DNA Flow Cytometry in Pheochromocytoma and Paraganglioma

Woo-Hee Jung, Woo-Ick Yang, Chanil Park and In Joon Choi

Flow cytometric DNA analysis was performed on 19 adrenal pheochromocytomas and 6 extra-adrenal paragangliomas in parallel with clinical and histopathological review to determine the usefulness of this technique to predict biologic behavior of these tumors. In pheochromocytomas and paragangliomas, tetraploidy or near-tetraploidy occurred in 32% and 33% and aneuploidy in 10% and none respectively. A case of malignant pheochromocytoma had diploid DNA content. Occurrence of aneuploidy or tetraploidy is frequent in clinically benign tumors in conjunction with a marked degree of nuclear atypia and cannot be a predictor of malignancy.

Key Words: Adrenal gland, pheochromocytoma, paraganglioma, flow cytometry, DNA content, histopathology

Adrenal pheochromocytomas and extra-adrenal paragangliomas frequently show striking nuclear pleomorphism regardless of their biologic behavior. In addition, capsular invasion, vascular invasion within the tumor, atypical mitoses and necrosis may all be seen in clinically benign tumors. Therefore, the only absolute criterion of malignancy is distant metastasis of the tumor. The incidence of malignancy is rare (under 5 percent) especially in pheochromocytoma, when multifocal tumors are rigorously excluded.

Previous reports suggest that nuclear DNA aneuploidy may be a useful marker of malignancy in these tumors (Klein et al. 1985; Hosaka et al. 1986). However, one report indicates that aneuploid DNA content is not a specific marker of malignancy in adrenal pheochromocytomas (Amberson et al. 1985).

In our study, flow cytometric DNA analysis was performed retrospectively on 19 specimens of pheochromocytoma and 6 paraganglioma. We wished to characterize the pattern of flow cytometric DNA histograms in pheochromocytomas and paragangliomas and to find the relationships of nuclear DNA ploidy pattern (DNA index) and proliferative compartment (%SG2M) to age, sex, primary site, multiplicity, histopathologic findings, clinical or biochemical function of tumor and clinical behavior.

MATERIALS AND METHODS

Adrenal pheochromocytomas from 3 patients and extra-adrenal paragangliomas from 6 patients diagnosed between 1974 and 1989 were retrieved from the files of Department of Pathology, Yonsei University College of Medicine, Seoul, Korea. Six cases (case # 1–6) of pheochromocytoma provided by Department of Pathology. The Childrens Hospital, Boston, MA were added. The medical records, gross descriptions, and microscopic slides stained with hematoxyline-eosin and with special stains in selected cases, were reviewed. Follow-up information was obtained by review of medical records and personal communication with patients' primary physicians. The duration of clinical follow-up has ranged from 10 months to 8 years. One patient...
(case #20) diagnosed with malignant pheochromocytoma had histologically proven distant metastasis and has been alive with the disease for two years. One patient (case #2) with multicentric tumor was included in this study.

**Age and Sex of Patients**

Range: 11 to 65 years (median: 32 years)
- 15 males and 10 females

**Number of Tumors by Primary Site**

- Adrenal: 19 (Right, 5; Left, 12; Bilateral, 2)
- Neck: 3 Mediastinum: 1 Retroperitoneum: 2

**Histologic Evaluation**

The architectural and cytologic features of each tumor, i.e., histologic pattern, presence of brown fat within the periadrenal soft tissue, cell size and shape, capsular and vascular invasion, necrosis, nuclear atypia, mitotic activity, and cytoplasmic hyaline globules were reviewed. Nuclear atypia was defined by hyperchromasia and enlargement of nuclei with polyplid form, and the degree of nuclear atypia was divided into 3 grades. If less than 10% of tumor cells showed nuclear atypia, it was called slight nuclear atypia and if more than 50% of tumor cells showed nuclear atypia, it was called marked. If it was in between, it was called moderate.

**Tissue Specimens**

Formalin fixed, paraffin embedded samples of tumor were selected for flow cytometric DNA analysis. The surgically removed adrenal glands obtained from patients with renal cell carcinoma or benign adrenal disease, e.g., hyperplasia or cysts were used as control tissue.

**Flow Cytometric DNA Analysis**

Flow cytometric DNA analysis (DNA FCM) was performed on isolated nuclei using a modification of the method of Headley et al (1985). Two or three 50 micron sections cut from the tissue blocks were deparaffinized in Histo-Clear (National Diagnostics, Manville, NJ) and rehydrated in a series ofgraded alcohols. Disaggregation of nuclei was accomplished by treatment with 2.5 mL of 0.5% pepsin (Sigma Chemical Corp., St. Louis, MO) at pH 1.5 at 37°C for 30 minutes with intermittent vortexing. Digestion was stopped by adding 1 mL of a 0.005% peptostatin solution (Sigma Chemical Corp. St. Louis, MO). The smaples were then centrifuged at 2,000 rpm, washed twice with Dulbecco's phosphate buffered saline (Sigma Chemical Corp., St. Louis, MO), and incubated with freshly prepared 0.5 mL of RNase (2.50 mg/mL; Worthington Biochemical, Freehold, NJ) at 37°C for 30 minutes. The samples were filtered through a 50 micron nylon mesh filter (Small Parts Inc., Miami, FL), and stained with 0.025% propidium iodide (Sigma Chemical Corp. St. Louis, MO) at 50 µL/mL. The isolated nuclei were adjusted to a concentration of 1 to 3×10⁶/mL by diluting with Dulbecco's phosphate buffered saline. Nuclei prepared and stained in parallel from formalin-fixed, paraffin embedded normal adrenal glands which included medulla served as controls.

Nuclei were analyzed in a Epics V FACS Analyser (Coulter, Hialeah, FL) with at least 10,000 nuclei read per sample. Data was analyzed using the Mult parameter Data Acquisition and Display System (MDADS Epics Division, Coulter Electronics, Hialeah, FL).

Single parameter histograms were utilized in the evaluation of the tumors. The first G0/G1 peak was assumed to be the diploid population and assigned a DNA index of 1.0 (ratio of nuclear DNA of sample to nuclear DNA of diploid control cells). DNA aneuploidy was defined by the presence of a distinct, separate second peak to the right of the first G0/G1 peak followed by a low G2M peak in the hexaploid to octaploid range. The half-peak coefficient of variance (CV) (a measure of quality control) as calculated for G0/G1 peaks (MDADS program) ranged from 5.36% to 15.88% (median 8.31%) with a mean of 8.93% and standard deviation 2.58%.

The DNA index was calculated for all nonaneuploid and aneuploid populations. The proportion of cells in the S and G2M phases of the cell cycle (%SG2M) was used as an estimate of the compartment of proliferative activity of the tumor. G2M peaks were identified as small humps to the right of the G0/G1 peaks. In the case of hyperdiploid tumors, only the second G0/G1 peak (greater DNA index) was used in these calculations, because it is assumed that only second peak consists entirely of abnormal cells.

**Statistical Analysis**

The chi-square test was used for statistical evaluation. A difference was regarded as statistically significant if p was less than 0.05.
<table>
<thead>
<tr>
<th>Case #</th>
<th>Age/Sex Site</th>
<th>Catecholamine Function</th>
<th>Histologic &amp; Flow Cytometric Findings</th>
<th>Pattern</th>
<th>Cell size cell shape</th>
<th>Capsule invasion</th>
<th>Vascular invasion</th>
<th>Necrosis</th>
<th>Nuclear Atypia</th>
<th>DNA Index</th>
<th>Mitosis</th>
<th>%SG,M</th>
<th>Follow-up (yr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11/M Lt. Adrenal</td>
<td>Clinical + Biochemical + Periadrenal brown fat + Hyaline globule +</td>
<td>Alveolar</td>
<td>Large polygonal</td>
<td>–</td>
<td>–</td>
<td>Focal</td>
<td>+ + +</td>
<td>2.1</td>
<td>Frequent Atypical</td>
<td>25</td>
<td>A&amp;W(6/12)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12/M Lt. Adrenal</td>
<td>+ + + –</td>
<td>Alveolar</td>
<td>Large polygonal</td>
<td>+</td>
<td>–</td>
<td>– + +</td>
<td>1.53</td>
<td>Frequent Atypical</td>
<td>42</td>
<td>A&amp;W(8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12/M Lt. Adrenal</td>
<td>+ + – +</td>
<td>Trabecular</td>
<td>Large polygonal</td>
<td>+</td>
<td>+</td>
<td>Focal</td>
<td>+ + +</td>
<td>2.1</td>
<td>Atypical Atypical</td>
<td>39</td>
<td>A&amp;W(1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13/M Lt. Adrenal</td>
<td>NA NA – –</td>
<td>Mixed</td>
<td>Small &amp; large polygonal</td>
<td>+</td>
<td>+</td>
<td>– +</td>
<td>2.1</td>
<td>–</td>
<td>–</td>
<td>51</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14/M Bilateral</td>
<td>+ + + –</td>
<td>Diffuse</td>
<td>Small &amp; large polygonal</td>
<td>–</td>
<td>–</td>
<td>– + +</td>
<td>2.0/2.0</td>
<td>–</td>
<td>–</td>
<td>42/34</td>
<td>A&amp;W(18)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>14/M Rt. Adrenal</td>
<td>+ + – +</td>
<td>Mixed</td>
<td>Small round &amp; spindle</td>
<td>–</td>
<td>–</td>
<td>Focal</td>
<td>+ + +</td>
<td>2.1</td>
<td>Rare Atypical Atypical</td>
<td>28</td>
<td>A&amp;W(3)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>14/F Lt. Adrenal</td>
<td>+ + + –</td>
<td>Diffuse</td>
<td>Small round</td>
<td>–</td>
<td>–</td>
<td>– +</td>
<td>1.0</td>
<td>–</td>
<td>24</td>
<td>A&amp;W(6.6/12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>29/M Rt. Adrenal</td>
<td>– + – +</td>
<td>Diffuse</td>
<td>Large Polygonal</td>
<td>–</td>
<td>–</td>
<td>– + +</td>
<td>1.86</td>
<td>–</td>
<td>–</td>
<td>35</td>
<td>A&amp;W(4)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>31/F Rt. Adrenal</td>
<td>– + – +</td>
<td>Mixed</td>
<td>Large polygonal</td>
<td>+</td>
<td>–</td>
<td>– +</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>19</td>
<td>A&amp;W(3.2/12)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>34/M Lt. Adrenal</td>
<td>+ + – +</td>
<td>Trabecular</td>
<td>Large polygonal</td>
<td>+</td>
<td>–</td>
<td>Focal</td>
<td>+ + +</td>
<td>1.0</td>
<td>–</td>
<td>41</td>
<td>A&amp;W(2.6/12)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>45/M Lt. Adrenal</td>
<td>+ + – –</td>
<td>Diffuse</td>
<td>Small polygonal</td>
<td>–</td>
<td>–</td>
<td>– +</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>22</td>
<td>A&amp;W(3.1/12)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>46/F Lt. Adrenal</td>
<td>+ + + –</td>
<td>Diffuse</td>
<td>Large polygonal small spindle</td>
<td>+</td>
<td>–</td>
<td>– +</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>28</td>
<td>A&amp;W(4.6/12)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>51/M Lt. Adrenal</td>
<td>+ + – +</td>
<td>Trabecular</td>
<td>Small &amp; large polygonal</td>
<td>–</td>
<td>–</td>
<td>+/+ +</td>
<td>1.0</td>
<td>–</td>
<td>13</td>
<td>A&amp;W(1.2/12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>52/F Rt. Adrenal</td>
<td>+ + – +</td>
<td>Diffuse</td>
<td>Large polygonal small spindle</td>
<td>+</td>
<td>–</td>
<td>– + +</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>28</td>
<td>A&amp;W(2.2/12)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>52/F Lt. Adrenal</td>
<td>+ + – –</td>
<td>Diffuse</td>
<td>Small polygonal &amp; spindle</td>
<td>+</td>
<td>–</td>
<td>– +</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>20</td>
<td>A&amp;W(3.9/12)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>56/F Bilateral</td>
<td>– – – –</td>
<td>Trabecular</td>
<td>Small polygonal large spindle</td>
<td>+</td>
<td>+</td>
<td>Extensive</td>
<td>1.0/1.0</td>
<td>–</td>
<td>–</td>
<td>24/18</td>
<td>AWD(2)</td>
<td></td>
</tr>
<tr>
<td>Case #</td>
<td>Age/Sex</td>
<td>Site</td>
<td>Clinical</td>
<td>Biochemical</td>
<td>Periadrenal brown fat</td>
<td>Hyaline globule</td>
<td>Catecholamine Function</td>
<td>Pattern</td>
<td>Cell size</td>
<td>Cell shape</td>
<td>Capsule invasion</td>
<td>Vascular invasion</td>
<td>Necrosis</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>--------------------</td>
<td>----------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>----------</td>
</tr>
<tr>
<td>21</td>
<td>58/F</td>
<td>Lt. Adrenal</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Diffuse</td>
<td>Large polygonal &amp; spindle</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>22</td>
<td>58/F</td>
<td>Rt. Adrenal</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Diffuse</td>
<td>Small round</td>
<td>-</td>
<td>+</td>
<td>Focal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>23</td>
<td>62/M</td>
<td>Lt. Adrenal</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Trabecular</td>
<td>Large polygonal small spindle</td>
<td>+</td>
<td>-</td>
<td>Focal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Paragangliomas (N=6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>20/M</td>
<td>Posterior mediastinum</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>+</td>
<td>Mixed</td>
<td>Small round large polygonal</td>
<td>+</td>
<td>-</td>
<td>Focal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>29/M</td>
<td>Neck</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>-</td>
<td>Diffuse</td>
<td>Large polygonal</td>
<td>-</td>
<td>-</td>
<td>Focal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>32/F</td>
<td>Neck</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>-</td>
<td>Trabecular</td>
<td>Small round</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>39/F</td>
<td>Neck</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>-</td>
<td>Alveolar</td>
<td>Small round</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>24</td>
<td>64/M</td>
<td>Retroperitoneum</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>-</td>
<td>Diffuse</td>
<td>Large &amp; small polygonal</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>65/F</td>
<td>Retroperitoneum</td>
<td>+</td>
<td>-</td>
<td>NA</td>
<td>-</td>
<td>Trabecular</td>
<td>Large &amp; small polygonal</td>
<td>+</td>
<td>-</td>
<td>Focal</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

NA: Not Available  
A&W: Alive & Well  
AWD: Alive with Disease
RESULTS

The clinical, biochemical, histopathologic and flow cytometric data of each patient are summarized in Table 1. The cases are arranged by adrenal and non-adrenal origin and by increasing age at diagnosis.

DNA Index of Tumors

Nuclear DNA histogram patterns of 25 patients with pheochromocytomas or paragangliomas including normal control adrenal gland are depicted in Fig. 1. Fifteen (60%) of the tumors showed DNA histograms that resembled the DNA histograms observed for non-tumor control samples of normal human adrenal glands and were defined as diploidy with DNA index of 1.0. Two (8%) of the patients showed a distinct DNA aneuploid peak with DNA index of 1.5 and 1.8 respectively. Eight (32%) of the tumors showed substantial increases (quantitatively greater than 20% of total nuclei) in and around the 4C peak and were defined as DNA tetraploidy with DNA index of 1.9 to 2.1. All aneuploid and tetraploid tumors had diploid lines. There was no hypertetraploidy. The distribution of DNA index in pheochromocytomas and paragangliomas is depicted in Fig. 2. In pheochromocytomas and paragangliomas, tetraploidy or near-tetraploidy occurred in 32% and 33% and aneuploidy in 10% and none respectively. A case of malignant pheochromocytoma had diploid DNA content.

DNA Index Related to Age and Sex of Patients

The distribution of DNA index related to age and sex of patients is depicted in Fig. 3. Of eight patients less than 20 years of age at diagnosis, seven (88%) were males, six with tetraploid tumors and one with a triploid tumor. The tumor of the single

---

Fig. 1. Nuclear DNA histogram patterns of pheochromocytomas & paragangliomas.
Woo-Hee Jung et al.

Fig. 2. Distribution of DNA index (DNAl) in pheochromocytoma & paraganglioma.
In pheochromocytomas and paragangliomas, tetraploidy or near-tetraploidy occurs in 32% and 33%, and aneuploidy in 10% and none respectively. A case of malignant pheochromocytoma has disloid DNA content.

Fig. 3. DNA index related to age & sex.
All patients with hyperdiploid tumors are male and hyperdiploid tumors are significantly more common in patients less than 20 years of age (p < 0.005).

female in this group was diploid. Of ten patients with aneuploid or tetraploid tumors, nine (90%) were less than 30 years of age, and all were males. Hyperdiploid tumors were significantly more common in patients less than 20 years of age (P < 0.005) and in male patients (P < 0.005).

Fig. 4. Degree of nuclear atypia related to DNA index of tumor.
Marked nuclear atypia is significantly correlated with the hyperdiploid DNA content of the tumor (p < 0.005).

Degree of Nuclear Atypia Related to DNA Index of Tumor
Of ten tumors with marked nuclear atypia, eight (80%) had aneuploid or tetraploid DNA content,
and all six tumors with slight nuclear atypia had diploid DNA content (Fig. 4). Marked nuclear atypia is significantly correlated with hyperdiploid tumors (p<0.01) but not with mitotic rate of tumor.

%SG2M Related to Mitotic Rate and Ploidy of Tumor

For the 25 tumors, the %SG2M ranged from 13% to 51%, with mean and standard deviation (S.D.) of 28.4% and 9.19%, respectively. The mean value of %SG2M of control tissue was 13.0%. Of six tumors showing rare or frequent mitotic rate, five of which were combined with atypical mitosis, only three had more than the mean value (28.4%) of % SG2M cells. Of ten hyperdiploid tumors, seven contained more than the mean value (28.4%) of % SG2M cells. As indicated in Fig. 5, a higher %SG2M was significantly correlated with hyperdiploid tumors (P<0.001) but not with mitotic rate of tumor.

DISCUSSION

Most pheochromocytomas are benign tumors that can be treated by adrenalectomy. Approxi-
terms of cellular kinetics and are assumed to be metabolically less active to divide and proliferate than diploid or aneuploid cells. In conclusion, pheochromocytomas and paragangliomas share a propensity for tetraploidy with other endocrine tumors (Klein et al. 1985; Bronner et al. 1988) and the occurrence of aneuploidy or tetraploidy is frequent in clinically benign tumors in conjunction with a marked degree of nuclear atypia and cannot be a predictor of malignancy.

As shown in Fig. 3, hyperdiploid tumors occurred exclusively in males and younger patients. However, the association of young age and the male sex with hyperdiploidy might be a happenstance and further studies need to be established whether our findings are typical, even though there is a report that malignant paragangliomas were significantly more common in men (Linnova et al. 1990).

Mitosis is very infrequently found in these tumors: 19 of 25 tumors show no mitosis. Three cases show rare mitotic activity, i.e. the mitotic count is less than one per ten high power fields, and three show frequent mitotic activity, i.e. more than one per ten high power fields. In various kinds of tumors (Gansler et al. 1986; Badalament et al. 1987; Bauer et al. 1987; Dressler et al. 1988; Kallioniemi et al. 1988), the percentage of cells in the S and G2/M phases of cell cycle (% SG2M) showed a highly significant association with clinical outcome in conjunction with ploidy pattern. Whereas mitotic counting in histologic sections provides an imprecise estimate of the M compartment of cell cycle, flow cytometric DNA analysis rapidly and more precisely determines the percentage of cells in the S and G2/M compartments, some of which cannot be discernible by light microscopy. In these tumors, mitoses are uncommon. This may be reflected by the fact that %SG2M is usually at or near "background" of control tissue levels and high %SG2M is not clearly a predictor of malignancy.

Histologically, alveolar (Zellballen) patterns similar to that of carotid body were infrequent (3 of 25 tumors), and diffuse patterns were most commonly observed in this series (11 of 25 tumors). It is possible that most adrenal or non-adrenal paragangliomas are originally of alveolar type but lose this pattern as they expand.

One report (Medeiros et al. 1985) indicated that necrosis, extensive and confluent in all malignant pheochromocytomas, was variable and focal in the benign ones. Additionally, all of the malignant tumors were composed of small cells. Only one case showing extensive tumor necrosis in our series was malignant, one which was composed exclusively of small polygonal cells. This confirms findings of other investigators (Hosada et al. 1976; Shapiro et al. 1984).

To evaluate the catecholamine function of the tumor, clinical symptoms and signs and laboratory data for biochemical function were investigated. Furthermore, the presence of periadrenal brown fat tissue was considered to be important, because it is suggested that catecholamine induced stress stimulates the appearance of brown fat (Melicow, 1957). Intracytoplasmic hyaline globules have been reported in normal and hyperplastic adrenal medulla as well as in pheochromocytomas and extralateral paragangliomas. The significance of the hyaline globule is not known, but some investigators have associated them with secretory activity. In our study, most of the tumors with hyaline globules turned out to have either clinical or biochemical catecholamine function, and the hyaline globule is better than periaxial fat in terms of predicting catecholamine function on a histologic basis.

In conclusion, neither ploidy pattern or %SG2M can be a predictor of malignancy in pheochromocytomas and paragangliomas, and the association of young age and the male sex with hyperdiploidy requires confirmation. This study provides new observations on the predictive value of certain flow cytometric and histologic parameters in clinically malignant pheochromocytomas and extra-adrenal paragangliomas.

Acknowledgements: We thank to Dr. G.F. Vawter Department of Pathology, The Children's Hospital, Boston, MA for providing pediatric cases (case #1-6).

REFERENCES

Bauer KD, Lincoln ST, Vera-Roman JM, Wallemark CB, Chmiele JS, Madurski ML, Murad T, Scarpelli DG:
DNA Flow Cytometry in Pheochromocytoma and Paraganglioma


Hedley DW, Friedlander ML, Taylor IW. Application of DNA flow cytometry to paraffin embedded archival material for the study of aneuploidy and its clinical significance. Cytometry 6: 327-333, 1985


Linnoila RI, Keiser HR, Steinberg SM, Lack EE: Histopathology of benign versus malignant sympathoadrenal paragangliomas; clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol 21: 1168-1180, 1990


