Histopathological Criteria for Paediatric Adrenocortical Carcinoma

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Abstract

Introduction: Adrenocortical carcinoma (ACC) is diagnosed in paediatric patients at 5 months after symptom onset on average, and 38\% die during the first 2.5 years of follow-up. This study aimed to compare the accuracy of Weiss, Van Slooten, and Wieneke histopathological ACC classifications for predicting follow-up prognosis in a paediatric population. Methods: Data were retrieved from medical records of 57 patients aged <18 years who underwent surgical treatment for ACC with surgical follow-up over 6 months or death due to ACC. They were classified into either good (without recurrence/death due to ACC) or poor (with recurrence/death due to ACC) prognosis group. Two expert pathologists classified the ACC surgical specimens according to the Weiss, Van Slooten, and Wieneke criteria. Results: The median follow-up duration was 126 (18–225) months in 38 males (66.7\%) and 19 females (33.3\%) (median age: 3 [1–6.5] years). The good prognosis group was younger than the poor prognosis group (median age: 3 [1.5–6.2] years vs. 5 [2–10] years). Seventeen (29.8\%) patients in the poor prognosis group died due to ACC within the first 50 months of surgical follow-up; the earliest death occurred in the fourth follow-up month, and the majority of deaths occurred within 24 months of follow-up. The accuracies of Weiss, Van Slooten, and Wieneke classification systems were 40\%, 47\%, and 77\%, respectively. Discussion/Conclusion: The Wieneke classification showed the best accuracy but was not sufficiently precise to establish reliable prognosis for ACC in the paediatric population. The Wieneke classification had approximately 95\% sensitivity and negative predictive value.

Keywords
Adrenal glands · Pathology · Neoplasms · Classification · Carcinoma · Paediatrics

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Introduction

Adrenal tumours, excluding neuroblastoma, are sporadic in childhood and adolescence, with an incidence of 1.5 million/year, corresponding to 0.2\% of all malignant tumours in this age group [1, 2]. The International Pedi-
Adrenocortical Tumor Registry (IPACTR) revision in 2004 reported that adrenocortical carcinoma (ACC) is diagnosed at 5 months after symptom onset on average, and 38% of patients do not survive during the first 2.5 years of follow-up, reaching only 54% of the overall survival during the first 5 years of follow-up [3, 4]. The IPACTR was created to be specific and develop knowledge of the epidemiological and clinical patterns of paediatric ACC. By using specific histopathological criteria from the paediatric population, the IPACTR improved outcomes by updating the ACC prognostic staging specific to this population, which had followed those available for adults [5].

ACC in childhood and adolescence is still being classified according to the histopathological Weiss criteria developed for adults, which have no specificity for prognostic issues and are not entirely recommended for the paediatric population [6–8]. In an attempt to create a classification for the paediatric population, Wieneke established specific criteria by modifying the Weiss criteria and adding morphometric data to build a new algorithm that achieves superior specificity for the diagnosis and prognosis of ACC. The Wieneke criteria were validated by three retrospective studies [9–12].

Considering the importance of clinical prognosis based on histopathological diagnosis for the establishment of therapeutic management, this study aimed to prospectively assess and compare the accuracy of three histopathological ACC classifications – namely, Weiss, Van Slooten, and Wieneke criteria – for predicting follow-up outcomes of this disease in the paediatric population. This study is a 35-year series of surgical patients with ACC.

Materials and Methods

After receiving exemption for disclosure and consent to retrieve the medical records and after obtaining approval from our Institutional Review Board (protocol number: HCFMRP-USP 3019/2010), data were retrieved from the medical records of 63 patients who underwent surgical treatment for ACC and followed up at a single academic institution in the countryside of São Paulo, Brazil, from January 1975 to December 2010. Six patients were excluded from this study, because they did not attain the minimum surgical follow-up or did not have surgical specimens at the institutional pathology laboratory for the review of histopathological criteria.

We evaluated age, ethnicity, sex, clinical characteristics, patient follow-up, functionality (laboratory tests), histopathological patterns (established criteria for ACC), and morphological traits (size, weight) of the surgically removed tumours. Any recurrence of the disease was identified at patient follow-up.

Table 1. Histopathological classification comparing the Weiss, Van Slooten, and Wieneke scoring system according to prognosis group

| Histopathological criteria          | Follow-up |
|------------------------------------|-----------|
|                                    | poor prognosis | good prognosis |
| Weiss                              |            |                |
| Malignant                          | 16         | 33             |
| Benign                             | 1          | 7              |
| Van Slooten                        |            |                |
| Malignant                          | 17         | 30             |
| Benign                             | 0          | 10             |
| Wieneke                            |            |                |
| Malignant                          | 16         | 12             |
| Benign                             | 1          | 28             |

The inclusion criteria were as follows: age <18 years, confirmed histological ACC diagnosis, surgical treatment for ACC, and surgical follow-up after surgery for at least 6 months or death due to ACC before 6 months of follow-up. Only two children received a follow-up that was less than 12 months in the poor prognosis group. The exclusion criteria were as follows: age ≥18 years, surgical follow-up shorter than 6 months except for death due to ACC, and histological diagnosis for other tumours of the adrenal gland (neuroblastoma, ganglioneuroma, pheochromocytoma, and metastasis).

Two expert pathologists from the same academic institution, who were not aware of the patients’ clinical status, reviewed the ACC surgical specimens of all 57 patients included in this study. The slides for surgical specimens were constructed from 5-mm paraffin block slices of the sample stained with haematoxylin and eosin. The pathologists classified the specimens according to the Weiss, Van Slooten, and Wieneke criteria. Subsequently, the 57 patients were assigned to either the good prognosis group (without recurrence/decease due to ACC) or poor prognosis group (with recurrence/decease due to ACC).

Statistical Analyses

Quantitative variables are presented as medians and interquartile ranges. The ability of each classification to distinguish the evolution of patients was based on sensitivity, specificity, positive and negative prognostic values, and positive and negative likelihood ratios. Statistical significance was set at $p < 0.05$, and 95% confidence intervals were presented as a measure of precision. Data analyses were performed using GraphPad Prism version 8.0.3 (GraphPad Software, San Diego, CA, USA).

Results

The median follow-up time in 57 patients included in this study was 126 [18–225] months in 38 females (66.7%) and 19 males (33.3%) (median age: 3 [1–6.5] years). The median age was lower in the good prognosis group (3 [1.5–6.2] years) than in the poor prognosis group (5 [2–
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10 years). Ethnically, 52 patients (91.2%) were white, 5 (8.8%) were black, and none were Asian. The patients were allocated to either the good prognosis group or the poor prognosis group according to their follow-up outcomes and were designated as having benign or malignant ACC following the Weiss, Van Slooten, and Wieneke histopathological system scores (p < 0.001) (Table 1).

Overall, 17 (29.8%) patients in the poor prognosis group died because of ACC. All deaths occurred within the first 50 surgical months of follow-up; the earliest death occurred in the fourth follow-up month, and the majority of deaths occurred within 24 months of follow-up (Fig. 1). The relapse rate with 24 and 50 months of follow-up was 43 and 40 patients, respectively (Fig. 1). The accuracy of evaluation for each histopathological system score revealed that the Wieneke score was superior to the Weiss and Van Slooten scores (Table 2).

Histopathological diagnosis of an adrenal cortical tumour strives to define whether it is malignant. Such diagnosis has been carried out using a multiparametric scoring system developed for adults but used as well for children and adolescents worldwide (i.e., Weiss and Van Slooten criteria), with only one system developed for children and adolescents only, but not for adults (i.e., Wieneke criteria) [13]. The histopathological patterns used to describe the malignant potential of adrenal cortical tumours in the paediatric population differ from those used in adults. However, diagnosing ACC remains challenging in children. Immunohistochemistry and genomic tests have been used to collaborate with the identification of adrenal cortical tumour prognosis, but with no meaningful achievement yet [13]. This study identified a mortality rate of 29.8%, which is in the range of 20–50% [14–16]. The high mortality rate of ACC calls attention to the importance of developing a reliable prognostic classification that provides better guidance to patients, families, and healthcare providers. In 2016, Bulzico et al. [17] analysed the database of the National Cancer Institute (INCA) of Brazil and found that almost 30% of patients considered sufficiently treated with surgery for ACC presented with disease recurrence during follow-up.

Weiss et al. [18] developed the largest scoring system available for diagnosing ACC in 1984, using the following nine histopathological parameters: high nuclear grade (Fuhrman III or IV), mitotic index >5/50 high-power field, atypical mitosis, lack of clear cytoplasm ≥25%, diffuse architecture >1/3 of tumour, necrosis, venous invasion, sinusoidal invasion, and capsular invasion. Each pa-

**Table 2. Accuracy comparing Weiss, Van Slooten, and Wieneke scoring system**

| Classification parameters | Weiss | Van Slooten | Wieneke |
|---------------------------|-------|-------------|---------|
| Sensitivity, %            | 100   | 94          | 94      |
| Specificity, %            | 17    | 94          | 70      |
| Positive predictive value, %| 36    | 32          | 57      |
| Negative predictive value, %| 100   | 87          | 96      |
| Likelihood ratio +        | 1.33  | 1.14        | 3.13    |
| Likelihood ratio –        | 0     | 0.35        | 0.08    |
| Accuracy, %               | 40    | 47          | 77      |

+, positive; −, negative.
rameter receives a score of 0 if it is absent and 1 if it is present, providing a total score ranging from 0 to 9. Analysing 43 patients with ACC for 5 years, Weiss identified those who scored ≥4 developed metastasis, therefore considered ACC, while those who scored ≤2 did not develop metastasis were considered to have nonmalignant neoplasia. In 1989, Weiss et al. [19] reviewed their study and reduced the score threshold to ≥3 for a diagnosis of ACC. In 1985, Van Slooten et al. [20] proposed their own score for adrenal cortical tumours based on seven histological parameters and designated different weights to each parameter: regressive changes (necrosis, haemorrhage, fibrosis, calcification), 5.7; lack of normal structure, 1.6; moderate or marked nuclear atypia, 2.1; nuclear hyperchromasia, 2.6; abnormal nucleoli, 4.1; mitotic index >2/10 high-power field, 9.0; and capsular/vascular invasion, 3.3. Hence, the score can range from 0 to 28.4, and if it reaches >8, it suggests a malignant adrenal cortical tumour. Later, using the same parameters as those by Van Slooten, Aubert et al. [21], van’t Sant et al. [22] and Pennanen et al. [23] (Helsinki score) attributed different weights to the criteria of Weiss et al. [19], modifying the final score and its threshold to define the adrenal cortical tumour as malignant or not, in an attempt to increase the accuracy of the method. All of these efforts work for adults.

ACC in the paediatric population suggests different carcinogenic mechanisms than those in adults. In addition, adrenal cortical tumours present with a less aggressive pattern in children and adolescents than in adults, even though they are malignant more than 80%–90% of the time in the paediatric population [4]. In 2003, Wieneke et al. [9] provided a scoring system to diagnose ACC in the paediatric population (<20 years) supported by the following parameters: tumour weight >400 g, tumour size >10.5 cm, extension into periadrenal soft tissue and/or adjacent organs, invasion into the vena cava, venous invasion, capsular invasion, presence of tumour necrosis, mitotic index >15/20 high-power field, and presence of atypical figures. The presence of up to two of these criteria supports a benign evolution, three open evolution, and four or more ACC [9].

In this 35-year series with 57 patients under 18 years of age, we identified a higher incidence of ACC in females, approximately 2/3 of all cases, similar to the Surveillance, Epidemiology, and End Results (SEER) database with 85 patients in a series of 35 years. The median age of the patients in our series was 3 years; however, the median age in the poor prognosis group was 5 years, again similar to the SEER data. The National Cancer Database (NCDB) and population studies in Europe identified a worse prognosis for ACC in a paediatric population ≥4 years old [24–27]. In a study of 58 patients, an Italian group showed a survival free of disease for patients ≥12 years, 9.44 times worse than those <4 years and 7.79 overall [11].

In 2018, Erickson demonstrated the challenge of diagnosing ACC by using the criteria provided by Weiss, Van Slooten, and Wieneke, their variants, complements, and/or upgrades developed in an attempt to increase the accuracy of the methods; even adding immunohistochemistry and genomic tests did not enable them to reach their goal [13]. In our 35-year series with 57 patients, 17 died who were classified as having poor prognosis and comprised almost 1/3 of the poor prognosis group. All patients died in the first 50 months after surgery, and the majority died within the first 24 months after surgery, similar to those reported in the literature.

All three scoring systems used to diagnose ACC in this series showed high sensitivity (94–100%) despite their low specificity (17–70%). In this scenario, despite the high positive predictive value, the low specificity resulted in a large number of children treated surgically by only two experienced surgeons and classified by the three scoring systems, as ACC had a benign follow-up with good prognosis. By taking this into account, the Wieneke criteria showed the best performance, placing a low number of patients (n = 12) who were considered to have ACC in the good prognosis group. However, based on the Wieneke criteria, one patient was considered to be “non-ACC” who developed the malignant pattern and was therefore placed in the poor prognosis group. In our series, the Wieneke criteria showed an accuracy of 77% for classifying adrenal cortical tumours in children, which was not as good as expected. However, Gupta et al. [28] analysed 41 patients at the Mayo Clinic in a 67-year series and showed an accuracy of 100% for the Wieneke index, as compared to 29% and 33% for the Weiss and modified Weiss criteria, respectively. Although the Wieneke index in our series was much better than the Weiss and Van Slooten criteria developed to classify adrenal cortical tumours in the adult population, the Wieneke index exhibited a performance less than that of flipping a coin, achieving an accuracy of 77%, as compared to an accuracy of 40% for the Weiss criteria and 47% for the Van Slooten criteria (Fig. 2).

Jehangir et al. [29] reported that the Wieneke criteria accurately predict the clinical course in childhood ACC considering the gold standard in their pathological characterization. However, Picard et al. [30] stated that they believe the Wieneke scoring system is not sufficient enough to guide perioperative treatment recommenda-
tions, calling attention to the requirement of small series and urging for further independent studies to validate the conclusion made by Jehangir et al. [29]. We do agree with Picard et al. [30] and have added our series results to the table published by Jehangir et al. [29], showing clinically malignant/pathologically benign and clinically benign/pathologically malignant tumours (Table 3).

All three histopathological criteria for diagnosing ACC showed very good sensitivity, making them reliable in terms of appropriately predicting and defining patients in the good prognosis group. Only the Van Slooten criteria placed all ACC patients with ACC in the poor prognosis group, whereas the Weiss and Wieneke criteria diagnosed one patient as “non-ACC” who belonged to poor prognosis group. However, with respect to all patients included in the good prognosis group, almost 75% of them were diagnosed by the Weiss and Van Slooten criteria as having ACC, whereas the Wieneke criteria diagnosed ACC in only 33%. The need for close follow-up in all children diagnosed with ACC is usually not welcome among families and healthcare providers. We understand that the allocation in the good prognosis group may have occurred owing to adequate surgical treatment and not because of a lack of histopathological classification. We also understand that, if possible, we should spare families from such a psychological burden. Therefore, despite the lack of the best histological criteria for diagnosing ACC in the paediatric population, we must use the best available criteria for that population.

This study has many limitations, starting with being a retrospective design. Surgery is a unique treatment that can modify the natural history of the adrenal cortical tumour, and biopsy is not recommended for this disease, making a prospective study to check the accuracy of the scoring system impossible. We also know that many children allocated as having an ACC had good prognosis because the disease was adequately treated with the surgery, which makes the accuracy of these three systems unreliable. However, this is a 35-year series of 57 patients with a rare disease, turning it into one of the largest series in the world with a long follow-up.

The accuracy of the Weiss and Van Slooten classifications were not greater than that of the odds of flipping a coin, and these criteria should be avoided to classify adrenal cortical tumours in the paediatric population. The Wieneke classification was better than the Weiss and Van Slooten, but the accuracy was not good enough to establish a reliable prognosis for ACC in the paediatric population. However, the Wieneke classification has been the best for the child and adolescent population to date.

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**Table 3. Cumulative analysis of the literature where Wieneke scoring system was used published by Jehangir et al. [29] and added Paschoalin et al. data on last line**

| Criteria                  | Clinically and pathologically malignant | Clinically benign pathologically malignant | Clinically malignant pathologically benign | Clinically and pathologically benign |
|---------------------------|----------------------------------------|------------------------------------------|------------------------------------------|-------------------------------------|
| Wieneke et al. [9]        | 18                                     | 10                                       | 0                                        | 37                                  |
| Chatterjee et al. [12]    | 5                                      | 0                                        | 0                                        | 9                                   |
| Magro et al. [10]         | 6                                      | 1                                        | 0                                        | 13                                  |
| Ru et al.                 | 6                                      | 1                                        | 0                                        | 13                                  |
| Giovannoni et al.         | 5                                      | 0                                        | 0                                        | 2                                   |
| Jehangir et al. [29]      | 7                                      | 0                                        | 0                                        | 14                                  |
| **Total (n = 81)**        | **48**                                 | **12**                                   | **0**                                    | **87**                              |
| Paschoalin et al. [this study] | **16**                                | **11**                                   | **1**                                    | **29**                              |

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![Fig. 2. Histogram of the accuracy of the Van Slooten, Weiss, and Wieneke scoring systems containing minimum and maximum confidence intervals.](image)
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Statement of Ethics

This study protocol was reviewed and approved by our Institutional Review Board: Hospital Das Clinicas Da Faculdade De Medicina De Ribeirao Preto Da Universidade De Sao Paulo (protocol number HCFMRP-USP 3019/2010). The study was granted with an exemption by the Research Ethics Committee of Ribeirão Preto Clinical Hospital of Ribeirão Preto Medical School of University of São Paulo regarding the requirement for the acquisition of written informed consent from patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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References

1 Ribeiro RC, Figueiredo B. Childhood adrenocortical tumours. Eur J Cancer. 2004 May; 40(8):1117–26.
2 Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Clinical review: prevalence and incidence of endocrine and metabolic disorders in the United States - a comprehensive review. J Clin Endocrinol Metab. 2009 Jun;94(6):1853–78.
3 Ribeiro RC, Sandrini Neto RS, Schell MJ, Lacerda L, Sambaio GA, Cat I. Adrenocortical carcinoma in children: a study of 40 cases. J Clin Oncol. 1990 Jan;8(1):67–74.
4 Michalkiewicz E, Sandrini R, Figueiredo B, Miranda EC, Caran E, Oliveira-Filho AG, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol. 2004 Mar; 22(5):838–45.
5 Ribeiro RC, Pinto EM, Zambetti GP, Rodrigues-Galinho C. The international pediatric adrenocortical tumor registry initiative: contributions to clinical, biological, and treatment advances in pediatric adrenocortical tumors. Mol Cell Endocrinol. 2012 Mar;351(1):37–43.
6 Almeida MQ, Fragoso MC, Lotfi CF, Santos MG, Nishi MY, Costa MH, et al. Expression of insulin-like growth factor -II and its receptor in pediatric and adult adrenocortical tumors. J Clin Endocrinol Metab. 2008 Sep; 93(9):3524–31.
7 Lima Lde O, Lerario AM, Saldanha I, Anton B, Ladenson PW, Almeida MQ, Domenice S, et al. Clinical and molecular aspects of a pediatric metachronous adrenocortical tumor. Arq Bras Endocrinol Metabol. 2011 Feb;55(1):72–7.
8 Sakoda A, Mushtaq I, Levitt G, Sebire NJ. Clinical and histopathological features of adrenocortical neoplasms in children: retrospective review from a single specialist center. J Pediatr Surg. 2014 Mar;49(3):410–5.
9 Wieneke JA, Thompson LD, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunohistochemical analysis of 83 patients. Am J Surg Pathol. 2003 Jul;27(7):867–81.
10 Magro G, Esposito G, Cecchetto G, Dall’Igna P, Marcato R, Gambini C, et al. Pediatric adenocortical tumors: morphological diagnostic criteria and immunohistochemical expression of matrix metalloproteinase type 2 and human leucocyte-associated antigen (HLA) class II antigens. Results from the Italian Pediatric Rare Tumor (TREP) Study project. Hum Pathol. 2012 Jan;43(1):31–9.
11 Dall’Igna P, Virgine C, De Salvo GL, Bertorelli K, Indolfi P, De Paoli A, et al. Adrenocortical tumors in Italian children: analysis of clinical characteristics and P53 status. Data from the national registries. J Pediatr Surg. 2014 Sep;49(9):1367–71.
12 Chatterjee G, DasGupta S, Mukherjee G, Sen-gupta M, Roy P, Arun I, et al. Usefulness of Wieneke criteria in assessing morphologic characteristics of adrenocortical tumors in children. Pediatr Surg Int. 2015 Jun;31(6):563–71.
13 Erickson LA. Challenges in surgical pathologoy of adrenocortical tumours. Histopathology. 2018 Jan;72(1):82–96.
14 Schlick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol. 1999 Dec;6(8):719–26.
15 Meyer A, Niemann U, Behrend M. Experience with the surgical treatment of adrenal cortical carcinoma. Eur J Surg Oncol. 2004 May;30(4):444–9.
16 Erdogan I, Deutschbein T, Jurowich C, Kroiss M, Ronchi C, Quinkler M, et al. The role of surgery in the management of recurrent adrenocortical carcinoma. J Clin Endocrinol Metab. 2013 Jan;98(1):181–91.

17 Bulzico D, de Faria PA, de Paula MP, Bordallo MA, Pessoa CH, Corbo R, et al. Recurrence and mortality prognostic factors in childhood adrenocortical tumors: analysis from the Brazilian National Institute of Cancer experience. Pediatr Hematol Oncol. 2016 May; 33(4):248–58.

18 Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol. 1984 Mar; 8(3):163–9.

19 Weiss LM, Medeiros LJ, Vickery AL. Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol. 1989 Mar;13(3):202–6.

20 van Slooten H, Schaberg A, Smeenk D, Moolenaar AJ. Morphologic characteristics of benign and malignant adrenocortical tumors. Cancer. 1985 Feb;55(4):766–73.

21 Aubert S, Wacrenier A, Leroy X, Devos P, Carnaille B, Proye C, et al. Weiss system revisited: a clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. Am J Surg Pathol. 2002 Dec;26(12):1612–9.

22 van’t Sant HP, Bouvy ND, Kazemier G, Bonjer HJ, Hop WC, Feeders RA, et al. The prognostic value of two different histopathological scoring systems for adrenocortical carcinomas. Histopathology. 2007 Aug;51(2):239–45.

23 Pennanen M, Heiskanen I, Sane T, Remes S, Mustonen H, Haglund C, et al. Helsinki score-a novel model for prediction of metastases in adrenocortical carcinomas. Hum Pathol. 2015 Mar;46(3):404–10.

24 McAteer JP, Huaco JA, Gow KW. Predictors of survival in pediatric adrenocortical carcinoma: a surveillance, epidemiology, and end results (SEER) program study. J Pediatr Surg. 2013 May;48(5):1025–31.

25 Kerkhofs TM, Ettaieb MH, Verhoeven RH, Kaspers GJ, Tissing WJ, Loeffen J, et al. Adrenocortical carcinoma in children: first population-based clinicopathological study with long-term follow-up. Oncol Rep. 2014 Dec; 32(6):2836–44.

26 Gulack BC, Rialon KL, Englum BR, Kim J, Talbot LJ, Adibe OO, et al. Factors associated with survival in pediatric adrenocortical carcinoma: an analysis of the national cancer data base (NCDB). J Pediatr Surg. 2016 Jan; 51(1):172–7.

27 Xu X, Sergi C. Pediatric adrenal cortical carcinomas: Histopathological criteria and clinical trials. A systematic review. Contemp Clin Trials. 2016;50:37–44.

28 Gupta N, Rivera M, Novotny P, Rodriguez V, Bancos I, Lteif A. Adrenocortical carcinoma in children: a clinicopathological analysis of 41 patients at the mayo clinic from 1950 to 2017. Horm Res Paediatr. 2018;90(1):8–18.

29 Jehangir S, Nanjundaiah P, Sigamani E, Burad D, Manipadam MT, Lea V, et al. Pathological prognostication of paediatric adrenocortical tumors: is a gold standard emerging? Pediatric Blood Cancer. 2019 Apr;66(4):e27567.

30 Picard C, Orbach D, Dijoud F. Reply to "Pathological prognostication of paediatric adrenocortical tumors: is a gold standard emerging?" Pediatric Blood Cancer. 2019 Jun;66(6):27710.