

# Adrenal Cortical Neoplasms in Children: Why So Many Carcinomas and Yet So Many Survivors?

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## ABSTRACT

Adrenal cortical neoplasms in children are represented by a disproportionate number of cases that have been diagnosed pathologically as adrenocortical carcinomas (ACCs)—as many as 90% of all cortical tumors in some pediatric series. Like other solid malignancies of childhood, over half of ACCs present in the first 4 years of life in over 50% of cases. Most are sporadically occurring neoplasms, but ACCs are a manifestation of Beckwith-Wiedemann and Li-Fraumeni syndromes. Despite the fact that the microscopic features are often quite atypical and identical in many respects to ACCs in adults, the clinical outcome is favorable in 70% or more of cases. Tumor weight is seemingly a significant determinant in prognosis at a threshold of greater than 400 g. A risk assessment system is proposed that incorporates tumor weight, localization of tumor to the gland without invasion into the surrounding tissues or organs, and absence of metastasis.

**Key words:** adrenal gland, adrenocortical adenoma, adrenocortical carcinoma, Beckwith-Wiedemann syndrome, Li-Fraumeni syndrome, p53

## INTRODUCTION

Adrenal cortical carcinoma (ACC) is a problematic neoplasm, as evidenced by the numerous published reports over the years detailing aspects of its clinical diagnosis, management, and pathology. Most studies have focused upon ACC in adults, since the majority of these neoplasms are diagnosed in individuals between the ages of 30 and 50 years [1–4]. However, it is recognized that ACC has a bimodal age distribution, with the initial peak in the 1st decade of life. Thus, ACC can be grouped with the other

solid, organ-based malignant neoplasms of childhood [5–7].

Despite the acknowledged infrequency of adrenocortical neoplasms in children, there is a substantial corpus of literature, often entitled “adrenal cortical tumors or neoplasms,” that becomes synonymous with ACC [8–15]. Although ACC in childhood constitutes fewer than 1% of all malignancies in the pediatric age population, it accounts for 12% of all primary carcinomas in children [16,17]. Unlike other carcinomas in children, which are seen in older children, most ACCs are diagnosed before the child is 6 years of age [10,11,13,16]. There is no other age-comparable example among the other carcinomas in children, but this period of life (newborn to 4 years old) is the one in which the majority of the unique pediatric solid malignancies are diagnosed.

The incidence of ACCs in children and adults is comparable and ranges from 0.5 to 2.0 cases per million, except in southern Brazil, where girls under 4 years old have an age-standardized rate of 4.7 cases per million [6,18–20]. The average age at diagnosis of ACC in adults is 53 years, with a modest male predilection [4]. Slightly over 50% of ACCs in adults have spread locally or metastasized at diagnosis, with a 5-year survival of 35% to 40% [4]. In another series [21] only 11% of patients were alive without evidence of disease at 5 years. Adrenal cortical carcinomas in adults are typically in excess of 250 g, and as many as 20% of ACCs weigh more than 1 kg [4,21].

## WHAT CONSTITUTES A PRIMARY CARCINOMA OF THE ADRENAL CORTEX?

The answer to this query would seem obvious until one considers that the adrenal cortical neoplasms share with other endocrine tumors an element of uncertainty with regard to the morphologic distinction between a benign and potentially malignant neoplasm, based upon the pathologic features of the primary tumor. It is unnecessary to look beyond the adrenal gland for an example of a

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**Table 1. Various pathologic features of pediatric adrenocortical neoplasm<sup>a</sup>**

	Benign (9 cases)	Malignant (51 cases, B)	Malignant (23 cases, M)
Vascular invasion	0	20	12
Capsular invasion	0	24	15
Architecture			
Alveolar		2	8
Diffuse/solid	8	44	19
Tubular	2	27	16
Necrosis			
Present	1 (11%)	30 (59%)	22 (96%)
Absent	8	21	1
Weight (g, mean)	82	268	631
Stage (path)			
T1 or T2	9 (100%)	45 (88%)	14 (61%)
Dead of disease	0	0	21 (100%)

B indicates benign clinical behavior; M, malignant clinical behavior.

<sup>a</sup>Adapted from tables 4 through 6 in Michalkiewicz and colleagues [38].

primary neoplasm whose pathologic features are not necessarily predictive of its clinical behavior, the pheochromocytoma [22–24]. Proliferation and molecular genetic markers have been examined in pheochromocytomas with some correlation between malignant behavior and MIB-1/Ki-67 expression, with similar results in studies of adrenal cortical neoplasms [25–29].

Numerous pathologic studies of adrenal cortical neoplasms have evaluated the tumors for the presence or absence of several microscopic features: (1) architecture or pattern, (2) cytologic atypia or nuclear grade, (3) mitotic activity, (4) atypical mitotic figures, (5) necrosis and its pattern, (6) presence of intersecting fibrous bands, and (7) vascular and/or capsular invasion [30–36]. It is generally acknowledged that no one pathologic feature of the tumor itself is diagnostic of malignancy, as witnessed by the widely applied Weiss system [33]. One recent study [37] has incorporated the various morphologic features of 3 different published histopathologic systems and compared them to their own “stepwise discriminate diagnosis” system, with mitotic activity as the critical 1st step in the algorithm. All of these studies except for 2 have included only cortical neoplasms in adults; both studies with the inclusion of pediatric cases have concluded that histopathologic criteria were unreliable in predicting outcome in children [32,36].

When standard pathologic criteria are applied to cortical neoplasms in children, the seemingly inevitable result is that the overwhelming majority of tumors are interpreted to be ACCs. The 2 largest pediatric series of adrenocortical tumors, from the International Pediatric Adrenocortical Tumor Registry (IPATR) [37] and the Armed Forces Institute of Pathology (AFIP) [38], have reported that 228 (90%) of 254 cases and 74 (89%) of 83 cases, respectively, met the particular pathologic criteria

for the ACC. A recent study of 33 adrenocortical neoplasms in children between the ages of 2 months and 8 years were studied pathologically utilizing 5 widely known pathologic grading systems; 3 of these, the Van Slooten [31], Weiss [33], and Hough [30] systems, classified the tumors as carcinomas in 100%, 94%, and 64% of cases, respectively [35]. The unavoidable conclusion is that adrenocortical neoplasms in children have a number of pathologic features that are associated with malignant behavior in cortical neoplasms in adults.

The AFIP study [38] is enlightening from the perspective of clinicopathologic correlation and prognosis in 83 adrenocortical neoplasms in children between the ages of 4 months and 19 years. Histologic criteria for malignancy consisted of 11 features that were adapted from several previously cited systems [30,31,33]. Three clinicopathologic categories emerged from their clinicopathologic analysis: benign (9 cases), malignant pathology and benign behavior (51 cases), and malignant pathology and malignant behavior (23 cases); there were 74 (89%) malignant adrenocortical tumors on the basis of histopathologic features, yet almost 70% of these children had a benign course [38]. The findings from this study can be summarized in the following manner: 89% of all cortical neoplasms were pathologically malignant, but 69% were clinically benign (Table 1).

Michalkiewicz and colleagues [37] (from the IPATR) acknowledged that “because consistent histologic criteria were not used to classify pediatric adrenocortical tumors as benign (adenoma) or malignant (carcinomas), these data were not examined as prognostic factors.” Older children (those greater than 5 years old) with tumors weighing in excess of 200 g and tumor spread beyond the gland into contiguous structures or spillage of tumor had a substantial reduction in survival to approximately 50%.

## WHAT IS THE PURPOSE AND ROLE OF THE PATHOLOGIC EXAMINATION OF AN ADRENOCORTICAL NEOPLASM IN A CHILD?

We can probably agree that it is necessary to establish that the adrenal tumor is cortical in nature. However, the weight and the dimensions of the tumor are essential and are arguably more predictive than any one histologic feature of the tumor itself, other than spread beyond the gland, either locally or as a metastasis. Documentation of the tumor's localization to the gland is important in pathologic staging of the disease. However, microscopic capsular or vascular invasion does not have apparent prognostic significance (see Table 1). Cagle and associates [32] reported that the size was the "only predictor of malignancy in pediatric tumors." None of the tumors in children weighing less than 100 g behaved in a malignant fashion, and only 1 of 6 tumors weighing less than 500 g was clinically malignant in their series [32]. In the IPATR study [37], the 5-year event free survival in children whose tumors weighed under 200 g was 88%, but this rate was only 48% in those tumors weighing in excess of 200 g. Weight was correlated with outcome in the AFIP study when the tumor averaged less than 300 g (Table 1). Authors of a large adult-based study [39] have reported that a size threshold of 4 cm and greater is correlated with a doubling of the likelihood of malignancy.

A review of our own 39 cases of adrenocortical neoplasms in children revealed the histologic diversity beyond the 3 patterns of the AFIP study [38] of alveolar, diffuse/solid, and tubular with the addition of the fibrohyaline and endodermal sinus-yolk sac-like patterns (Fig. 1A-F). These histologic patterns are found with some frequency in a single tumor and do not have any prognostic significance per se [38].

Wieneke and colleagues [38] also reported that necrosis was present in virtually 100% of malignant-behaving neoplasms but was also a feature in slightly more than 50% of all benign-behaving neoplasms, including the subset of "benign" ACCs (Table 1 and Fig. 2). Cagle and colleagues [32] also emphasized that "benign" adrenocortical neoplasms in children are more likely to be mitotically active, to have moderate to severe pleomorphism, to contain foci of necrosis, and to have broad fibrous bands compared with their presumed adult counterparts (Fig. 3A-D).

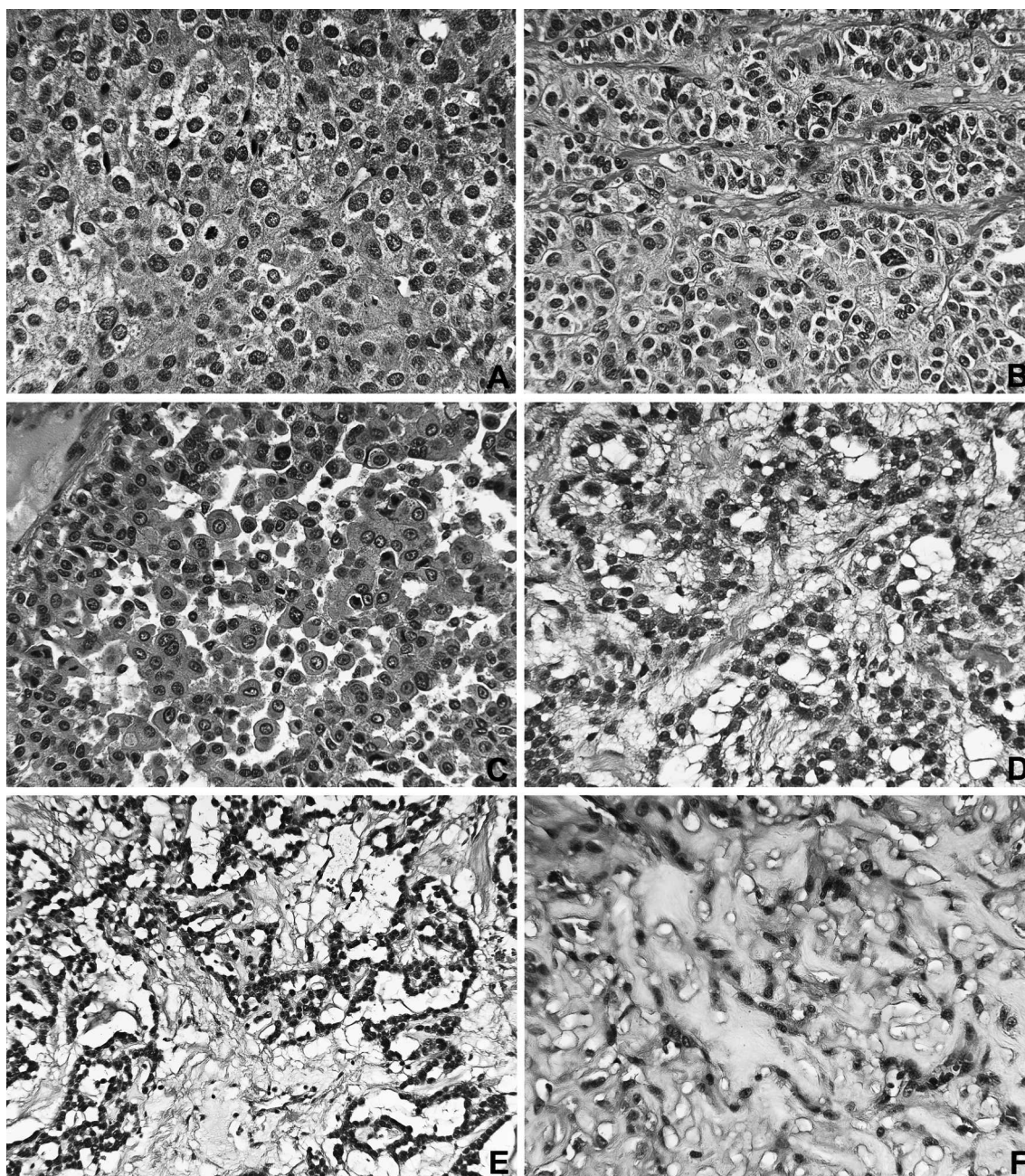
Our experience with adrenocortical neoplasms has been included in a review of adrenalectomies in children less than 15 years of age between 1989 and 2008 (Table 2). Not unexpectedly, the most common diagnosis was neuroblastoma, but there were a total of 39 (1 case with bilateral tumors) adrenocortical neoplasms in children between the ages of 7 days and 12 years at diagnosis (mean age of 3 years and median age of 2 years). Most tumors were diagnosed between the ages of 7 days and 4 years (29/38 patients, 76%). There were 11 males and 27 females. Only 4 of these cases originated from the St Louis Children's Hospital, whereas the others (34/38) were

consultation cases, as a reflection of the problem that these cases present to all. Virtually every case had at least 1 and typically more than 1 microscopic feature that is included among those associated with malignancy, including nuclear pleomorphism, mitotic activity, and atypical mitotic figures (Fig. 3A-D). Weights were documented on 34 cases, with a mean weight of 194 g and a median weight of 60 g (range: 4 to 2280 g). There was a mean increase in weight with age, but curiously the median weight decreased with the age group, as the largest tumors were found in children who were >1 year at diagnosis, but they were eliminated in the calculation of the median age (Table 3). There were only 3 tumors that weighed in excess of 400 g (620, 910, 2280 g); these latter 3 tumors were among 7 tumors that were originally interpreted as ACCs and that have behaved as such. In retrospect, the other 4 cases would probably qualify today as an atypical or intermediate-risk adrenal cortical neoplasm since this designation includes those adrenocortical tumors with more than 1 microscopic feature associated with ACC and a tumor weight of less than 400 g.

## PATHOLOGIC STAGING

As though the difficulties with the pathology of adrenocortical neoplasms in children are not enough, there is no standardized system for tumor staging in either adults or children. The Cancer Staging Manual of the American Joint Committee on Cancer does not include such a system, so that it has been necessary for various authors to devise their own [40] (Table 4). The tumor stages of the IPATR series are compared to provide some sense of the distribution of cases (Table 5) [37,38,41]. Some perspective is provided by the fact that approximately 50% of adults with ACCs have stage IV disease upon presentation, in contrast to 15% or less of cases in children [4,21,37,38]. In the IAPTR staging, completely resected tumors weighing in excess of 200 g are labeled stage II tumors, whereas stage II tumors in the AFIP study utilizing the Lack staging system have invaded beyond the adrenal, with or without extension into contiguous organs [37,38,41]. It is important to take note of the particular system of pathologic staging in order to compare study results.

After the pathologic staging of an adrenocortical neoplasm, the question remains regarding the prognosis of the tumor based upon various pathologic features if the tumor has been completely resected as either a stage I tumor in the Lack or IPATR classification or a stage II tumor in the IPATR system if the tumor weighs in excess of 200 g [37,38,41]. Can the overall more favorable clinical outcome for those neoplasms interpreted pathologically as ACCs in children, as compared with their presumed counterparts in adults, be explained by the overall lower pathologic stages in children? Tucci and associates [42] have presented just such an argument in a review of 34 children with ACC, of whom 17 (50%) had

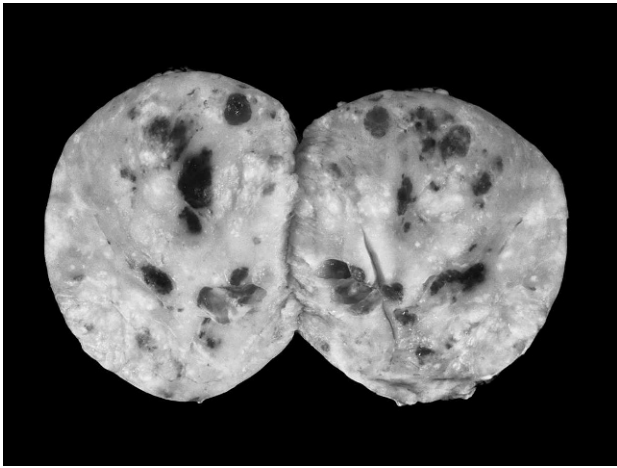


**Figure 1.** These 6 microscopic fields represent some of the histologic patterns encountered among the adrenal cortical neoplasms from our file, occurring in children. These patterns are not mutually exclusive but can be seen in conjunction with any one of the others in a single neoplasm. **A.** Solid pattern of formless sheets of relatively monotonous rounded cortical cells. **B.** Trabecular pattern of small groups of cells separated by delicate fibrovascular septa. Note the large cell with a hyperchromatic nucleus. **C.** Alveolar pattern with individual tumor cells separated from each other and surrounded by apparent epithelial-lined spaces. **D.** Glandular pattern with gland-like structures containing pale extracellular material. **E.** Endodermal sinus or yolk-sac tumor-like pattern with the reticulated appearance and individual profiles resembling Schiller-Duval bodies. Note the pale hyaline stroma. **F.** Hyaline myxoid pattern with compressed, delicate strands of tumor cells in a pale staining stroma.

stage I or stage II tumors, defined as a completely resected neoplasm measuring less than or greater than 5 cm in diameter without local invasion. The 5-year survival rate was 100% (5/5 cases) and 86% (12/14 cases), respectively, for stage I and II tumors. Keeping in mind the difference between the IPATR and AFIP studies [37,38] on the eligibility criteria for stage II, 76% and 100% of adrenocortical neoplasms were stage I and stage II tumors

(Table 5). The argument could be made that the low stage of adrenocortical neoplasms in children is the explanation for the more favorable prognosis, which ranges from 60% to 70% disease-free survival [43–47].

Other than the morphologic verification of the adrenal neoplasm as cortical in type, it would appear that individual histopathologic features of the tumor are largely insensitive in the differentiation of a benign from a



**Figure 2.** An adrenal cortical neoplasm presenting in a 6-month-old female with Cushing syndrome. The tumor weighed 83 g. Multiple foci of hemorrhage and necrosis are present on cut surface. In addition to the necrosis, this tumor showed marked cytologic atypia, including enlarged, bizarre-appearing cells (see Figures 3A–D as examples) and numerous mitotic figures. This child, now 7 years old, is alive and well.

**Table 2. Adrenalectomy in children (1989 to 2008)<sup>a</sup>**

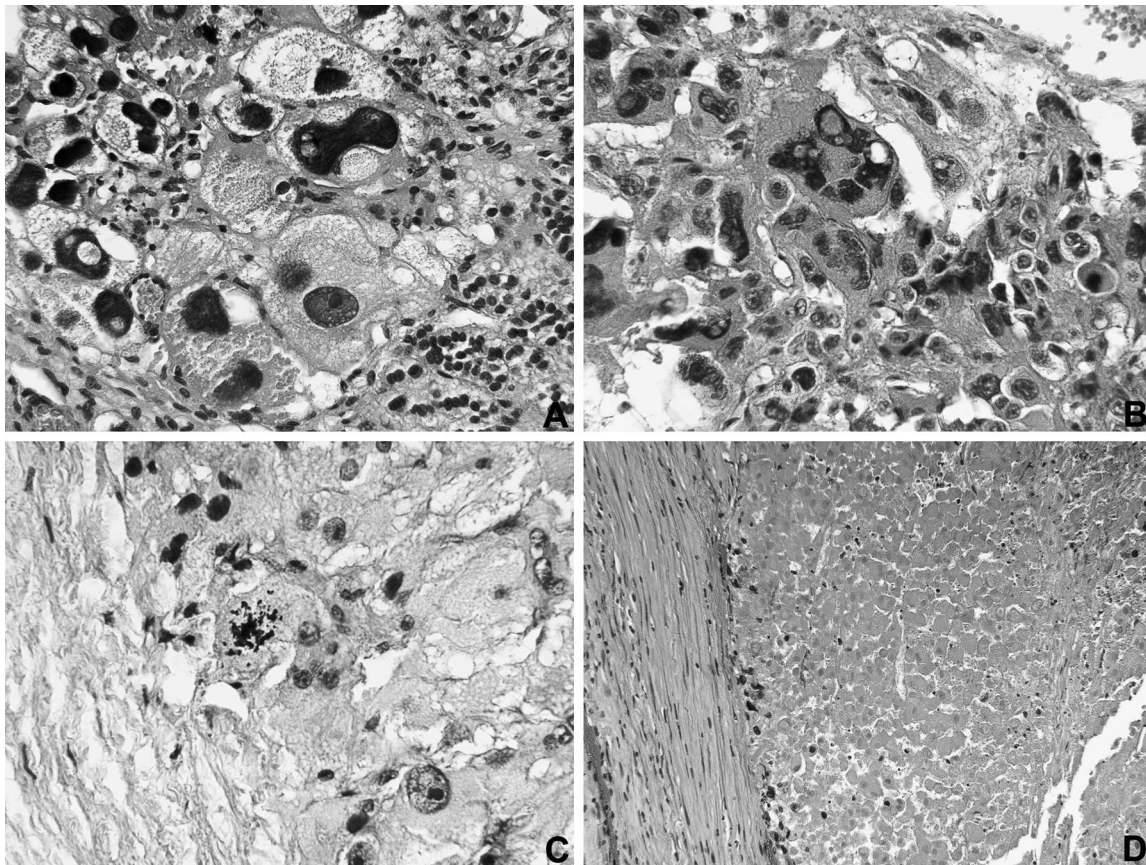
	No.	% of Total
Neuroblastic tumors (all types)	66	45
Cortical neoplasms <sup>b</sup>	39	27
Incidental adrenalectomy	18	12
Cyst	5	3
Wilms tumor (direct extension)	4	3
Pheochromocytoma	4	3
Soft tissue neoplasms <sup>c</sup>	4	3
Intra-adrenal Wilms tumor	2	1
Teratoma	2	1
Pigmented micronodular hyperplasia	1	<1
Total	146	~100

<sup>a</sup>From the Lauren V. Ackerman Laboratory of Surgical Pathology, Barnes-Jewish and St Louis Children's Hospitals, Washington University Medical Center, St Louis, MO.

<sup>b</sup>A total of 39 adrenal cortical neoplasms; 1 child had bilateral tumors.

<sup>c</sup>One case each of malignant rhabdoid tumor, leiomyoma, desmoplastic small round cell tumor, and epithelioid hemangioendothelioma.

malignant cortical neoplasm. It is now understandable why the IPATR study and others [37,48] have not incorporated the pathologic type or histologic features of adrenocortical neoplasms into the outcome analysis. In the AFIP study [38] there were no tumor-associated deaths among 51



**Figure 3.** Four microscopic fields from adrenal cortical neoplasms, all weighing less than 100 g, showing some of the "malignant" features in otherwise benign-behaving neoplasms. **A.** Large, bizarre-appearing cells with hyperchromatic nuclei and intranuclear pseudoinclusions. **B.** Large, multinucleated tumor giant cell among smaller tumor cells, also with nuclear atypia. **C.** An example of an atypical mitotic figure. **D.** Zonal necrosis bordered by a broad fibrous band.

**Table 3. Weight of adrenal cortical neoplasms and age at diagnosis**

Age (years)	No.	Range (GM)	Mean (GM)	Median (GM)
<1	7	25–88	51	70
1–3	17	5–910	111	40
≥4	10	4–2280	383	37
	34 <sup>a</sup>			

<sup>a</sup>Weight unknown for 5 cases (includes one of the bilateral tumors).

(69%) of 74 cases involving pathologically malignant adrenocortical neoplasms.

Weight of the tumor is a central factor in the risk assessment of adrenocortical neoplasms in children since there is a consistent correlation between prognosis and tumor size [32,37,38]. It appears that tumor weight is the most critical gross or microscopic attribute of the tumor to correlate with clinical outcome, although the critical weight cutoffs have tended to vary between studies [32,37,38]. There are 3 weights and ranges of importance: 200 g or less, 200 to 400 g, and 400 g or greater. We have incorporated these weights into proposed risk assessment groups for those tumors confined to the adrenal gland (Table 6). It is obvious that any adrenal cortical neoplasm that has directly invaded into the surrounding tissues and/or organs or that has metastasized is an ACC regardless of its size or microscopic features. Most neoplasms in children are confined to the gland and are completely respectable, as in all of our 38 cases, including the 1 child with bilateral tumors, from our own experience. Virtually every one of these neoplasms had atypical, if not “malignant,” histologic features. We are proposing that those tumors that weigh 200 g or less are low-risk neoplasms and that those weighing between 200 and 400 g should be assigned to an intermediate risk category. Among our 34 cases with recorded weights, 27 (79%) were low-risk neoplasms, 4 (12%) were intermediate-risk tumors, and 3 (9%) were high-risk tumors. The children

**Table 4. Staging of adrenocortical neoplasms**

I—Tumor less than or equal to 5 cm, no invasion (T1), Lack [38,41]
Tumor greater than 5 cm (T2), Lack [41]
Tumor completely resected with negative margins, weight ≤200 g, no metastasis (IPATR [37])
II—Tumor of any size, local invasion without involvement of adjacent organs (T3), Lack [38,41]
Tumor of any size with invasion of adjacent organs (T4), Lack [38,41]
Tumor completely resected with negative margins, weight >200 g, no metastasis (IPATR [37])
III—Any tumor with regional lymph node metastasis, Lack [38,41]
Residual or inoperable tumor (IPATR [41])
IV—Any tumor with distant metastasis Lack [38,41]
Hematogenous metastasis at presentation (IPATR [37])

**Table 5. Stage of pediatric adrenocortical neoplasms compared to adult experience**

IAPTR [37]	AFIP [38]	Adult [41]
Stage I—112 (44%)	68 (82%)	3%
Stage II—80 (32%)	15 (18%)	29%
Stage III—25 (10%)	0 (0%)	19%
Stage IV—37 (15%)	0 (0%)	49%
	254 (~100%)	83 (~100%)

IAPTR indicates International Adrenal Pediatric Tumor Registry; AFIP, Armed Forces Institute of Pathology.

with the latter 3 tumors represent the only tumor-associated deaths to date. Those adrenal cortical neoplasms weighing less than 400 g with microscopic invasion into the immediate surrounding soft tissues, but that are completely resected, would be assigned to the intermediate category as well. The high-risk category includes the ACC, and the remainder are low-risk (adenoma) or intermediate-risk tumors (atypical adrenal cortical neoplasm). The label of ACC would be restricted to those 10% to 30% of neoplasms that weigh in excess of 400 g or that demonstrate invasion of adjacent organs or have metastasized [37,38,49].

It was not until one of our more recent cases of an adrenocortical neoplasm in a 7-year-old boy that intraoperative tumor spillage was an issue. Tumor spillage involving the peritoneal surfaces in the case of a Wilms tumor is one criterion for stage III disease, regardless of the local features of the tumor itself [50]. Solid and pseudopapillary tumor of the pancreas and juvenile granulosa cell tumor of the ovary are complicated by abdominal or pelvic recurrences if the tumor is allowed to contaminate surrounding structures intraoperatively [51,52]. A subset of children in the IPATR study [37] who had intraoperative spillage of tumor were compared to those without this complication, with a statistically significant reduction in the 2-year and 5-year event-free survival rates.

**Table 6. Proposed risk groups for adrenocortical neoplasms in children**

Risk	Criteria
Low	Any cortical neoplasm confined to the adrenal gland and weighing less than 200 g
Intermediate	Any cortical neoplasm confined to the gland and weighing between 200 and 400 g Any cortical neoplasm weighing less than 400 g with microscopic invasion into surrounding soft tissues, completely resected, and no evidence of metastatic spread
High	Any cortical neoplasm weighing in excess of 400 g or with direct gross invasion into adjacent organs like the liver, spleen, or kidney or with metastatic spread

## SYNDROMIC ASSOCIATIONS AND MOLECULAR GENETICS

Adrenocortical neoplasms in children may be associated with Li-Fraumeni syndrome (LFS) and Beckwith-Wiedemann syndrome (BWS) [53,54]. One of our 38 cases occurred in a child with BWS. There were no documented examples of LFS. In southern Brazil, the incidence of adrenocortical tumors in children is extremely high (3.4 to 4.2 cases per  $10^6$  children-years versus 0.3 to 0.5 cases elsewhere); a specific p53 mutation (R337H) has been detected in these children, one that predisposes them to adrenocortical neoplasms, most of which have been interpreted as ACCs [55]. The parental carrier rate approaches 35%, and this germ-line mutation is distinct from the ones associated with the classic LFS. These kindreds are not at risk for the various other neoplasms of LFS. The penetrance of adrenocortical tumors in these kindreds is approximately 10%. One of the hallmarks of adrenocortical tumors in LFS is their presentation before 10 years of age [56,57]. In sporadically occurring adrenocortical tumors in children, germ-line mutations in p53 have been detected in parents without other familial manifestations of LFS. Varley and associates [58] have concluded that there are some p53 alleles with a low penetrance (considerably lower than in LFS) for the predisposition to develop adrenocortical neoplasms in affected children.

The cytomorphologic features of the adrenocortical neoplasms are reminiscent of the cells of the fetal adrenal cortex, which are larger than the adult cortical cells, have abundant eosinophilic cytoplasm, and are cytomegalic with large, prominent nuclei. Cytomegaly is one of the features of adrenocortical neoplasms in children, and a characteristic feature of BWS is the presence of adrenal cytomegaly [59]. As noted earlier, there is a predilection to the development of adrenocortical neoplasms in BWS, whereas there is a perturbation in the 11p15.5 imprinted gene cluster through the mechanism of uniparental disomy, usually involving paternally derived duplications [60]. One of the genes in this cluster is the overexpressed paternal IGF2. Overexpression of IGF2 is found in 80% of adrenocortical tumors in children, which is thought to be responsible for the phenotype of the fetal adrenal cortex, and the mutant p53 results in defective apoptosis, the mechanism of fetal cortical involution [61].

There remains the apparent limited or benign clinical behavior of adrenocortical neoplasms, especially in children less than 5 years of age, whose tumors infrequently extend beyond the adrenal gland yet have various histopathologic features that are found in ACCs in adults. Do adrenal cortical neoplasms in children, the majority of which are diagnosed in the 1st 4 years of life, arise from a cell more like those of the fetal than the adult cortex? Does this explain in part the limited biologic potential of these neoplasms, despite the presence of impressively atypical microscopic features that may be a manifestation of biological regression rather than progression to a malignancy?

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