Prognostic Value of the Stage 4S Metastatic Pattern and Tumor Biology in Patients With Metastatic Neuroblastoma Diagnosed Between Birth and 18 Months of Age

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A B S T R A C T

Purpose

Patients with neuroblastoma younger than 12 months of age with a 4S pattern of disease (metastases limited to liver, skin, bone marrow) have better outcomes than infants with stage 4 disease. The new International Neuroblastoma Risk Group (INRG) staging system extends age to 18 months for the 4S pattern. Our aim was to determine which prognostic features could be used for optimal risk classification among patients younger than 18 months with metastatic disease.

Methods

Event-free survival (EFS) and overall survival were analyzed by log-rank tests, Cox models, and survival tree regression for 656 infants with stage 4S neuroblastoma younger than 12 months of age and 1,019 patients with stage 4 disease younger than 18 months of age in the INRG database.

Results

Unfavorable biologic features were more frequent in infants with stage 4 disease than in infants with 4S tumors and higher overall in those age 12 to 18 months (although not different for stage 4 v 4S pattern). EFS was significantly better for infants younger than 12 months with 4S pattern than with stage 4 disease ($P < .01$) but similar for toddlers age 12 to 18 months with stage 4 versus 4S pattern. Among 717 patients with stage 4S pattern, patients age 12 to 18 months had worse EFS than those age younger than 12 months ($P < .01$). *MYCN*, 11q, mitosis-karyorrhexis index (MKI), ploidy, and lactate dehydrogenase were independently statistically significant predictors of EFS and more highly predictive than age or metastatic pattern. *MYCN*, 11q, MKI, histology, and 1p were combined in a survival tree for improved risk stratification.

Conclusion

Tumor biology is more critical than age or metastatic pattern for prognosis of patients age younger than 18 months with metastatic neuroblastoma and should be considered for risk stratification.

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INTRODUCTION

Stage 4S neuroblastoma is a unique category of metastatic disease in infants. Originally described in 1971,¹ the definition (clarified by International Neuroblastoma Staging System [INSS]) categorizes infants younger than 12 months of age with metastases limited to the liver, skin, and bone marrow (< 10% replacement with tumor cells) as having stage 4S disease, hereafter referred to as 4S pattern. The primary tumor must be localized (INSS 1 or 2), without infiltration across the midline or contralateral lymph node involvement.²

Patients with 4S disease (7% to 10% of neuroblastoma)³ have a more favorable outcome than

other patients with metastatic neuroblastoma, often demonstrating spontaneous maturation and regression. Estimated survival rates of 70% to 90% have been reported, and these tumors are usually associated with favorable biologic features.⁴⁻⁷ Unfortunately, a subgroup of patients with stage 4S disease and unfavorable prognostic features—including *MYCN* amplification, chromosomal aberrations (loss of heterozygosity [LOH] 1p, aberration 11q, gain 17q), diploidy, and age younger than 2 months at diagnosis—has significantly worse outcomes.^{3,4,8-14}

The upper age limit defining 4S disease has been debated as a result of recent reports demonstrating more favorable outcomes for patients with metastatic

Fig 1. Analytic cohort. INRG, International Neuroblastoma Risk Group.

neuroblastoma diagnosed between 12 and 18 months of age.^{15,16} Recently, the International Neuroblastoma Risk Group (INRG) developed consensus guidelines for a modified staging system based on clinical and radiologic criteria. The INRG increased the upper limit of age from 12 to 18 months for 4S disease (now designated Ms), defined as metastases limited to skin, liver, and bone marrow (< 10%) without cortical bone involvement and either L1 or L2 stage tumors, including large unresectable primary tumors that cross the midline.¹⁷ These patients were then stratified by biologic features for risk classification. The current study uses the INRG database of 1,675 patients with metastatic neuroblastoma age 0 to 18 months to determine whether biologic and clinical features better than the younger-than-12-months age cutoff and 4S metastatic pattern can be identified to categorize patients with good outcomes.

METHODS

Patients

The INRG database contains information on 8,800 unique patients who provided consent for and were enrolled onto cooperative clinical trials between January 1, 1990, and December 31, 2002, by cooperative groups from multiple countries.¹⁷ Requirements for eligibility into the INRG database include confirmed pathologic diagnosis of neuroblastoma excluding ganglioneuroma,¹⁸ age 21 years or younger at diagnosis, and available data for disease and survival outcomes.

From this database, we identified 3,425 patients with INSS stage 4 and 656 patients with INSS stage 4S disease (Fig 1). Among patients with stage 4 disease, 654 were age younger than 12 months (infants) and 365 were age 12 to 18 months (toddlers) at diagnosis. With regard to patients with stage 4S disease, all 656 were younger than 12 months of age (by definition). These 1,675 patients formed our analytic cohort. We divided the patients with stage 4 disease age 12 to 18 months into two groups—those with (n = 61) and without (n = 304) 4S pattern of metastasis—independent of size of primary tumor or extent of bone marrow involvement.

Statistical Considerations

Factors evaluated in tests of association and survival analyses were as follows: *MYCN* gene amplification,^{19,20} 11q aberration, 1p aberration, ploidy, grade, mitosis-karyorrhexis index (MKI), lactic dehydrogenase (LDH), primary site (adrenal v not adrenal), and initial treatment (surgery

and observation v more intensive therapies). Both 11q and 1p chromosomal abnormalities were detected using fluorescence in situ hybridization or polymerase chain reaction. Using flow cytometry, ploidy was reported as less than or equal to one or more than one; all patients with more than one were classified as hyperdiploid. Histology is often used to categorize tumors as favorable or unfavorable. Because the INPC and Shimada classification systems incorporate age into their categorization, there is a duplication of the prognostic contribution when both age and histology are used as risk factors.^{18,21} Therefore, we used tumor grade (differentiated v poorly or undifferentiated) and MKI (low or intermediate v high) to evaluate tumor histology. For LDH, median value was used to dichotomize the cohort; LDH less than 580 U/L was classified as low, and 580 U/L or greater was classified as high.

Fisher's exact tests were performed for prognostic factors versus metastatic pattern. For event-free survival (EFS), time to event was calculated as time from enrollment to first occurrence of relapse, progressive disease, secondary malignancy, or death as a result of any cause or to time of last patient contact, if no event occurred. For overall survival (OS), time to event was time from enrollment until death or time of last contact, if alive. Survival was estimated using the Kaplan-Meier method,²² and subgroups were compared by log-rank test. EFS and OS are expressed as the 5-year estimate plus or minus SE.²³

A Cox model on EFS was used to explore the possibility of a better age cutoff to define stage 4S disease.²⁴ The subset of 717 patients with stage 4S metastatic pattern (ie, including some stage 4 patients > 1 year of age) was repeatedly divided into two age groups. *P* values and hazard ratios for older versus younger patients were calculated, whereby the optimal age cutoff was statistically significant and maximized the difference in EFS between older and younger patients (ie, largest hazard ratio). The selected age cutoff was used in other Cox models to test binary age in combination with one biologic factor at time, and another model was used to identify all factors independently predictive of EFS.

Survival tree regression was used to determine if biologic factors could improve risk groupings for patients younger than 18 months of age with metastases, either in addition to or in combination with age and metastatic pattern.^{21,25,26} Proportional hazards assumption was confirmed by visual inspection of survival curves and plots of log(time) versus log[−log(S[time])].

RESULTS

EFS and OS by Age and Pattern of Metastases

In the overall cohort of patients age 0 to 18 months with metastases, 5-year EFS and OS (± SE) were 70% ± 2% and 75% ± 1%,

respectively (Table 1). Five-year EFS was significantly higher for patients with 4S pattern of metastases ($77\% \pm 2\%$) compared with patients with stage 4 pattern of metastases ($64\% \pm 2\%$; $P < .001$; Table 1; Fig 2A). Five-year EFS was also significantly higher for stage 4S

pattern age younger than 12 months ($79\% \pm 2\%$) than for stage 4 pattern age younger than 12 months ($70\% \pm 2\%$; $P < .001$; Fig 2B). In contrast, EFS for toddlers age 12 to 18 months with stage 4S pattern ($55\% \pm 8\%$) was not significantly different from EFS for toddlers with stage 4 pattern ($50\% \pm 4\%$; $P = .39$; Fig 2C). EFS was also improved for younger patients age younger than 12 months compared with that for patients age 12 to 18 months, overall (Fig 2D), and within each metastatic pattern (Figs 2E, 2F). OS paralleled EFS in all cases.

Distribution of Clinical and Biologic Characteristics

To understand these differences in outcome, we assessed associations of age and pattern of metastases with poor prognostic features (Table 2). For patients with stage 4S pattern, the proportion of patients with unfavorable features was significantly higher among toddlers (age 12 to 18 months) than infants (age < 12 months) for *MYCN* amplification, 1p aberration, unfavorable histology, high MKI, and high LDH. However, the proportion with adrenal primary was higher for patients age younger than 12 months than for those age 12 to 18 months. In comparing infants versus toddlers within the subgroup with stage 4 pattern, a significantly higher proportion of patients age 12 to 18 months had unfavorable features: *MYCN* amplification, diploidy, unfavorable histology, and high MKI. In contrast to stage 4S pattern, in stage 4 pattern, more toddlers than infants had an adrenal primary.

In infants, unfavorable biologic prognostic features were also significantly more frequent in stage 4 than stage 4S pattern, including *MYCN* amplification, diploidy, 1p aberration, unfavorable histology, high MKI, and high LDH. Adrenal primary was observed in more infants with stage 4S pattern compared with stage 4 pattern. In contrast, the proportion of unfavorable prognostic features was not significantly different between toddlers with stage 4 and toddlers with 4S pattern, except for adrenal primary, which was more common in stage 4 pattern.

The following subgroups had a significantly higher proportion of patients who received initial treatment with chemotherapy or other intensive therapy: among infants, more stage 4 than 4S pattern; toddlers, more stage 4S than stage 4 pattern; within stage 4S pattern, more toddlers than infants.

EFS and OS by Prognostic Factors

In the cohort of patients age 0 to 18 months with metastatic disease, univariate analyses revealed that both EFS and OS were statistically significantly worse for toddlers and patients with stage 4 pattern, *MYCN* amplification, diploidy, unfavorable histology, high MKI, 1p LOH or aberration, high LDH, and adrenal primary (Table 1; Appendix Tables A1-A4, online only). EFS was worse for patients with 11q LOH or aberration ($P = .0376$), but OS was not ($P = .55$). Patients whose initial treatment plan included chemotherapy or more intensive therapy had lower EFS ($P < .001$) and OS ($P < .001$; Table 1). Grade of differentiation did not seem to affect prognosis in this cohort and was excluded from the other analyses.

Distribution of Outcome by Age

We next evaluated the prognostic impact of age within the cohort of patients with metastatic disease age 0 to 18 months. Five-year EFS for patients younger than age 19 days with metastatic disease was less than 71% for all subgroups; the subgroup with the lowest EFS was made up of those 7 to 18 days of age with stage 4 pattern (58% at 5 years; Appendix Fig A1, online only). The most favorable outcomes were in patients diagnosed at 19 to 38 days of age. Thereafter, EFS gradually decreased with increasing

Table 1. EFS and OS in Patients With Metastatic Neuroblastoma < 18 Months of Age (n = 1,675)

Characteristic	Patients		5-Year EFS		5-Year OS	
	No.	%	± SE (%)	P	± SE (%)	P
All patients	1,675		70 ± 2		75 ± 1	
Pattern of metastatic disease						
Stage 4S	717	43	77 ± 2	< .001	84 ± 2	< .001
Stage 4	958	57	64 ± 2		69 ± 2	
Age, months						
< 12	1,310	78	75 ± 2	< .001	82 ± 1	< .001
12-18	365	22	51 ± 3		53 ± 3	
<i>MYCN</i> amplification						
No	1,070	79	83 ± 2	< .001	90 ± 1	< .001
Yes	282	21	28 ± 4		32 ± 4	
Unknown	323					
Ploidy						
> 1 (hyperdiploid)	548	73	81 ± 3	< .001	87 ± 2	< .001
≤ 1 (diploid, hypodiploid)	206	27	59 ± 6		63 ± 6	
Unknown	921					
Histology						
Favorable	592	79	86 ± 2	< .001	92 ± 2	< .001
Unfavorable	156	21	38 ± 6		39 ± 6	
Unknown	927					
MKI						
Low, intermediate	513	84	84 ± 2	< .001	90 ± 2	< .001
High	100	16	38 ± 7		38 ± 7	
Unknown	1,062					
11q						
Normal	145	80	77 ± 6	.0376	84 ± 5	.55
Aberration	36	20	54 ± 16		83 ± 13	
Unknown	1,494					
1p						
Normal	284	73	83 ± 3	< .001	91 ± 3	< .001
Aberration	105	27	43 ± 7		49 ± 7	
Unknown	1,286					
LDH, U/L						
< 587	427	43	83 ± 2	< .001	91 ± 2	< .001
≥ 587	555	57	60 ± 3		64 ± 3	
Unknown	693					
Initial treatment						
Surgery and observation	254	21	86 ± 3	< .001	95 ± 2	< .001
Chemotherapy and transplantation	967	79	64 ± 2		71 ± 2	
Unknown	454					
Primary tumor location						
Nonadrenal primary	586	36	75 ± 2	.0011	81 ± 2	< .001
Adrenal primary	1,022	64	67 ± 2		72 ± 2	
Unknown	67					
Grade of neuroblastoma differentiation						
Differentiating	54	8	76 ± 6	.79	83 ± 5	.53
Undifferentiated	590	92	75 ± 3		81 ± 3	
Unknown	1,031					

Abbreviations: EFS, event-free survival; LDH, lactic dehydrogenase; MKI, mitosis-karyorrhexis index; OS, overall survival.

Fig 2. Event-free survival (EFS) comparisons by age and stage. EFS by stage for (A) all patients age 0 to 18 months with metastatic disease ($n = 1,675$), (B) infants age younger than 12 months ($n = 1,310$), and (C) toddlers age 12 to 18 months ($n = 365$). EFS by age for (D) all patients ($n = 1,675$), (E) patients with stage 4 pattern ($n = 958$), and (F) patients with stage 4S pattern ($n = 717$).

age in both 4 and 4S pattern, although EFS was lower for stage 4 pattern in almost every age group (Appendix Fig A1).

Within the cohort of patients with 4S pattern, we sought to determine whether the 365-day age cutoff maximized the outcome difference between younger and older patients. For patients with 4S pattern, those younger than 19 days of age had a 1.5 times greater risk of an event than patients 20 to 547 days of age, and those 365 days of age or older had a 2.31 times greater risk of an event than those who were younger than 365 days of age (Appendix Table A5, online only). No optimal age cutoff was identified, because the maximum hazard ratio was

for the oldest group; risk for an event gradually increased with increasing age. Any choice of age cutoff greater than 226 days would be reasonable, so we made no change to the existing 365-day cutoff.

Multivariable Analysis

In univariate analyses, all factors were statistically significantly predictive of EFS except for grade of differentiation (Table 1). Significance of each factor was maintained when each was tested in combination with age in a multivariable Cox model (ie, testing to see if age and given factor were independently predictive of EFS; Table 3). In a

Table 2. Association of Risk Factors by Pattern of Metastases Within Age Subgroups and by Age Within Pattern of Metastases Subgroups

Unfavorable Tumor Feature	Total % of Patients* (n = 1,675)	Age (months)				Pattern of Metastases			
		< 12 (n = 1,310)		12 to 18 (n = 365)		Stage 4S (n = 717)		Stage 4 (n = 958)	
		4S v 4 Pattern (%)	P	4S v 4 Pattern (%)	P	Age < 12 v 12 to 18 Months (%)	P	Age < 12 v 12 to 18 Months (%)	P
MYCN amplified	21	8 v 20	< .001	39 v 48	NS	8 v 39	< .001	20 v 48	< .001
Diploidy	27	21 v 28	.0323	32 v 41	NS	21 v 32	NS	28 v 41	.0178
11q aberration	20	10 v 21	NS	38 v 34	NS	10 v 38	.06	21 v 34	NS
1p aberration	27	16 v 30	.0036	50 v 46	NS	16 v 50	.0032	30 v 46	NS
Unfavorable histology	21	7 v 23	< .001	52 v 48	NS	7 v 52	< .001	23 v 48	< .001
Grade: undifferentiated	92	93 v 90	NS	91 v 92	NS	93 v 91	NS	90 v 92	NS
High MKI	16	4 v 17	< .001	50 v 43	NS	4 v 50	< .001	17 v 43	< .001
High LDH	57	44 v 63	< .001	67 v 72	NS	44 v 67	.0059	63 v 72	NS
Adrenal primary	64	73 v 56	< .001	43 v 66	.0008	73 v 43	< .001	56 v 66	.0032
Initial treatment: chemotherapy or other intensive	79	58 v 93	< .001	100 v 92	.0476	58 v 100	< .001	93 v 92	NS

NOTE. Bold font indicates significance.

Abbreviations: LDH, lactate dehydrogenase; MKI, mitosis-karyorrhexis index; NS, not significant ($P > .05$).

*No. of unknown patients excluded when calculating percentages with given characteristic.

multivariable Cox model testing more than two variables, *MYCN*, 11q, MKI, ploidy, and LDH were independently predictive of EFS (Appendix Table A6, online only).

A survival tree regression model identified *MYCN* amplification as the most highly prognostic factor, more so than age or metastatic pattern (Fig 3). Among patients with *MYCN* amplified tumors, MKI and then metastatic pattern (in low/intermediate MKI patients) were the most statistically significant predictors of outcome. Among those with *MYCN* nonamplified tumors, 11q was the most highly significant predictor of outcome. Among patients with 11q aberration, histology was significant, and in patients with normal 11q, 1p was significant. Of the 18 patients age 12 to 18 months with 4S pattern and *MYCN* nonamplified, normal 11q tumors, 5-year EFS and OS were $87.4\% \pm 10.3\%$ and 100.0%, justifying their inclusion as very low risk in the INRG.

DISCUSSION

In this study, we have demonstrated that overall outcome for patients with neuroblastoma and stage 4S pattern is superior to that for patients with stage 4 pattern, and outcome for older patients is in general worse than that for younger patients (with exception of patients < 19 days of age). Age and metastatic pattern are highly significant prognostic factors.^{21,27} However, age serves as a surrogate for evolving tumor biology in growing children, so it is not surprising that tumor biology is shown here to be more important than metastatic pattern or age. In patients younger than 18 months old with metastases, *MYCN* gene amplification, 11q aberration, MKI, 1p aberration, histology, and metastatic pattern can be used to classify patients into subgroups that are statistically significantly different in terms of outcome. The reason that toddlers age 12 to 18 months have similar EFS regardless of metastatic pattern seems to be because of similar frequencies of unfavorable biologic features for stage 4 and 4S pattern in the toddler age group.

INSS stage 4S has been established as having superior outcome compared with historical results with INSS stage 4 disease in infants younger than 12 months of age.^{3,4} However, *MYCN* gene amplification has been shown to be an extremely important prognostic factor in

infants with metastatic neuroblastoma in multiple cooperative studies, for infants with both stage 4S^{3,9} and stage 4 disease.²⁸⁻³⁰ Infants with either stage 4 or 4s neuroblastoma and *MYCN* gene amplification have a 2-year EFS of less than 30% despite intensive therapy,^{28,30} whereas those without *MYCN* amplification may have a 2-year survival of greater than 90% with minimal or no chemotherapy.^{29,31} Because of the rarity of *MYCN* amplification in infants with 4S neuroblastoma (0% to 10%), it has been difficult to show without the help

Table 3. Bivariate Analysis of Risk Factors in Stage 4S Metastatic Pattern

Risk Factor (category of increased risk)	Sample Size	Hazard Ratio	95% CI	P
Age (12 to < 18 months)	717	2.3	1.5 to 3.5	< .001
Age	564	NS		.33
MYCN (amplified)		4.1	2.6 to 6.2	< .001
Age	85	NS		.30
11q (aberration)		5.0	1.6 to 15.7	.0052
Age	196	NS		.68
1p (LOH)		3.3	1.7 to 6.6	< .001
Age	305	2.8	1.3 to 6.5	.0127
Ploidy (diploid)		1.9	1.0 to 3.8	.05
Age	337	NS		.87
Histologic classification (unfavorable)		4.3	2.2 to 8.4	< .001
Age	296	2.4	1.2 to 5.0	.0139
Grade (differentiated)		NS		.77
Age	282	NS		.67
MKI (high)		2.9	1.2 to 7.1	.0183
Age	460	2.1	1.3 to 3.6	.0040
LDH (≥ 580 U/L)		2.4	1.6 to 3.6	< .001
Age	677	2.3	1.5 to 3.5	< .001
Adrenal primary site (Yes)		NS		.59
Age	545	2.1	1.3 to 3.3	.0029
Initial treatment (chemotherapy and intensive therapy)		1.7	1.1 to 2.6	.0161

Abbreviations: LDH, lactate dehydrogenase; LOH, loss of heterozygosity; MKI, mitosis-karyorrhexis index; NS, not shown because not statistically significant.

Fig 3. Survival tree regression analysis of patients with neuroblastoma younger than 18 months of age with metastatic disease (n = 1,675; event-free survival [EFS] ± SE). AMP, amplified; LOH, loss of heterozygosity; MKI, mitosis-karyorrhexis index.

of a large series such as the INRG database that *MYCN* status is prognostic independent of age and other factors. The favorable outcome for patients with stage 4 pattern without *MYCN* amplification was also extended to toddlers age 12 to 18 months. Two cooperative group analyses showed that this subgroup had a significantly superior survival to older patients with stage 4 disease as well as to those of the same age with *MYCN* gene amplification.^{15,16} These findings prompted the revised INRG age limit for 4S metastatic pattern now designated Ms.¹⁷

In addition to *MYCN*, the other independently prognostic factors were 11q, MKI, ploidy, and LDH, despite the fact that a number of patients lacked information on these biologic variables. Within particular subsets in the survival tree, metastatic pattern, histology, and 1p were also significant. Attiyeh et al³² reported 11q and 1p aberrations as independent unfavorable risk factors in a study of 915 patients, regardless of clinical risk classification. This study included nine of 50 patients with stage 4S and 11q aberration, although this small group was not analyzed separately. Spitz et al³³ compared 11q aberration in localized and 4S disease and found metastatic relapse rates to be 30% when 11q aberration was present and 3% with normal 11q status. Although a relatively low proportion of patients in our INRG series had assessment of 11q aberration (181 of 1,675 patients age < 18 months with metastases), the effect of 11q was so strong that even in this small sample, we found significance in multivariable analysis. Patients younger than 12 months or 12 to 18 months of age with *MYCN* amplified or 11q LOH tumors would not be considered low-risk patients and would warrant more intensive therapy despite the 4S pattern. Excluding such patients, there were only 18 patients who were age 12 to 18 months with *MYCN* not amplified and normal 11q tumors, with 5-year EFS and OS of 87.4 ± 10.3% and 100.0%, respectively.

Previous analyses of 4S disease have found unfavorable histology to be associated with decreased survival.^{4,9} Diploid tumors have also been associated with poorer outcomes, but the prognostic benefits of hyperdiploid tumors seem to be limited to infants and toddlers age 12 to 18 months without *MYCN* amplification.¹⁵ Elevated serum LDH may indicate increased tumor burden and has been identified as an independent poor prognostic factor.^{3,9}

In our evaluation of infants with stage 4S disease, we found that risk of an event was high for patients of very young age, that the age subgroup with the best outcome was approximately 19 to 38 days, and that risk of an event increased gradually after age 38 days. Although the definition of young age varies by study, multiple groups have reported that infants younger than 2 to 3 months old have poorer OS than older infants.^{3,4,9} Massive hepatomegaly in these infants can lead to respiratory, renal, and gastrointestinal impairment as well as coagulation abnormalities.³ In the analysis by Nickerson et al⁴ of 80 infants with 4S disease, five of the six recorded deaths occurred in infants younger than 2 months of age who had rapidly progressive abdominal disease. A literature review of 119 4S cases found that in 33 deaths, 11 of 12 deaths resulting from hepatomegaly occurred in infants diagnosed in the first 4 weeks of life.¹³ These young infants with liver enlargement often are treated early and are at greater risk of death, thus explaining the observation in our INRG study that initial treatment is an unfavorable prognostic factor, as noted by others.³

Although this analysis used the largest cohort of patients with 4S metastatic pattern younger than 18 months of age, missing data and the rarity of some of the biologic tumor features resulted in some limitations. For example, some of the contributing groups at certain times allowed patients with so-called 4S disease younger than 12 months with tumors that crossed the midline as well as bone marrow involvement of more than 10%, characteristics that would have excluded patients from 4S categorization by the INSS definition; less than 10% bone marrow involvement was not required for any patient in the 12- to 18-month-old group with 4S pattern, because these patients were not defined as INSS 4S. It is unknown whether the size and stage of primary tumor are important in assigning 4S designation, but our study has shown that the pattern of metastases is less critical for risk group definitions than biologic variables. The most recent European infant protocols have used the metastatic pattern excluding macroscopic bone metastases but ignoring the primary tumor size as criteria for minimizing therapy in infants with metastatic neuroblastoma.²⁹ Finally, a variety of different treatment regimens were used, and thus, we were unable to adjust for treatment effect on EFS and OS. Acquisition of more complete data on biologic tumor features will be

critical for future clinical trials to provide improved assignment of treatment intensity and greater insight into the role of biologic and clinical tumor features on patient survival.

In conclusion, although the INSS stage 4S metastatic pattern has a more favorable outcome than stage 4 pattern in the age group of 0 to 18 months, biologic categorization of risk, particularly by *MYCN*, *MKI*, *11q*, *1p*, and histology, is more critical than metastatic pattern to assign risk-adapted therapy. In addition, infants in the very young age group (ie, age younger than 19 days) may require different management.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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