Adrenocortical tumors (ACT) are very aggressive endocrine neoplasms whose incidence is quite low. Little is known about their pathogenesis, clinical presentation, and optimal treatment. In recent years, however, new information has been derived from the International Pediatric Adrenocortical Tumor Registry (IPACTR), and new clues to its pathogenesis have emerged. To provide an overview of the available data that may apply to pediatric ACT, we reviewed the epidemiology, pathogenesis, and treatment of ACT in adults and in children. Germline TP53 mutation is almost always the predisposing factor in childhood ACT. A unique germline mutation (TP53−R337H) has been described in Southern Brazil, where the incidence of ACT is 10–15 times the general incidence. Childhood ACT typically present during the first 5 years of life and has female predominance. Hormone hyperproduction is almost universal, and most patients present with virilization. Two-thirds of patients have resectable tumors. Surgery is the definitive treatment for ACT, and a curative complete resection should always be attempted. Cisplatin-based chemotherapy with mitotane is indicated for unresectable or metastatic disease, although its impact on overall outcome is slight. In childhood ACT, age, tumor size, and tumor resectability are the most important prognostic indicators. Outcome is stage-dependent: patients with small, resectable tumors have survival rates in excess of 80%, whereas the outcome for patients with unresectable disease is dismal. Patients with large, resectable tumors have an intermediate outcome. Childhood ACT are rare, but their unique epidemiology appear to implicate novel oncogenic pathways that are unique to the pediatric population. Multi-institutional and prospective studies are necessary to further our understanding of the pathogenesis and to improve outcomes. Pediatr Blood Cancer 2005;45:265–273.

Key words: adrenocortical carcinoma; adrenocortical tumors; children; p53 mutations

Epidemiology of Childhood Adrenocortical Tumors

ACT follow a bimodal age distribution, with peaks during the first and fourth decades [3]. In the US, only 25 new cases are expected to occur annually, for an estimated annual incidence of 0.2–0.3 cases per million [1]. Internationally, however, the incidence of ACT appear to vary substantially; it is particularly high in southern Brazil, being approximately 10–15 times that observed in the US. Most cases occur in the contiguous states of Sao Paulo and Paraná. The cause of this higher rate has not been identified. However, as discussed below,
predisposing genetic factors have been implicated in most cases. In patients from either Brazil or the US, germline TP53 mutations are almost always the predisposing factors [2,4]. Patients with Beckwith-Wiedemann and hemihyperplasia syndromes have a predisposition to cancer, and as many as 20% of their neoplasms are ACT [5]. In contrast, less than 1% of children with ACT have these syndromes [6]. ACT have also been reported in association with other genetic diseases such as congenital adrenal hyperplasia [7].

**Biology of Adrenocortical Tumors**

The molecular mechanisms of tumorigenesis of the adrenal cortex are not well understood; Kirshner has recently reviewed the available information [8]. Carcinogenesis is a multistep process, and the pathogenesis of ACT may combine dedifferentiation and unchecked proliferation induced through the activation of hormonal or growth factor signaling receptors. Adrenocortical cells respond to signaling through a G protein-coupled receptor (GPCR), the melanocortin-2 receptor (MC2R), and the resulting activation of a c-AMP-dependent kinase (PKA) and signal transduction via phosphorylation in the cytoplasm and nucleus. Abnormalities in the ACTH-MC2R-PKA pathway have been hypothesized to lead to abnormal growth and proliferation [8]. However, no MC2R or PKA mutations have been found in ACT [9,10], and current evidence does not support a role for this pathway in the initiation of neoplastic transformation. Interestingly, there is strong evidence that in adrenal cells, this pathway inhibits proliferative signals initiated through other signaling pathways [11]. In that case, ACTH would be a differentiation-maintaining factor, whose involvement in the pathogenesis of ACT should involve loss of function. In fact, Reincke et al. [12] reported loss of heterozygosity (LOH) at the MC2R locus and an associated decrease in receptor expression in adrenocortical carcinomas but not adenomas. The role of the ACTH-MC2R-PKA system in the pathogenesis of ACT is still poorly defined.

In 1966, reporting on the association between congenital abnormalities and cancer, Miller concluded “when diseases are found together more often than can be attributed to chance, each can be studied in the light of what is known of the other for clues to etiology” [13]. A number of pediatric tumors, including ACT, are associated with congenital abnormalities. The frequency of ACT is second only to that of Wilms tumor in patients with Beckwith-Wiedemann syndrome (BWS) [6]. Genetic alterations associated with BWS are mapped to regions of chromosome band 11p15 designated BWS chromosomal regions (BWSCR) 1, 2, and 3 [6]. Insulin-like growth factor (IGF)-II is mapped to BWSCR1. The birth weight of patients with BWS is dependent on the expression level of IGF-II, and the phenotype of mutant mice overexpressing IGF-II overlaps with BWS [14]. The IGF signaling pathway has many important roles in normal cell growth and development. IGF-I functions almost exclusively postnatally, whereas IGF-II has a more important role during fetal development and a minimal role after birth. Two IGF receptors (IGF1R and IGF2R) recognize both ligands. The strong association of BWS, IGF-II, and ACT suggests that IGF-II participates in tumorigenesis, and some studies have shown increased IGF-II protein and mRNA in ACT [15,16]. The IGF-II gene is regulated by maternal genomic imprinting, such that adult expression comes almost exclusively from the paternal allele. There is evidence of genetic alteration (usually LOH) at this locus that leads to specific deletion of the maternal allele and often the gain of a second copy of the paternal allele [17].

Consistent overexpression of the IGF1R has been shown in ACT cells [18]. Interestingly, the antiproliferative effect of ACTH is blunted in ACT cell lines overexpressing IGF1R [19]. Further, transgenic mice expressing IGF-II postnatally develop adrenal hyperplasia but not frank malignancy [20]. Taken together, the evidence strongly suggests that the IGF system is involved in adrenal growth and tumorigenesis. An interesting anecdotal report describes a 78-year-old patient with IGF-II-induced hypoglycemic attacks that led to the diagnosis of ACT; after tumor resection, the patient’s IGF-II levels normalized and the hypoglycemia resolved [21]. High local IGF-II levels combined with elevated IGF1R expression would provide a significant growth advantage, but additional steps are required for neoplastic transformation [8,19].

Members of the epidermal growth factor receptor (EGFR) family are known to participate in the pathogenesis of some carcinomas. EGFR expression has been identified in approximately 90% of ACT [22,23]. The available information suggests that this system plays a permissive but nonspecific role in transformation of adrenal cells [8,22,23].

The hypothetical multistep transformation process also requires intracellular signaling abnormalities other than dedifferentiation- and proliferation-inducing signals. TP53 mutations appear to underlie such abnormalities in most cases, and ACT are strongly associated with germline TP53 mutations. ACT are the tumors most increased in frequency in families with Li-Fraumeni syndrome [24,25], suggesting that germline TP53 mutations exert tissue-specific effects. A wide spectrum of germline TP53 alterations have been described in ACT, and these mutations may contribute to the etiology of more than 80% of cases in children [4,26]. De novo TP53 mutations are also observed, and relatives of children with ACT may have a high incidence of cancer [4,26]. In North American children, the spectrum of germline
TP53 mutations and the mechanisms and types of functional LOH in ACT are quite diverse, although germline mutations occur primarily in the TP53 DNA-binding domains (exons 4–8) [4,26,27]. In the Brazilian cases, by contrast, the patients’ families do not have a high incidence of cancer, and a single mutation in exon 10 of the TP53 gene is consistently observed. This mutation encodes an arginine in place of histidine at codon 337 (TP53–R337H) within the tetramerization domain. The families of these children do not share common ancestry, and the R337H mutation does not appear to be a common polymorphism among southern Brazilians. Further, the penetrance of this mutation is low (only 10%–15% of carriers develop ACT), and it appears not to predispose carriers to other malignancies later in life [2]. The wild-type allele is deleted in these tumors, and the mutant p53 protein accumulates in the nucleus. Functional analyses have shown that the mutant TP53 retains transactivation function and can induce apoptosis [2]. However, the mutant tetramerization domain is less stable than the wild-type domain. Its sensitivity to slightly increased pH suggests that a unique physiological condition within adrenal cortical cells contributes to the observed tissue-restricted pathogenesis [28].

Additional genetic alterations may be necessary for malignant transformation. ACT are characterized by a high frequency of chromosomal gains and amplifications, and several chromosomal subregions containing candidate proto-oncogenes are affected [29,30]. In a series of nine cases in Southern Brazil, the most consistent findings were a gain of all or part of chromosome arm 9q (8 cases) and amplification of band 9q34 (5 cases) [30]. Preliminary data from bacterial artificial chromosome (BAC) array analyses also reveal homozygous deletion of a region on chromosome band 10p21 in 80% of the pediatric ACT examined. A combination of microarray gene expression and BAC array analyses should more specifically identify the factors and pathways that are corrupted during ACT progression.

Finally, the early age of onset and the distinctive clinical features of childhood ACT suggest that they arise in the fetal zone of the fetal adrenal cortex. The fetal zone occupies 85% of the adrenal cortex during embryonic development and is oriented toward dehydroepiandrosterone production. A constitutional TP53 mutation may, therefore, increase the risk of neoplastic transformation in the fetal adrenal cortex but not in the definitive adrenal cortex.

Clinical Characteristics of Adrenocortical Tumors

The clinical characteristics, treatment, and outcome of ACT have been described mainly in adults; because there are few reports about pediatric ACT, it is difficult to discriminate features unique to either age group. At presentation, patients typically have signs and symptoms of overproduction of androgens (virilization) and/or cortisol (hypercortisolism or Cushing syndrome). Rarely, hyperestrogenism (feminization) or aldosteronism (Conn syndrome) may be the presenting clinical manifestation. Mixed syndromes reflecting oversecretion of several adrenocortical hormones are frequent. Most patients have functional tumors [3,31–37], although as many as 50% may produce mainly hormonal precursors with low bioactivity [35]. The degree and type of endocrine disturbance appear to be related to patient age [3,33]. Older patients tend to have a much higher incidence of nonfunctional tumors, whereas more than 90% of childhood ACT are functional [33,38–40]. Adults usually have mixed virilization-hypercortisolism syndromes, whereas virilization syndrome is the most common presentation in children [33,38–40]. Other presenting symptoms include abdominal pain in 50% or fewer patients and, less frequently, weight loss [32]. Most patients (50%–60%) present with large tumors and advanced regional or metastatic disease [31–37,41]. Distant metastases usually involve the liver, lungs, kidneys, and bone, in that order. The diagnosis of ACT is straightforward. Because most patients have an endocrine syndrome, elevated blood or urine concentration of adrenocortical hormones and a suprarenal mass usually suggest a preoperative diagnosis of ACT. Imaging studies are necessary for adequate staging and surgery planning. Magnetic resonance and computed tomography of the primary site are necessary to detect invasion of adjacent structures, which may require resection during the curative procedure. The tumors characteristically have a thin pseudocapsule and areas of calcification and necrosis [42]. Vascular invasion is very common, and patients should be examined for intra caval tumor thrombus before surgery. Because ACT are metabolically active, fluorodeoxyglucose positron emission tomography (FDG-PET) imaging is increasingly used [43,44]. Although its value has not been evaluated in detail, it may have a role in the detection of recurrent disease.

The distinction between benign (adenomas) and malignant (carcinomas) tumors can be problematic. In fact, adenoma and carcinoma appear to share multiple genetic aberrations and may represent points on a continuum of cellular transformation [29,30]. Macroscopically, adenomas tend to be well defined and spherical, and they never invade surrounding structures. They are small by definition (usually <200 g). Microscopically, they may resemble normal adrenal cortex and are composed of cells with round, regular nuclei and abundant clear to light pink cytoplasm, arranged in a sinusoidal, trabecular, or solid pattern with prominent vasculature, resembling the normal zona reticularis or zona fasciculata. By contrast, carcinomas have macroscopic features suggestive of malignancy; they are larger, and they show...
Adrenocortical Tumors in Children

Despite the rarity of childhood ACT, its clinical and pathologic characteristics have been well characterized in recent years [38–40,50–52]. Significant information has been obtained from the International Pediatric Adrenocortical Tumor Registry (IPACTR) (www.stjude.org/ipactr), established in 1990 by the St. Jude Children’s Research Hospital International Outreach Program, as a joint effort with the Hospital de Clínicas in Curitiba, Brazil. The registry has served as an information-exchange web site, and more than 250 patients have been registered to date [53].

Childhood ACT typically present during the first 5 years of life (median age, 3–4 years), although there is a second, smaller peak during adolescence [38,50,51,53]. Female sex is consistently predominant (female: male ratio 1.5:1) [50,51,53]. Because pediatric ACT are almost universally functional, they cause endocrine disturbances, and a diagnosis is usually made 5–8 months after the first signs and symptoms emerge [39,50,53]. Virilization syndrome is seen, alone or in combination with hypercortisolism, in approximately 90% of patients. Isolated Cushing syndrome is very rare (5% of patients). Half of the patients have severe hypertension at presentation, and hypertensive crisis resulting in seizures is the presenting feature in 10% of cases [38,50,51,53]. Nonfunctioning tumors are rare in children, although they appear to be more common in adolescents and young adults [53].

At the time of diagnosis, two-thirds of pediatric patients have limited disease (tumors are completely resected), and the remaining patients have either unresectable or metastatic disease [53]. As with adult ACT, histologic differentiation of adenomas and carcinomas is difficult. However, approximately 10%–20% of pediatric cases are adenomas [50,53]. To identify features of pediatric ACT that are suggestive of malignancy, Bugg et al. analyzed histology, ploidy, proliferative index, and tumor size in 54 cases [52]. The histologic criteria for malignant tumors were the mitotic index, the presence of confluent necrosis and atypical mitoses, and the nuclear grade, as previously defined by Weiss [45,47]. The most statistically significant predictors of outcome were tumor histology and tumor weight (100 g). Ploidy and proliferative index were not predictive of outcome [52].

Three studies have analyzed factors predictive of malignant clinical behavior of childhood ACT. In a review of 88 children, Wieneke et al. found that tumor size >10.5 cm or >400 g, local invasiveness (infiltration of soft tissues and vena cava), and malignant histologic features (necrosis, atypia, and high mitotic rate) were predictors of malignant behavior, although only invasion of the vena cava, necrosis, and high mitotic rate retained their prognostic value in a multivariate analysis [50]. In an analysis of 40 cases in Southern Brazil, Ribeiro et al. [38] found tumor volume >200 mL or weight >80 g, and age >3.5 years, to be associated with worse outcome, although only tumor size was independently predictive. This study’s findings also suggested that higher urinary levels of 17-OH-corticosteroids are associated with more aggressive disease [38]. Similarly, in an analysis of 254 patients registered in the IPACTR, the most important favorable prognostic factors were age <3 years, tumor weight <200 g, virilization, and stage I disease [53].

The available data suggest that tumor size is especially important in children; patients with small tumors have an excellent outcome with surgery alone, regardless of histologic features [38,50,52–54]. In fact, some authors have reported that children with nonmetastatic ACT have a better prognosis than adults [33]. A staging system based on disease extent and tumor size has been proposed on the basis of these findings (Table I) [51]. The overall probability of 5-year survival for children with ACT is reported to be 54%–74% [50,51,53]. Data from the
IPACTR show the staging system to be highly predictive of outcome in children with stage I or stage IV disease: more than 90% of patients with stage I disease, but only 10% of those with stage IV disease, are long-term survivors. Predicting the prognoses of patients with intermediate-stage disease is much more difficult. Despite presumed complete tumor resection, local recurrence is the most common adverse event in patients with stage II disease (30%–50% of cases). Patients with stage III or stage IV disease have an extremely poor outcome (Figure 1).

**Treatment of Adrenocortical Tumors**

**Surgery.** Surgery is the mainstay of treatment for ACT. In fact, low disease stage and complete tumor resectability are the most important prognostic factors. A curative complete resection may be attempted in patients with local or regional disease (70%–75% of cases) [31,32,35,36,41,55]. However, despite attempted curative surgery, adults with locoregional disease have a 5-year survival rate of only 30%–40% [32,34–37,41,48]. The pattern of recurrence is locoregional (15%–25%), combined local and distant (25%–30%), or distant alone (50%) [32,41,56]. However, the increasing availability and quality of imaging allows diagnosis at an earlier stage, and the success of curative resection appears to be improving [31,32].

![Fig. 1. Probability of 5-year event-free survival according to disease stage at the time of diagnosis in 254 patients with adrenocortical tumor enrolled in the International Pediatric Adrenocortical Tumor Registry (from Michalkiewicz et al. Clinical and outcome characteristics of children with adrenocortical tumors. An analysis of 254 cases from the International Pediatric Adrenocortical Tumor Registry J Clin Oncol 2004, 22:838–845. Reprinted with permission from the American Society of Clinical Oncology.)](image)

Surgery is usually performed using a transabdominal approach. En bloc resection including the adjacent structures invaded by the tumor is required for good local control. Nephrectomy and resection of liver segments and portions of the pancreas may be included. Because of tumor friability, rupture of the capsule with resultant tumor spillage is frequent (approximately 20% of initial resections and 43% of resections after recurrence) [51,53]. There have been anecdotal reports of ruptured ACT as a cause of acute abdomen in children [57]. When the diagnosis of ACT is suspected, laparotomy and a curative procedure are recommended rather than fine-needle aspiration, to avoid the risk of tumor rupture [58]. Infiltration of the vena cava by tumor thrombus occurs in 20% of patients and may make radical surgery difficult [32,53]. For this reason, the vena cava should be palpated by the surgeon before resection of the primary mass is attempted. A combined thoracic and abdominal approach may be required in cases of extensive tumor thrombus. Often, spillage cannot be avoided. Large tumors tend to adhere to adjacent structures (e.g., vena cava) and have large necrotic and friable areas that promote rupture of the capsule during radical excision. The same is true for tumor thrombus, which may contaminate the peritoneal cavity when the vessel is opened.

**Mitotane and other antineoplastic agents.** Chemotherapy with mitotane or systemic agents is indicated for advanced disease or high risk of recurrence, although it has a small impact on overall outcome. Mitotane, an insecticide derivative that produces adrenocortical necrosis, has been used extensively to treat adult ACT. Mitotane both inhibits biosynthesis of corticoids and destroys the adrenocortical cells. At low doses, mitotane suppresses the secretion of adrenal steroids, providing symptomatic improvement and partial regression of endocrine dysfunction in most patients with functional tumors [35]. Higher doses (>3 g/day) are required for an adrenolytic effect [31,33]. Approximately 20%–30% of patients with advanced disease have objective responses to mitotane alone [31,33,35,59,60]. Although long-term remission is possible [61], most responses are transient and the prolongation of survival is uncertain [33,35,62]. In children, the use of mitotane for advanced ACT has not been evaluated systematically. Complete responses have been reported in children with advanced or metastatic ACT but appear to be rare [63–65].

The antitumor effect of mitotane is influenced by its pharmacokinetics and by whether therapeutic exposure is maintained for prolonged periods. Serum concentration reaches a plateau after 8–12 weeks of treatment [33,60] and antitumor responses occur only when serum concentration >14 μg/mL is maintained for a prolonged period [55,59,60]. Therapeutic levels are achieved in only 50%–60% of patients [55,60]. The severe gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain) and
neurologic (somnolence, lethargy, ataxia, depression, and vertigo) toxic effects of mitotane limit patient compliance [33,35,59]. Neurologic toxicity is closely correlated with plasma concentration >20 μg/mL, and close monitoring and dose adjustment may decrease the incidence of toxicity [59,60].

An alternative to high-dose mitotane is administration of low doses for more prolonged periods. Some authors have reported good results with low-dose mitotane (2–3 g/day). With appropriate monitoring, therapeutic levels can be achieved after 3–5 months of therapy [66,67]. This approach limits side effects, which are dependent on serum levels [59], and significantly improves compliance. A therapeutic level can be reached with the lowest effective dose by proceeding in stepwise increments [67].

Because mitotane is adrenolytic, all patients receiving this agent should be considered to have severe adrenal insufficiency. Often, nausea and vomiting are caused by adrenal insufficiency rather than by mitotane, and adequate control of adrenal insufficiency increases mitotane tolerance. The cells in the zona fasciculata (which produce cortisol) are most greatly affected, although the cells in the zona glomerulosa (which produce aldosterone) are also compromised. Hydrocortisone and fludrocortisone must be given to prevent glucocorticoid and mineralocorticoid deficiency, respectively. Although dexamethasone replacement therapy has been widely used for adrenal insufficiency, it is not recommended for children receiving mitotane. Mitotane increases the metabolic clearance of glucocorticoids [68,69], and administration of hydrocortisone plus fludrocortisone allows independent adjustment of glucocorticoid and mineralocorticoid dosage. This independent adjustment is especially crucial during episodes of infection and chemotherapy. In addition to causing adrenal insufficiency, mitotane can interfere with the metabolism of other hormones, including thyroid and parathyroid hormones. Thyroxine replacement may be necessary. Another striking complication of mitotane is gynecomastia, which resolves after the medication is stopped.

Chemotherapeutic agents other than mitotane have been evaluated less extensively in ACT. Cisplatin as a single agent may induce responses in approximately 25% of patients with advanced disease [70]. Cisplatin-based regimens have been evaluated by various investigators. Regimens that combine cisplatin with doxorubicin and either cyclophosphamide [71] or 5-fluorouracil [72] have resulted in response rates of 20%–40%. Cisplatin has also been investigated in combination with etoposide [33,73,74]. The combination of doxorubicin, etoposide, and vincristine without cisplatin appears to induce an inferior antitumor effect [75]. Because of cisplatin’s renal dose-limiting toxicity, Ayass and coworkers substituted carboplatin for cisplatin given in combination with etoposide to a 17-month-old boy with ACT that had metastasized to the brain and chest. After complete resection of the primary tumor and eight cycles of etoposide and carboplatin, the metastatic disease responded completely and the patient survived long-term.

Adrenocortical carcinoma cells express P-glycoprotein (Pgp) [76,77], and mitotane causes reversion of the multidrug-resistance phenotype in vitro [78], with maximum Pgp inhibition at 15 μg/mL [59,62]. These findings provide a strong rationale for the combination of mitotane with etoposide-containing regimens [79,80]. Responses have been observed in 53% of patients treated with mitotane and cisplatin, etoposide, and doxorubicin [80]. However, other studies have failed to confirm these positive results [75]. Abraham et al. found that rhodamine efflux from CD56⁺ cells (a surrogate marker of Pgp inhibition) was not impaired in patients receiving chemotherapy and mitotane, even at therapeutic drug levels; therefore, mitotane may inhibit Pgp poorly in vivo [75].

Other treatments. The use of radiotherapy in pediatric ACT has not been consistently investigated. ACT are generally considered to be radioresistant [33]. Furthermore, because many children with ACT carry germline TP53 mutations that predispose to cancer, radiation may increase the incidence of secondary tumors. Driver et al. reported that three of five long-term survivors of pediatric ACT died of secondary sarcoma that arose within the radiation field [40]. For most patients with metastatic or recurrent disease that is unresponsive to mitotane and chemotherapy, repeated surgical resection is the only alternative. However, given the infiltrative nature of the disease, complete resection is difficult to achieve. Image-guided tumor ablation with radiofrequency current offers a valid alternative for these patients. Radiofrequency ablation is a minimally invasive and safe treatment for patients in whom surgery may not be possible. Using this technique, Wood et al. reported responses in 53% of the patients treated; these results suggest that radiofrequency ablation has a role in the management of this aggressive malignancy [81].

A Collaborative Research Initiative for Childhood Act

Cooperative multi-institutional efforts have been pivotal in the advancement of pediatric oncology during the past several decades. Rare pediatric tumors, however, have remained research orphans, and children with these rare malignancies have yet to benefit from group-wide initiatives. In recent years, the Children’s Oncology Group (COG) has made a commitment to develop research programs in rare childhood malignancies. Part of this effort is a collaboration between COG and Brazilian institutions to develop a study protocol for childhood ACT (ARAR0332) (Table II). This protocol will investigate three main clinical questions: (1) the efficacy of surgery alone for stage I tumors; (2) the role of retroperitoneal lymph node resection in reducing local recurrence of
chemotherapy have been studied mainly in adults. In the childhood ACT is not well-established; mitotane and peritoneal lymph node dissection.

With stage II tumors will undergo a mandatory retro-

of the initial surgery will be performed. However, patients with stage I tumors have an excellent outcome with tumor resection alone, and only lymph node sampling at the time of surgery. The ARAR0332 study will investigate the incidence of retroperitoneal lymph node involvement with large tumors. The ARAR0332 protocol will also investigate the incidence and prognostic implications of intraoperative tumor spillage and determine whether adjuvant chemotherapy should be explored in future trials.

Even after complete resection, larger tumors are associated with an increased risk of recurrence, both locoregional and distant, in adults and children [41,53]. We hypothesize that this finding reflects tumor spread into the regional lymph nodes. The lymph node drainage of the adrenal gland is complex. An extensive subserosal network of lymphatic channels surrounds the gland, and these channels cross at several levels, and in different directions, within the fascia and connective tissue. The lymph nodes are not routinely sampled during surgery, although the incidence of lymph node involvement is reported to be as high as 40% in adults with ACT [36,82]. It is, therefore, possible that residual tumor in the lymph nodes contributes to relapse, particularly for those patients with large tumors. The ARAR0332 study will investigate the incidence of retroperitoneal lymph node involvement in childhood ACT, and its impact on outcome. Patients with stage I tumors have an excellent outcome with tumor resection alone, and only lymph node sampling at the time of the initial surgery will be performed. However, patients with stage II tumors will undergo a mandatory retroperitoneal lymph node dissection.

The role of chemotherapy in the management of childhood ACT is not well-established; mitotane and chemotherapy have been studied mainly in adults. In the ARAR0332 study, patients with unresectable or metastatic disease will be treated with mitotane and a cisplatin-based chemotherapy regimen.

The ARAR0332 protocol will also attempt to provide further insight into the biology of ACT. In addition to the near-requisite germline TP53 mutations, a number of consistent chromosomal gains (e.g., 9q34 amplification in ~90% of cases) and losses (e.g., 18q21) have been observed in childhood ACT [30,83]. These genetic alterations presumably favor the expression of tumor-promoting oncogenes while eliminating potential tumor suppressors. Genomic DNA analyses (e.g., single nucleotide polymorphism analysis) used with microarray gene expression profiling should allow identification of the genes that cooperate with p53 inactivation to promote development of ACT. No effective therapies have yet been established for this rare childhood tumor, but efforts to define its oncogenic pathways should open new potential chemotherapeutic strategies to exploration.

TABLE II. Proposed Treatment on the COG ARAR 0332 Protocol

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<th>Stage</th>
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<td>II</td>
<td>Surgery</td>
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<td>III</td>
<td>RPLN dissection</td>
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<td>Mitotane</td>
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<td>Surgery + RPLN dissection</td>
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RPLN, retroperitoneal lymph node; CDDP, cisplatin; ETO, etoposide; and DOX, doxorubicin.

stage II tumors; and (3) the impact of mitotane and cisplatin-based chemotherapy for unresectable and metastatic disease.

Available information from adults and from the IPACTR indicates that patients with small, completely resectable tumors (stage I) can be cured with surgery alone. Tumor spillage remains a frequent problem for these patients, and its clinical relevance has not been prospectively studied in pediatric ACT, although retrospective data from the IPACTR suggest that tumor spillage is associated with a worse prognosis [53]. Therefore, the ARAR0332 protocol will also investigate the incidence and prognostic implications of intraoperative tumor spillage and determine whether adjuvant chemotherapy should be explored in future trials.

Even after complete resection, larger tumors are associated with an increased risk of recurrence, both locoregional and distant, in adults and children [41,53]. We hypothesize that this finding reflects tumor spread into the regional lymph nodes. The lymph node drainage of the adrenal gland is complex. An extensive subserosal network of lymphatic channels surrounds the gland, and these channels cross at several levels, and in different directions, within the fascia and connective tissue. The lymph nodes are not routinely sampled during surgery, although the incidence of lymph node involvement is reported to be as high as 40% in adults with ACT [36,82]. It is, therefore, possible that residual tumor in the lymph nodes contributes to relapse, particularly for those patients with large tumors. The ARAR0332 study will investigate the incidence of retroperitoneal lymph node involvement in childhood ACT, and its impact on outcome. Patients with stage I tumors have an excellent outcome with tumor resection alone, and only lymph node sampling at the time of the initial surgery will be performed. However, patients with stage II tumors will undergo a mandatory retroperitoneal lymph node dissection.

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