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Adrenocortical tumors in Italian children: Analysis of clinical characteristics and P53 status. Data from the national registries ☆,☆☆

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ABSTRACT

Aim: Adrenocortical tumors are very rare in children. The distinction between adenoma and carcinoma is complex because of their clinical/histological characteristics. The analysis of the cases registered in two consecutive Italian Studies is described, in order to provide additional insight into their nature and possibly identify benign and malignant lesions.

Materials and Methods: The analysis includes patients registered from?? 1.1982 to 6.2011 into two consecutive Italian protocols.

Results: Fifty-eight children (age 2–210 months) were evaluated. Endocrine manifestations were the most frequent symptoms. Stage distribution at diagnosis was: ST I 35, ST II 17, ST III 1, ST IV 5. Treatment consisted in mitotane for ST II, mitotane + chemotherapy for ST III/IV. Forty-four patients are alive without evidence of disease, 1 is alive with disease, 12 died of disease and 1 because of cardiomyopathy. The Wienecke score system was applied in 24 patients with good significance. A p53 mutation was found in 7 cases, and it was diagnostic for Li–Fraumeni syndrome in 2 benign tumors.

Conclusions: The results highlight the importance of a complete excision to obtain the cure of patients. The efficacy of chemotherapy is controversial, however it was able to control the disease in 4 patients in ST II. The value of the Wienecke score system in predicting patients' outcome was confirmed. p53 mutation was more frequent in malignant tumors and represented the sentinel of the Li–Fraumeni syndrome.

Adrenocortical tumors (ACTs) in childhood represent about 0.2% of all pediatric malignancies. The incidence varies across geographic regions and is remarkably high in southern Brazil [1,2]. The female/male ratio is 2/1 and the age incidence curve is characterized by two peaks, the first under 3 years, the second during adolescence [3,4].

The high prevalence of p53 tumor suppressor gene mutations has been proposed as predisposing factor in Brazil and United States, both in the sporadic forms and in those associated with Li–Fraumeni syndrome [5–8].

Most children (80%) have secreting tumors with signs of virilisation [9]. The surgical excision represents the gold standard of treatment. In advanced stages, chemotherapy, which usually includes cisplatin, etoposide, doxorubicine (CED) and mitotane (*o*,*p*'-DDD: 1,1-dichloro-2-*o*-chlorophenil)-2-(*p*-chlorophenil)ethane), an insecticide derivative that produces adrenocortical necrosis, may be utilized [10–12].

It is generally recognized that no one pathologic feature can predict the outcome [5], and the tumor weight has been considered

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the only liable prognostic parameter (with variations of the weight cut-off in the different studies) [4,13].

The analysis of the cases registered in two consecutive Italian Studies is described, in order to provide additional information of the nature of ACT in a cohort of children from a European country.

1. Materials and Methods

The analysis includes patients ≤18 years, registered into the retrospective study, carried out under the auspices of the Italian Association of Pediatric Hematology-Oncology, and the ongoing prospective National study (TREP; Rare Tumors in Pediatric Age), started in 2000 [14]. All information concerned clinical findings (symptoms and hormonal assessment), diagnostic work up, surgical treatment, histology, staging, follow-up and events. For every patient, moreover, an informed consent was obtained, which included the permission for data management. Patients were classified according to the staging system utilized for other pediatric series [9,13,1], and treated accordingly: ST I (radical excision and tumor volume <200 cm^3 and subsequent normalization of hormonal blood level): no treatment; ST II (excision with microscopic residual or tumor spillage or regional nodes positive or tumor volume >200 cm^3 or high hormonal blood level persisting after surgery): mitotane; ST III (excision with macroscopic residual) and ST IV (metastases): mitotane plus CED. Patients included in the retrospective study had been assigned to the same staging system. The surgical approach in the two studies was the same. If we consider chemotherapy, the treatment, even if not identical, included the same chemotherapic agents, such as cisplatin and mitotane, in different combinations; however in the TREP study it was standardized through guidelines that have been used by every Centre since 2000.

1.1. Histology, immunohistochemistry, molecular analysis

Histology could be reviewed in 24 cases of the new study, and tumors were categorized according to the Wienecke criteria (Table 1) [4]. These data have been object of a recent pathological study [15].

Immunostaining for p53 (CLONE D07, DAKO) was performed using automated immunostainer Bondmax, according to manifacturer's protocols: nuclear staining in more than 10% of cells was considered positive.

The more frequently mutated regions of TP53 gene were studied by polymerase chain reaction (PCR) using primer pairs specific for each exon [10,16,17]. The amplified products were sequenced by fluorescent capillary electrophoresis analysis (ABI PRISM 310 genetic analyzer, Applied Biosystems, CA).

1.2. Statistical analysis

The statistical analysis evaluated the impact of the clinical characteristics on patients' survival (age, sex, tumor's volume, tumor's diameter, symptoms, stage and surgery). Tumor progression, relapse, occurrence of second malignancy, or death for any cause was considered for event-free survival (EFS). Disease outcome was also analyzed in term of overall survival (OS). Crude survival curves were estimated by the Kaplan Meier method and 5-year estimates were reported for descriptive purpose. Heterogeneity in survival among strata of selected variables was assessed through the Log-rank Test. A multivariate Cox proportional hazards model was performed to identify factors associated with the risk of developing events or death. Multivariate hazard ratios (HRs), with 95% CI, were computed considering factors that turned out to be statistically significant at univariate analysis, applying a backward variable selection. The statistical analyses were performed using SAS 9.2 software.

Table 1
Proposed criteria for malignancy of adrenal cortical neoplasms in pediatric patients (Wienecke, 2003).

Tumor weight of > 400 g
Tumor size > 10.5 cm
Extension into periadrenal soft tissues and/or adjacent organs
Invasion into vena cava
Venous invasion
Capsular invasion
Presence of tumor necrosis
> 15 mitoses per 20 HPF
Presence of atypical mitotic figures

Tumors are defined as malignant when ≥ 4 criteria are present; in the presence of 3 or <3 criteria, tumors are defined undetermined and benign, respectively.

2. Results

2.1. Clinical and pathologic findings

From January 1982 to June 2011, 58 children (39 females, 19 males) were registered into the studies. Age at diagnosis ranged from 2 to 210 months (median 61). In 47 cases, the endocrine manifestations, especially virilisation, were the most frequent symptoms. In 1 patient, the tumor was detected in the prenatal period. Stage distribution at diagnosis was: ST I 35, ST II 17, ST III 1, ST IV 5. According to Wienecke scoring system, 13 tumors were benign, 9 malignant, 2 undetermined. Clinical characteristics and treatment are summarized in Table 2.

ST I. Thirty-three patients (94.2%) reached a complete remission (CR) and are alive without disease (FU 23–119 months, median 71); 2, from the retrospective study, developed local recurrence (LR) and died of disease 4 and 26 months after diagnosis respectively, despite chemotherapy in 1 and a second surgery in the other. One patient was lost to follow-up. The median maximum tumor volume was 31 cm^3.

Table 2
Clinical characteristics of patients according to stage.

	STAGE I (35 pts)	STAGE II (17 pts)	STAGE III and IV (6 pts)	TOTAL (58 pts)
Age				
<4 yrs	21	5	0	26
≥4 yrs–≤12 yrs	12	8	2	22
>12 yrs	2	4	4	10
Sex				
Males	9	5	5	19
Females	26	12	1	39
Symptoms				
Non-endocrine	5	3	3	11
Endocrine non-Cushing	22	8	0	30
Cushing sdr.	8	5	3	16
Surgery (on primitive tumor)				
Complete resection	35	5	1	41
Microscopical residuals	0	12	3	15
Macroscopical residuals/biopsy	0	0	2	2
Maximum diameter (cm)				
median	5	10	12	6
range	2–10	2.5–24	6–25	2–25
Volume (cm^3)				
median	31	209.5	196.5	76
range	4–176	8–1381	21–3556	4–3556
Chemotherapy (1st line)				
Mitotane	0	6	0	6
CED +/− Mitotane	0	1	4	5
other regimens	2	2	1	5
Further treatments (2nd line)				
Chemotherapy	0	4	1	5
Radiotherapy	1	1	0	2
Surgery	1	2	0	3
Outcome				
Not Evidence of Disease	33	12	0	45
Alive With Disease	0	0	1	1
Dead Of Disease	2	5	5	12

In the patients who died, the tumor volumes were 128 and 113 cm^3. **ST II**. Eleven patients (64.7%) are in CR (FU 3–139 months, median 34). Seven (6 from TREP) received mitotane, 4 (3 from TREP) did not, due to Center decision: 1 (tumor rupture) manifested LR and was treated with surgery only; 1 had an excision with microscopic residue after a laparoscopy procedure (CR at 65 months after diagnosis). Five patients died of disease, 2 despite chemotherapy. Three were not treated (1 because of allergy to mitotane) and developed local and distant metastases. One (in CR after surgery) died because of dilatative cardiomyopathy. Tumor volume was bigger than 200 cm^3 in 4. **ST III**. The only child with a tumor infiltrating the perivertebral tissue, did not receive any treatment after surgery, for Center decision, and is alive with disease at 48 months from diagnosis. **ST IV**. After surgery on the primary tumor (2 complete, 1 microscopic residue, 2 biopsy), all 5 children received chemotherapy: CED plus mitotane in 4, adriamicin, vinblastin, melphalan, etoposide, mitotane in 1. All died of disease from 2 to 13 months after diagnosis.

2.2. p53 immunostaining and molecular analysis

The analysis was carried on 20 cases with available material. Immunostaining for p53 was positive in 7 cases, of which 3 did not have evidence of p53 mutation. In 7/20 (2 benign, 5 malignant), a TP53 mutation was detected at the sequencing analysis (Table 3). A germ line mutation was documented and a diagnosis of Li–Fraumeni syndrome was obtained only in 2 patients, a 7.8 year old boy affected by a large malignant tumor and a 2 year old girl, with a 5.5 cm tumor (Table 3). The lack of normal tissue or blood samples of patients enrolled into the retrospective study and some of those enrolled in the prospective did not allow to investigate whether the mutation were somatic or germline.

2.3. Outcome analysis

EFS and OS curves are shown in Fig. 1. Age <4 years, maximum diameter <5 cm, volume <200 cm^3, low stage and complete surgical excision were related to a better OS and EFS at univariate analysis (Table 4). Cox regression model indicated that only age <4 years and volume <200 cm^3 were independently associated to good prognosis. Patients with tumor volume ≥200 cm^3 were at a 5-fold higher risk of developing an event (HR = 5.47; 95% CI: 1.60–18.72) and 3-fold higher risk of death. Patients ≥12 years were found to have 9.44-fold higher risk for worse EFS (95% CI: 1.79–49.85) compared to age <4 years, and 7.79-fold higher risk for worse OS (95% CI: 1.44–42.23).

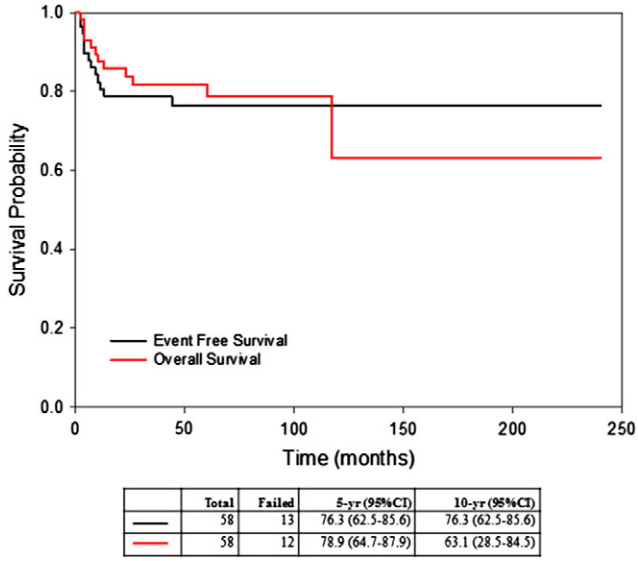
3. Discussion

ACTs are very rare tumors in children, but their incidence in Italy cannot be established because of the lack of a "population based" cancer registry [14]. Interestingly, the National TREP study, for the first time, could enroll 40 patients since 2000, however, a considerable number of adolescents, who are often treated in Centers for adults, might have been missed [18].

Table 3
TP53 mutations and immunohistochemistry in 7 patients.

Patients	Exon	Codon	Nucleotide	Mutation	p53 IHC	Wienecke	FU
1	5	175	G/A	R175H	+	M	Dod
2	5	177	C/T	P177S	NA	M	Ned
3	5	179	A/G	H179R	+	B	Ned
4	8	273	G/A	R273H	NA	B	Ned
5	8	276	G/A	A276T	NA	M	Dod
6	10	342	C/T	R342X	+	M	Dod
7	10	342	C/T	R342X	+	M	Dod

NA: not available; M: malignant; B: benign; Dod: dead of disease; Ned: non evidence of disease.



	Total	Failed	5-yr (95%CI)	10-yr (95%CI)
——	58	13	76.3 (62.5-85.6)	76.3 (62.5-85.6)
——	58	12	78.9 (64.7-87.9)	63.1 (28.5-84.5)

Fig. 1. Event-free Survival and Overall Survival.

The criteria utilized for distinguishing benign and malignant lesions in adults, including for example the histological parameters of the Weiss score [19] or some immunohistochemical features, such as the expression of the proliferation antigen Ki67 [20], have not been helpful in predicting the biological behavior of these tumors in children [4,21], and the research of characteristics able to define the nature of lesions in this age group has been the main matter of discussion in the recent years [2,4,13,21–23]. Tumor weight or tumor size has traditionally been considered as the only valid prognostic parameters, and various cut-offs have been proposed throughout the years [1,4,11,13,22,24,25]. Dehner et al. suggested the importance of the vena cava invasion as the only independent predictor of unfavourable outcome, but proposed the tumor weight as the main prognostic indicator, defining as high risk tumors those weighing more than 400 g [2]. In our experience, the scoring system suggested by Wienecke in 2001, which included tumor weight, vena cava invasion and other histological features (Table 1) [4], was a strong predictor of prognosis, and a volume less than 200 cm^3 positively correlated with OS and EFS [13,22]. It is true that in the group of patients who died the tumor was less than 200 cm^3 in 5, but two of them were infants, for whom it should be taken into account the different proportion between body weight and tumor size.

Low stage and complete surgical excision were also related to a better OS and EFS at univariate analysis.

The complete excision of the tumor at diagnosis may actually cure the patient, and in our series, it was the only treatment in 37 patients, A complete surgical excision should also be obtained after chemotherapy, removing part of organs, if involved by the tumor, and after the occurrence of relapse and some authors even suggest repeated resections of recurrent local or distant lesions [26,27]. If we consider ST II patients, the impact of positive lymph nodes on survival has not been so far fully investigated, but relapses in these sites were described in our series, as well as in others [9,28], leading us to strongly recommend their biopsy. The significance of microscopic residue is also not completely understood, but it is clearly correlated to tumor biology: 5 patients STII (and III) did not receive any other treatment except surgery, indicating that the lesion might have had benign characteristics, and 1, who had tumor spillage during a laparoscopic procedure, is alive after chemotherapy [29].

As already mentioned, the efficacy of chemotherapy is controversial. In adults, divergent results have been obtained using mitotane,

Table 4
Kaplan–Meier analysis for Event Free Survival and Overall Survival (univariate analysis).

		5-year EFS			5-year OS		
Characteristic	N	N. failed	5-yr EFS (95% CI)	*p-value*	N. failed	5-yr OS (95% CI)	*p-value*
Sex							
Male	19	5	72.9 (46.4–87.8)	0.5083	5	78.2 (51.7–91.2)	0.3148
Female	39	8	78.4 (61.2–88.6)		7	80.0 (62.1–90.0)	
Age, years							
<4	26	2	91.8 (71.1–97.9)	0.0007	2	91.2 (68.9–97.7)	0.0016
4–12	22	5	74.6 (48.4–88.8)		4	85.9 (62.4–95.2)	
≥12	10	6	40.0 (12.3–67.0)		6	33.3 (6.3–64.6)	
Maximum diameter (cm)[a]							
<5	16	–	100.0 (−)	0.0009	–	100.0 (−)	0.0016
5–10	24	5	78.3 (55.4–90.3)		5	78.0 (55.0–90.2)	
≥10	14	7	49.0 (21.6–71.7)		7	42.3 (8.7–73.8)	
Volume (cm^3)[a]							
<200	43	6	85.7 (70.9–93.3)	0.0002	6	85.3 (70.1–93.1)	0.0013
≥200	11	6	45.4 (16.7–70.7)		6	42.4 (8.2–74.5)	
Symptoms[a]							
Non-endocrine	11	4	59.6 (24.1–82.9)	0.0545	3	71.6 (35.0–89.9)	0.0339
Endocrine non-Cushing	30	3	89.5 (70.8–96.5)		3	92.2 (72.2–98.0)	
Cushing sdr.	16	6	62.5 (34.8–81.1)		6	57.3 (26.3–79.3)	
Stage							
I	35	2	94.3 (79.0–98.5)	<0.0001	2	94.0 (78.1–98.5)	<0.0001
II	17	6	54.4 (21.8–78.4)		5	65.5 (29.2–86.5)	
III–IV	6	5	–		5	–	
Surgery							
Complete resection	41	5	87.7 (73.0–94.7)	0.0085	5	89.9 (75.1–96.1)	0.0110
Microscopical residuals	15	7	42.4 (13.3–69.4)		6	47.1 (14.8–74.4)	
Macroscopical residuals/biopsy	2	1	–		1	–	

[a] Missing values excluded.

with a response rate of 10%–60% [11,30], and this is observed also in some pediatric experiences [6,31]. This drug is utilized, especially in case of inoperable tumors, preferably associated to cisplatin, etoposide and doxorubucine [12,28,32–35]. In our series, mitotane was able to control the disease in 8 patients, alone or in association with other drugs, however, it did not obtain any result in 11 patients who died. New drugs and regimens have been recently investigated with the aim to defeat the expression of high levels of multidrug resistance protein MDR1 of ACT (tariquidar, bevacizumab, gefinitib) [10]. Gemcitabine plus metronomic 5-FU or apecitabine has generated some interest as second- or third-line therapy [35].

The molecular pathways involved in the pathogenesis of ACT are poorly understood, although mutations of p53 tumor suppressor gene with loss of function of the protein appear to play an important role in tumor development and progression in pediatric cases [5,7]. Data from the most recent Surveilance, Epidemiology and End-Results (SEER, 2011) program, demonstrated that adrenocortical carcinomas occur in 68% of patients carrying a p53 germline mutation in the first 4 years of life and in 92% of those in the pediatric age-group, while a germline p53 mutation is found in 50% to 80% of malignant ACTs in children [36]. In Brazilian children the TP53 R337H germline mutation is characteristic and is found in 98% of tumors [36]. Outside Brazil, this mutation is exceptionally rare, and in our series it was never found, while mutations involving the common hot spots were present in 35% of tumors (57% of malignant and 15% of benign ACTs): in 2 cases, tumors presented a hot spot mutation at codons 175 (exon 5) and 273 (exon 8), in the other 5, less frequent mutations, equally functionally inactivating, were found. In particular, a nonsense mutation in exon 10 (R342X) was detected in 2 tumors, characterized by aggressive behaviour. This very rare mutation has been reported in different sporadic adult malignancies with a frequency of 0.32%, and only in one pediatric ACT, arising in the context of Li–Fraumeni syndrome [37]. It is intriguing that the 3 ACTs carrying a p53 mutation with a benign clinical behavior occurred in children in the first 2 years of life, suggesting that the early detection is responsible for a favorable prognosis. The absence of p53 mutation in the majority of cases in our series raises the question whether these ACTs carry germline lesions, so far unknown, in other components of the p53, and/or of the apoptotic pathways [38]. Moreover, direct post-translational modification of the p53 protein at multiple sites might be involved in determining its function and might explain also the positive immunostaining for p53 in non-mutated tumors. As reported in other studies, also in our series, a positive immunostaining for p53 was found in 3 non-mutated tumors, all with a benign clinical course.

In conclusion, pediatric ACTs have a better prognosis compared to adults' tumor, but, when malignant, they may be very aggressive. The results in our series highlight the importance of the complete surgical excision. Despite the general approach improved in the last years, the prognosis for advanced disease is still poor, and the controversial efficacy of chemotherapy warrants the future use of new targeted therapies.

Although no clinical and pathologic features may define malignant and benign forms, the findings in our series could confirm the value of the Wienecke score system in predicting patients' outcome. The p53 mutations are more frequent in malignant tumors and represent a sentinel event of a Li–Fraumeni syndrome.

The prospect to increase the recruitment of patients in the TREP study would favor future knowledge and possible modifications of the guidelines. The ongoing cooperation with European groups, moreover, will shed new light in the comprehension of the biological mechanisms of these rare tumors, defining their more appropriate treatment.

References

[1] Sandrini R, Ribeiro RC, De Lacerda L. Childhood adrenocortical tumors. J Clin Endocrinol Metab 1997;82:2027–31.
[2] Dehner LP, Hill DA. Adrenal cortical neoplasms in children: why so many carcinomas and yet so many survivors? Pediatr Dev Pathol 2009;12:284–91.
[3] Ribeiro RC, Sandrini Neto R, Shell MJ, et al. Adrenocortical carcinoma in children: a study of 40 cases. J Clin Oncol 1990;8:67–74.

[4] Wienecke 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;27:867–81.
[5] 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;98:9330–5.
[6] Rodriguez-Galindo C, Figueiredo BC, Zambetti GP, et al. Biology, clinical characteristics and management of adrenocortical tumors in children. Pediatr Blood Cancer 2005;45:265–73.
[7] Wagner J, Portwine C, Rabin K, et al. High frequency of germline p53 mutations in childhood adrenocortical cancer. J Natl Cancer Inst 1994;86:1707–10.
[8] Custódio G, Komechen H, Figueiredo FRO, et al. Molecular epidemiology of adrenocortical tumors in southern Brazil. Mol Cell Endocrinol 2012;351:44–51.
[9] Ribeiro RC, Figueiredo B. Childhood adrenocortical tumors. Eur J Cancer 2004;40:1117–26.
[10] Kirschner LS. Emerging treatment strategies for adrenocortical carcinoma: a new hope. J Clin Endocrinol Metab 2006;91:14–21.
[11] Williamson SK, Lew D, Miller G, et al. Phase II evaluation of Cisplatin and Etoposide followed by Mitotane at disease progression in patients with locally advanced or metastatic adrenocortical carcinoma. Cancer 2000;881:159–1165.
[12] Berruti A, Terzolo M, Pia A, et al. Mitotane associated with etoposide, doxorubicin and cisplatin in the treatment of advanced adrenocortical carcinoma. Cancer 1998;83:2194–200.
[13] Michalkievicz E, Sandrini R, Figueiredo B, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the international pediatric adrencortical tumor registry. J Clin Oncol 2004;22:838–45.
[14] Ferrari A, Bisogno G, De Salvo GL, et al. Italian Study on Rare Tumours in Paediatric Age (TREP); Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). The challenge of very rare tumours in childhood: the Italian TREP project. Eur J Cancer 2007;43:654–9.
[15] Magro G, Esposito G, Cecchetto G, et al. Pediatric adrenocortical 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;43:31–9.
[16] Varley JM, McGown G, Thorncroft M, et al. Are there low-penetrance TP53 alleles? Evidence from childhood adrenocorticals tumors. Am J Hum Genet 1999;65:995–1006.
[17] Bertorelle R, Esposito G, Del Mistro A, et al. Association of p53 gene and protein alterations with metastases in colorectal cancer. Am J Surg Pathol 1995;19:463–71.
[18] Pastore G, De Salvo GL, Bisogno G, et al. Evaluating access to pediatric cancer care centers of children and adolescents with rare tumors in Italy: the TREP Project. Pediatr Blood Cancer 2009;53:152–5.
[19] Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenal cortical tumors. Am J Surg Pathol 1984;8:163–9.
[20] Orhan D, Kale G, Çağlar M, et al. Histone mRNA in situ hybridization and Ki-67 immunohistochemistry in pediatric adrenocortical tumors. Virchows Arch 2006;448:591–6.
[21] Faria AM, Almeida MQ. Differences in the molecular mechanism of adrenocortical tumorigenesis between children and adults. Mol Cell Endocrinol 2012;351:52–7.
[22] Klein JD, Turner CG, Gray FL, et al. Adrenal cortical tumors in children: factors associated with poor outcome. J Pediatr Surg 2011;46:1201–7.
[23] Dehner LP. Pediatric adrenocortical neoplasms. Am J Surg Pathol 2003;27:1005–7.
[24] Weiss LM, Medeiros LJ, Vickery Jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol 1989;13:202–6.
[25] Bugg MF, Ribeiro RC, Roberson PK, et al. Correlation of pathologic features with clinical outcome in pediatric adrenocortical neoplasia. A study of a Brazilian population. Brazilian Group for Treatment of Childhood Adrenocortical Tumors. Am J Clin Pathol 1994;101:625–9.
[26] Shulick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol 1999;6:719–26.
[27] De León DD, Lange BJ, Walterhouse D, et al. Long-term (15 years) outcome in an infant with metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 2002;87:4452–6.
[28] 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.
[29] Tucci Jr A, Martins ACP, Haylton JS, et al. The impact of tumor stage on prognosis in children with adrenocortical carcinoma. J Urol 2005;174:2338–42.
[30] Hanna AM, Tuan HP, Askergard-Giesmann JR, et al. Outcome of adrenocortical tumors in children. J Pediatr Surg 2008;43:843–8.
[31] Rescorla FJ. Malignant adrenal tumors. Semin Pediatr Surg 2006;15:48–56.
[32] Allolio B, Fassnacht M. Adrenocortical carcinoma: clinical update. J Endocrinol Metab 2006;91:2027–37.
[33] Zancanella P, Pianovski MAD, Oliveira B, et al. Mitotane associated with cisplatin, etoposide and doxorubicin in advanced childhood adrenocortical carcinoma. J Pediatr Hematol Oncol 2006;28:513–24.
[34] Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007;156:2372–80.
[35] Sperone P, Ferrero A, Daffara F, et al. Gemcitabine plus metronomic 5-fluorouracil or capecitabine as a second-/third-line chemotherapy in advanced adrenocortical carcinoma: a multicenter phase II study. Endocr Relat Cancer 2010;17:445–53.
[36] Wasserman JD, Zambetti GP, Malkin D. Towards an understanding of the role of p53 in adrenocortical carcinogenesis. Mol Cell Endocrinol 2012;351:101–10.
[37] Fiszer-Maliszewska L, Kazanowska B, Padzik J. p53 tetramerization domain mutations: germline R342X and R342P, and somatic R337G identified in pediatric patients with Li–Fraumeni syndrome and a child with adrenocortical carcinoma. Fam Cancer 2009;8:541–6.
[38] Herbet M, Feige JJ, Thomasa M. Insights into the role of genetic alterations in adrenocortical tumorigenesis. Mol Cell Endocrinol 2009;300:169–74.