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Review

Childhood adrenocortical tumours

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Abstract

Childhood adrenocortical tumours (ACT) constitute only about 0.2% of all paediatric malignancies. However, the incidence of ACT varies across geographic regions and is remarkably high in southern Brazil. At presentation, most children show signs and symptoms of virilisation, which may be accompanied by manifestations of the hypersecretion of other adrenal cortical hormones. Fewer than 10% of patients with ACT show no endocrine syndrome at presentation; these are often older children and adolescents. ACT is commonly associated with constitutional genetic abnormalities, particularly mutations of the *P53* gene. Histological features are used to classify the tumours as adenomas or carcinomas; however, the distinction between these two subtypes is often difficult. The extent of disease is best evaluated by computed tomography or magnetic resonance imaging; the role of positron-emission tomographic scans has not been defined. Cure of ACT requires complete tumour resection. The role of chemotherapy or radiotherapy has not been established, although definitive responses to several anticancer drugs have been documented. Among patients who undergo complete tumour resection, favourable prognostic factors include age <4 years, smaller tumour size, signs of virilisation alone at presentation, and adenomatous tumour histology. Some children with ACT show abnormalities of growth and development at the time of presentation, but these usually resolve after surgery.

Keywords: Paediatric adrenocortical tumours; Adrenal cortex tumours

1. Epidemiology

Carcinomas are generally rare in children and adolescents. In the United States, Surveillance Epidemiology and End Results (SEER) data from the National Cancer Institute show that only about 1.3% of all childhood carcinomas and only about 0.2% of all childhood malignancies are adrenocortical tumours (ACT) [1]. Unlike paediatric carcinomas in general, which show a progressive increase in incidence with age, ACT has a peak incidence between ages 0 and 4 years. The frequency of ACT is 0.4 per million during the first 4 years of life, and it decreases to 0.1 per million during the subsequent 10 years. It then rises to 0.2 per million during the late teens and reaches another peak during the fourth decade of life. This pattern is consistent with the concept that paediatric ACT comprises at least two distinct disease groups [2].

Worldwide, the incidence of ACT differs across geographic regions. Although many cancer registries do not provide useful information about such rare diseases as ACT, the known incidence per million children of less than 14 years of age ranges from 0.1 in Hong Kong and Bombay to 0.4 in Los Angeles to 3.4 in southern Brazil [3–8].

2. Constitutional syndromes associated with ACT

Paediatric ACT is usually associated with constitutional genetic abnormalities (Table 1) [9–11]. On the basis of case reports of sporadic ACT in multiple siblings and the familial occurrence of ACT accompanied by diverse other neoplasms, Miller [12] first suggested that paediatric ACT

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Table 1
Constitutional genetic abnormalities associated with adrenal cortical tumours (ACT)

Condition	Tumour types	Observations
Li–Fraumeni syndrome and other germline *P53* mutations	Adenomas, carcinomas	10% of these tumours are ACT
Hemihypertrophy	Adenomas, carcinomas	20% of these tumours are ACT
Beckwith–Wiedemann syndrome	Adenomas, carcinomas	ACT is the second most common tumour (approx. 15% of children with this syndrome)
Carney complex	Primary pigmented nodular adrenocortical disease	ACT occurs in approx. 25% of patients Common in children.
Congenital adrenal hyperplasia	Adenoma, carcinoma (very rare)	Testicular tumours of heterotopic adrenal cortical tissue
Multiple endocrine neoplasia I	Nodules, adenomas, carcinomas	Median age of patients with carcinomas is 40 years

has a genetic basis. Li and Fraumeni observed a remarkably high frequency of ACT (4 cases, or 10%) among 44 malignancies in children from families in which diverse cancers segregated in an autosomal-dominant pattern [13,14]. In 1990, Malkin and colleagues [15] screened five of these families and found germline mutations clustered in exon 7 of the *P53* gene in all five. It is now well recognised that most of the constitutional genetic abnormalities in young children with ACT are germline mutations in various exons of *P53*. In fact, it is likely that more than 90% of young children with ACT have an inherited *P53* mutation. For example, Varley and colleagues [16] found germline p53 mutations in 9 of 13 cases of paediatric ACT selected without reference to the family's history of cancer. In southern Brazil, the frequency of a specific *P53* mutation (R337H) is 98% (55/56) in children younger than 4 years (B. Figueiredo, personal communication). An evolving hypothesis is that some *P53* mutations have low penetrance for cancer susceptibility in general but are associated with an increased predisposition to paediatric ACT. In these cases, the families of children with ACT have had a relatively unremarkable cancer history [16,17]. The biological basis of this finding has only now begun to be elucidated [18]. Nonetheless, the presence of a germline *P53* mutation of any type appears to greatly increase the predisposition to childhood ACT. These observations underscore the importance of considering genetic testing and counselling for families of young children with ACT, which may be the first manifestation of Li–Fraumeni syndrome in a family. The American Society of Clinical Oncology has recently published genetic testing guidelines for physicians of patients with increased cancer susceptibility [19]. Older children and young adults with ACT do not appear to carry germline *P53* mutations [20].

Hemihypertrophy is also associated with childhood ACT, either alone or as one of multiple somatic abnormalities. The incidence of hemihypertrophy is estimated to be 1 in 86 000 live births, with a predominance in females and an association with increased birth weight [21]. Recently, Hoyme and colleagues [22] reported the results of a prospective multicentre study of the incidence of neoplasia in children with isolated hemihypertrophy. Ten tumours were reported in nine children. Six patients had Wilms' tumour, two had ACT, one had hepatoblastoma, and one had leiomyosarcoma. Thus, approximately 20% of tumours occurring in children with hemihypertrophy are ACT, a frequency much higher than the rate of 0.1% among sporadic paediatric malignancies.

Beckwith–Wiedemann syndrome is a complex cancer-susceptibility disorder first described in 1963 [23]. It is characterised by omphalocele, macroglossia, macrosomia, neonatal hypoglycaemia, ear pits or ear creases, and midline abdominal-wall defects. The estimated frequency of Beckwith–Wiedemann syndrome is 1 in 13 700 [24], although the true frequency may be greater because of undiagnosed milder cases. Most cases are sporadic, but about 15% show autosomal-dominant inheritance. In families in which more than one sibling is affected, linkage analysis has shown that the disease cosegregates with chromosome band 11p15 [25]. Genomic imprinting and epigenetic mechanisms also play a role in the etiology of Beckwith–Wiedemann syndrome. Children with this syndrome are at increased risk of malignant and benign tumours, including Wilms' tumour, ACT, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma. ACT is the second most common tumour in Beckwith-Wiedemann syndrome (15% of patients) [26].

Carney complex is a rare familial cancer-predisposition syndrome inherited as an autosomal-dominant trait [27]. Linkage analysis has shown at least two genetic loci, 2p16 and 17q22-24, to be associated with Carney complex [28–30]. Primary pigmented nodular adrenocortical disease, which occurs in about 25% of affected individuals (most of them children or young adults), is the main endocrine manifestation of Carney complex. The nodules, which strongly express the neuroendocrine marker synaptophysin, are composed primarily of eosinophilic, lipid-poor cells similar to those of the zona reticularis [31]. It is not known whether these nodules represent a true malignancy, although they have shown loss of heterozygosity for *PRKAR1A* in some cases [32,33].

Congenital adrenal hyperplasia (CAH) is the result of inherited deficiency of enzymes of the steroidogenic pathway. Impaired cortisol and/or aldosterone production and increased production of ACTH and androgens account for the protean clinical manifestations of this disorder [34]. More than 90% of cases of congenital adrenal hyperplasia (frequency, 1 in 10 000–15 000 newborns) are caused by deficiency of the steroid enzyme 21-hydroxylase, which is encoded by the *CYP21* gene [35]. ACT are described only rarely in patients with congenital CAH [36–39]. Types of adrenal tumour in these cases include carcinoma, adenoma, myelolipoma, and haemangioma. Chronic stimulation of the adrenal gland by ACTH is thought to contribute to tumorigenesis.

Multiple endocrine neoplasia type 1 is a rare familial cancer syndrome characterised by neoplasms of several endocrine glands [40,41]. The frequency of multiple endocrine neoplasia type 1 in the population has been estimated to be 1 in 10 000 to 1 in 10 0000. The gene (*MEN1*) responsible for this disorder is located at chromosome band 11q13 and encodes a protein termed menin [42]. Approximately 35% of patients with multiple endocrine neoplasia type 1 have adrenal nodules. This prevalence is much higher than that of adrenal 'incidentalomas' in individuals without multiple endocrine neoplasia type 1 (approximately 9%). In a recent study of 66 patients with confirmed germline *MEN1* mutations, 18 patients (26.8%) had adrenal tumours [41]. 10 patients had non-functional benign ACT, three had cortisol-secreting benign adrenal tumours, and one had pheochromocytoma. The remaining four patients developed adrenocortical carcinoma; three of which were functional. All 4 patients were more than 30 years of age. Thus, germline *MEN1* mutations are an unlikely cause of paediatric ACT.

3. Somatic mutations in ACT

Although some children and most adults with ACT do not carry any of the known germline mutations, ACT cells often show non-random, acquired chromosomal changes. These observations suggest that multiple genes and genetic pathways are involved in predisposition to tumours of the adrenal cortex and to their progression.

Comparative genomic hybridisation has been used in an attempt to identify genetic patterns in ACT. This method detects amplification or deletion of chromosomal areas. The first study that used such hybridisation to analyse adult ACT found losses involving chromosomal regions 2, 11q, and 17p (50%), and gains at chromosomes 4 and 5 (50%) [43]. Sidhu and colleagues [44] confirmed some of these findings in adult ACT. They found the most common gains on chromosomes 5 (46%), 12 (38%), 19 (31%), and 4 (31%), and the most common losses at 1p (62%), 17p (54%), 22 (38%), 2q (31%), and 11q (31%). The findings of these studies were consistent only for losses in 17p and 11q and gains in chromosomes 4 and 5, which findings were also consistent with the report of James and colleagues [45]. Many chromosomal gains and losses have been described in children, but the most striking finding is a consistent gain in the number of copies of chromosomal region 9q34 [45,46]. Our most recent findings support the idea that gains and losses are independent of tumour type (carcinoma vs. adenoma) or the presence of a germline *TP53* mutation [46]. The genetic instability noted in these and many other tumours may be linked to defects in mismatch-repair genes that cause replication error phenotypes [47], and different replication-error genes may be expressed in the tumours of children and adults.

4. Clinical manifestations

A recent review of 254 children enrolled in the International Pediatric Adrenocortical Tumor Registry [20] showed that signs of virilisation were the most common clinical manifestation (84.2% of patients). The presenting features of virilisation include pubic hair, facial acne, clitoromegaly, voice change, facial hair, hirsutism, muscle hypertrophy, growth acceleration, and increase in penis size. Virilisation was observed either alone (virilising tumours, 55% of patients) or accompanied by clinical manifestations of the overproduction of other adrenal cortical hormones, including glucocorticoids, androgens, aldosterone, or oestrogens. These findings are consistent with those of other reports from diverse continents [8,48–54]. About 10% of patients showed no clinical evidence of an endocrine syndrome at presentation (non-functional tumours). Finally, overproduction of glucocorticoids alone (Cushing syndrome) was evident in only 5.5% of patients. Conversely, most adults with ACT show evidence of either Cushing syndrome or non-functional tumours at presentation [55,56]. Primary hyperaldosteronism (Conn syndrome) and pure feminisation occur very rarely.

The rate of tumour growth and the rate of tumour dissemination to other organs are variable. Some patients have a prolonged history of virilisation before a sizeable mass is detected, whereas others have relatively rapid tumour growth. In one extreme case, the estimated tumour weight increased at a rate of 400 g per month. Most patients have localised or regional disease at the time of diagnosis. The International Pediatric ACT Registry data show localised disease in 192 of the 254 reported patients. Metastatic disease was found at presentation in less than 5% of cases.

About one-third of patients present with hypertension, which is usually caused by excess glucocorticoid production. In the absence of hypercortisolism, hypertension is rarely caused by increased concentrations of

mineralocorticoid (Conn syndrome) or plasma renin activity. Hypertension caused by plasma renin activity is likely to reflect the compression of renal vessels rather than tumour secretion of renin, although renin production by ACT has been reported [57]. Regardless of the mechanism, hypertension should be treated aggressively, because if left untreated it can lead to hypertensive encephalopathy, seizure, and possibly death. After tumour resection, the hypertension typically resolves within a week.

5. Laboratory evaluation

The initial laboratory evaluation for suspected ACT is unique among evaluations for paediatric tumours. Because the tumour cells may secrete a number of adrenal hormones, either alone or in combination, it is possible to establish an endocrine profile of most paediatric ACT. Hormones that are oversecreted by ACT include androgens, glucocorticoids, mineralocorticoid and oestrogen. These tumour markers allow close monitoring for tumour recurrence. Typically, plasma hormones return to normal within 7 days after complete tumour resection. Adrenal cortex hormones should be monitored monthly during the first year after resection (the period of most frequent relapse) and every 3–4 months during the second and third years. It is important to note that tumour recurrence should be suspected when hormone levels progressively increase, even if they remain within normal limits. In such cases, unexpected changes in stature, weight, pubic hair, or other clinical signs are strong indicators of tumour relapse.

Laboratory investigation also helps to distinguish physiological adrenarche or CAH from ACT, especially in the case of small tumours. Typically, patients with adrenarche have elevated basal concentration of DHEA-S and androstenedione, while those with CAH may show increased basal or ACTH-stimulated peak concentration of 17-OH-progesterone [58]. A striking decrease in serum DHEA-S, androstenedione, and testosterone after administration of dexamethasone may help to distinguish adrenarche from ACT, especially when image analysis reveals a very small adrenocortical mass.

In most cases, the signs and symptoms of virilisation and Cushing syndrome abate over a period of several weeks or months after tumour resection. The persistence of hypertension seven or more days after tumour resection may reflect the administration of excess hydrocortisone replacement therapy, rather than residual tumour.

6. Pathology

Paediatric ACT comprises two main histopathological subtypes, adenoma and carcinoma. Adenomas, which represent about 10–15% of childhood ACT, are almost always functional. Macroscopically, adenomas tend to be well demarcated without extension into adjacent tissues. They usually have an ovoid or spherical shape and a uniform colour that varies from yellow to brown. Tumour size is relatively small (<10 cm), and tumour weight reportedly ranges from 11 g to 210 g [59,60]. Microscopically, adenomas tend to be encapsulated without evidence of necrosis and to show any of a variety of morphological patterns. Usually, they comprise oval or polygonal cells with eosinophilic cytoplasm that resemble the compact cells of the normal zona reticularis and/or clear cells of the normal zona fasciculata. Occasionally, areas of haemorrhage and calcification are noted. There are usually fewer than two mitotic figures per high-power field. Some adenomas show fibrosis or broad fibrous bands traversing the tumour.

Carcinomas usually have gross features suggestive of a malignant tumour. They tend to be large with marked lobulation and extensive necrotic and/or haemorrhagic areas. Because of these features, carcinomas are friable and commonly rupture during surgery. The bosselated tumour appearance results from the presence of broad fibrous bands. On cross-section, the tumour is soft and has a variegated appearance, ranging from yellow to dark brown in colour. Microscopically, carcinomas are composed of medium-sized to large cells with eosinophilic cytoplasm, arranged in large or small alveolar clusters. On high-power examination, the typical characteristics include numerous mitotic figures with features of atypical cell division; distorted architecture; broad fibrous bands; prominent cellular pleomorphism and nuclear atypia; extensive areas of necrosis, haemorrhage, and calcification; and vascular and capsular invasion.

Although adenoma and carcinoma are histologically distinct entities, their clinical distinction is less clear. A substantial number of patients with tumours classified as malignant (carcinoma) also have a benign clinical course.

7. Imaging studies

Because more than 90% of children with ACT have clinical and laboratory evidence of endocrine dysfunction, imaging studies are unlikely to contribute to the differential diagnosis of adrenal neoplasia in that age group. However, imaging studies are of great importance for surgical planning and disease staging. Adequate imaging studies, including magnetic resonance (MR), computed tomography (CT), and ultrasound (US) studies, are necessary to allow the surgeon to detect invasion of local structures (including liver, pancreas, and diaphragm), metastasis, and involvement of the vena cava. In the last case, it is important to determine the extent of tumour thrombus. Moreover, imaging can

be used to provide other prognostic information, such as tumour size, extension into adjacent structures, vascular invasion, and thrombosis. A thin-collimation CT scan, MR imaging, and US examination should be obtained for each patient before surgery. Because the liver and lungs are the most common sites of metastasis, CT scans of chest and abdomen are recommended for all newly diagnosed patients. The skeleton and central nervous system are involved in a few cases. Technetium bone scans are typically obtained in the initial evaluation of children with ACT. Imaging of the central nervous system is not routinely performed at presentation.

On CT imaging, which is most commonly performed, ACT is usually well demarcated with an enhancing peripheral capsule [61]. Large tumours usually have a central area of stellate appearance caused by haemorrhage, necrosis, and fibrosis. This stellate zone is hyperintense on T_2-weighted MR imaging and STIR images. Calcifications, which can range from small focal inclusions to extensive linear and amorphous deposits, are common. Because CT scans may miss tumour extension via the vena cava into the right atrium, US or MR imaging should complement CT scans, particularly when there is compression or thrombosis of the inferior vena cava. US can demonstrate involvement of the inferior vena cava when CT and MR imaging appear normal [62]. Because ACT is metabolically active, whole-body fluorodeoxyglucose (FDG)-positron-emission tomographic (PET) imaging is increasingly used in patients with ACT [63,64]. Although FDG-PET is unlikely to add information to that obtained with CT or MR imaging of the primary tumour and its regional extension, it can disclose distant metastases that are not readily detected by CT or MR imaging. FDG-PET can also detect tumour recurrence in areas that routine follow-up imaging may miss. However, this technique has not been systematically evaluated in paediatric ACT. Very rarely, invasive techniques such as arteriography and venography have been used to complement CT, MR, and US imaging. None of these imaging methods can reliably distinguish between adenoma and carcinoma or between malignant or benign tumours in children.

8. Treatment

Surgery is the only mode of therapy documented as effective for treating paediatric ACT. Curative surgical resection should be considered for every child with ACT. Surgery is performed by a transabdominal approach, usually by using an ipsilateral subcostal incision, which may be modified to a chevron or bilateral subcostal incision. *En bloc* resection, which may include the kidney, portions of the pancreas and/or liver, or other adjacent structures, may be necessary in rare cases of large, locally invasive tumours. A thoracoabdominal incision is indicated in rare cases.

Because of extensive tumour necrosis, haemorrhage, and fibrosis, ACT is particularly friable and is susceptible to intraoperative tumour rupture and spillage. To avoid a possible adverse effect on outcome, the tumour should be carefully manipulated during surgery. CT imaging can be particularly useful to the surgeon in identifying necrotic areas of tumour prior to surgery. Spontaneous tumour rupture [65] and tumour rupture after percutaneous biopsy [66] have been also reported. Therefore, needle biopsy should be avoided in children with ACT.

Before tumour resection, the inferior vena cava should always be palpated to detect thrombus. If infradiaphragmatic thrombus is evident, it can be extracted during the initial surgery. If the thrombus extends above the diaphragm and into the atrium, a cardiovascular surgeon may be involved in the surgical intervention. In such cases, a sternal-split incision and extracorporeal circulation may be required [67–69].

In adults, laparoscopic extirpation of small benign adrenal tumours is increasingly used [70]. This method was recently reported in the case of a paediatric patient [71]. However, we are aware of paediatric cases in which this technique has led to tumour rupture during the procedure and subsequent relapse. Therefore, the laparoscopic method is feasible but should be avoided in the management of paediatric ACT.

The role of regional lymph-node dissection in paediatric ACT has not been evaluated, but it has been advocated because patients with large tumours commonly experience local relapse. An ipsilateral modified node dissection is performed, extending from the renal vein to the level of bifurcation of the common iliac vessel. If there are contralateral clinically enlarged lymph nodes, they should be removed as well.

Surgical resection of recurrent local and distant disease is also important. In the latter case, multiple surgical resections may be necessary to render patients free of disease. This aggressive approach is associated with prolonged survival, particularly when combined with chemotherapy.

The role of chemotherapy has not been systematically evaluated in childhood ACT. Mitotane (1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane; *o*, *p*'-DDD), an isomer of the insecticide *p*, *p*′-DDD, specifically induces adrenocortical necrosis [72,73]. Mitotane has been used to treat advanced metastatic ACT prior to surgery in cases of inoperable tumours, after surgery in patients at high risk of relapse (adjuvant chemotherapy), and to control symptoms associated with increased production of adrenal hormones. In adults, objective responses to mitotane (mostly partial responses) are obtained in 15–60% of patients [74–76]. The wide variation in response rates may in part reflect the

pharmacokinetics of mitotane. Haak and colleagues have suggested that tumour response is greater when the plasma concentration of mitotane is above 14 mg/l [77].

Little information is available about the use of mitotane in children, but response rates appear to be similar to those seen in adults with ACT [50,78,79]. Complete and durable responses have been described in a few patients [80–82]. Between 1990 and 1995, we conducted a study of the efficacy and toxicity of mitotane as adjuvant therapy for newly diagnosed childhood ACT at high risk of relapse. 32 patients were treated at a dosage $\leqslant 8$ g/m^2 per day. About 50% of these children had relapses, a rate similar to that historically obtained in patients with a comparable tumour burden at diagnosis (unpublished data). Because of poor tolerance and compliance, it was impossible to determine the efficacy of adjuvant therapy with this agent. Mitotane toxicity was significant, causing nausea, vomiting, anorexia, diarrhoea, somnolence, mental confusion, ataxia, blurred vision, headaches, and renal and hepatic dysfunction, as reported by others [83–86].

The endocrine-associated toxicity of mitotane deserves special attention. Because mitotane is adrenolytic, all patients receiving this agent should be considered to have severe adrenal insufficiency. 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 are 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, and administration of hydrocortisone plus fludrocortisone allows independent adjustment of glucocorticoid and mineralocorticoid deficiencies. Independent adjustment of the dosage of these medications is especially critical during episodes of infection. In addition to causing adrenal insufficiency, mitotane can also interfere with the metabolism of other hormones, including thyroid and parathyroid hormones. Thyroxine replacement is commonly necessary in these children. Another striking complication of mitotane is gynaecomastia, which resolves after the medication is stopped. Recently, a reduction of the daily dose of mitotane to achieve a serum concentration between 14 and 20 mg/l has been advocated [87,88] in the hope of reducing the side-effects while retaining the efficacy of mitotane. The duration of mitotane treatment has not been defined. It has ranged from several months to more than 10 years in different studies. The available information does not allow conclusions about the optimal duration of treatment. Because paediatric ACT usually relapses within 6–8 months after surgery, continuation of mitotane therapy for 8 months to 1 year is reasonable.

Other chemotherapeutic agents, including 5-fluorouracil, etoposide, cisplatin, carboplatin, cyclophosphamide, doxorubicin, and streptozocin, have been used alone or in combination to treat ACT, with varied results. The most recent trials have investigated the efficacy of a combination of cisplatin and etoposide with or without doxorubicin. The response rate is approximately 30%, with very few complete responses [88–91]. Mitotane is usually given during the treatment period, partly because of its ability to reverse multidrug resistance by inhibiting P-glycoprotein-mediated drug efflux [92]. The best results of combination chemotherapy have been reported by Italian investigators [93] who administered cisplatin, etoposide, and doxorubicin in conjunction with a relatively low dose of mitotane. 15 of 28 patients had measurable responses, including two complete responses. Recently, Khan and colleagues [94] conducted a phase II study of intravenous streptozocin given in combination with mitotane to patients with either completely resected or residual disease. About 30% of patients with measurable disease had responses, and patients who received the chemotherapy appeared to have a greater probability of survival than did the control group, although the number of patients was small. There has been no formal trial of conventional chemotherapy agents in paediatric ACT, but the available case reports and the experience of the International Pediatric Adrenocortical Tumor Registry suggest that a subset of paediatric ACT is chemotherapy sensitive. The combination used most often in paediatrics consists of cisplatin and etoposide given in conjunction with mitotane. At St. Jude, 3 of 7 patients with relapsed or metastatic disease who have been treated with this combination are long-term survivors and are likely to be cured (unpublished observation). Patients at other institutions in the United States have received similar combination therapy with complete tumour responses, including the disappearance of pulmonary metastasis. However, these anecdotal observations should be superseded by systematic studies to determine the overall rate of response to this combination chemotherapy.

9. Prognostic factors

The clinical value of prognostic-factor analysis depends on the efficacy of the available therapy. Because surgery is the only known effective treatment for childhood ACT, complete tumour resection is the single most important prognostic indicator. Patients who have residual disease after surgery have a dismal prognosis. Of 57 patients in the international ACT registry who had distant or local gross or microscopic residual disease after surgery, only eight have remained free of disease. Conversely, the long-term survival rate is

around 75% for children with completely resected tumours. Among patients who are free of residual disease after surgery, tumour size has prognostic value. Registry data showed that among 192 such patients, those with tumours >200 g had an event-free survival estimate of 39%, compared to 87% for those with smaller tumours. Tumour size, as measured by weight, volume, or largest diameter, has been consistently associated with prognosis in several studies of ACT [4,59]. The weight used as a discriminator (i.e. the threshold value) in many of these studies has varied considerably. For example, Wieneke and colleagues [59] found that weight >400 g was associated with poor prognosis in a univariate analysis. In other studies, weight <200 g identified a group of patients with a very good prognosis [95]. The type of adrenal hormone secreted by the tumour is also associated with prognosis. Children whose tumours produce excess glucocorticoid appear to have a worse prognosis than children who have pure virilising manifestations. However, these observations require confirmation, because many of the patients studied did not have complete assessment of plasma adrenal hormones. Young age has also been associated with a better outcome.

It is likely that adding other predictive factors can further refine prognostic-factor analysis. For example, rupture of the tumour pseudocapsule during surgery and invasion of the vena cava were found to be associated with poor prognosis even among patients who had completely resected tumours, but these variables have yet to be prospectively analysed. Moreover, some histological tumour features, such as vascular or capsular invasion, extensive necrosis, and marked mitotic activity, were independently associated with prognosis in a recent study [59]. Classification schemes or disease staging systems to guide therapy are still evolving in paediatric ACT. Sandrini and colleagues [8] have proposed a staging system that includes tumour volume and resectability. This scheme has the advantage of distinguishing two groups—those with completely excised tumours less than 200 cm^3 (stage I disease) and those with distant metastasis (stage IV disease)—that have vastly different outcomes. However, the intermediate groups, stages II and III, are heterogeneous and are likely to include different prognostic categories. It is likely that this scheme will be further refined for purposes of treatment and prognosis as more information becomes available.

10. Integration of known prognostic factors with treatment options

Children with small, completely resected tumours have an excellent prognosis. Small tumours are those that measure ⩽5–10 cm in their largest diameter or that weigh ⩽100–200 g. These patients, regardless of any clinical or biological feature, require no further treatment; the expected relapse rate is <10%. At the other extreme are patients with residual or metastatic disease. These patients require multimodality therapy with surgery and intensive chemotherapy. Although little information is available, a combination of orally administered mitotane with intravenous etoposide and cisplatin should be considered for these patients. Whether doxorubicin adds to the efficacy of this regimen is at present uncertain. These modalities should be coordinated, since chemotherapy should be most effective in patients with minimal tumour burden. Between these two groups are patients who have completely resected tumours but are at high risk of relapse. Mitotane given alone appears not to influence the outcome of these patients, but adjuvant combination chemotherapy has not been systematically evaluated. Because treatment failure in these patients usually takes the form of local relapse, it is possible that more extensive primary surgery, including retroperitoneal nodal dissection, may improve their prognosis. Finally, there is a small group of patients who have a very large abdominal mass that cannot be safely resected. Typically, these tumours do not invade adjacent structures or produce distant metastasis, despite their size. For these patients, mitotane is recommended to induce tumour shrinkage and improve the odds of complete tumour excision. These tumours may differ biologically from those that produce regional and distant metastasis.

11. Future directions

Because of the rarity of childhood ACT, it is unlikely that a single institution or even a single country could accrue enough patients to advance knowledge of this disease. An international database was developed in 1990; to date, information on the clinical and biological characteristics and outcome of more than 250 cases of paediatric ACT has been collected and analysed [20]. Recently, a protocol to request tumour samples as well as clinical information was formalised. This capability will facilitate investigators' access to tumour material. Finally, the Children's Oncology Group has approved a clinical trial designed to establish uniform guidelines for the treatment of children with ACT. Two Brazilian institutions located in the region that has an increased incidence of ACT will participate in the study. We strongly believe that only through extensive international participation and collaboration can the outcome of rare tumours such as paediatric ACT be improved and sufficient tumour material collected to allow elucidation of the mechanisms of tumorigenesis.

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