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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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. © 2001 American Cancer Society.

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. 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. This is an age-linked classification that adopts the basic concept of the Shimada system, which was developed originally in 1984. The prognostic significance and biologic relevance of the International Classification have been discussed in detail by the International Neuroblastoma Pathology Committee in preceding articles.

Modifications and differences between the original Shimada classification and the International Classification 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 groups defined by age, Evans clinical stage, and tumor biology (MYCN status, histopathology according to the original Shimada classification, and serum ferritin level). 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 $\leq 1$ 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 Classification 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-
Ganglioneuroblastoma, nodular (Schwannian
Ganglioneuroma (Schwannian stroma-dominant) FH

The log-rank statistic was used to compare study entry were estimated by using the Kaplan–Meier
Prognostic Analysis

The tumors in the ganglioneuroma category were classified 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.
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

### Table 2

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical stage</th>
<th>Age at diagnosis</th>
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<tr>
<td>Neuroblastoma (Schwannian stroma-poor) category (N = 630)</td>
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<td>Undifferentiated subtype</td>
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<td>High MKI</td>
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<td>Poorly differentiated subtype</td>
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<td>Low MKI</td>
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<td>Intermediate MKI</td>
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<td>High MKI</td>
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<td>Differentiating subtype</td>
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<td>Low MKI</td>
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<td>Intermediate MKI</td>
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<td>High MKI</td>
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<td>Ganglioneuroblastoma, Intermixed (Schwannian stroma-rich) category</td>
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<td>Maturing</td>
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<td>Mature</td>
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<td>Ganglioneuroblastoma, nodular (composite: Schwannian stroma-rich/stroma-dominant and stroma-poor) category</td>
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<td>Total</td>
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MKI: mitosis-karyorrhexis index.
low MKI in patients age ≥ 5.0 years \( (n = 18 \text{ patients; } 20.8\% \text{ EFS; } 27.0\% \text{ OS}) \), tumors with intermediate MKI in patients age ≥ 1.5 years \( (n = 68 \text{ patients; } 17.8\% \text{ EFS; } 26.6\% \text{ OS}) \), and tumors with high MKI in patients of all ages \( (n = 125 \text{ patients; } 30.2\% \text{ EFS; } 37.5\% \text{ OS} ; \ P < 0.0001 \text{ for EFS; } P < 0.0001 \text{ for OS}) \). Again, the results indicated that two different prognostic subsets were distinguished by the age-linked evaluation of the MKI classes \( (P < 0.0001 \text{ for EFS; } P < 0.0001 \text{ for OS}) \).

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 \( (n = 364 \text{ patients; } 90.4\% \text{ EFS; } 97.8\% \text{ OS}) \) and the UH subgroup \( (n = 266 \text{ patients; } 26.9\% \text{ EFS; } 35.6\% \text{ OS}) \), in the neuroblastoma category are summarized in Figure 2 \( (P < 0.0001 \text{ for EFS; } P < 0.0001 \text{ for OS}) \). 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 \text{ for EFS; } P = 0.0002 \text{ for}

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**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.
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 (123 FH tumors: 93.6% EFS; 98.9% OS; 20 UH tumors: 64.2% EFS; 82.1% OS; P = 0.0093 for EFS; P = 0.0003 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
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 Classification 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).
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-

**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.
Based on the results of this study as well as of our previous studies, 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.

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 patients. 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 $\geq 5.0$ 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 $\geq 5.0$ years should have morphologic characteristics of either ganglioneuroblastoma, intermixed (Schwannian stroma-rich) or ganglioneuroma (Schwannian stromadominant). It also should be noted here that no
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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