A Surgical Approach to Adrenocortical Tumors in Children: The Mainstay of Treatment
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**Background**: Adrenocortical tumors (ACTs) are rare in the pediatric population. The pathogenesis, prognostic indicators, and management of these tumors are still unclear because of its infrequent occurrence. This case series presents the surgical experience of the authors’ center over 29 years.

**Methods**: The medical records of children treated for ACTs between 1974 and 2003 were reviewed. Information on age, sex, presenting symptoms, hormonal levels, pathology, stage, treatment, and outcome was obtained.

**Results**: Nine children (5 girls, 4 boys) were treated for ACTs. The median age at presentation was 29 months (range, 5 months to 11 years). Endocrine dysfunction was found in 8 patients. Four presented with virilizing symptoms, 4 presented with both virilizing and Cushing’s symptoms, and 1 patient with Beckwith-Wiedemann syndrome was identified during routine screening. One was an adenoma, and 8 were carcinomas. Of the carcinomas, 3 were stage I, and 5 were stage II. The mean tumor weight was 125 g (range, 42 g to 336 g) with a mean volume of 139 cm³ (range, 30 cm³ to 626 cm³). All patients had complete excision of the tumor with spillage occurring in 2 cases. Lymph node biopsies were done in all but 2 patients. Two patients were treated with chemotherapy because of large tumor size and nodal involvement. All patients are doing well including those with tumor spillage.

**Conclusions**: This study shows that surgical excision continues to be the mainstay of treatment for ACTs. Extensive lymph node biopsy in small ACTs can probably be avoided given the generally good outcome with surgery alone. The role of adjuvant chemotherapy remains unclear because most of the children in our series were effectively treated with surgical resection only. Patients should be enrolled in multicenter trials to assess the added value of chemotherapy.

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INDEX WORDS: Adrenal carcinoma, adrenal adenoma, childhood adrenocortical tumor.

Both adrenocortical adenomas and carcinomas are considered in the literature under the heading of adrenocortical tumors. It often is difficult to distinguish between these 2 entities based on histopathologic features alone.1 These tumors are rare in the pediatric population, comprising less than 0.2% of all pediatric neoplasms and 6% of all pediatric adrenal tumors.2 The incidence of this disease varies depending on geographic location with one region of Brazil having the highest frequency.3 Malignant adrenocortical tumors are thought to have a poor prognosis in both adults and children.4 These tumors are more likely to be functional in children presenting with symptoms caused by increased levels of adrenal hormones. The heterogeneous nature and infrequency of this tumor have made it difficult to identify clear prognostic factors.3 Surgical resection plays an important role in the treatment of adrenocortical tumors. The added benefit of chemotherapeutic agents remains unclear given the low incidence of this malignancy.6 The goal of this study is to describe the presentation, management, and long-term outcome of patients who presented with adrenocortical tumors in our institution. In particular, the focus was on assessing the effectiveness of surgical excision and the need for lymph node biopsy in all patients.
patients showed signs of endocrine dysfunction. Four patients presented with virilizing symptoms alone. The other 4 had a mix of virilizing and Cushingoid symptoms. Symptoms of virilization include hirsutism, growth of pubic hair, acne, voice changes, clitoromegaly, and penile enlargement. The most common Cushingoid symptoms seen were hypertension, central obesity, buffalo hump, and a moon face. Patient 3 also had an abdominal mass on presentation. One patient with Beckwith-Wiedemann syndrome was identified during imaging done for screening purposes. The average duration of symptoms was 6 months (range, 2 to 12 months). The hormonal levels correlated with the clinical profile in all patients. Diagnosis of adrenal tumor was made using ultrasound imaging and computed tomography (CT) scan.

All neoplasms were unilateral, with 6 presenting on the left side and 3 on the right side. All patients underwent resection of the tumor, with spillage occurring in 2 patients. The mean tumor weight was 125 g (range, 42 g to 336 g) with a mean volume of 139 cm³ (range, 30 cm³ to 626 cm³). Lymph node biopsies were done in all but 2 patients, with positive findings in 2 patients. One was a patient with a large tumor size (336 g). The other was found in a patient with a relatively small primary tumor (70.2 g).

One patient was found to have an adrenocortical adenoma. Three patients had stage I carcinomas, and 5 patients had stage II carcinomas. Hormonal levels returned to normal postoperatively in all patients. In the last 2 years, we had 2 patients whose tumors were classified as stage II because of tumor size. However, they also had positive lymph nodes. These patients underwent a radical retroperitoneal lymph node dissection based on the belief that local control is important, and the role of chemotherapy is unclear at this time (Raul Ribeiro, personal communication). These 2 patients also received cisplatin and etoposide for a total of 8 cycles based on the protocol utilized at St Jude Children’s Research Hospital in Memphis.

All of our patients are alive with no recurrence of disease. One of the patients who received chemotherapy completed treatment more than 1 year ago, and the other patient just finished recently. The mean length of follow-up is 5.3 years, with a range of 6 months to 11 years. Table 2 details patient demographics.

### DISCUSSION

The current study confirms the literature findings with regard to the epidemiology of adrenocortical tumors. In a review of 520 cases, Ribeiro et al found that the median age at diagnosis of adrenocortical tumors in the pediatric

<table>
<thead>
<tr>
<th>Table 1. Staging Criteria for Pediatric Adrenocortical Tumors</th>
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<tbody>
<tr>
<td><strong>Stage</strong></td>
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<tr>
<td>Stage I</td>
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<tr>
<td></td>
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<tr>
<td>Stage II</td>
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<td></td>
</tr>
<tr>
<td>Stage III</td>
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<td>Stage IV</td>
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</tbody>
</table>

### Table 2. Patient Demographics

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age at Diagnosis (yr)</th>
<th>Sex</th>
<th>Duration of Symptoms (mo)</th>
<th>Clinical Presentation</th>
<th>Tumor Size and Weight</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>M</td>
<td>2</td>
<td>Virilization, Cushing</td>
<td>137cm³</td>
<td>70.2g</td>
<td>AC Stage II</td>
<td>Surgery + chemotherapy</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>F</td>
<td>9</td>
<td>Virilization, Cushing</td>
<td>626cm³</td>
<td>336 g</td>
<td>AC Stage II</td>
<td>Surgery + chemotherapy</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>F</td>
<td>3</td>
<td>Virilization, Cushing, abdominal mass</td>
<td>113cm³</td>
<td>60.2g</td>
<td>AC Stage II</td>
<td>Surgery</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>F</td>
<td>12</td>
<td>Virilization</td>
<td>277cm³</td>
<td>105.5g</td>
<td>AC Stage II</td>
<td>Surgery</td>
</tr>
<tr>
<td>5</td>
<td>1.6</td>
<td>M</td>
<td>4-6</td>
<td>Virilization</td>
<td>320cm³</td>
<td>219 g</td>
<td>AC Stage II</td>
<td>Surgery</td>
</tr>
<tr>
<td>6</td>
<td>2.4</td>
<td>M</td>
<td>8</td>
<td>Virilization</td>
<td>53cm³</td>
<td>43 g</td>
<td>AD</td>
<td>Surgery</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>F</td>
<td>3-4</td>
<td>Virilization, Cushing</td>
<td>65cm³</td>
<td>42 g</td>
<td>AC Stage I</td>
<td>Surgery</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>M</td>
<td>0</td>
<td>Asymptomatic (screening)</td>
<td>30cm³</td>
<td>-</td>
<td>AC Stage I</td>
<td>Surgery</td>
</tr>
<tr>
<td>9</td>
<td>1.6</td>
<td>F</td>
<td>2</td>
<td>Virilization</td>
<td>31.5cm³</td>
<td>-</td>
<td>AC Stage I</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Abbreviations: AC, Adrenocortical carcinoma; AD, adrenocortical adenoma.
population was 3 years, with less than 10% of tumors presenting in patients 15 years or older. In our study, 8 of the 9 patients were less than 3 years of age. Adrenocortical tumors are more common in girls than in boys with a 2.5:1 female to male ratio.¹⁰ In our study, there was a slight female predominance.

Predisposing genetic factors can be found in certain patients with adrenocortical tumors. Two syndromes in particular have a clear association with this type of tumor. Li-Fraumeni syndrome is associated with mutations of the p53 gene. Beckwith-Wiedemann syndrome is associated with mutations in the 11p15 region.¹⁰ One patient in our series had Beckwith-Wiedeman syndrome. His tumor was identified during imaging done for screening purposes. The presence of p53 mutations was not looked at in our patients.

Unlike in the adult population, most adrenocortical tumors in children are hormonally active.¹ All of our patients except for one presented with evidence of a hormonally active tumor. It may be postulated that the patient with Beckwith-Wiedeman might have had symptoms had his tumor not been detected early by routine screening. The presenting symptoms vary depending on the specific hormones secreted by the tumor. This may lead to a wide range of presenting signs and symptoms. Other studies have shown that 80% to 90% of patients present with virilizing features, either alone or in combination with Cushingoid features.⁵,⁶,¹¹ Isolated hyperadrenocorticalism was present in only 8% of patients.⁵ Aldosterone- and estrogen-secreting tumors are rare in children.⁹,¹² The presentation of our patients is consistent with these literature findings, with the overwhelming majority of patients presenting with a virilizing syndrome, either alone or in combination with Cushing’s syndrome. None of our patients had increased cortisol level in isolation. One patient had increased levels of estrogen as well as increased cortisol and androgens.

The diagnosis of adrenocortical tumors is based on clinical findings, biochemical abnormalities, and radiologic imaging. Laboratory tests are done to measure levels of hormones secreted by the tumor. These are useful both for diagnostic purposes and for follow-up. Various imaging modalities have been used in the past to establish the diagnosis of adrenocortical tumors. Currently, CT and ultrasound scans are the principal diagnostic modalities used. CT scan has been shown to be more sensitive than ultrasonography in tumor identification and localization. In one series of 28 patients, ultrasound scan did not identify the mass in 11% of cases.⁶ However, ultrasound scan is useful to evaluate tumor extension into the inferior vena cava and right atrium.⁵ In our series of patients, ultrasound imaging was done in 6 patients with identification of all 6 tumors. Magnetic resonance imaging (MRI) is also being used increasing, although its benefit over CT scan remains to be determined. MRI can be used to differentiate between adrenal adenomas and carcinomas, although this distinction can be difficult in some cases.¹³ On MRI, adenomas usually have a higher fat content than carcinomas. As well, the entire lesion in adenomas loses signal on opposed-phase T₁ images compared with carcinomas, in which only a portion of the lesion shows a signal loss.¹⁴ Surgical treatment has long been the cornerstone of therapy for adrenocortical tumors. It is the only therapy that unquestionably cures or prolongs survival significantly.¹⁵ It is important to remember that these patients need perioperative steroid coverage. All of our patients underwent complete surgical resection, which was complicated by spillage in 2 of our patients. In one study, tumor friability led to rupture of the capsule and tumor spillage in 20% of cases.⁶ The need for lymph node biopsy for staging and for prognosis has not been addressed clearly in the literature. In our patient series, lymph node biopsy was done in all but 2 patients with positive nodes found in 2 patients. One patient had a large primary tumor (336 g) with extensive nodal involvement. The other patient had a fairly small tumor (70.2 g). The former patient currently is free of disease; however, given his relatively recent diagnosis, his long-term outcome remains to be seen.

According to the experience at St Jude (R. Ribiero, personal communication), the presence of positive lymph nodes portends a poor prognosis, and the recommendation is to widely sample the lymph nodes at the time of primary tumor excision and to proceed with radical lymph node dissection (RLND) when the biopsy result is positive. The last 2 patients we had with positive nodes have been treated in this manner.

Other adjunctive therapeutic modalities have been tried in the treatment of adrenocortical tumors. Radiotherapy was shown to have limited success in one study.¹⁶ Given the relatively small number of patients with such tumors, the optimal use of chemotherapy has yet to be determined. Mitotane, an insecticide derivative that causes adrenocortical necrosis, has been used in adults, but its efficacy in children has not been well studied.

This drug has significant toxicity, affecting mostly the gastrointestinal and neurological systems. After its use, steroid markers in the blood cannot be followed as an indication of tumor relapse because mitotane interferes with steroid metabolism. A response rate of 30% to 38% has been shown in a few small studies, although these results have not been consistent.¹⁶-¹⁸ Chemotherapy with combinations of other agents has been tried. A combination of etoposide and cisplatin was used successfully in a small series of 5 patients.¹⁹ Chemotherapy generally is reserved for patients with recurrent or metastatic disease or those at high risk of relapse.¹⁰ St Jude Children’s
Research Hospital currently has an open protocol for these patients, in which mitotane, cisplatin, and etoposide are the chemotherapeutic agents used for high-risk patients. We currently are in the process of opening this protocol in our institution, and we treat our patients according to it. Two of our patients had stage II disease with extensive lymph node involvement and received 8 cycles of cisplatin and etoposide.

Differentiation between benign and malignant adrenocortical tumors is difficult. Various histologic classification systems based on cytologic abnormalities have been proposed. Prognostic factors have been difficult to determine given the rarity of adrenocortical tumors. A young age at diagnosis seems to be a good prognostic factor, with an 82% long-term survival rate in children less than 2 years of age. In contrast, children older than 2 years of age have a survival rate of 29%. Most of the patients in our study were less than 2 years of age, which may contribute to the good overall outcome of our patients. The other factor explaining our results is that none of our patients presented with advanced disease.

From previous reports it is clear that incomplete resection has a negative effect on outcome. In children, the 2-year survival rate jumped from 46% for all adrenocortical tumors to 67% for those who underwent a complete surgical excision. All of the patients in our series underwent complete surgical excision. The 2 patients with intraoperative spillage have no evidence of recurrence; however, the duration of follow-up has been short.

The prognostic importance of histology versus tumor weight continues to be controversial. In a comparison between adult and pediatric adrenocortical tumors, it was found that histologic features are not reliable prognosticators in children because even benign pediatric adrenocortical tumors often show elements suggestive of malignancy. Lefevre et al also concluded earlier that histologic classification is not of prognostic significance. Others have found that patients with adenomas generally have a better outcome, although cure often is possible for patients with carcinomas. Tumor size seems to be of prognostic significance. A study by Michalkiewicz et al showed that patients with a tumor weight less than 100 g or a volume of less than 200 cm³ have an excellent prognosis with a 90% disease-free survival at a median follow-up of 2.3 years. There were virtually no survivors in patients with metastatic stage IV disease.

The optimal treatment of pediatric adrenocortical tumors has yet to be determined. Our study shows, as in previous studies, that complete surgical resection continues to be the mainstay of treatment for this tumor. The need for lymph node biopsy and RLND has not been properly assessed in other studies. Our data suggest that it may not be necessary in completely resected small tumors given the good prognosis for early-stage disease. Whether RLND and chemotherapy for more advanced disease will have a significant impact on local recurrence and survival needs to be addressed in a larger patient population, and consequently we encourage centers to open available protocols in their own institution.

REFERENCES


