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International neuroblastoma pathology classification adds independent prognostic information beyond the prognostic contribution of age

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ABSTRACT

Age has been used as a prognostic factor for patients with peripheral neuroblastic tumours (pNTs). The latest analysis disclosed a cut-off around 18 months for the optimal prognostic distinction. The International Neuroblastoma Pathology Classification (INPC) distinguishes favourable and unfavourable histology based on the age-appropriate evaluation of histologic indicators (grade of neuroblastic differentiation, mitosis-karyorrhexis index) in the categories of neuroblastoma and ganglioneuroblastoma, nodular. This study showed that age tested by using 3 different cut-offs (12, 18, 24 months) was prognostically significant. INPC remained prognostically significant regardless of the age group to which it was applied. Prognostic effects of age and histologic indicators were independently significant, i.e., age had prognostic ability beyond that of histologic indicators, and histologic indicators had prognostic ability beyond that of age. Due to the fact that INPC incorporated age factor (18, 60 months) in the system, it served better than age by itself for prognostic distinction of pNT patients.

1. Introduction

Peripheral neuroblastic tumours (pNTs including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) are common solid tumours in infancy and childhood.[1] Because of their diverse clinical behaviours: such as involution/spontaneous regression, maturation, and aggressive progression, they were often described as "enigmatic" in the past.[2] The unpredictable nature and variable clinical behaviours of pNTs have been recognized for decades, and there currently are concerted efforts to identify reproducible and robust prognostic factors that allow treatment to be tailored to the individual cases. The Children's Oncology Group (COG) neuroblastoma biology study uses front-end prognostic factors for predicting their clinical behaviours and classifies the patients into low-, intermediate-, and high-risk groups for the purpose of protocol assignment.[3] These factors include age at diagnosis,[4] International Neuroblastoma Staging

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System (INSS) clinical stage,[5,6] *MYCN* status,[7,8] DNA index,[9] and the International Neuroblastoma Pathology Classification (INPC).[10,11]

Patient age at diagnosis in particular has long been recognized as a powerful indicator of clinical behaviour of pNTs: Sutow[12] first reported, in 1958, the significantly better outcome of patients younger than 2 years at diagnosis, and Gross[13] showed that the survival of infants was significantly better than that of children older than 12 months. Since then, many clinical trials, including recent studies conducted by the COG,[3,14,15] have used 12 months at diagnosis as a cut-off to discriminate risk of the patients with pNTs. More recently, however, Schmidt[16] and George RE[17] reported an excellent outcome in a subset of patients with stage IV neuroblastoma who were between 12 and 18 months old at diagnosis. Furthermore, the latest analysis by London,[18] using statistical models with more than 3500 cases combined from the previous Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) studies, showed that prognostic impact by age was continuous in nature and that an optimal cut-off for prognostic distinction was between 460 and 600 days of age at diagnosis with a minimum *P*-value at 18.8-months.

The INPC was established in 1999[10,11] by adopting the original system proposed by Shimada[19] and revised in 2003.[20] The INPC distinguishes favourable histology (FH) group and unfavourable histology (UH) group by applying the concept of age-dependent (age-appropriate) normal ranges of morphologic features: such as Schwannian stromal development, grade of neuroblastic differentiation and mitosis-karyorrhexis index (MKI). Tumours in the FH group are Neuroblastoma (NB), poorly differentiated subtype with either a low or an intermediate MKI (<18 months of age); Neuroblastoma (NB), differentiating subtype with a low MKI (<60 months of age); Ganglioneuroma, intermixed (GNBi); and Ganglioneuroma (GN). Tumours in the latter 2 categories of the FH group are usually diagnosed in older children even over 60 months of age. In contrast, tumours in the UH group have morphologic feature(s) outside of the normal ranges for the age of the individual patients: such as undifferentiated subtype (any age), poorly differentiated subtype ($\geqslant$18 months), differentiating subtype ($\geqslant$60 months), high MKI (any age), intermediate MKI ($\geqslant$18 months), and low MKI ($\geqslant$60 months) in the NB category. The last category of the INPC is Ganglioneuroblastoma, nodular (GNBn: a composite tumour with a ganglioneuromatous/ganglioneuroblastomatous component and a neuroblastoma component), and the prognostic grouping of the given tumour is determined by evaluating grade of neuroblastic differentiation and MKI of the neuroblastomatous nodule(s) using the same age-dependent criteria described above.[20]

As described above, based on the latest reports, the COG neuroblastoma biology study is now considering changing the age cut-off from 12 months to 18 months in their new risk-grouping scheme for patient stratification and protocol assignment. This movement prompted us to conduct our study, and we examined if the age factor with different cut-offs could directly affect prognostic significance of the INPC where age at diagnosis is already incorporated as a guideline to determine prognostic impact of histologic features.

2. Patients and methods

A total of 911 patients with pNTs, enrolled concurrently on the CCG-3881 and CCG-3891 studies from August 1, 1991 to August 1, 1995 were analyzed in this study. This cohort was a portion of the patients included in the previous study by London.[18] The CCG-3881 protocol was designed for the low-risk patients (biopsy/surgery alone)[21] and for the intermediate-risk patients (moderate intensity adjuvant chemotherapy in addition to biopsy/surgery).[22] The CCG-3891 protocol was for the high-risk patients, and included aggressive treatment with or without bone marrow transplantation.[23] Among those cases, 746 tumours were centrally reviewed histopathologically and classified into FH or UH group by using INPC at the Pathology Reference Laboratory, Department of Pathology and Laboratory Medicine, Childrens Hospital Los Angeles (Los Angeles, CA, USA). The remaining 165 cases were not evaluated prognostically by the central review due to sampling problems (limited amount and/or severe crush artifact) or no samples submitted for the review. Appropriate informed consent procedures were followed, with consent being obtained from patient's parents or guardians.

First, prognostic effects by the age for all 911 patients were tested at 3 different cut-off points of 12 months, 18 months, and 24 months at the time of diagnosis. Then survival rates of the patients in the FH group and UH group according to the INPC ($N = 746$) were analyzed, and then compared among the cohorts based on these different age cut-offs: i.e., FH < or $\geqslant$12 months (365 days) vs. UH < or $\geqslant$12 months; FH < or $\geqslant$18 months (547 days) vs. UH < or $\geqslant$18 months; and FH < or $\geqslant$ 24 months (730 days) vs. UH < or $\geqslant$24 months.

2.1. *Statistical analysis*

Tests of association were performed using a chi-squared test. For univariate prognostic analyses, event-free survival (EFS) rates and overall survival (OS) rates from study entry were calculated by the Kaplan–Meier method[24] at the Children's Oncology Group Data Statistics Center (Arcadia, CA, and Gainesville, FL, USA). As was done by London[18] the 'events' considered were: relapse, disease progression, second malignancy, and death (whichever came first). The log-rank statistic[25] was used to compare the EFS and OS probabilities of the individual prognostic subgroups. Survival rates for EFS and OS are quoted as the 9-year rate ± standard errors (per Peto[26]).

Multivariable analyses were performed using a Cox proportional hazards regression model,[27] and terms with $P < 0.05$ were considered statistically significant.

3. Results

Table 1 compares the overall study cohort of 911 patients and the sub-cohort of 746 patients whose tumours were evaluated by the central pathology review. The patients are segregated by CCG study, clinical stage, INPC evaluation, and age at diagnosis. A separate analysis (data not shown) demonstrated no significant differences between the two cohorts, in terms of the average age at diagnosis, distribution of cases by clinical stage, overall EFS, and overall OS. It was noted that, regardless of the age cut-offs, the older age groups always included

Table 1 – Study cases

	No.	Age cut-off (at the time of diagnosis)					
		<12 months	⩾12 months	<18 months	⩾18 months	<24 months	⩾24 months
Protocol[1]							
CCG-3881	500	334	166	391	109	416	84
CCG-3891	411	16	395	72	339	122	289
Clinical stage[2]							
I, II, IVS	309	201	108	236	73	253	56
III, IV	602	149	453	227	375	285	317
Histopathology[3]							
FH	427	278	149	341	86	365	62
UH	319	25	294	57	262	96	223

Histopathology: a total of 746 cases reviewed according to the International Neuroblastoma Pathology Classification; FH: favourable histology; UH: unfavourable histology; NE: not evaluable Patient distributions in Protocol Assignment[1], Clinical stage[2], and Histopathology Classification[3]: always significantly different between age groups ($p < 0.0001$).

significantly more numbers of cases in 3891 studies, in the advanced clinical stages (stage III and IV), and in the UH group than the younger age groups ($P < 0.0001$ for all comparisons). Tumour category and subtype for the 746 cases are listed in the Table 2.

Due to the use of age-dependent ranges for morphologic features in defining INPC, there are distinctly different patterns for age distribution of the patients in the FH and UH groups (Fig. 1). The majority of the cases in the FH group were diagnosed in the first year of life, with the numbers sharply declining afterwards. In contrast, the number of UH tumours began to increase late in the first year of life, with a peak incidence between 24 and 30 months of age at diagnosis in this series. These two curves crossed between 18 months and 24 months of age.

When survival rates for all cases ($N = 911$) were analyzed, both EFS and OS were significantly ($P < 0.0001$) different between age groups for cut-offs at 12, 18, and 24 months (see EFS curves in Fig. 2a–c): 81.5 ± 9% EFS and 90.7 ± 6% OS for patients <12 months vs. 41.1 ± 5% EFS and 45.4 ± 5% OS for patients ⩾12 months; 77.2 ± 8% EFS and 84.9 ± 6% OS for patients <18 months vs. 35.5 ± 5% EFS and 40.3 ± 5% OS for patients ⩾18 months; 73.9 ± 7% EFS and 81.1 ± 6% OS for patients <24 months vs. 31.6 ± 4% EFS and 36.4 ± 6% OS for patients ⩾24 months. Prognostic differences in EFS and OS rates between the age groups by these 3 age cut-offs were also significant among the 746 cases with histopathology evaluation (data not shown). The INPC also significantly ($P < 0.0001$) distinguished FH with an excellent prognosis (EFS 89.3 ± 6%; OS 96.1 ± 3%) and UH with a worse prognosis (EFS 26.8 ± 5%, OS 32.2 ± 5%) (EFS curves in Fig. 2d).

INPC had prognostic significance within age group, regardless of the cut-off used to make the two age groups (Fig. 3).

Table 2 – Tumour category and subtype according to the INPC

Category/Subtype	FH	UH
NB		
Undiff. and low MKI	0	2
Undiff. and intermediate MKI	0	1
Undiff. and high MKI	0	7
Poorly diff. and low MKI	233	69
Poorly diff. and intermediate MKI	58	63
Poorly diff. and high MKI	0	114
Diff. and low MKI	63	2
Diff. and intermediate MKI	10	4
Diff. and high MKI	0	4
GNB, Intermixed	30	0
GNB, Nodular	23	53
GN, Maturing subtype	10	0
Total	427	319

INPC: International Neuroblastoma Pathology Classification; FH: favourable histology; UH: unfavourable histology; NB; neuroblastoma (Schwannian Stroma-poor) category; Undiff.: undifferentiated subtype; Poorly diff.: poorly differentiated subtype; Diff.: differentiating subtype; GNB, Intermixed: ganglioneuroblastoma, intermixed (Schwannian stroma-rich) category; GNB, Nodular: ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-poor and stroma-poor) category; GN: ganglioneuroma category; MKI: mitosis-karyorrhexis index.

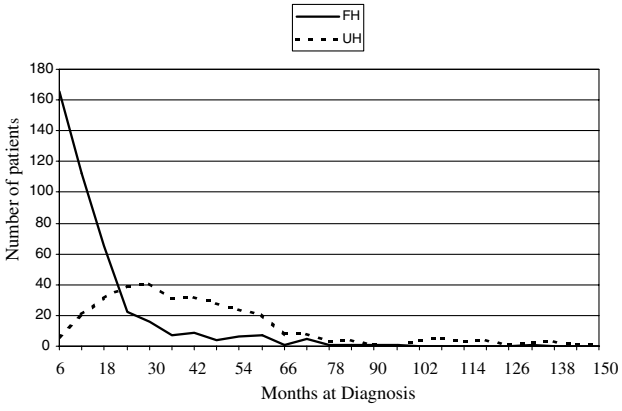

Fig. 1 – Age distribution of the patients with peripheral neuroblastic tumours. FH: patients in the favourable histology group, UH: patients in the unfavourable histology group.

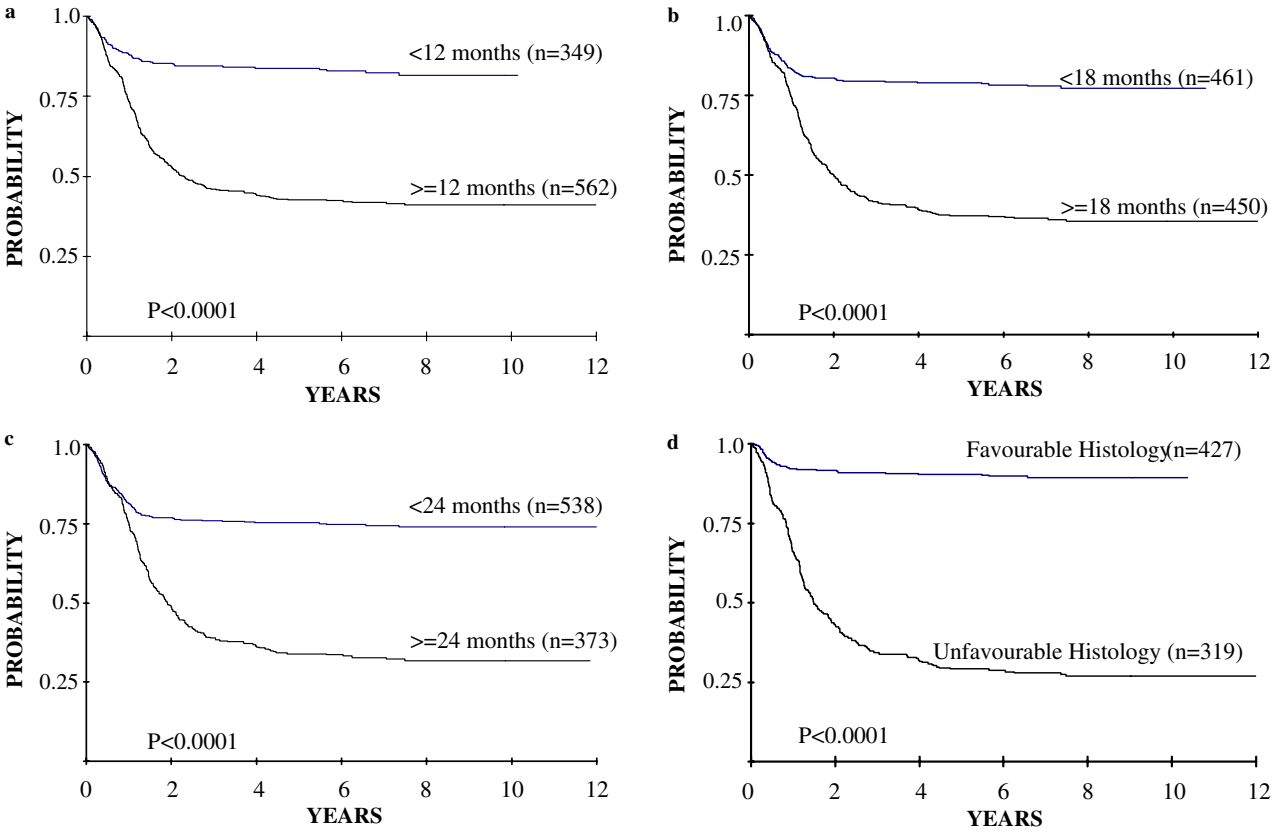

Fig. 2 – Kaplan–Meier curves for event-free survival by age-cut off at: (a) 12 months, (b) 18 months, and (c) 24 months at diagnosis; and (d) by the International Neuroblastoma Pathology Classification.

Within each age group, FH predicted an excellent prognosis and UH predicted a poor clinical outcome ($P < 0.0001$). Survival rates (EFS and OS) for patients <12 months with FH tumours were 88.5 ± 8% and 96.6 ± 4%, and for those <12 months with UH tumours were 40.2 ± 22% and 54.7 ± 21%. Whereas survival rates (EFS and OS) for patients ⩾12 months with FH tumours were 90.6 ± 8% and 95.1 ± 6% and for those ⩾12 months with UH tumours were 25.7 ± 5% and 30.2 ± 5%. Survival rates (EFS and OS) for patients <18 months with FH tumours were 88.9 ± 7% and 96.4 ± 4%, and for those <18 months with UH tumours were 31.7 ± 13% and 38.4 ± 13%. Whereas survival rates (EFS and OS) for patients ⩾18 months with FH tumours were 90.6 ± 9% and 95.0 ± 7%, and for those ⩾18 months with UH tumours were 31.7 ± 13% and 38.4 ± 13%. Survival rates (EFS and OS) for patients <24 months with FH tumours were 89.1 ± 4% and 96.3 ± 4%, and for those <24 months with UH tumours were 36.8 ± 9% and 41.9 ± 9%. Whereas survival rates (EFS and OS) for patients ⩾24 months with FH tumours were 90.3 ± 11% and 94.9 ± 8%, and for those ⩾24 months with UH tumours were 22.7 ± 5% and 28.0 ± 6%.

With multivariable analysis, we performed a comparison of the independent prognostic ability of age and INPC (Table 3, Model A) versus age and the underlying components of INPC: i.e., two histologic features of grade of neuroblastic differentiation and MKI (Table 3, Model B). Each Model was run on the same cohort of $n = 698$ patients with diagnostic categories neuroblastoma or ganglioneuroblastoma, nodular where those two histologic features were critical for prognostic evaluation. In Model A, the INPC criteria (using 2 age cut-offs of 18 and 60 months) added independent prognostic information beyond the prognostic contribution of age by itself. In Model B, we removed the redundant (confounding) effect of age, yet still included the important histologic information: age, grade of neuroblastic differentiation, and MKI were independently prognostic of outcome.

4. Discussion

This is the first study reporting a relationship in detail between the age factor and the age-linked histopathological classification for pNTs. The latest report clearly indicated that historical benchmark of age cut-off point at one year for prognostic distinction of the patients with pNTs was too low, and suggested that a new cut-off should be greater than 12 months and could be set around 18 months of age.[18] Whereas, the INPC is based on a unique system where prognostic impact of the individual histologic features depends on the patient's age at diagnosis, and it uses 2 age cut-offs at 18 months (547 days) and 60 months (1826 days) old.[10,11]

First, we confirmed that all 3 cut-offs tested in this study (12 months, 18 months, and 24 months) significantly distinguished favourable and unfavourable clinical outcomes. We did not attempt to perform an exhaustive search for an optimal age cut-off within the relatively small number of cases in our series. Regardless of the cut-off points, more patients in

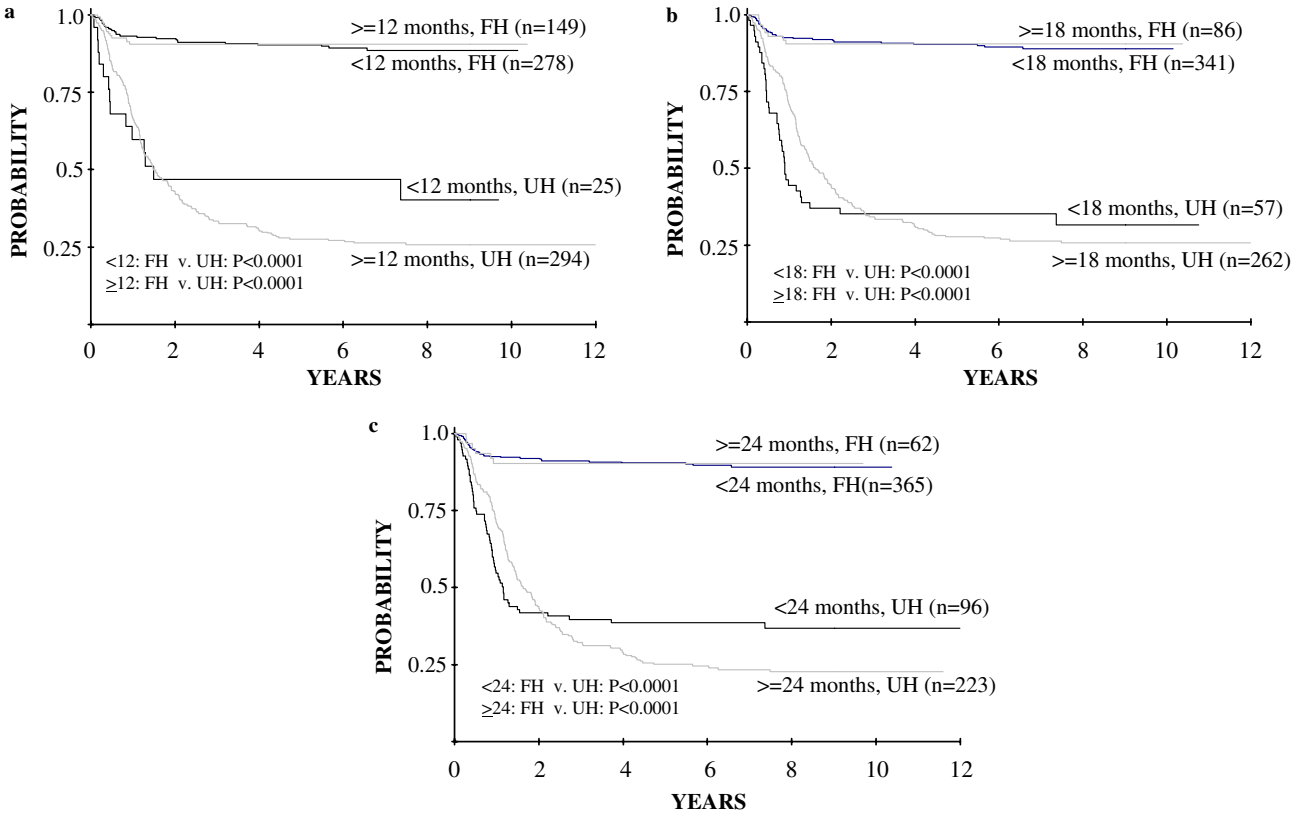

Fig. 3 – Kaplan–Meier curves for event-free survivals showing prognostic significance of the International Neuroblastoma Pathology Classification (FH: favourable histology, UH: unfavourable histology) within different age groups (a) <12 months, ⩾12 months; (b) <18 months, ⩾18 months; and, (c) <24 months, ⩾24 months. Within each age group, FH patients have statistically significantly higher EFS than UF patients ($P < 0.0001$).

Table 3 – Multivariable models to assess independent prognostic ability of age and INPC

Cohort	Model	*n*	Hazard ratio	*p*-value[a]
Patients with diagnostic categories of neuroblastoma or ganglioneuroblastoma, nodular	A	698		
	Age 18–60 months (547–1825days)		0.92	0.6088
	Age ⩾ 60 months (1826 days)		1.00	0.9894
	INPC		10.86	<0.0001
	B	698		
	Age 18–60 months (547–1825 days)		3.74	<0.0001
	Age ⩾ 60 Months (1826 days)		5.01	<0.0001
	Grade (poorly diff., undiff.)		2.14	0.0024
	MKI (intermediate, high)		2.15	<0.0001

Grade: grade of neuroblastic differentiation; poorly diff.: poorly differentiated subtype; undiff.: undifferentiated subtype; MKI: mitosis-karyorrhexis index.
a Likelihood ratio test from the Cox proportional hazards model.

the younger age groups had favourable prognostic indicators (stages I, II, IVS and FH) than those in the older age groups. In contrast, more patients in the older age group had unfavourable prognostic factors (stages III, IV and UH) than those in the younger age groups. Patients in the younger age groups were more frequently treated according to the CCG-3881 protocol, and patient in the older age groups were more often treated by the CCG-3891 protocols.

Since the age is one of the built-in components of the INPC, it would be inappropriate to assess individual prognostic contributions in one risk model where these two factors (age and INPC) are included at the same time, and especially when they share the same age cut-off of 18 months. In this study, we clearly demonstrated that INPC retains prognostic significance regardless of age group. FH patients had statistically significantly higher EFS than UH patients did within all

age groups: i.e., within < or ⩾12 months; within <18 or ⩾18 months; and within <24 or ⩾24 months.

The multivariable model results showed that INPC has prognostic information over and above that of age. Conversely, the same can be said of age, that age has prognostic information over and above that of the underlying components of INPC: grade of neuroblastic differentiation and MKI. All components (age, grade of neuroblastic differentiation and MKI) contributing to the evaluation system of INPC had independent prognostic information.

Recent advances in clinical, translational, and basic research[2,28] suggest that genomic aberrations in tumour cells could provide more sensitive and specific prognostic information for developing our future strategy in pNT patient management. Age is a surrogate for increasing risk for failure in the developmentally dynamic environment of a young patient. As additional prognostic factors are identified, age will eventually be replaced by these factors. We believe that pNTs are a good model for analyzing histopathologic changes as manifestations of various genomic aberrations. For example, reports demonstrating significant relationship between *MYCN* amplification and histopathology[29–31] and between trkA expression and histopathology[32] in pNTs have already been published. In this respect, the age-linked histopathology classification can be a key and the most important risk factor for this complicated disease in infants and young children.

Three age cut-offs were tested, and regardless of the choice of age cut-off, the prognostic ability of INPC was retained. Three critical components in INPC: i.e., age, grade of neuroblastic differentiation, and MKI, had independent prognostic ability. INPC, using an evaluation system by combination of these 3 components, served better than age by itself for prognostic distinction of the pNT patients.

Conflict of interest statement

None declared.

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