated. 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.<sup>1</sup> 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.<sup>17</sup> 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 SIOOPEN 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 SIOPEX Infant Neuroblastoma Study suggests that preoperative chemotherapy (or time) can decrease the incidence of IDRFs by 35% to 40%.<sup>18</sup> 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.<sup>1</sup> 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<sup>19,20</sup>). 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<sub>M</sub>, stage 2A<sub>M</sub>, and so on),<sup>3</sup> 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,<sup>21,22</sup> 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.<sup>23</sup> 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 SIOPEX 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.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

**Table A1.** The INRG Task Force: Participants of the INRG Meeting (Whistler, Canada, September 17-19, 2005)

Name	Country and Cooperative Group	Role
Susan L. Cohn	United States, COG	Chair
Andrew D.J. Pearson	United Kingdom, SIOPEN	Chair
Statistics committee		
Wendy B. London	United States, COG	Chair
Emanuele S.G. d'Amore	Italy, SIOPEN	
Andreas Faldum	Germany, GPOH	
Barbara Hero	Germany, GPOH	
Tomoko lehara	Japan, JANB/JINCS	
David Machin	United Kingdom, SIOPEN	
Veronique Mosseri*	France, SIOPEN	
Michel Peuchmaur	France, SIOPEN	
Hiroyuki Shimada	United States, COG	
Biology committee		
Peter F. Ambros	Austria, SIOPEN	Chair
Inge M. Ambros*	Austria, SIOPEN	
Garrett M. Brodeur	United States, COG	
Jerome Couturier	France, SIOPEN	
Michelle Haber	Australia	
Javed Khan	United States, COG	
John M. Maris	United States, COG	
Akira Nakagawara	Japan, JANB/JINCS	
Gudrun Schleiermacher	France, SIOPEN	
Frank Speleman*	Belgium, SIOPEN	
Ruediger Spitz	Germany, GPOH	
Nadine Van Roy	Belgium, SIOPEN	
Metastatic disease committee		
Katherine K. Matthay	United States, COG	Chair
Klaus Beiske	Norway, SIOPEN	
Sue Burchill	United Kingdom, SIOPEN	
Irene Cheung	United States, COG	
Francesco Giammarile	France, SIOPEN	
Eiso Hiyama	Japan	
Jean Michon	France, SIOPEN	
Robert C. Seeger	United States, COG	
Barry Shulkin	United States, COG	
Surgery committee		
Tom Monclair	Norway, SIOPEN	Chair
Hervé Brisse	France, SIOPEN	
Giovanni Cecchetto	Italy, SIOPEN	
Keith S.J. Holmes	United Kingdom, SIOPEN	
Michio Kaneko	Japan, JANB/JINCS	
Jed G. Nuchtern	United States, COG	
Dietrich von Schweinitz	Germany, GPOH	
Senior advisors		
Frank Berthold	Germany, GPOH	
Victoria Castel	Spain, SIOPEN	
Robert P. Castleberry*	United States, COG	
Nai-Kong Cheung	United States, COG	
Bruno De Bernardi	Italy, SIOPEN	
Helen Irving	Australia, COG	
Ruth Ladenstein	Austria, SIOPEN	
C. Patrick Reynolds	United States, COG	
Jinhua Zhang	China	
Young investigators		
Julie R. Park	United States, COG	
Roswitha Schumacher-Kuckelkorn	Germany, GPOH	
Thorsten Simon	Germany, GPOH	
Hidetaka Niizuma	Japan, JANB/JINCS	
Toby Trahair	Australia	
William Guy Forbeck Research Foundation		
Jennifer Forbeck	United States	
John T. Kemshead	United Kingdom	

Abbreviations: COG, Children's Oncology Group; SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group; GPOH, German Pediatric Oncology and Hematology Group; JANB/JINCS, Japanese Advanced Neuroblastoma Study Group/Japanese Infantile Neuroblastoma Co-operative Study Group.

\*International Neuroblastoma Risk Group Task Force members not present at the Whistler meeting.