

International Neuroblastoma Pathology Classification for Prognostic Evaluation of Patients with Peripheral Neuroblastic Tumors

A Report from the Children's Cancer Group

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Supported in part by grant CA 13539 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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Received May 18, 2001; revision received July 23, 2001; accepted July 24, 2001.

BACKGROUND. The International Neuroblastoma Pathology Classification was established in 1999 for the prognostic evaluation of patients with neuroblastic tumors (NTs).

METHODS. Pathology slides from 746 NTs (the Children's Cancer Group [CCG]-3881 and CCG-3891 studies) were evaluated according to the International Classification. First, prognostic effects of the morphologic indicators (grade of neuroblastic differentiation: undifferentiated [U], poorly differentiated [PD] and differentiating [D]; and mitosis-karyorrhexis index [MKI]: low [L-MKI], intermediate [I-MKI], and high [H-MKI]) for tumors in the neuroblastoma (NB) category were tested. Then, prognostic significance of the International Classification for all NTs in four categories (neuroblastoma [NB]; ganglioneuroblastoma, intermixed [GNBi]; ganglioneuroma [GN]; and ganglioneuroblastoma, nodular [GNBn]) was analyzed. Finally, age distribution of the patients in the four categories as well as three subtypes (based on the grade of differentiation) in the NB category was compared.

RESULTS. There were 630 NB tumors, 30 GNBi tumors, 10 GN tumors, and 76 GNBn tumors. In the NB category, prognostic effects of the indicators (three grades of differentiation and three mitosis-karyorrhexis index [MKI] classes: low [L], intermediate [I], and high [H]) were affected significantly by the age of the patients. The age-linked evaluation of the indicators according to the International Classification successfully distinguished two prognostic subgroups: the favorable histology (FH) subgroup (PD/D and L/I-MKI tumors in patients age < 1.5 years, D and L-MKI tumors in patients ages 1.5–5.0 years; 90.4% 5-year event free survival [EFS]) and the unfavorable histology (UH) subgroup (U and/or H-MKI tumors in patients of any age, PD and/or I-MKI tumors in patients ages 1.5–5.0 years, any grade of differentiation, and any MKI class in patients age ≥ 5 years; 26.9% EFS) ($P < 0.0001$). The International Classification also distinguished the FH group (FH subgroup with NB, GNBi, and GN tumors) and the UH group (UH subgroup with NB and GNBn tumors) for all NTs (90.8% EFS and 31.2% EFS, respectively; $P < 0.0001$) and provided independent prognostic information on both patient age and disease stage ($P < 0.0001$). Among patients with FH tumors, the median ages of patients with the PD and D subtype tumors in the NB category were 0.43 years (range, 0–1.50 years) and 1.50 years (range, 0.02–4.65 years), respectively, and the median ages of patients with GNBi and GN tumors were 3.51 years (range, 0.96–14.85 years) and 4.80 years (range, 1.94–17.05 years), respectively. In contrast, patients with UH tumors generally were older when they were diagnosed, and with median ages of 2.99 years (range, 1.30–8.84 years) for patients with U subtype tumors, 2.59 years (range, 0.0–12.57 years) for patients with PD subtype tumors, 2.16 years (range, 0.35–9.90) for patients with D subtype tumors, and 3.26 years (range, 0.57–15.90 years) for patients with GNBn tumors.

CONCLUSIONS. This study confirmed the prognostic significance of the International Classification, substantiated age-linked prognostic effects of the morphologic indicators for patients with the tumors in the NB category, and supported the concept of an age-appropriate framework of maturation for patients with the tumors in the FH group. *Cancer* 2001;92:2451-61.

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KEYWORDS: neuroblastic tumors, histopathology, International Neuroblastoma Pathology Classification, Shimada system, prognosis, differentiation, mitosis-karyorhexis index, age.

Peripheral neuroblastic tumors (NTs), including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas, make up one of the most common groups of solid tumors in childhood.¹ In 1999, the International Neuroblastoma Pathology Classification (the International Classification) was established to standardize the terminology and the criteria for the prognostic evaluation of morphologic features of NTs.^{2,3} This is an age-linked classification that adopts the basic concept of the Shimada system, which was developed originally in 1984.⁴ The prognostic significance and biologic relevance of the International Classification have been discussed in detail by the International Neuroblastoma Pathology Committee in preceding articles.^{2,3}

Modifications and differences between the original Shimada classification⁴ and the International Classification^{2,3} are summarized as follows: 1) Individual categories have corresponding grades of Schwannian stromal development in parenthesis: such as neuroblastoma (Schwannian stroma-poor); ganglioneuroblastoma, intermixed (Schwannian stroma-rich); ganglioneuroma (Schwannian stroma-dominant); and ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor). 2) There are three subtypes; i.e., undifferentiated, poorly differentiated, and differentiating, in the tumors of the neuroblastoma category (the original Shimada classification included only two subtypes of undifferentiated and differentiating). 3) There are two subtypes, maturing and mature, in the ganglioneuroma category and the *ganglioneuroblastoma, well differentiated* subtype in the original Shimada classification is now renamed *ganglioneuroma, maturing subtype*.

In this report, we present the results of our pathology review by applying the International Classification to a large number of patients from the Children's Cancer Group (CCG) studies, confirming its prognostic significance and supporting the concept of an age-linked framework of the morphologic features in this disease.

MATERIALS AND METHODS

A total of 911 patients with NTs were enrolled on the CCG-3881 and CCG-3891 studies from August 1, 1991 to August 1, 1995. Treatment protocols of these two studies depended on risk groups⁵⁻⁹ defined by age, Evans clinical stage,¹⁰ and tumor biology (MYCN status,¹¹ histopathology according to the original Shimada classification,⁴ and serum ferritin level¹²). The CCG-3881 protocol included biopsy or surgery alone for low-risk patients and biopsy or surgery plus chemotherapy for intermediate-risk patients. The CCG-3891 protocol had aggressive treatment with or without bone marrow transplantation for high-risk patients. Appropriate informed consent procedures were followed, and consent was obtained from parents or guardians.

Among these 911 patients, pathology slides from 746 tumors that were either biopsied or removed surgically prior to chemotherapy and/or irradiation, were reviewed centrally and evaluated according to the International Classification. Hematoxylin and eosin-stained sections from these patients (1-42 sections from each tumor; median, 6 sections per tumor) were available for this study. A total of 165 patients were excluded from this study: They included 102 unassessable patients due to a limited amount of tissue for the histopathology evaluation, 61 patients with no pathology slides available for the review, and 2 patients with incorrect diagnoses (hepatoblastoma and adrenal hematoma). Of these patients who were excluded, 101 patients (61.2%) were diagnosed age \geq 1 year and had Stage IV disease, so that the data in this series underrepresented this group of patients.

Histologic Evaluation

Histologic features were evaluated and recorded by the reviewer pathologists (H.S., S.U., Y.M., Y.H., A.N., and S.G.) according to the International Classification³ without knowing clinical information (see Table 1). The individual tumors were classified into four categories: neuroblastoma (Schwannian stroma-poor); ganglioneuroblastoma, intermixed (Schwannian stroma-rich); ganglioneuroma (Schwannian stroma-domi-

TABLE 1
International Neuroblastoma Pathology Classification

Category and subtype	Prognostic group
Neuroblastoma (Schwannian stroma-poor)	
Undifferentiated	FH and UH subgroups, based on the combination of age, grade of neuroblastic differentiation, and MKI class (see Fig. 2)
Poorly differentiated	
Differentiating	
Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)	FH
Ganglioneuroma (Schwannian stroma-dominant)	FH
Maturing	
Mature	
Ganglioneuroblastoma, nodular (Schwannian stroma-rich/stroma-dominant and stroma-poor)	UH ^a

FH: favorable histology; UH: unfavorable histology; MKI: mitosis-karyorrhexis index.

^a Tumors in this category were classified into an unfavorable histology group according to the International Neuroblastoma Pathology Classification. However, two prognostic subsets, i.e., favorable and unfavorable, are distinguished based on the results of our recent study.¹⁷

nant); and ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor). The tumors in the neuroblastoma category were further divided into three subtypes—undifferentiated, poorly differentiated, and differentiating—based on the grade of neuroblastic differentiation. Three mitosis-karyorrhexis index (MKI) classes (low, < 2% or < 100/5000 mitotic and karyorrhectic cells; intermediate, 2–4% or 100–200/5000 mitotic and karyorrhectic cells; and high, > 4% or > 200/5000 mitotic and karyorrhectic cells) also were distinguished in the tumors of the neuroblastoma category. The tumors in the ganglioneuroma category were classified into two subsets: maturing and mature.

Prognostic Analysis

Event free survival (EFS) and overall survival (OS) from study entry were estimated by using the Kaplan–Meier method.¹³ The log-rank statistic was used to compare the EFS and OS probabilities of the individual prognostic groups. EFS and OS, if not otherwise listed in the text, represent calculated rates at 5 years from study entry. First, prognostic effects of the morphologic indicators (grade of neuroblastic differentiation and MKI) for the tumors in the neuroblastoma category were tested individually. Then, age-linked prognostic effects of these indicators were analyzed by using the age cut-off points (age 1.5 years and 5.0 years at the time of diagnosis) according to the International Classification. Based on the combination of the grade of neuroblastic differentiation and the age of the patients, the tumors were classified into five dif-

ferent prognostic subgroups, i.e., undifferentiated subtype in patients of any age, poorly differentiated subtype in patients age < 1.5 years, poorly differentiated subtype in patients age ≥ 1.5 years, differentiating subtype in patients age < 5.0 years, and differentiating subtype in patients age ≥ 5.0 years. Based on the combination of the MKI classes and the age of the patients, there were also five different subgroups for prognostic analysis: low MKI at age < 5.0 years, low MKI at age ≥ 5.0 years, intermediate MKI at age < 1.5 years, intermediate MKI at age ≥ 1.5 years, and high MKI at any age.

To test the prognostic effects of the International Classification, all NTs were classified into either a favorable histology (FH) group or an unfavorable histology (UH) group according to the Shimada system. FH tumors in the neuroblastoma category were put into the FH subgroup and included 1) poorly differentiated or differentiating subtype tumors with low or intermediate MKI (age < 1.5 years) and 2) differentiating subtype tumors with low MKI (age < 5.0 years), whereas UH tumors in the neuroblastoma category were put into the UH subgroup and included 1) undifferentiated subtype tumors (any age), 2) poorly differentiated subtype tumors (age ≥ 1.5 years), 3) high MKI (any age), 4) intermediate MKI (age ≥ 1.5 years), and 5) all neuroblastoma tumors (age ≥ 5 years with any grade of neuroblastic differentiation and any class of MKI). Regardless of the patient's age, tumors in the ganglioneuroblastoma, intermixed category and the ganglioneuroma category were classified into the FH group, whereas tumors in the ganglioneuroblastoma, nodular category were classified into the UH group.^{2–4}

Analysis of Age Distribution

Defining NTs according to the age-linked framework of tumor maturation is the primary concept of the International Classification. By using the patients in this series, the age distribution of the patients with NTs of different categories (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) and subtypes (undifferentiated, poorly differentiated, and differentiating in the neuroblastoma category) were compared by testing the median age between all pairwise combinations using the Mann–Whitney test.¹⁴

RESULTS

Histologic features of all 746 tumors are listed in Table 2, which also shows a breakdown of the patients according to the clinical stage and age distribution.

TABLE 2
International Neuroblastoma Pathology Classification for Patients in the Children's Cancer Group 3881/3891 Study

Classification	Clinical stage					Age at diagnosis		
	I	II	III	IV	IV-S	< 1.5 yrs	1.5-5.0 yrs	≥ 5 yrs
Neuroblastoma (Schwannian stroma-poor) category (N = 630)								
Undifferentiated subtype								
Low MKI	2	0	0	1	1	0	1	1
Intermediate MKI	1	0	0	1	0	0	1	0
High MKI	7	0	0	2	5	0	4	1
Poorly differentiated subtype								
Low MKI	302	50	59	63	92	38	233	15
Intermediate MKI	121	9	12	24	64	12	58	11
High MKI	115	0	3	24	88	0	62	4
Differentiating subtype								
Low MKI	65	14	28	18	3	2	26	2
Intermediate MKI	14	1	5	4	3	1	10	1
High MKI	3	1	0	0	2	0	3	0
Ganglioneuroblastoma, Intermixed (Schwannian stroma-rich) category								
	30	6	16	8	0	0	4	8
Ganglioneuroma (Schwannian stroma-dominant) category								
Maturing	10	4	3	3	0	0	0	5
Mature	0	0	0	0	0	0	0	0
Ganglioneuroblastoma, nodular (composite: Schwannian stroma-rich/stroma-dominant and stroma-poor) category								
	76	6	17	14	39	0	15	15
Total	746	91	143	162	297	53	400	63

MKI: mitosis-karyorrhexis index.

Prognostic Effects of the Morphologic Indicators for Tumors in the Neuroblastoma (Stroma-poor) Category

There were significant differences in prognosis for the three different grades of differentiation among the patients with tumors in the neuroblastoma category: The EFS and OS rates for patients with undifferentiated, poorly differentiated, and differentiating tumor subtypes were 30.0%, 61.0%, and 81.4%, respectively, for EFS ($P = 0.0009$) and 50.0%, 69.0%, and 87.3%, respectively, for OS ($P = 0.0017$) (Fig. 1a, Table 3). Furthermore, the prognostic effects of the grade of neuroblastic differentiation were affected significantly by patient age at the time of diagnosis. For patients with tumors of the poorly differentiated subtype, the EFS (82.9%) and OS (89.6%) rates for patients age < 1.5 years ($n = 340$ patients) were significantly better compared with patients age ≥ 1.5 years (25.4% and 35.2%, respectively; $n = 198$ patients). For patients with tumors of the differentiating subtype, EFS (84.5%) and OS (90.8%) rates of patients age < 5.0 years ($n = 79$) also were significantly better compared with the EFS and OS rates (both 0%) of patients age ≥ 5.0 years ($n = 3$ patients). There were only 10 patients who were diagnosed with tumors of the undifferentiated subtype, and they had a poor prognosis regardless of their age (30.0% EFS, 50.0% OS). These results indicated

that two different prognostic subsets, i.e., a favorable subset, including *poorly differentiated subtype tumors in patients age < 1.5 years* and *differentiating subtype tumors in patients age < 5.0 years*, and an unfavorable subset, including *undifferentiated subtype tumors in patients of any age*, *poorly differentiated subtype tumors in patients age ≥ 1.5 years*, and *differentiating subtype tumors in patients age ≥ 5.0 years*, were determined by age-linked evaluation of the grade of neuroblastic differentiation in the tumors of the neuroblastoma category ($P < 0.0001$ for EFS; $P < 0.0001$ for OS) (see Fig. 1b; Table 3).

Figure 1c shows that three MKI classes had significantly different prognostic effects: The EFS and OS rates for low MKI, intermediate MKI, and high MKI were 79.1%, 50.4%, 30.2% ($P < 0.0001$) and 86.3%, 60.6%, 37.5% ($P < 0.0001$), respectively. When EFS and OS were analyzed for the five prognostic subgroups based on the combination of MKI and age of the patients, two prognostic subsets were distinguished (Fig. 1d; Table 3): A subset consisting of tumors with low MKI in patients age < 5.0 years ($n = 351$ patients; 82.1% EFS; 89.2% OS) and tumors with intermediate MKI in patients age < 1.5 years ($n = 68$ patients; 84.9% EFS; 94.0% OS) had a significantly better prognosis than the other subset, which consisted of tumors with

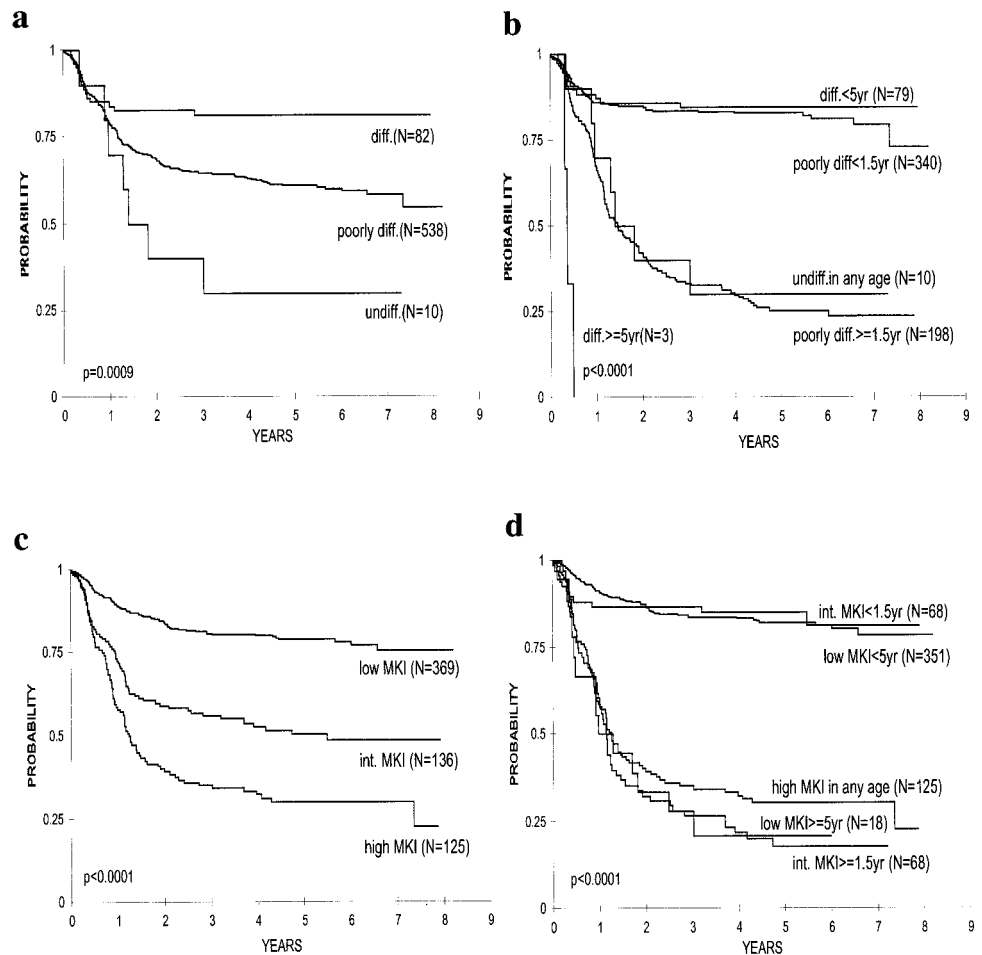


FIGURE 1. Event free survival by morphologic indicators for patients with tumors in the neuroblastoma category. (a) Prognostic effects by three different grades of neuroblastic differentiation for all age groups. (b) Age-linked prognostic effects by three different grades of neuroblastic differentiation. (c) Prognostic effects by three different mitosis-karyorrhexis index (MKI) classes for all age groups. (d) Age-linked prognostic effects of three MKI classes. diff.: differentiating subtype; poorly diff.: poorly differentiated subtype; undiff.: undifferentiated subtype; int. MKI: intermediate MKI. For the numbers of patients at risk at 1 year, see Table 3.

low MKI in patients age ≥ 5.0 years ($n = 18$ patients; 20.8% EFS; 27.0% OS), tumors with intermediate MKI in patients age ≥ 1.5 years ($n = 68$ patients; 17.8% EFS; 26.6% OS), and tumors with high MKI in patients of all ages ($n = 125$ patients; 30.2% EFS; 37.5% OS; $P < 0.0001$ for EFS; $P < 0.0001$ for OS). Again, the results indicated that two different prognostic subsets were distinguished by the age-linked evaluation of the MKI classes ($P < 0.0001$ for EFS; $P < 0.0001$ for OS).

The results of these analyses confirmed the system used by the International Classification for prognostic evaluation, i.e., the age-linked assessment of the two morphologic indicators (grade of neuroblastic differentiation and MKI) for tumors in the neuroblastoma category (see Materials and Methods, above). The distinctions between two large prognostic subgroups, the FH subgroup ($n = 364$ patients; 90.4% EFS; 97.8% OS) and the UH subgroup ($n = 266$ patients; 26.9% EFS; 35.6% OS), in the neuroblastoma category are summarized in Figure 2 ($P < 0.0001$ for EFS; $P < 0.0001$ for OS). Further analysis of prognostic distinction by FH or UH subgroup stratified by both

disease stage and patient age (where the cut-off points are at either age < 1 year and age ≥ 1 year or at ages < 1.5 years, 1.5–5.0 years, and ≥ 5.0 years) showed that the stratified log-rank P value was < 0.0001 for both EFS and OS.

Prognostic Significance of the International Neuroblastoma Pathology Classification for All Neuroblastic Tumors (Neuroblastoma; Ganglioneuroblastoma, Intermixed; Ganglioneuroma; and Ganglioneuroblastoma, Nodular)

Two prognostic subgroups, favorable and unfavorable, as discussed above, were distinguished clearly for patients with tumors in the neuroblastoma category. It was noted that there were no deaths from patients with tumors in the ganglioneuroblastoma, intermixed category (93.2% EFS; 100% OS) or with tumors in the ganglioneuroma, maturing category (100% EFS; 100% OS), in contrast to a significantly poor prognosis in patients with tumors in the ganglioneuroblastoma, nodular category (46.8% EFS; 59.1% OS) in this series ($P < 0.0001$ for EFS; $P = 0.0002$ for

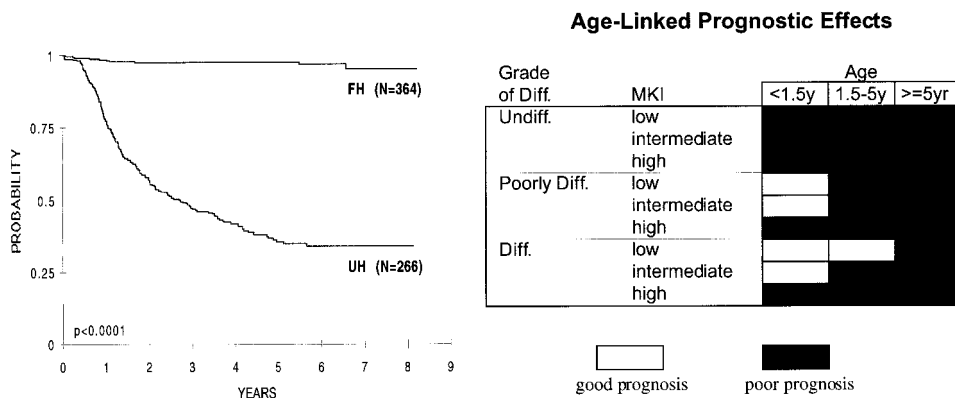


FIGURE 2. Prognostic distinctions according to the International Neuroblastoma Pathology Classification for patients with tumors in the neuroblastoma category. (Left) Event free survival for patients with tumors in the favorable histology subgroup (FH) and the unfavorable histology subgroup (UH) in the neuroblastoma category. (Right) Summary of age-linked prognostic effects by two morphologic indicators: the grade of neuroblastic differentiation (Grade of Diff.: Undiff., undifferentiated; Poorly Diff., poorly differentiated; and Diff., differentiating) and mitosis-karyorrhexis index (MKI; low, intermediate, and high). The numbers of patients at risk at year are shown in Table 3.

OS). In summary, 404 tumors (neuroblastoma, FH subgroup [364 patients]; ganglioneuroblastoma, intermixed [30 patients]; ganglioneuroma, maturing [10 patients]) were classified into the FH group, and 342 tumors (neuroblastoma, UH subgroup [266 patients]; ganglioneuroblastoma, nodular [76 patients]) were classified into the UH group according to the International Classification. The patients with FH tumors had a 90.8% EFS rate and a 98.0% OS rate. Patients with UH tumors had a significantly worse prognosis, and their EFS and OS rates were 31.2% ($P < 0.0001$) and 40.8% ($P < 0.0001$), respectively (Fig. 3a).

Figure 3b-f and Table 4 show the distinct prognostic effects of FH and UH groups by clinical stage. There were 91 patients with Stage I disease (80 FH tumors: 93.6% EFS; 100% OS; 11 UH tumors: 72.7% EFS; 81.8% OS; $P = 0.0166$ for EFS; $P < 0.0001$ for OS); 143 patients with Stage II disease (123 FH tumors: 86.6% EFS; 99.1% OS; 20 UH tumors: 64.2% EFS; 82.1% OS; $P = 0.0093$ for EFS; $P = 0.0003$ for OS); 162 patients with Stage III disease (93 FH tumors: 96.8% EFS; 98.9% OS; 69 UH tumors: 63.8% EFS; 67.5% OS; $P < 0.0001$ for EFS; $P < 0.0001$ for OS); 297 patients with Stage IV disease (55 FH tumors: 90.9% EFS; 92.7% OS; 242 UH tumors: 17.9% EFS; 28.9% OS; $P < 0.0001$ for EFS; $P < 0.0001$ for OS); and 53 patients with Stage IV-S disease (all FH tumors: 85.6% EFS; 96.2% OS).

Age Distribution of the Patients

Among patients with tumors in the FH group, the maturation grades gradually advanced according to the age of the patients: The median age of patients with tumors in the neuroblastoma, poorly differentiated category was 0.43 years (range, 0-1.5 years); the

median age of patients with tumors in the neuroblastoma, differentiating category was 1.5 years (range, 0.02-4.65 years); the median age of patients with tumors in the ganglioneuroblastoma, intermixed category was 3.51 years (range, 0.96-14.85 years); and the median age of patients with tumors in the ganglioneuroma, maturing category was 4.80 years (range, 1.94-17.05 years; $P < 0.0001$ for neuroblastoma, poorly differentiated vs. differentiating; $P < 0.0001$ for neuroblastoma, differentiating vs. ganglioneuroblastoma, intermixed; $P = 0.1298$ for ganglioneuroblastoma, intermixed vs. ganglioneuroma, maturing). There were no statistically significant differences in age distribution between histologic subtypes among UH tumors in the neuroblastoma category: The median age of patients with tumors of the undifferentiated subtype was 2.99 years (range, 1.30-8.84 years); the median age of patients with tumors of the poorly differentiated subtype was 2.59 years (range, 0.0-12.57 years); and the median age of patients with tumors of the differentiating subtype was 2.16 years (range, 0.35-9.90 years). However, those patients with tumors in the ganglioneuroblastoma, nodular category (median, 3.26 years; range, 0.57-15.90 years) were diagnosed at a significantly older age than children with UH tumors in the neuroblastoma category ($P = 0.0414$). It was noted that the patients with UH tumors in the neuroblastoma category, regardless of their subtypes (undifferentiated, poorly differentiated, or differentiating), generally were older than the patients with FH tumors (poorly differentiated and differentiating subtypes) in the same category ($P < 0.0001$). Patients with tumors in the ganglioneuroblastoma, nodular category in the

TABLE 3
Follow-Up Information for Patients with Neuroblastoma (Schwannian stroma-poor) Tumors According to Morphologic Indicators and Favorable or Unfavorable Histology Subgroup: Numbers of the Patients at Risk at Year for Figure 1 and 2

Year	Figure 1								
	0	1	2	3	4	5	6	7	8
Differentiation									
Diff	82	67	64	61	50	32	20	7	—
Poorly diff	538	417	358	320	256	179	94	38	2
Undiff	10	7	4	4	2	2	2	1	—
Age-linked differentiation									
Diff, age < 5 yrs	79	67	64	61	50	32	20	7	—
Poorly diff, age < 1.5 yrs	340	285	276	256	207	146	76	30	2
Diff, age ≥ 5 yrs	3	—	—	—	—	—	—	—	—
Poorly diff, age ≥ 1.5 yrs	198	132	82	64	49	33	18	8	—
Undiff, any age	10	7	4	4	2	2	2	1	—
MKI									
Low MKI	369	323	299	271	222	151	80	32	2
Int MKI	136	97	79	72	55	39	22	7	—
High MKI	125	71	48	42	31	23	14	7	—
Age-linked MKI									
Low MKI, age < 5 yrs	351	314	293	267	220	149	80	32	2
Int MKI, age < 1.5 yrs	68	57	57	54	42	31	17	5	—
Low MKI, age ≥ 5 yrs	18	9	6	4	2	2	—	—	—
Int MKI, age ≥ 1.5 yrs	68	40	22	18	13	8	5	2	—
High MKI, any age	125	71	48	42	31	23	14	7	—

Year	Figure 2								
	0	1	2	3	4	5	6	7	8
Histology subgroup									
Favorable	364	328	320	300	242	167	90	33	2
Unfavorable	266	163	106	85	66	46	26	13	0

Diff: differentiating; Poorly diff: poorly differentiated; Undiff: undifferentiated; MKI: mitosis-karyorrhexis index; Int. MKI: intermediate MKI.

UH subgroup were similar in age distribution to the patients with tumors in the ganglioneuroblastoma, intermixed or ganglioneuroma, maturing categories in the FH subgroup ($P = 0.2128$).

DISCUSSION

This is the first report presenting the results of a histopathologic review and discussing the morphologic features in detail on a large series of patients with NTs using the International Neuroblastoma Pathology Classification^{2,3} after its establishment. The International Classification successfully distinguished two prognostic groups; i.e., the FH and UH groups. Many of the patients with FH tumors (256 of 404 patients; 63.4%) presented with nonadvanced stages disease (Stage I or II) or with Stage IV-S disease, whereas the majority of patients with UH tumors (311 of 342 patients; 90.9%) had advanced clinical stage disease (Stage III or IV). However, the International Classifi-

cation provided prognostic information independently from both clinical stage and age of the patients.

The International Classification defines NT morphologically based on the concept of tumor maturation^{5,15-18} and classifies NTs into four different categories: neuroblastoma (Schwannian stroma-poor); ganglioneuroblastoma, intermixed (Schwannian stroma-rich); ganglioneuroma (Schwannian stroma-dominant); and ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor). The International Classification also uses two morphologic indicators, i.e., grade of neuroblastic differentiation and MKI, as prognostic indicators for tumors in the neuroblastoma category. This study demonstrated that three grades of neuroblastic differentiation (undifferentiated, poorly differentiated, and differentiating) had significantly different prognostic effects, as did three MKI classes (low, intermediate, and high).

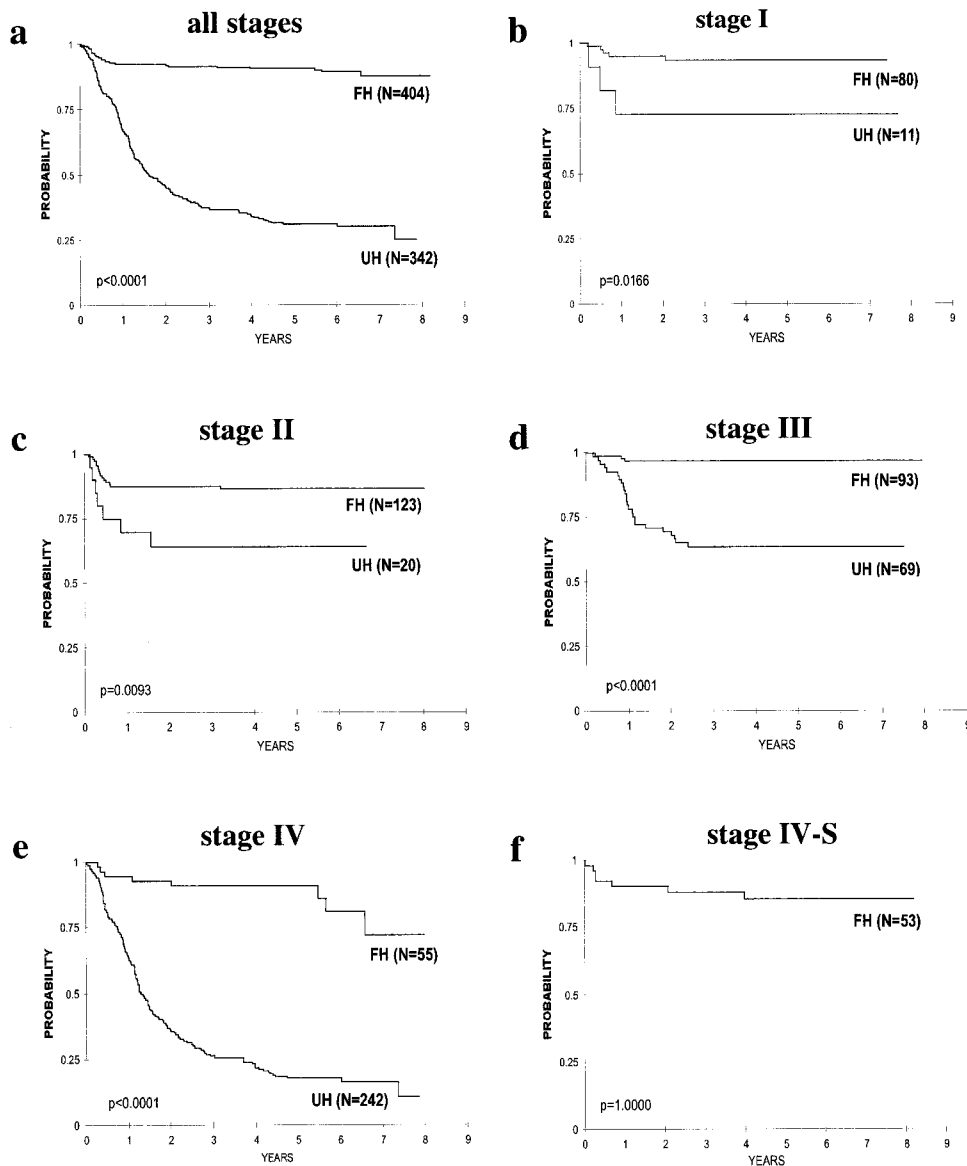


FIGURE 3. Event free survival for all patients with peripheral neuroblastic tumors (neuroblastoma; ganglioneuroblastoma, intermixed; ganglioneuroma; ganglioneuroblastoma, nodular) according to the International Neuroblastoma Pathology Classification. FH: favorable histology, UH: unfavorable histology. (a) Patients with tumors in all stages. (b–f) Patients with individual stage of tumor. The numbers of patients at risk at 1 year are listed in Table 4.

According to the International Classification, however, these morphologic indicators have different prognostic effects linked to the different patient age groups (any age, age < 1.5 years, ages 1.5–5.0 years, and age ≥ 5.0 years). The results of this study proved clearly the significance of the age-linked prognostic effects of these indicators according to the Shimada system: Patients with tumors in the neuroblastoma category were classified into the FH subgroup (those with tumors of the poorly differentiated or differentiating subtype with low or intermediate MKI in children age < 1.5 years and those with tumors of the differentiating subtype with low MKI in children ages 1.5–5.0 years) or into the UH subgroup (those with tumors of the undifferentiated subtype and/or with high MKI in children of any age; those with

tumors of the poorly differentiated subtype and/or with intermediate MKI in children ages 1.5–5.0 years; and those with tumors in this category in children ages ≥ 5.0 years).

It should be noted here that age cut-off values (ages 1.5 years and 5.0 years at the time of diagnosis) used in the International Classification are different from the age cut-off value (age 1 year at the time of diagnosis) commonly used in clinical risk grouping for patients with NTs. Those cut-off values in the International Classification were determined based on the prognostic effects of the morphologic indicators: They were designed to serve as a guideline or framework for defining host (growth)-tumor (morphologic changes) relations but not for use directly for the purpose of prognostic prediction. In con-

TABLE 4
Follow-Up Information for Patients with All Neuroblastic Tumors According to Favorable or Unfavorable Histology Grouping by the International Neuroblastoma Pathology Classification: Numbers of the Patients at Risk at Year of Figure 3

	Year								
	0	1	2	3	4	5	6	7	8
All stages									
FH	404	365	352	329	267	183	97	34	2
UH	342	228	152	120	93	63	34	15	0
Stage I									
FH	80	73	69	62	45	37	17	5	—
UH	11	8	8	6	6	5	3	2	—
Stage II									
FH	123	104	100	92	73	47	31	12	1
UH	20	13	10	9	6	4	1	—	—
Stage III									
FH	93	90	89	89	75	51	24	9	—
UH	69	54	48	41	38	29	16	8	—
Stage IV									
FH	55	52	51	46	42	28	14	5	—
UH	242	153	86	64	43	25	14	5	—
Stage IV-S									
FH	53	46	43	40	32	20	11	3	1
UH	0	—	—	—	—	—	—	—	—

FH: favorable histology; UH: unfavorable histology.

trast, age cut-off values in the clinical risk grouping, by itself, serves as one of the prognostic factors. Based on the results of this study as well as of our previous studies,²⁻⁴ the cut-off ages of 1.5 years and 5.0 years worked best for evaluation of the histologic changes reflecting prognosis of the patients. For future study, however, we should look for more precise parameters for defining biologically significant relations between host (patient) and tumor (NT).

Those patients with tumors in the ganglioneuroblastoma, intermixed category or in the ganglioneuroma, maturing category generally had nonaggressive tumors that did not cause a fatal outcome. In contrast, the patients with tumors in the ganglioneuroblastoma, nodular category had a significantly poor clinical outcome. Recently, by using patients from the same data base used for the CCG-3881 and CCG-3891 studies, we successfully distinguished two distinct prognostic subsets, favorable and unfavorable, in the tumors of the ganglioneuroblastoma, nodular category. The distinction is based on histopathologic evaluation of the nodular neuroblastomatous component by applying the same age-linked histologic features (grade of neuroblastic differentiation and MKI) used in prognostic determination for the tumors in the neuroblastoma category.¹⁹

This study also confirmed the primary concept

of the International Classification, i.e., age-linked maturation sequences for defining NTs in the FH group. The patients with tumors in the FH group were distributed among various age groups, but their tumors showed histologic features of gradually advanced maturation from the poorly differentiated subtype to the differentiating subtype in the neuroblastoma category; to the ganglioneuroblastoma, intermixed category; and to the ganglioneuroma, maturing category according to the age of the patients (see Fig. 4). The allowable frequency of nuclear abnormality defined by MKI in the tumors of the neuroblastoma category also decreased, depending on the age of the patients²⁰: A low MKI indicated a good prognosis in patients up to age 5 years at the time of diagnosis, and an intermediate MKI indicated a good prognosis in patients up to age 1.5 years at the time of diagnosis, whereas a high MKI was linked to a poor prognosis in any age. Tumors in the neuroblastoma category, when diagnosed in children age ≥ 5.0 years, all are classified into an unfavorable subgroup regardless of their grade of neuroblastic differentiation and MKI class. To be classified into an FH group, tumors in children age ≥ 5.0 years should have morphologic characteristics of either ganglioneuroblastoma, intermixed (Schwannian stroma-rich) or ganglioneuroma (Schwannian stroma-dominant). It also should be noted here that no

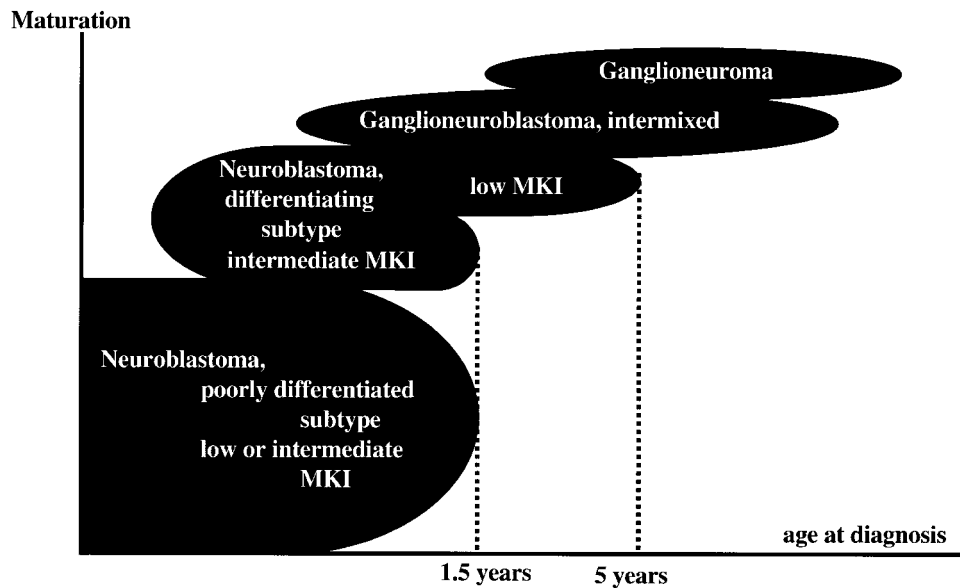


FIGURE 4. Age-linked framework for patients with peripheral neuroblastic tumors in the favorable histology group. For patients with tumors in the neuroblastoma category, age-linked effects of two morphologic indicators (grade of neuroblastic differentiation and mitosis-karyorrhexis index [MKI]) need to be evaluated according to the International Neuroblastoma Pathology Classification (see text). Patients with tumors in the ganglioneuroblastoma, intermixed category and in the ganglioneuroma category (tumors that usually are diagnosed in older children compared with tumors in the neuroblastoma category) have tumors in the favorable histology group. In contrast, patients with tumors in the ganglioneuroblastoma, nodular category (not found in this figure), which also are diagnosed in older children, have tumors in the unfavorable histology group.

tumors in the ganglioneuroblastoma, intermixed category or in the ganglioneuroma category had increased mitotic and karyorrhectic activities. In summary, this study confirmed the prognostic significance of the International Classification, substantiated the age-linked prognostic effects of the morphologic indicators (grade of neuroblastic differentiation and MKI) for patients with tumors in the neuroblastoma category, and supported the concept of an age-appropriate framework of maturation for patients with tumors in the FH group.

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