Different Karyotypic Patterns in Early and Advanced Stage Neuroblastomas

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ABSTRACT

Of 23 untreated and 7 treated (relapsed) neuroblastomas, 14 (11 untreated, 3 treated) had modal chromosome numbers in the diploid (45 to 51), 9 (8 untreated, 1 treated) in the triploid (60 to 77), and 6 (3 untreated, 3 treated) in the hypotetraploid (81 to 88) range, and one (untreated) had hypertriploidy (100). The near-or-pseudodiploid and hypotetraploid tumors were characterized by numerous structural abnormalities, most frequently of 1p, and frequent presence of double minutes or homogeneously staining regions. The near-triploid tumors were characterized by three almost complete haploid sets of chromosomes, and few structural abnormalities. N-myc amplification was found in five of the near-or-pseudodiploid or hypotetraploid tumors but in none of the near-triploid tumors. Most near-triploid tumors were found in infants at stage I or II, and the near-or-pseudodiploid or hypotetraploid tumors in children at stage III or IV mostly 1 year old or older. Among the untreated patients, all 8 with a near-triploid tumor were alive with no evidence of the disease, and the 11 with a near-or-pseudodiploid tumor had a median survival of only 376 days (P < 0.05), 7 of the 11 being dead. Thus, the near-triploid patients had well recognized favorable prognostic factors and an excellent prognosis, and the near-or-pseudodiploid patients had unfavorable prognostic factors and a dismal prognosis. The hypotetraploid tumors seemed to have karyotypic and clinical features in common with the near-or-pseudodiploid tumors. We presume that the near-triploid tumors and the near-or-pseudodiploid or hypotetraploid tumors may constitute distinctly different subcategories within neuroblastomas.

INTRODUCTION

Various chromosome studies on neuroblastomas have reported presence of dmin and/or hsr in most neuroblastoma cell lines and xenografts (1-3) and less common presence of such abnormalities in neuroblastoma tissues. They have also reported abnormalities of the short arm of chromosome 1 in 70% of patients (1, 2). In the chromosome studies on neuroblastoma tissues reported in the literature (1, 2), however, most samples were obtained from bone marrow or metastatic tumors, and few from primary tumors.

Clinically, neuroblastoma patients are classified into 2 groups: one has an excellent prognosis with minimal therapy and the other has a very poor prognosis despite aggressive therapy (4). The stage or extent of the disease and the age of the patient at diagnosis are known to be good prognostic factors in neuroblastoma patients (5). Recently, with the use of flow cytometry, Look et al. (6) studied DNA contents of neuroblastomas obtained from patients under 1 year of age and found that hyperdiploidy was more common in early stage neuroblastomas than in advanced-stage neuroblastomas. More recently, strong association of N-myc amplification and rapid progression of the tumor have been established (7).

We studied cytogenetic and clinical features of 30 evaluable neuroblastoma patients, including 9 who were found through a mass screening program for neuroblastoma in infants (8). We found that karyotypes of early stage neuroblastomas were in the triploid range and had few structural changes and that those of advanced-stage neuroblastomas were in the diploid or hypotetraploid range and had numerous structural changes, including those of the short arm of chromosome 1, and dmin and/or hsr. The remarkably different karyotypic patterns were closely related to the different biological and prognostic characteristics of neuroblastomas. These findings suggest that the triploid tumors and near-or-pseudodiploid or hypotetraploid tumors belong to fundamentally different subcategories within neuroblastomas.

MATERIALS AND METHODS

Patients and Treatment. Chromosomes were studied from neuroblastoma cells of 52 infants or children under 13 years of age who were admitted to various institutions between February 1977 and November 1985, mostly (45 of them) after January 1983. The tumor material was obtained at the time of diagnosis from 39 cases, of which 12 were found through a mass screening program for neuroblastoma in infants (8), and at the time of relapse or in the terminal stage from the other 13 patients. Chromosome studies were performed at Saitama Cancer Center to which place samples obtained at other institutions were transferred. Clinical data were recorded for each patient; they included age, sex, site of the primary tumor, stage of the disease (9), and survival time recorded in days on March 31, 1986. Patients at stage I or II were treated with surgery and chemotherapy consisting of cyclophosphamide, vincristine, and doxorubicin, and those at stage III or IV were treated with multidrug chemotherapy consisting of cyclophosphamide, vincristine, doxorubicin, cisplatin, and teniposide with or without surgery.

Chromosome Studies. The tumors excised from patients were minced with scissors and were cultured in plastic flasks containing ES medium (Nissui Seiyaku, Tokyo, Japan) with 15% fetal calf serum. The cells were harvested within 96 h from the start of culture. Bone marrow cells were cultured for 24 h in plastic flasks containing RPMI 1640 medium with 20% fetal calf serum and were harvested. Chromosomes were analyzed by means of regular Giemsa staining and quinacrine banding techniques. We defined abnormal clones as 2 or more metaphase cells with identical structural and/or numerical abnormalities. Karyotypes were described according to ISCN (1985) (10).

Determination of N-myc Gene Amplification. DNA was isolated in 11 patients from the same tumor that was used for chromosome study and in two patients from a cell line which had been established from the tumor that was used for chromosome study. The DNA was digested with EcoRI, electrophoresed in horizontal agarose gel, and transferred onto nitrocellulose filters. The presence or absence of N-myc gene amplification, which was represented by a 2-kilobase EcoRI fragment, was examined with the Southern blotting method using the probe NB-19-21 (11).

Statistical Analyses. Patients were classified into different groups on the basis of the karyotypic abnormalities that their neuroblastomas exhibited. Significance of the difference in age or clinical stage between chromosomally different groups of patients was examined with the χ² test.
RESULTS

Karyotypic Characteristics. Chromosomes of the tumor tissues were successfully studied on 30 patients (Tables 1 and 2), of whom were studied after January 1983.

Of the 23 untreated tumors, 11 had modal chromosome numbers in the diploid range (45 to 51). This group of tumors was characterized by numerous structural chromosome abnormalities. The most frequently observed were those of the short arm of chromosome 1 (Ip). Their abnormalities (Fig. 3), and only one (Patient 105) had an abnormality of the short arm of chromosome 1 (Ip). Their abnormalities were successfully studied with the banding method. They had few structural chromosome abnormalities. The most frequently observed were those of the short arm of chromosome 1 (Ip). Numerous dmin were observed in 5, 19, 26, 184, and 46) had a translocation of an unknown chromosome segment onto Ip. Numerous abnormalities were observed in 5, 19, 26, 184, and 46).

Eight untreated tumors had modal chromosome numbers in the triploid range (61 to 77). Six of the 8 tumors were successfully studied on 30 patients (Tables 1 and 2), of whom were studied after January 1983.

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Fig. 1. Q-banded karyotype of a cell from Patient 130. \(\text{\textasciitilde}\) abnormal chromosome 1 with an unknown segment in band p32. Thirty double minutes were observed in the cell. The karyotype is described in Table 1.

Fig. 2. Q-banded partial karyotypes of cells from Patients 26, 19, 184, 46, and 139. The first 4 patients had a translocation of an unknown chromosome segment onto 1p, and the last patient had a reciprocal translocation between chromosomes 1 and 11. The detailed karyotypes are described in Table 1.

another patient had hsr, and a third patient had dmin and hsr in their tumor tissues, which were never seen in the same cell (Figs. 4 and 5). These characteristics were similar to those of the untreated near-or-pseudodiploid or hypotetraploid tumors. One tumor (Patient 91) had no dmin, hsr, and 1p abnormalities but had a near-triploid karyotype with a pattern of numerical chromosome changes similar to that of the untreated near-triploid tumors.

Correlation of Karyotypic Pattern with Patient's Age, Stage of Disease, and Survival. Clinical data on each patient are sum-

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summarized in Table 2. Nine of the 11 untreated patients with a near-or-pseudodiploid tumor were 1 year old or older. Seven of the 8 untreated patients with a near-triploid tumor were under 1 year of age. There was a significant difference in age between the 2 karyotypically different groups of patients ($P < 0.01$).

Of the 11 untreated patients with a near-or-pseudodiploid tumor, 4 were at stage III and the other 7 were at stage IV. Of the 8 untreated patients with a near-triploid tumor, 4 were at stage I, 3 were at stage II, and only one was at stage III. There was a significant difference in the distribution of the clinical stages between the 2 groups ($P < 0.01$).

All 8 untreated patients with a near-triploid tumor were alive and 11 untreated patients with a near-or-pseudodiploid tumor had the median actuarial survival of 376 days. The difference between the survival times was significant ($P < 0.05$) (Fig. 6).

The median actuarial survival of 7 untreated patients with dmin or hsr, both of which were observed exclusively in the near-or-pseudodiploid or the hypotetraploid patients, was 252 days, and the actuarial survival of 16 untreated patients without dmin or hsr was 58% at 957 days. Again, the difference was significant ($P < 0.001$) (Fig. 7).

Correlation of Karyotypic Pattern with N-myc Gene Amplification. The presence or absence of N-myc gene amplification was examined in 10 untreated tumors, one treated tumor, and 2 cell lines derived from untreated tumors. The amplification was detected in 2 untreated tumors with pseudodiploidy or hypotetraploidy, one treated tumor with pseudodiploidy, and 2 cell lines with near- or pseudodiploidy, but not in the 5 untreated tumors with near-triploidy and in 3 untreated ones with near- or pseudodiploidy or hypotetraploidy. Five of the 13 patients examined had dmin and/or hsr; N-myc amplification was observed in 4 (Patients 26, 68, 73, and 184) of the 5 but not in the other (Patient 130). One patient (Patient 46) showed N-myc amplification but did not have dmin nor hsr.

DISCUSSION

In the study of chromosomes in neuroblastomas, we found a remarkable difference in the karyotypic pattern between tumors obtained from early stage patients and those from advanced-stage patients. The pattern of the former tumors was characterized by modal chromosome numbers in the triploid range, few structural abnormalities, and absence of dmin or hsr, and that of the latter tumors by modal chromosome numbers in the diploid or hypotetraploid range, numerous structural abnormalities including those of 1p, and frequent presence of dmin
Fig. 4. Q-banded karyotype of a cell from Patient 68. Arrows, 3 abnormal chromosome 1s. Two normal chromosome 6s are seen. Twenty-five double minutes were observed in the cell. The karyotype is described in Table I.

or hsr. Most relapsed tumors showed a karyotypic pattern similar to that of the untreated advanced-stage tumors.

In previous reports on chromosomes in neuroblastomas (1, 2), there were many cases with near- or pseudodiploidy, and some with hypotetraploidy, but few with near-triploidy. The lack of data on near-triploid karyotypes in neuroblastomas may be related to the fact that samples for chromosome study were often taken from bone marrow or metastatic tumor of patients 1 year old or older (1, 2). In the present study, near-triploid karyotypes were usually seen in early stage primary tumors of infants, most of which were found in the presymptomatic period through a mass screening program for neuroblastoma in infants.

The grouping that we have created of neuroblastoma patients shows an excellent correlation of the karyotype with already recognized prognostic factors including the patient's age and the stage of the disease; i.e., patients under 1 year of age show far better survivals than those 1 year old or older and patients at stage I or II do better than those at stage III or IV (4, 5).

The near-triploid tumors were seen in patients under 1 year old, and in those at stage I or II, with only one exceptional case in each. The two exceptional patients, one 19 months old and the other at stage III at the time of diagnosis are both alive after 28 and 7 months, respectively. The karyotypic pattern may be a more important prognostic factor than the patient's age or the stage of the disease in some neuroblastoma patients. In only one case (Patient 91), near-triploid karyotypes were observed in a metastatic epipulmonary tumor which was studied at the age of 9 months. Fifteen months have passed without further recurrence since the resection of the tumor. Thus, all patients who had a near-triploid tumor are showing an excellent prognosis.

In contrast, most patients with a near- or pseudodiploid or hypotetraploid tumor were 1 year old or older and all were at stage III or IV at the time of diagnosis. Usually, patients of this karyotypic group had a dismal prognosis. The great majority of the relapsed tumors also showed a karyotypic pattern similar to that of the untreated near- or pseudodiploid or hypotetraploid tumors. These findings suggest that most of the relapsed patients may have had a neuroblastoma with a near- or pseudodiploid or hypotetraploid karyotype rather than one with a near-triploid karyotype when they first developed the disease. In our previous study on 8 neuroblastoma xenografts (3), 7 showed a near- or pseudodiploid karyotype, and the remaining one showed a mosaicism of a near-diploid and a hypotetraploid karyotype. In the last case, the near-diploid cell had a 1p−chromosome, and the hypotetraploid cell had 2 of the same 1p−chromosomes. These findings indicate that xenografts may readily be established from tumors with a near- or pseudodiploid or hypotetraploid karyotype, but probably not from tumors with a near-triploid karyotype and that hypotetraploid cells may arise from near- or pseudodiploid cells probably through endomitosis.

Look et al. (6) studied DNA content of neuroblastomas from 35 infants. They found hyperdiploid tumors in 12 of 13 patients at stage A or B (I or II), in 7 of 20 patients at stage C or D (III or IV), and in all 4 patients at stage IVS. Their data obtained...
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Fig. 5. Q-banded karyotype of another cell from Patient 68. Arrows, 3 abnormal chromosome 1s which are the same as those in the cell of Fig. 3. One normal chromosome 6 and one abnormal chromosome 6 with hsr in band p21 are seen. No double minutes were observed in the cell. Inset, a pair of chromosome 6s from another cell.

by means of flow cytometry showed some similarity to ours obtained with chromosome analysis, although we suggest that some of their hyperdiploid tumors may have had triploid or tetraploid chromosome numbers. Unfortunately, we did not study chromosomes of stage IVS tumors. It is tempting to suggest that the karyotypic pattern of the IVS tumors may be similar to that of early stage infant tumors that we have characterized.

The site of the primary tumor was also suggested to have prognostic influence (5); i.e., patients with adrenal tumors had a poorer prognosis than those with nonadrenal tumors. However, there was no significant association between the nonadrenal nature and near-triploidy in the present study; 5 of the 9 triploid tumors occurred in the adrenal.

Recently, N-myc gene amplification has been shown in advanced-stage neuroblastomas but not in early stage tumors (7). Of the tumors in which N-myc copy number was examined in the present study, none with near-triploidy showed an increased N-myc copy number, but the majority of the tumors with near- or pseudodiploidy or with hypotetraploidy showed N-myc gene amplification. The amplified N-myc was shown to be present in dmin or hsr of neuroblastoma cells (11). This finding that substantiated in the present study. Thus, 4 of the 5 tumors that showed N-myc amplification had dmin or hsr. Our data showed that the patients with dmin or hsr had shorter survival times than those without them. Therefore, it is predictable that neuroblastoma patients with dmin or hsr may have N-myc gene amplification and a poor prognosis.

In conclusion, in the chromosome study of neuroblastoma tissues from infants and children, we found 2 different karyotypic patterns; one was near-triploid and the other was near- or pseudodiploid or hypotetraploid. The former pattern, which had been scarcely reported previously, was almost always associated with stage I or II tumors and the latter unexpectedly with stage III or IV or relapsed tumors of children mostly 1 year old or older. The close association of the stage and the chromosome ploidy may indicate that we are possibly missing the stage I or II tumors with pseudo- or near-diploidy or hypotetraploid probably because of the rapid progression of such tumors. From the cytogenetic viewpoint, it is almost
## Table 2 Some clinical and cytogenetic findings of patients with neuroblastomas

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age*</th>
<th>Sex</th>
<th>Stage</th>
<th>Site of primary tumor</th>
<th>Survival (days) after initial diagnosis</th>
<th>Material for chromosome study</th>
<th>Modal chromosome no.</th>
<th>Ip abnormality</th>
<th>dmin</th>
<th>hsr</th>
<th>N-myc amplification</th>
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<td><strong>Untreated</strong></td>
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<tr>
<td>57</td>
<td>1 yr 11 mo</td>
<td>M</td>
<td>IV</td>
<td>Adrenal (r)</td>
<td>199</td>
<td>Bone marrow</td>
<td>45</td>
<td>+</td>
<td>+</td>
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<td></td>
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<td>60*</td>
<td>8 mo</td>
<td>M</td>
<td>III</td>
<td>Adrenal (l)</td>
<td>770*</td>
<td>Primary tumor</td>
<td>46</td>
<td>+</td>
<td>+</td>
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<td>50%</td>
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<td>130</td>
<td>1 yr 8 mo</td>
<td>M</td>
<td>III</td>
<td>Adrenal (l)</td>
<td>258+</td>
<td>Primary tumor</td>
<td>46</td>
<td>+</td>
<td>+</td>
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<td></td>
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<td>26</td>
<td>1 yr</td>
<td>F</td>
<td>IV</td>
<td>Adrenal (l)</td>
<td>409</td>
<td>Primary tumor</td>
<td>46</td>
<td>+</td>
<td>+</td>
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<tr>
<td>38</td>
<td>1 yr</td>
<td>F</td>
<td>IV</td>
<td>Retropertioneum (l)</td>
<td>376</td>
<td>Metastatic lymph node</td>
<td>46</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>19</td>
<td>1 yr 3 mo</td>
<td>M</td>
<td>IV</td>
<td>Abdomen</td>
<td>366</td>
<td>Primary tumor</td>
<td>46</td>
<td>+</td>
<td>+</td>
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<tr>
<td>20</td>
<td>5 yr</td>
<td>F</td>
<td>IV</td>
<td>Adrenal (r)</td>
<td>125</td>
<td>Primary tumor</td>
<td>46</td>
<td>+</td>
<td>+</td>
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<tr>
<td>184</td>
<td>1 yr 8 mo</td>
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<td>IV</td>
<td>Adrenal (l)</td>
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<td>Bone marrow</td>
<td>46</td>
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<td>III</td>
<td>Chest (l)</td>
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<td>Primary tumor</td>
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<td>Mediastinum</td>
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<td>51</td>
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<td><strong>Near-triploid</strong></td>
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<tr>
<td>31</td>
<td>1 yr</td>
<td>F</td>
<td>II</td>
<td>Retropertioneum (r)</td>
<td>957+</td>
<td>Primary tumor</td>
<td>61</td>
<td>-</td>
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<tr>
<td>127*</td>
<td>9 mo</td>
<td>M</td>
<td>III</td>
<td>Retropertioneum (r)</td>
<td>276+</td>
<td>Primary tumor</td>
<td>66</td>
<td>-</td>
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<tr>
<td>92*</td>
<td>8 mo</td>
<td>M</td>
<td>I</td>
<td>Adrenal (r)</td>
<td>444+</td>
<td>Primary tumor</td>
<td>66</td>
<td>-</td>
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<tr>
<td>141</td>
<td>5 mo</td>
<td>F</td>
<td>II</td>
<td>Cervical ganglion (r)</td>
<td>144+</td>
<td>Primary tumor</td>
<td>68</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>78*</td>
<td>9 mo</td>
<td>M</td>
<td>I</td>
<td>Adrenal (l)</td>
<td>550+</td>
<td>Primary tumor</td>
<td>70</td>
<td>-</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>124</td>
<td>10 mo</td>
<td>F</td>
<td>I</td>
<td>Sympathetic ganglion (r)</td>
<td>291+</td>
<td>Primary tumor</td>
<td>71</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>105*</td>
<td>7 mo</td>
<td>F</td>
<td>I</td>
<td>Adrenal (r)</td>
<td>389+</td>
<td>Primary tumor</td>
<td>74</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>137*</td>
<td>10 mo</td>
<td>M</td>
<td>II</td>
<td>Adrenal (r)</td>
<td>179+</td>
<td>Primary tumor</td>
<td>77</td>
<td>?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Hypotetraploid</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>139</td>
<td>7 mo</td>
<td>M</td>
<td>III</td>
<td>Retropertioneum (r)</td>
<td>195+</td>
<td>Primary tumor</td>
<td>84</td>
<td>+</td>
<td></td>
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<tr>
<td>24</td>
<td>2 yr</td>
<td>F</td>
<td>IV</td>
<td>Adrenal (r)</td>
<td>670</td>
<td>Metastatic lymph node</td>
<td>85</td>
<td>-</td>
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<tr>
<td>73</td>
<td>1 yr 4 mo</td>
<td>M</td>
<td>IV</td>
<td>Adrenal (r)</td>
<td>252</td>
<td>Primary tumor</td>
<td>88</td>
<td>+</td>
<td>+</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>66*</td>
<td>10 mo</td>
<td>F</td>
<td>I</td>
<td>Adrenal (l)</td>
<td>674+</td>
<td>Primary tumor</td>
<td>100</td>
<td>-</td>
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<td><strong>Hypertetraploid</strong></td>
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</tr>
<tr>
<td>71</td>
<td>5 yr</td>
<td>M</td>
<td>III</td>
<td>Adrenal (l)</td>
<td>347+ (619+)</td>
<td>Abdominal tumor</td>
<td>45</td>
<td>+</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>134</td>
<td>4 yr</td>
<td>M</td>
<td>IV</td>
<td>Abdomen</td>
<td>843+ (193+)</td>
<td>Metastatic tumor</td>
<td>46</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>1 yr 8 mo</td>
<td>M</td>
<td>III</td>
<td>Abdomen</td>
<td>1021 (31)</td>
<td>Abdominal tumor</td>
<td>46</td>
<td>+</td>
<td>+</td>
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<td>50</td>
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<tr>
<td>91</td>
<td>3 mo</td>
<td>M</td>
<td>III</td>
<td>Adrenal (l)</td>
<td>620+ (458+)</td>
<td>Metastatic tumor</td>
<td>60</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 yr 11 mo</td>
<td>M</td>
<td>IV</td>
<td>Mediastinum</td>
<td>762 (39)</td>
<td>Bone marrow</td>
<td>81</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>4 yr</td>
<td>M</td>
<td>IV</td>
<td>Adrenal (r)</td>
<td>830 (113)</td>
<td>Bone marrow</td>
<td>82</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>3 yr</td>
<td>M</td>
<td>IV</td>
<td>Unknown</td>
<td>365 (4)</td>
<td>Bone marrow</td>
<td>84</td>
<td>-</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Age and stage at initial diagnosis are shown also for the treated patients.

1. left; r, right.

2. The patient was found to have neuroblastoma by a mass screening program.

3. + after survival, patient is alive.

4. N-myc amplification was examined on the cell line which was established from the tumor utilized for chromosome study.

5. Numbers in parentheses, survival after chromosome study.

---

**Fig. 6.** Actuarial survival curves of 8 patients with near-triploidy and 11 patients with pseudo- or near-diploidy. The difference in the survival times between the 2 patient groups was significant ($P < 0.05$).

**Fig. 7.** Actuarial survival curves of 7 patients with dmin or hsr and 16 patients without them. The difference in the survival times between the 2 patient groups was significant ($P < 0.001$).
impossible to imagine that a near-triploid tumor will evolve to a near-or-pseudodiploid or hypotetraploid tumor during the course of the disease. From these findings, it would be reasonable to assume that the triploid tumors and near-or-pseudodiploid or hypotetraploid tumors belong to fundamentally different subcategories within neuroblastomas.

ACKNOWLEDGMENTS

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Different Karyotypic Patterns in Early and Advanced Stage Neuroblastomas

Yasuhiko Kaneko, Naotoshi Kanda, Nobuo Maseki, et al.


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