Management of Adrenal Tumors in Pediatric Patients

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KEYWORDS

• Pediatric • Adrenal • Neoplasm • Cancer • Tumor • Child

KEY POINTS

- Adrenal tumors in children can be benign, malignant, or pseudotumors.
- Adrenal tumors are considered rare, frequently have a genetic underpinning, and are often hormone producing.
- Diagnostic algorithms depend on history, physical findings, biochemical testing, and radiologic analyses.
- Regardless of tumor type, surgery plays an essential role in their treatment, and surgical principles should be followed in order to avoid complications and contribute to better cure and survival rates.
- Ongoing surveillance after treatment is mandated in almost all cases.

INTRODUCTION

Adrenal tumors in children are caused by a wide variety of conditions and may be diagnosed from the fetal stage onwards.[1–4] From an embryologic perspective, the adrenal fetal cortex and medulla are formed by 7 weeks' gestation. The cortex comes from the mesoderm, whereas the medulla is derived from the ectoderm/neural crest. As such, adrenal tumors identified within the gland have different histopathologic origins and resultant symptoms. Neoplasms of the adrenal gland are classified and discussed here in an anatomic framework.

PRIMARY TUMORS

Cortex

Adrenocortical tumors (ACTs) are rare but aggressive endocrine neoplasms when carcinomas, comprising 0.2% of all pediatric malignancies.[5] Only 10% to 20% of pediatric cases are benign adenomas. The estimated worldwide incidence is about 0.3 new cases per million individuals per year.[6] However, in the south and southeast regions of

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Brazil, ACT incidence rates are 15 to 20 times higher than those described in other countries. This ACT cluster in Brazil is caused by the presence of a founder TP53 mutation in this population.[7,8] Germline TP53 mutations are present in more than 80% of ACTs in children, and they underlie signaling abnormalities that are strongly associated with ACT. ACTs are also the most frequent neoplasms identified in families afflicted with Li-Fraumeni syndrome. De novo TP53 mutations are also observed, and relatives of children with ACT may have a higher incidence of cancer.[9] In North American children, the spectrum of germline TP53 mutations and the mechanisms and types of functional loss of heterozygosity in ACT are diverse, although germline mutations occur primarily in the TP53 DNA-binding domains (exons 4–8).[9] By contrast, in the Brazilian cases, 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.[9] The penetrance of this mutation is low (only 10%–15% of carriers develop ACT), and it seems not to predispose carriers to other malignancies later in life.[9] Therefore, additional genetic alterations may be necessary for malignant transformation. The early age of onset and the distinctive clinical features of childhood ACT suggest that they arise in the fetal zone of the adrenal cortex.[9] The fetal zone occupies 85% of the adrenal cortex during embryonic development and is oriented toward dehydroepiandrosterone production. A constitutional TP53 mutation may increase the risk of neoplastic transformation in the fetal adrenal cortex but not in the definitive adrenal cortex. The adrenal cortex is composed of 3 functional areas, defined as the glomerulosa, reticularis, and fasciculata zones. Complete differentiation of these areas occurs by the age of 3 years. Tumors can arise from all 3 zones, be benign (adenoma) or malignant (adenocarcinoma), and be hormone secreting. Neoplasms arising from the adrenal cortex are predominantly hormone secreting and can express mixed patterns of hormone production, which is explained by the embryologic zones of origin (aldosterone, granulosa; glucocorticoids, fasciculata; reticular, glucocorticoids and sex hormones). As such, ACT may present with virilization (precocious puberty, deepening voice, pubic and axillary hair, acne, genital growth), Cushing syndrome (hypertension, central obesity, buffalo pump, moon face, stretch marks), signs of hyperaldosteronism, or may be asymptomatic depending on the quantity of hormone produced. Because hormone-related symptoms generally are readily apparent, most patients in these situations have small, nonpalpable adrenal masses.

Therefore, the diagnosis of ACT is generally straightforward. Clinical presentation includes virilization and hypertension, and surgeons must be aware of the disease in order to make an early diagnosis. Because most patients have an endocrine syndrome, increased blood or urine concentrations 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 (MR) and computed tomography (CT) of the primary site are necessary to detect invasion of adjacent structures, lymph node enlargement, and tumor thrombus in the venous drainage, all of which may require resection during the curative procedure. The tumors characteristically have a thin pseudocapsule and areas of calcification and necrosis. Vascular extension occurs in 20% of cases, and patients should be examined for intracaval tumor thrombus.[10] Some cases are diagnosed incidentally by imaging studies performed for other purposes. Distant metastases usually involve the liver, lungs, kidneys, and bone, and, hence, dedicated radiologic studies are required to evaluate these anatomic areas. In general, PET with concurrent diagnostic CT is warranted for evaluating for distant metastases.

The need for tumor biopsy is not indicated unless there is a question of the diagnosis or if the tumor is unresectable. Hence, surgical dictum recommends primary resection

to prevent unnecessary tumor rupture, complete tumor staging with concurrent ipsilateral lymph node dissection, and tumor extirpation to control the overproduction of hormones. Hence, the authors strongly recommend that surgical excision should be done upfront whenever possible and that biopsies should be avoided.

Surgery is the only curative treatment modality in ACT, and, as such, it is the cornerstone of treatment. The goal in all cases is complete resection, including en bloc (partial) removal of adjacent organs if needed to achieve negative margins. The driving force behind this recommendation is the fact that patients with microscopic or macroscopic residual disease or metastatic disease have a dismal prognosis (**Fig. 1**). Before surgery, it is essential that the patients are properly prepared to avoid adrenal insufficiency in the perioperative period. As such, corticosteroids directed to both glucocorticoid and mineralocorticoid function are mandated. The reason for this recommendation is that, with the abrupt decrease in hormone production with surgical resection of the ipsilateral tumor (and if the adrenalytic agent mitotane is used in the adjuvant setting), the need for steroid supplementation in the perioperative and postoperative settings is absolute.

Meticulous and precise surgical technique is advised in all patients having resection of ACT and should include a complete discussion with the patient. A major concern is inadvertent tumor spillage because it increases the rate of recurrence and worsens prognosis by upstaging the patient and increasing therapy in the adjuvant setting, as shown in **Fig. 1**.

Known anatomic considerations and concerns need to be well understood and acknowledged by the surgeon too, because these issues can increase the risk of rupture.[11] ACT can present with a very thin capsule and be composed of gelatinous contents from intratumoral necrosis, which may also increase the risk of rupture and must be taken into account by the surgeon (**Figs. 2 and 3**A and B).

The decision on the type of surgery (open or closed) to perform in ACT is surgeon and case dependent. For smaller lesions, those with benign characteristics, those relegated to the gland, and in those without concern for spill, a closed or minimally

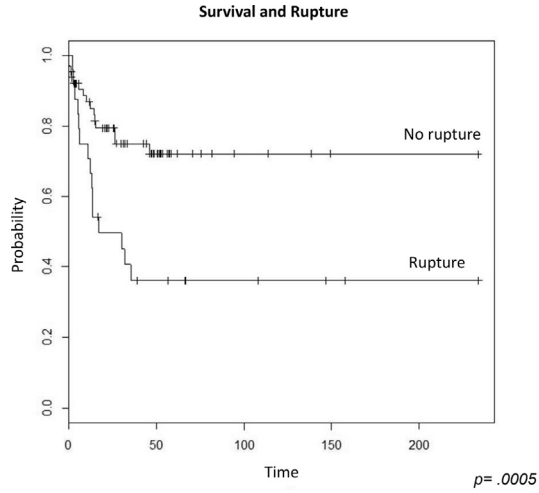

Fig. 1. Brazilian Pediatric ACT Cohort showing impact of tumor rupture on survival. Data analyzed on 151 Brazilian children diagnosed with ACT showed a statistically significant (P<.0005) reduction in survival when tumors were ruptured at surgery.

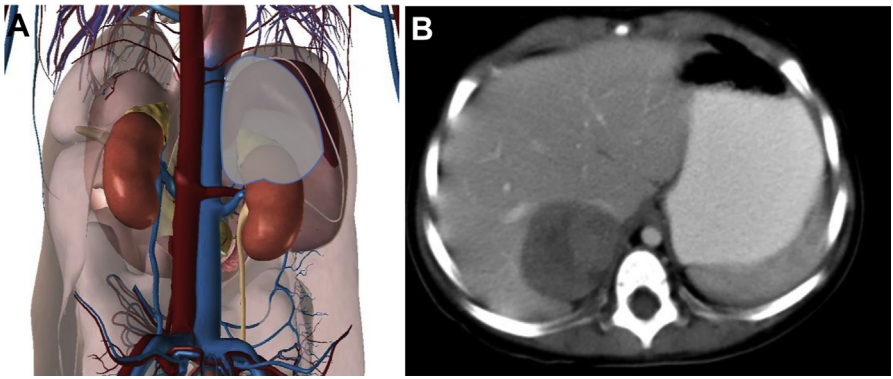

Fig. 2. Anatomic position of the right adrenal gland and the liver (*A*) and CT (*B*) showing the posterior view of the interface of the right adrenal gland with the liver with the right adrenal firmly adherent to the liver by fibrous union of the capsules, making it easier for the tumor rupture to occur.

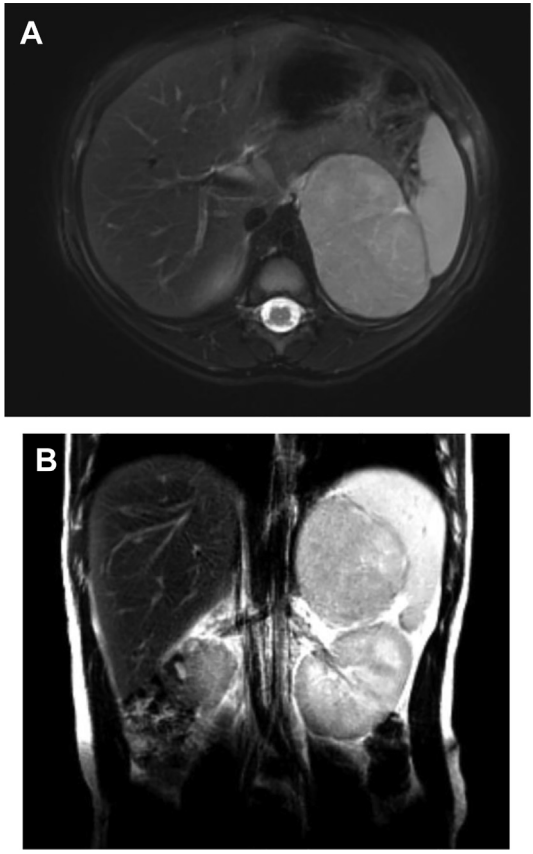

Fig. 3. Imaging comparison of 2 different ACT tumor consistencies. Radiologic comparison between 2 different tumor consistencies with the upper axial and coronal MRI (*A*) showing a homogeneous and solid lesion, whereas the lower images (*B*) shows a heterogeneous pattern and likely tenuous tissue consistency more prone to rupture.

invasive approach can be considered. The pros and cons of open and minimally invasive access (minimally invasive surgery [MIS]) are well known, but the surgeon must keep in mind that patients with ACT have inferior outcomes with higher relapse rates after MIS approaches, especially in large tumors. Thus, although feasible and tempting in many cases, the authors strongly recommend that laparoscopic resections should be carefully considered and performed in pediatric ACT in centers with experienced surgeons, high case volumes, and in patients with small tumors.

In larger tumors, tumors invading other organs, concern for intraoperative tumor rupture or spill, and tumors expected to be malignant ACT regardless of size and any sign of vascular involvement, an open approach should be prioritized. The open surgical approach can be done by laparotomy or a thoracoabdominal approach. A thoracoabdominal approach (**Fig. 4**) is recommended to decrease the risk of rupture and hemorrhage by widely opening the involved operative field and allowing access to the posterior structures of the retroperitoneum and body wall where perforation may be likely to occur, especially the large tumors that grow behind the liver. This approach is recommended for small tumors in this site as well, because the adrenal and liver capsules may be densely adherent and rupture can easily occur. Self-retaining liver retractors can be important tools to facilitate access and extirpation. In order to reach the adrenal glands, the surgeon must perform an ipsilateral (possibly bilateral) medial visceral rotation maneuver to mobilize the associated adjacent and overlying structures (surgeons also need to be able to mobilize the liver and the left and right triangular, falciform, and caudate ligaments) fully as well, so as to gain access to the right (or even left) adrenal gland. These maneuvers also allow access to the aorta, the vena cava, and their branches so as to achieve vascular control if required.

However, regardless of the technique used for the resection, the surgeon must be able to perform an ipsilateral retroperitoneal lymph node dissection (RPLND) as well for proper and complete staging of these tumors. Evidence of lymph node metastases (radiographically occult or not) upstages patients and intensifies adjuvant therapy. Because RPLND is a standard oncological principle, a careful understanding of the anatomic boundaries for this procedure need to be recognized and acted on. An RPLND should be performed to ensure adequate histopathologic staging. The lymphatic drainage of the adrenal gland includes the lymph node basins of the ipsilateral suprarenal space, kidney, and periaortic and paracaval regions, and these regions

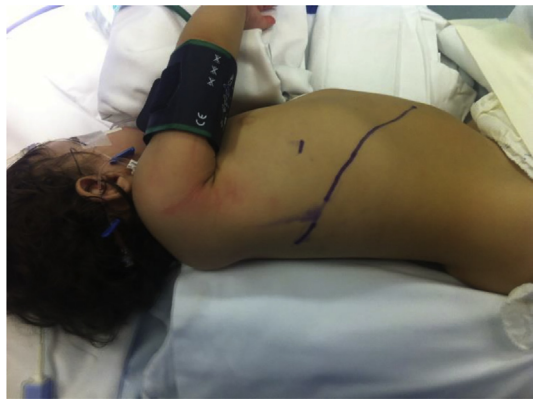

Fig. 4. Thoracolaparotomy incision. Representative image of a child undergoing open right adrenalectomy via a thoracolaparotomy incision.

should be included in a dissection. In order to determine the necessity of an RPLND as a formal component of treatment, the recently completed Children's Oncology Group (COG) ARAR0332 prospective trial is attempting to evaluate the necessity and results of RPLND in low-stage ACT. However, preliminary results have been inconclusive.[12]

Vascular extension is another surgical issue in ACT, because it is related to very poor prognosis and changes the surgical strategy considerably.[10] In some cases, cardiac bypass may be needed to achieve complete resection in those cases where the tumor thrombus ascends the vena cava to the level of the hepatic veins or more cephalad into the right atrium. It is important to evaluate this condition preoperatively with dedicated vascular imaging to assess the extent of the tumor thrombus. The tumor thrombus of ACT is also distinctive (**Fig. 5**), and **Table 1** outlines the qualitative differences between tumor thromboses in nephroblastoma and ACT. Considering the difficulties in resection that these features add, surgeons must be prepared to deal with these risks.

The benefit of primary tumor resection or debulking in general is yet to be defined in pediatric patients with metastatic ACT. In some cases, it may be indicated because of refractory hypertension and/or to relieve other symptoms of hormone overproduction. Aggressive locoregional debulking, including peritonectomy and metastasectomy, alone or in combination with hyperthermic intraperitoneal chemotherapy (HIPEC), is another consideration, but adequate data are lacking. Furthermore, pulmonary metastasectomy has been reported to have benefit, but the exact indications and in which patients (especially in children) have not been defined.[13]

Pathologically, small tumors can behave aggressively, suggesting that more specific prognostic factors should be considered other than simply tumor size. On histology, ACTs are classified as adenoma, indeterminate, or carcinoma.[14] Adenomas are associated with excellent prognosis because they are benign, but only about 20% of pediatric ACTs are classified as such.[9] However, the distinction between adenoma and carcinoma histopathologically is difficult,[15–18] and many times tumors are considered of indeterminate histology. If there is evidence of metastases and/or recurrence, then a diagnosis of carcinoma is obvious. To better define the malignant potential of ACT, a study is needed to quantitate markers of angiogenesis and lymphangiogenesis in ACT and controls.[19,20] From the angiogenic perspective, combined levels of vascular endothelial growth factor, endoglin, intratumoral microvessel density (MVD), and cluster of differentiation 34 (CD34) MVD were better able to predict prognosis in patients with indeterminate tumor histology. Inclusion of these components in the pathologic analysis of ACT may refine the classification in pediatric ACT.[19] No association was noted

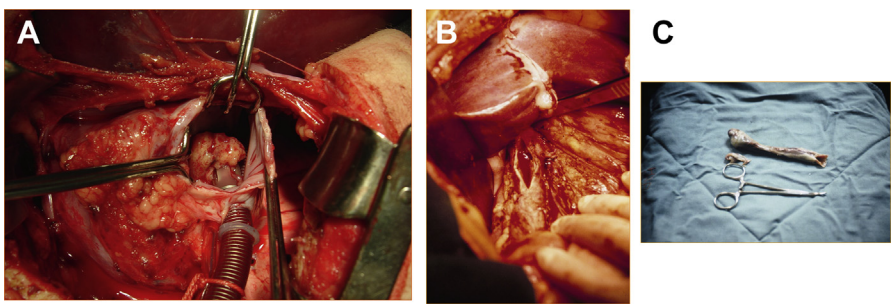

Fig. 5. Tumor thrombus in ACT and nephroblastoma. (*A–C*) Intracaval tumor thrombus. (*A*) The ACT tumor thrombus is a distinct mass and friable, whereas in nephroblastoma it is a plaquelike lesion adherent to the vessel wall. (*B*) Nephroblastoma in vivo, cavotomy; (*C*) ex vivo.

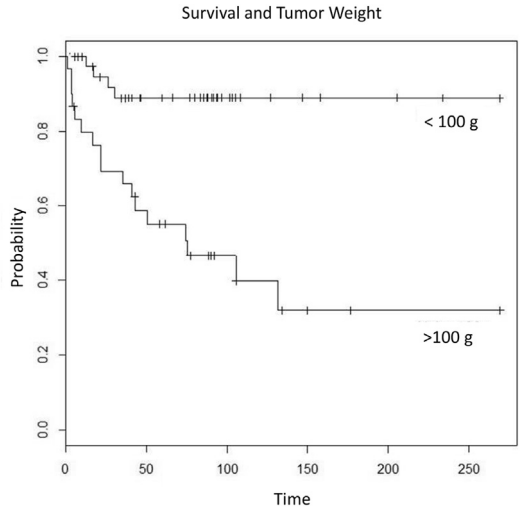

Fig. 6. Brazilian Pediatric ACT Cohort showing impact of tumor weight on survival. Data analyzed on 151 Brazilian children diagnosed with ACT showed a statistically significant (P = .004) reduction in survival with larger tumors.

between positive lymph nodes and relapsed disease. In contrast, the lymphatic vessel density was inversely associated with local relapse, indicating that pediatric adrenocortical carcinoma (ACC) may not disseminate through lymphatic vessels.[20]

Staging of ACT combines several components, including tumor size (Fig. 6), evidence of local-regional extra-adrenal disease, and metastases. Complete staging necessitates both radiologic and anatomic considerations. An ACT staging system[21] used in the most recent COG ARAR0332 is provided in Table 2. At present, tumor size and disease stage remain the primary prognostic factors of this disease,[15–18,21] because other prognostic factors have not been firmly established for pediatric ACT.

Based on staging, the treatment proposed by the recently completed COG ARAR0332 protocol is shown in Table 3. Multimodal therapies are recommended, including surgery, cytotoxic chemotherapy, and the primary adrenalytic agent

Table 1
Qualitative differences between tumor thromboses in nephroblastoma and adrenocortical tumors

	WT Thrombus	ACT Thrombus
Consistency	Firm	Friable
Thrombus Regression	Possible	Unlikely
Stage	No change	Changes staging (spillage)
Oncological Prognosis	No change	Very poor
Constitution (Viable Tumor Cells)	Skeleton with/without tumor cells	Tumor cells
Embolism	Possible	Likely
Surgical Complications	Rare	More often

Abbreviation: WT, wilms tumor (nephroblastoma).

Table 2
Adrenocortical tumor staging per Children's Oncology Group ARAR0332

Stage	Definition
I	Completely resected, small tumors (<100 g and <200 cm^3), with normal postoperative hormone levels
II	Completely resected, large tumors (>100 g and >200 cm^3), with normal postoperative hormone levels
III	Unresectable gross or microscopic disease Tumor spillage Patients with stage I and II tumors who fail to normalize hormone levels after surgery Patients with lymph node involvement
IV	Presence of distant metastases

mitotane. Outcomes for children with malignant stage I ACT are excellent with surgery only.[9,12] However, failure rates for patients with localized large tumors (stage II) remain high after surgery. Hence, systemic therapy should be considered for this group of patients after careful multidisciplinary review. Patients with stage III ACC have an acceptable outcome combining surgery and standard chemotherapy regimens. Unfortunately, patients with stage IV ACT continue to have poor outcomes and new treatments need to be developed for this high-risk group (**Fig. 7**). The combination of mitotane and chemotherapy as prescribed in COG ARAR0332 resulted in significant toxicity in an initial review, with one-third of patients being unable to complete the scheduled treatment.[12]

Treatment in high-volume specialized centers is advised because of the complex nature of this tumor. The authors recommend enrollment of children with ACT in clinical trials and research studies directed at the delineation of ACT biology and genetic profiles so as to guide future treatment initiatives.

Medulla

Pheochromocytoma(Pheo)/paraganglioma (PGL) (PP) are a constellation of neuroendocrine tumors defined by their anatomic location (adrenal vs extra-adrenal) and that trace their common cell of origin to the catecholamine-secreting enterochromaffin cell. These tumors originate in either the adrenal gland (Pheo) or in extra-adrenal organs (PGL) such as the sympathetic ganglia, carotid body, organ of Zuckerkandl, bladder,

Table 3
Treatment by adrenocortical tumor stage per Children's Oncology Group ARAR0332

Stage	Treatment
I	Surgery alone
II	Surgery + RPLND
III	Mitotane CDDP/ETO/DOX Surgery + RPLND
IV	Mitotane CDDP/ETO/DOX Surgery + RPLND

Abbreviations: CDDP, cisplatin; DOX, doxorubicin; ETO, etoposide.

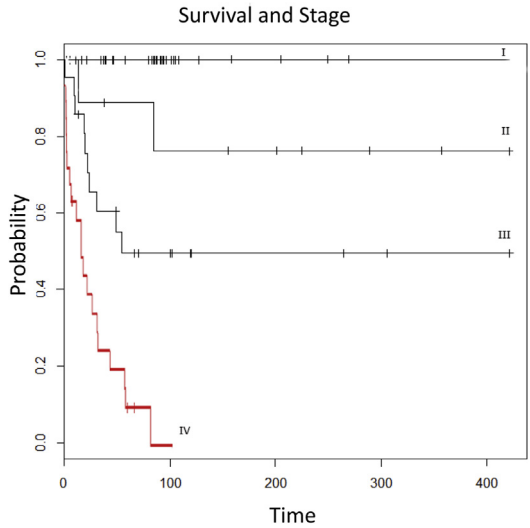

Fig. 7. Brazilian Pediatric ACT Cohort showing impact of tumor stage on survival. Data analyzed on 151 Brazilian children diagnosed with ACT showed a statistically significant (P = .0174) reduction in survival with increasing tumor stage.

or other locations as classified by the World Health Organization in 2017.[22] Some 85% are found in the adrenal medulla, and extrarenal sites account for the remainder.[23] They can also be sympathetic or parasympathetic, with the latter group being identified in the head and cervical regions primarily and being biochemically silent.[24] PP are rare, with an incidence of 0.6 per 100,000 person-years,[25] with approximately 10% occurring in children younger than 14 years, male individuals being affected at twice the rate as female, and extra-adrenal sites accounting for up to one-third of all pediatric cases.[26–29]

Regardless of the epidemiologic observations in these tumors, their genetic origins are traced to some 20 germline and/or somatic mutations that drive their oncogenesis in 3 distinct pathways: pseudohypoxic, kinase dependent, and Wnt-signaling clusters.[30] The pseudohypoxic pathway interferes with the normal regulation of hypoxia-inducible factor (HIF) signaling, whereby hypoxia is not the prime driver of the molecular events, but other components of the cellular milieu that mimic an oxygen-starved state. The genetic mutations found in this cohort include hypoxia-inducible factor 2-alpha (*HIF2a*), von Hippel-Lindau tumor suppressor (*vHL* [von Hippel-Lindau syndrome]), and Krebs cycle pathway components (eg, succinyl dehydrogenase [Carney triad, Carney-Stratakis syndrome], fumarate hydratase, malate dehydrogenase 2.) The kinase-dependent cluster involves the dysregulation of the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) cell survival pathway by inducing cell growth and subverting apoptotic regulation via a mitogen-activated protein kinase (MAPK)–dependent mechanism via mutations in *RET*, *NF1* (neurofibromatosis 1 syndrome), *H-RAS*, *K-RAS*, *MAX*, *ATRX*, and several others. The Wnt group of mutations includes *MAML3* and *CSDE1*, which exploit the processes of cell development, motility, and differentiation to promote cell growth and tumorigenesis. No matter the selective genetic perturbation involved, these 3 common pathways serve as a foundation for both diagnostic and therapeutic interventions with significant clinical impact regardless of age or clinical presentation.

Patient presentation can span the spectrum from incidentally found lesions in asymptomatic children to expected masses identified in genetically predisposed patients. Symptoms can include some combination of sweating, pallor, nausea, flushing, anxiety, weight loss/failure to thrive, headaches, dizziness, and/or urinary symptoms (proteinuria, hematuria, polyuria), but there is no one pattern or symptom identified as dominant save sustained hypertension, which is found in most.[28] However, adults have a classic pattern of paroxysmal hypertension that is not found in children.[24] These symptoms are secondary to catecholamine excess, and, depending on the organ in which the tumor arises, the biochemical profile is different. Only in the adrenal medulla can norepinephrine be converted to the epinephrine secondary to the action of phenylethanolamine N-methyltransferase (PNMT),[31] and, as such, identification of increased levels of epinephrine (or its metabolites) in the serum and urine indicate an adrenal origin of the tumor. In contradistinction, isolated, increased levels of epinephrine's precursors (norepinephrine and especially dopamine)indicate an extra-adrenal origin. However, dopaminergic tumors are generally physiologically silent, and hence they may grow unnoticed until physical signs or symptoms develop secondary to mass effect on adjacent structures.[32]

PP diagnosis begins with a thorough history and physical examination focusing on the symptoms. Documenting each symptom's severity, change over time, and duration is critical to establish a differential diagnosis. A complete examination (including serial vital sign measurements) is critical to identify subtle findings (papilledema, bruits, or subtle fullness) that may be present but overlooked in the setting of more obvious issues, such as hypertension and hematuria. Baseline laboratory testing is warranted, including urinary and plasma free metanephrines (metanephrine and normetanephrine),[33] methoxytyramine (for dopaminergic tumors),[32] and chromogranin A levels (especially with succinate dehydrogenase [SDH]–deficient tumors and tumor syndromes).[34] The degree of increase in some of these values can also be diagnostically significant; there are reports of levels of plasma free and urine metabolites greater than 4-fold greater than baseline being highly suggestive of a lesion.[35] Imaging begins with dedicated plain radiographs of the involved area of concern, in addition to dedicated ultrasonography. Identification of masses or lesions in specific locations is both possible and probable depending on the anatomic location of the mass (paraspinous, adrenal, cervical, and so forth), in addition to identifying other organ involvement (liver, lung, lymph nodes, and so forth). If ultrasonography or plain radiographs identify a suspected mass, or if there is a high index of suspicion, then a dedicated CT or MR study can be undertaken. MR and CT have both shown a high sensitivity for identifying these tumors (90%),[36] but MRI is the preferred modality in children secondary to absence of ionizing radiation and risk of second malignancies.[37] Even in children with a known genetic predisposition syndrome (NF1, vHL, SDH mutations) who may undergo surveillance via whole-body MR to identify occult tumors at regular intervals, a dedicated MR scan of the involved area of concern is likely to be needed to better characterize the tumor. PP can also be characterized and identified by various nuclear medicine studies (alone or in conjunction with MR or CT), including PET scanning with various moieties (fluorodopamine, fluorodeoxyglucose), ^{123}I-MIBG (meta-iodobenzylguanidine), or DOTA (dodecane tetraacetic acid) peptides. These nuclear medicine studies can identify the focal lesion in question, in addition to metastatic foci.

Treatment of PP, once identified, is surgery in almost all cases. Before any anesthetic, patients require the combined care of providers who understand the metabolic demands and hormonal effects of PP. Coordination between surgeon, endocrinologist, oncologist, and anesthesiologist is critical to appropriately initiate and escalate perioperative blockade before surgery. Preoperative assessment with an

electrocardiogram and echocardiogram is also important to show any effects on the heart (ventricular hypertrophy, conduction abnormalities) from long-standing tachycardia and hypertension.[38] The following protocol is used at this author's (C.B.W.) institution and has been found to be effective; however, there are many different drugs available. As such, the following discussion is simply one reference, and any institution of a treatment plan must include a multidisciplinary team well versed in these drugs because they can have profound sequelae if not managed properly. A goal reduction in the patient's blood pressure to less than 50% of expected for height, weight, and age is generally a recommend goal.[24] The optimization period begins with hyperhydration (1.5 times maintenance of fluid intake per day) and a high-salt diet (6–10 g/d) so as to assist in the prevention of postural hypotension in the setting of alpha blockade. Once fluid and dietary modifications have been established for 24 to 48 hours, alpha blockade is begun. Although many agents may be used, twice-daily doxazosin beginning at 1 mg per dose and escalated by 0.5 mg per dose per day over the course of a week to the point of development of orthostasis has proved to be effective, as previously reported.[28] Once postural hypotension is documented, assessment of the resting heart rate must occur, and the patient must be cautioned regarding sudden positional changes that may result in dizziness and subsequent inadvertent traumatic injury from falling. Beta blockade is initiated roughly 24 hours after optimal alpha blockade has been established, and ideally within 3 days of the proposed surgery date. A beta-1 selective agent (atenolol) is used, and a standing dosage established (0.5 mg/kg/d divided twice daily) and escalated (1 mg/kg/d) to keep the heart rate less than 100beats/min.[39] Approximately 24 hours before surgery, the child is admitted, begun on 1.5 times maintenance of 0.9% normal saline, while continuing all previously described components. If for any reason the blockade is not thought to be adequate, then careful escalation can be performed under the medical providers' care, possibly requiring admission to the intensive care unit. During surgery, parenteral alpha-antagonists and beta-antagonists are commenced using short-acting formulations and agents, in addition to having alpha-agonists and beta-agonists also available to support the patient with profound hypotension once the baseline circulating catecholamine production has ceased on tumor extirpation. These hypertensive medications (norepinephrine, epinephrine continuous infusions) may be required days to weeks postoperatively, and these patients require careful and ongoing observation and management in the immediate and longer-term perioperative periods secondary to the risk of cardiovascular and neurovascular sequelae.[40]

Whether attempted by open or closed techniques, the surgical principles are the same: complete extirpation of the tumor without damage to surrounding structures and assessment for any evidence of regional disease if indicated by preoperative evaluation or intraoperative assessment. Details regarding the nuances and technical steps for an open adrenalectomy are discussed earlier in this article. For a minimally invasive approach, appropriate port placement is critical. In general, 4 ports are required, with 2 being used by the surgeon to perform the dissection and resection, whereas the other 2 are used by the assistant to retract adjacent organs (liver, spleen, stomach, bowel) and operate the camera (transumbilical port site) (**Fig. 8**). These 4 ports are generally placed around the umbilicus, but they may be positioned anywhere on the anterior abdominal wall per surgeon's preference. Whether the patient is placed supine or on a small, ipsilateral flank roll is also a surgeon-specific decision. Furthermore, care should be taken to carefully and deliberately ligate (sutures, clips, fulguration, or a combination of techniques depending on the size of the vessel) the adrenal vein before extensive gland manipulation or dissection if possible, so as to minimize the uncontrolled release of catecholamines intraoperatively. For smaller tumors, bilateral tumors, or unilateral tumors

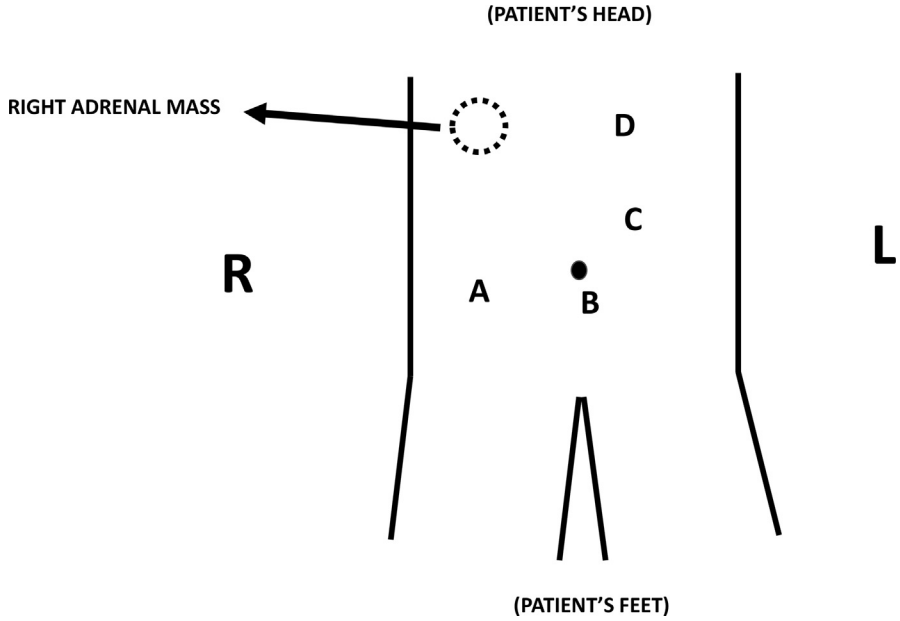

Fig. 8. Port placement for right adrenalectomy. The patient has a right adrenal mass, and the proposed port placement locations are shown for the primary surgeon (A and C) and the assistant (B). D, transumbilical port.

in children with known genetic predisposition syndromes where partial, cortical-sparing adrenalectomies are required when feasible, or if there is a question about the exact location of the mass within the adrenal and to ensure the mass is completely resected, intraoperative ultrasonography is an excellent adjuvant to define the anatomy and associated structures The results with this technique are excellent, with documented shorter operative times, less pain in the postoperative period, and a decreased length of stay in the hospital compared with open procedures.[41,42]

Treatment of nonmetastatic PP postoperatively requires primarily surveillance only, especially in patients with genetic predisposition syndromes who may develop other PP elsewhere over the course of time. Furthermore, any patient with a PP may have recurrence and/or metachronous metastases.[43,44] This surveillance is generally a combination of examinations, laboratory testing (urine and plasma catecholamine metabolites, chromogranin A levels, methoxytyramine levels) and radiological evaluations (whole-body MRI). There is no one regimen accepted or proposed in all cases, but those patients with genetic predisposition syndromes require lifelong surveillance.[27] Those nonsyndromic children require 10 years of observation postprocedure.[45]

The determination of malignancy in this disease cannot be made histopathologically despite several attempts to identify negative prognostic factors.[15,46,47] The definitive means of determining malignancy in PP is evidence of non–neural crest cell disease deposits, and malignancy is only identified in a minority (10%) of cases.[48] Treatment in metastatic PP involves a combination of catecholamine-induced symptom control, tumor debulking/destruction (surgical, percutaneous image guided, or both), cytotoxic chemotherapy, and radiopharmaceutical interventions.[49] When adjuvant therapies are required, referral to a dedicated, multidisciplinary care team is recommended.

PSEUDOTUMORS, MIMICS, AND THE UNEXPECTED

The adrenal gland is anatomically nestled in the retroperitoneum adjacent to and surrounded by several other organs from which tumors may arise and cause confusion about the origin of the neoplasm.[50] The kidney, pancreas, spleen, liver, stomach, sympathetic chain (schwannoma, paraganglioma, neuroblastic tumors, neurofibroma), and even the peritoneum (primary peritoneal cysts, inflammatory myofibroblastic tumors) and retroperitoneum (germ cell tumors, sarcomas [Ewing, liposarcoma, leiomyosarcoma], lymphomas, lipomas, fibrous tumors, echinococcus cysts, granulomatosis, xanthomatosis) may all serve as the originating organ from which a tumor may arise that compresses or interferes with identifying the adrenal gland as an uninvolved adjacent organ.[50–52]

In addition, a word of caution is needed when lesions are found incidentally antenatally or postnatally in any pediatric patient or any age. Clinicians must account for the identified lesion possibly being a focus of an ectopic organ from disordered embryogenesis (lung [pulmonary sequestrations, bronchogenic cysts], enteric duplications),[53] inborn errors of adrenal hormone synthesis (congenital adrenal hyperplasia),[54] or an adrenal hemorrhage[55] in evolution. These masses may be cystic, solid, or both, may be bilateral, may have characteristic echo or cross-sectional imaging features, and/or may have expected vascular inflow and outflow patterns that may help with the diagnosis. Hence, age may serve as a necessary component in the construction of a diagnostic algorithm.

SUMMARY

Pediatric adrenal neoplasms, although rare, span a broad differential from pseudotumors to frank malignancies. Considering the bivariate embryogenesis of the organ and its anatomic location, careful, multimodality diagnostic plans must be enacted to ensure the proper course of therapy is undertaken. Surgery is invariably required for both treatment of the benign entities and cure of the malignant tumors, and these children generally require fastidious and ongoing surveillance.

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DISCLOSURE

The authors have no disclosures to make of any kind.

CLINICS CARE POINTS

- As these tumors frequently produce hormones, careful biochemical evaluation and chemical manipulation and/or supplementation may be required in the preoperative, perioperative or postoperative periods.

- Adrenal tumors in children can be benign or malignant and hormone-secreting or not. Although adrenal tumors are considered rare, it is of essence to perform the right diagnosis to guide treatment.
- Adrenocortical tumors are more common in the Southeast of Brazil.
- Surgical principles for each type of tumor should be followed in order to avoid complications and contribute to better cure and survival rates.

REFERENCES

1. Carsote M, Ghemigian A, Terzea D, et al. Cystic adrenal lesions: focus on pediatric population (a review). Clujul Med 2017;90(1):5–12.
2. Słapa RZ, Jakubowski WS, Dobruch-Sobczak K, et al. Standards of ultrasound imaging of the adrenal glands. J Ultrason 2015;15(63):377–87.
3. Quinn E, McGee R, Nuccio R, et al. Genetic predisposition to neonatal tumors. Curr Pediatr Rev 2015;11(3):164–78.
4. Baudin E. Endocrine tumor board of gustave roussy. Adrenocortical carcinoma. Endocrinol Metab Clin North Am 2015;44(2):411–34.
5. Liou LS, Kay R. Adrenocortical carcinoma in children. Review and recent innovations. Urol Clin North Am 2000;27(3):403–21.
6. Ribeiro RC, Michalkiewicz EL, Figueiredo BC, et al. Adrenocortical tumors in children. Braz J Med Biol Res 2000;33(10):1225–34.
7. Ribeiro RC, Sandrini F, Figueiredo B, et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci U S A 2001;98(16):9330–5.
8. Pinto EM, Billerbeck AEC, Villares MCBF, et al. Founder effect for the highly prevalent R337H mutation of tumor suppressor p53 in Brazilian patients with adrenocortical tumors. Arq Bras Endocrinol Metabol 2004;48(5):647–50.
9. Rodriguez-Galindo C, Figueiredo BC, Zambetti GP, et al. Biology, clinical characteristics, and management of adrenocortical tumors in children. Pediatr Blood Cancer 2005;45(3):265–73.
10. Ribeiro RC, Schettini ST, Abib S de CV, et al. Cavectomy for the treatment of Wilms tumor with vascular extension. J Urol 2006;176(1):279–83 [discussion 283–84].
11. Donnellan WL. Surgical anatomy of adrenal glands. Ann Surg 1961;154(Suppl 6): 298–305.
12. Rodriguez-Galindo C, Pappo AS, Krailo MD, et al. Treatment of childhood adrenocortical carcinoma (ACC) with surgery plus retroperitoneal lymph node dissection (RPLND) and multiagent chemotherapy: Results of the Children's Oncology Group ARAR0332 protocol. J Clin Oncol 2016;34(15_suppl):10515.
13. Kemp CD, Ripley RT, Mathur A, et al. Pulmonary resection for metastatic adrenocortical carcinoma: the National cancer institute experience. Ann Thorac Surg 2011;92(4):1195–200.
14. Teinturier C, Pauchard MS, Brugières L, et al. Clinical and prognostic aspects of adrenocortical neoplasms in childhood. Med Pediatr Oncol 1999;32(2):106–11.
15. Hanna AM, Pham TH, Askegard-Giesmann JR, et al. Outcome of adrenocortical tumors in children. J Pediatr Surg 2008;43(5):843–9.
16. Klein JD, Turner CG, Gray FL, et al. Adrenal cortical tumors in children: factors associated with poor outcome. J Pediatr Surg 2011;46(6):1201–7.
17. Aubert S, Wacrenier A, Leroy X, et al. Weiss system revisited: a clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. Am J Surg Pathol 2002;26(12):1612–9.

18. Wieneke JA, Thompson LDR, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. Am J Surg Pathol 2003;27(7):867–81.
19. Dias AIB dos S, Fachin CG, Avó LRS, et al. Correlation between selected angiogenic markers and prognosis in pediatric adrenocortical tumors: Angiogenic markers and prognosis in pediatric ACTs. J Pediatr Surg 2015;50(8):1323–8.
20. Fachin CG, Bradley Santos Dias AI, Schettini ST, et al. Lymphangiogenesis in pediatric adrenocortical tumors. Pediatr Blood Cancer 2012;59(6):1071.
21. Ribeiro RC, Pinto EM, Zambetti GP, et al. The international pediatric adrenocortical tumor registry initiative: contributions to clinical, biological, and treatment advances in pediatric adrenocortical tumors. Mol Cell Endocrinol 2012;351:37–43.
22. Weltgesundheitsorganisation, Lloyd RV, Osamura RY, et al, editors. WHO classification of tumours of endocrine organs. 4th edition. Lyon (France): International Agency for Research on Cancer; 2017.
23. Lenders JWM, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. Lancet 2005;366(9486):665–75.
24. Bholah R, Bunchman TE. Review of pediatric pheochromocytoma and paraganglioma. Front Pediatr 2017;5:155.
25. Berends AMA, Buitenwerf E, de Krijger RR, et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. Eur J Intern Med 2018;51:68–73.
26. Fonkalsrud EW. Pheochromocytoma in childhood. Prog Pediatr Surg 1991;26:103–11.
27. Bausch B, Wellner U, Bausch D, et al. Long-term prognosis of patients with pediatric pheochromocytoma. Endocr Relat Cancer 2014;21(1):17–25.
28. Beltsevich DG, Kuznetsov NS, Kazaryan AM, et al. Pheochromocytoma surgery: epidemiologic peculiarities in children. World J Surg 2004;28(6):592–6.
29. Hodgkinson DJ, Telander RL, Sheps SG, et al. Extra-adrenal intrathoracic functioning paraganglioma (pheochromocytoma) in childhood. Mayo Clin Proc 1980;55(4):271–6.
30. Jochmanova I, Pacak K. Genomic landscape of pheochromocytoma and paraganglioma. Trends Cancer 2018;4(1):6–9.
31. Dobri GA, Bravo E, Hamrahian AH. Pheochromocytoma: pitfalls in the biochemical evaluation. Expert Rev Endocrinol Metab 2014;9(2):123–35.
32. Eisenhofer G, Goldstein DS, Sullivan P, et al. Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. J Clin Endocrinol Metab 2005;90(4):2068–75.
33. Lenders JWM, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287(11):1427–34.
34. Zuber S, Wesley R, Prodanov T, et al. Clinical utility of chromogranin A in SDHx-related paragangliomas. Eur J Clin Invest 2014;44(4):365–71.
35. Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J Clin Endocrinol Metab 2003;88(6):2656–66.
36. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 2004;89(2):479–91.
37. Brenner D, Elliston C, Hall E, et al. Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol 2001;176(2):289–96.
38. Turner MC, Lieberman E, DeQuattro V. The perioperative management of pheochromocytoma in children. Clin Pediatr (Phila) 1992;31(10):583–9.

39. Romero M, Kapur G, Baracco R, et al. Treatment of hypertension in children with catecholamine-secreting tumors: a systematic approach. J Clin Hypertens (Greenwich) 2015;17(9):720–5.
40. Mamilla D, Araque KA, Brofferio A, et al. Postoperative management in patients with pheochromocytoma and paraganglioma. Cancers (Basel) 2019;11(7). https://doi.org/10.3390/cancers11070936.
41. Miller KA, Albanese C, Harrison M, et al. Experience with laparoscopic adrenalectomy in pediatric patients. J Pediatr Surg 2002;37(7):979–82 [discussion 979–82].
42. Vargas HI, Kavoussi LR, Bartlett DL, et al. Laparoscopic adrenalectomy: a new standard of care. Urology 1997;49(5):673–8.
43. Plouin PF, Amar L, Dekkers OM, et al. European society of endocrinology clinical practice guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol 2016;174(5):G1–10.
44. Lam AK-Y. Update on adrenal tumours in 2017 world health organization (WHO) of endocrine tumours. Endocr Pathol 2017;28(3):213–27.
45. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014;99(6):1915–42.
46. Kimura N, Takayanagi R, Takizawa N, et al. Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2014;21(3):405–14.
47. Kimura N, Takekoshi K, Naruse M. Risk stratification on pheochromocytoma and paraganglioma from laboratory and clinical medicine. J Clin Med 2018;7(9). https://doi.org/10.3390/jcm7090242.
48. Edström Elder E, Hjelm Skog A-L, Höög A, et al. The management of benign and malignant pheochromocytoma and abdominal paraganglioma. Eur J Surg Oncol 2003;29(3):278–83.
49. Nölting S, Ullrich M, Pietzsch J, et al. Current management of pheochromocytoma/paraganglioma: a guide for the practicing clinician in the era of precision medicine. Cancers (Basel) 2019;11(10). https://doi.org/10.3390/cancers11101505.
50. Frey S, Caillard C, Toulgoat F, et al. Non-adrenal tumors of the adrenal area; what are the pitfalls? J Visc Surg 2020;157(3):217–30.
51. Shaikh F, Murray MJ, Amatruda JF, et al. Paediatric extracranial germ-cell tumours. Lancet Oncol 2016;17(4):e149–62.
52. Rashidi A, Fisher SI. Primary adrenal lymphoma: a systematic review. Ann Hematol 2013;92(12):1583–93.
53. White J, Chan YF, Neuberger S, et al. Prenatal sonographic detection of intra-abdominal extralobar pulmonary sequestration: report of three cases and literature review. Prenat Diagn 1994;14(8):653–8.
54. Bittman ME, Lee EY, Restrepo R, et al. Focal adrenal lesions in pediatric patients. Am J Roentgenol 2013;200(6):W542–56.
55. Velaphi SC, Perlman JM. Neonatal adrenal hemorrhage: clinical and abdominal sonographic findings. Clin Pediatr (Phila) 2001;40(10):545–8.