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Clinical and histopathological features of adrenocortical neoplasms in children: Retrospective review from a single specialist center

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ABSTRACT

Background/purpose: Adrenocortical tumors (ACTs) are rare in children and the extent to which histopathological features can predict clinical behavior remains uncertain. The aim of this study was to investigate the relationship between histopathological features (Weiss score), surgical approach, tumor size, underlying genetic predisposition syndrome, and outcome.
Methods: Twenty-nine ACTs treated at our institution between 1987 and 2011 were identified from a histopathology database. The histological features were categorized using the Weiss scoring system. For tumor staging, the UKCCSG staging system was utilized.
Results: At a median follow-up of 25 months, 19 patients (65.5%) survived without evidence of disease and 10 patients (35.5%) had died. There was a strong association between high Weiss score and both large tumor size ($P < 0.01$) and adverse outcome ($P < 0.01$). Outcome for stage I and IIA disease was significantly better compared to higher stage disease and/or tumor rupture ($P < 0.01$).
Conclusion: There is an association between high Weiss score, large tumor size, underlying genetic predisposition syndrome and an adverse outcome for pediatric ACTs. Regardless of histopathological findings, complete surgical resection, without tumor spillage, is optimal for survival. Genetic evaluation is recommended in patients with ACTs, particularly those with a high Weiss score.

Adrenocortical tumors (ACTs) are rare, with a worldwide incidence of 0.3/million for children younger than 15 years of age [1]. Previous studies have reported a range of prognostic factors related to their clinical behavior, including large tumor size, incomplete surgical resection and high stage at presentation being associated with worse outcome, whereas, in keeping with other endocrine neoplasms, cytological features are not a reliable prognostic marker [2–5]. However, the Weiss histopathological scoring system (Table 1A) does appear to be of some value in predicting malignant behaviour [6–10], although complete surgical resection remains the strongest predictor of survival. The aim of this study was to investigate the relationship between histopathological features (Weiss score), surgical approach, tumor size, underlying genetic disease, and outcome in a series of pediatric ACT cases managed at a specialist center.

1. Material and methods

Our institution is a tertiary referral center for pediatric conditions including pediatric tumors. A search of the histopathology and clinical databases identified 29 ACTs treated at the center between 1987 and 2011 in whom complete clinical information and histopathological specimens/reports were available for review. Clinical features of the patients were ascertained from the medical notes.

1.1. Data analysis

Overall and event-free survival (OS and EFS) curves were created using a Kaplan-Meier estimate and the groups were compared using a

Table 1A
Weiss scoring system. The presence of three or more criteria correlates with malignancy.

Histological criteria	Weight of criteria	
	0	1
Nuclear grade	1 and 2	3 and 4
Mitoses	<5/50 HPF*	≧5/50 HPF
Atypical mitoses	No	Yes
Clear cells	>25%	≦25%
Diffuse architecture	≦33% surface	>33% surface
Confluent necrosis	No	Yes
Venous invasion	No	Yes
Sinusoidal invasion	No	Yes
Capsular infiltration	No	Yes

(Tissier F. Best Pract Res Clin Endocrinol Metab 2010).
* HPF: high-power fields.

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Table 1B
The UKCCSG staging system for ACTs.

Stage	
I	Total excision of tumour, tumour volume <200 cm^3 (100 g) Absence of metastases and normal hormone levels after surgery
II	Microscopic, residual tumour, tumour volume >200 cm^3 (100 g) Persistently elevated adrenocortical hormone levels after surgery.
II	A: Children with resected tumours (>200 cm^3/100 g) – 50% surgically cured
II	B: Patients with microscopic residual disease or persistent hormone excess – 100% progression.
III	Gross residual or inoperable tumour
IV	Distant metastases

log-rank test. The duration of OS was measured from the date of diagnosis to the date of last follow-up or death resulting from any cause. The duration of EFS was measured from the date of operation to the date of last follow-up, local or distant relapse or death as a result of any cause. Histopathological features were reviewed by a specialist pediatric pathologist and classified according to the Weiss scoring system. The histopathological review was conducted blinded to all clinical details and outcome. To examine the efficacy of the Weiss scoring system, EFS curves were generated according to Weiss score = <3 and >3 respectively. The relationship between Weiss score, tumor size and outcome was examined with box-plot analysis and Mann-Whitney U tests. The significance of specific variables to predict outcomes was evaluated using chi square (Fisher's exact) tests. $P < 0.05$ was considered as statistically significant. For tumor staging, the UKCCSG staging system (Table 1B) was utilized. Tumor rupture (spillage) was considered as residual disease and cases upstaged to stage III. The EFS curves were compared between Stage I, IIA and Stage IIB, III, IV. The study was approved by the local research ethics committee as a retrospective clinical review.

2. Results

There were 15 girls and 14 boys with a median age at presentation of 2.2 years (range, 5 months to 15 years). All but 1 patient (97%) had clinical evidence of endocrine hyperfunction at presentation; 24 (83%) with virilization, 17 (59%) with Cushing's syndrome and 15 (52%) with hypertension. Nineteen (66%) showed a mixed endocrine presentation.

The median interval between the onset of symptoms and diagnosis was 6 months (range, 1 week to 6 years). Thirteen patients had a family history of malignancy and underlying genetic predisposition syndromes were identified in eight, including five with Li-Fraumeni syndrome or constitutional p53 mutation, and three with Beckwith-Wiedemann syndrome.

All patients underwent primary surgical excision. The median tumor weight was 61 g (range, 4–1566 g). Histopathological slides were available for review and blinded Weiss scoring was performed in 28/29, (report only available in 1 case) (Fig. 1). Surgical findings, pathological features, stage and outcome are shown in Table 2.

At median follow-up of 25 (range, 1–180 months), 19 patients (65.5%) survived without evidence of disease and 10 (35.5%) had died. Seven died of recurrent disease including local recurrence and distant metastases despite chemotherapy. One patient had intra-atrial and intra-hepatic extension of tumor at presentation and died in the immediate post-operative period owing to multi-organ failure. Two patients died of subsequent primary brain tumors (case 16; glioblastoma, case 27; medulloblastoma) with no local recurrence of ACT. Five-year OS and EFS estimates was 62.4% and 59.7%, respectively (Fig. 2A).

The EFS for patients with Weiss score = <3 and Weiss score >3 are shown in Fig. 3A. Tumors with a low Weiss score had a better outcome compared those with a high Weiss score ($P < 0.01$); tumors with a high Weiss score were usually associated with poor outcome (Fig. 3AB). The outlier in the surviving group with a high Weiss score had a complete resection without rupture (case 27). In contrast, the outlier with a low Weiss score but who died was a patient (case 9) with a genetic predisposition syndrome who suffered intraoperative tumor rupture and died following several local relapses.

The relationship between Weiss score and tumor size showed a statistically significant association ($P < 0.01$), with large tumors associated with higher Weiss scores (Fig. 3C, 3D).

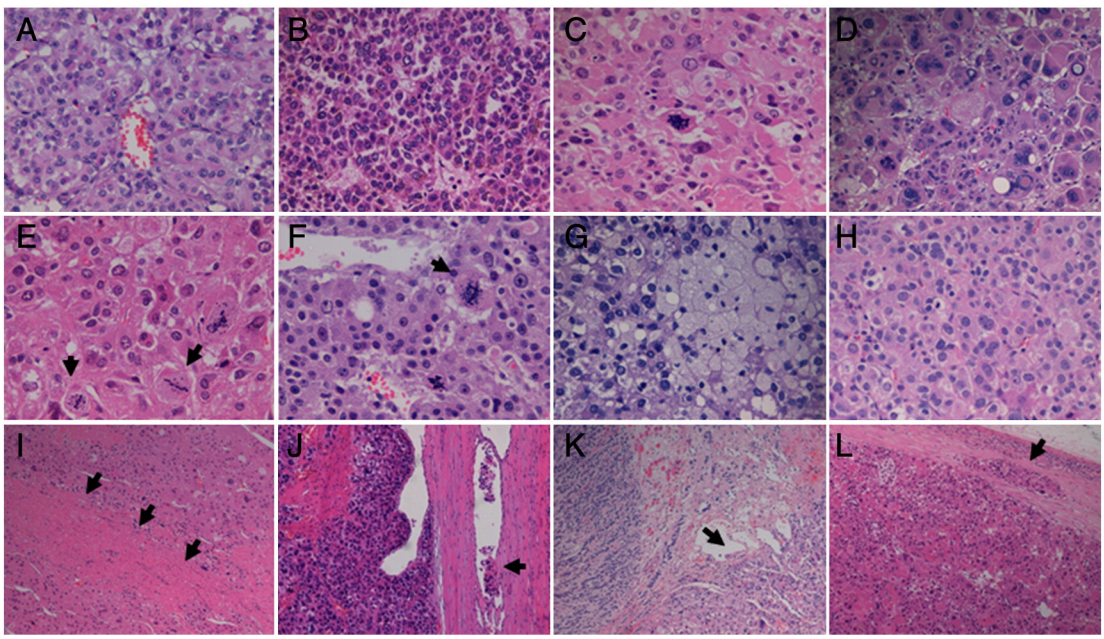

Fig. 1. Illustrations of features in the Weiss scoring system. Nuclear grades: A. Grade 1: Uniform round nuclei, homogenous, small size, no nucleoli. B. Grade 2: Nuclei slightly irregular, more voluminous, conspicuous nucleoli. C. Grade 3: Irregular large nuclei, with hyperchromasia along with marked variability in size and shape. Nucleoli are conspicuous. D. Grade 4: Monstrous cells with very irregular nuclei. (x400) Other categories. E: Mitoses. F: Atypical mitoses. G: Clear cell. H: Diffuse architecture. I: Confluent necrosis. J: Vascular invasion. K: Sinusoidal invasion. L: Capsular invasion. (E–I: ×400, J–L: ×100).