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SUPPLEMENT ARTICLE

Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations

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Abstract

Adrenocortical tumours (ACTs) are rare during childhood. A complete surgical resection provides the best chance of cure, but the role and efficacy of the adjuvant therapy are still controversial. Various histologic criteria of malignancy for ACTs adopted in children do not facilitate comparative studies and are not completely shared. Therefore, a sharp demarcation between benign and malignant lesions has not been recog-

Abbreviations: ACA, adrenocortical adenoma; ACC, adrenocortical carcinoma; ACT, adrenocortical tumours; CED, cisplatin, etoposide and doxorubicin; COG, Children's Oncology Group; EFS, event-free survival; EXPeRT, European Cooperative Study Group for Paediatric Rare Tumours; FRACTURE, Groupe Français Des Tumeurs Rares de l'Enfant; GPOH-MET, German Society for Pediatric Oncology and Hematology Malignant Endocrine Tumors Study; MDT, multidisciplinary team; NN1/NN2, vincristine, ifosfamide and doxorubicin/carboplatin and etoposide; OS, overall survival; PARTNER, Paediatric Rare Tumours Network - European Registry; PET, positron emission tomography; RPLND, retroperitoneal lymph node dissection; RT, radiotherapy; TREP, Tumouri Rari in Età Pediatrica; VRT, very rare tumour.

nised, making it difficult to identify who potentially needs perioperative therapy. This manuscript presents the internationally harmonised recommendations for the diagnosis and treatment of ACTs in children and adolescents, established by the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) group within the EU-funded project PARTNER (Paediatric Rare Tumours Network - European Registry).

KEYWORDS
adolescents, adrenocortical tumours, children, diagnosis, EXPeRT, guidelines, PARTNER, recommendations, therapy

1 | INTRODUCTION

Adrenocortical tumours (ACTs) account for approximately 0.2% of all childhood cancers, and the incidence is approximately 0.2 new cases per 1 million children/year.[1] They are frequently associated with germline pathogenic mutations in the tumour-suppressor gene *TP53*, in some cases predisposing to Li–Fraumeni syndrome.[2] The male/female ratio is 1/2 and the age incidence curve during childhood is characterised by two peaks, the first under 3 years and the second during adolescence.[1,3–5] The incidence may vary remarkably worldwide.[6,7] The higher incidence observed in the Brazilian population has been linked to a specific pathogenic variant of *TP53* gene (p.R337H), which is associated with adrenocortical carcinoma (ACC) limited to the paediatric age.[2,8,9]

ACTs comprise benign adenoma (ACA) and highly malignant carcinoma (ACC). Only about 20% of paediatric ACTs are classified as ACA and are associated with excellent prognosis. However, the distinction between adenoma and carcinoma is difficult both at the clinical and histopathologic level. The histologic Wieneke Index has been reported to have a stronger prognostic predictive value compared to other histologic prognostic scores used in adults.[1,6,7,10,11] Nevertheless, the prognostic stratification of paediatric ACTs is still a challenge due to their rarity, variable presentation, and difficulties in histologic definition. The 5-year survival for children with ACTs depends on stage and histology, varying from more than 80% for patients with small localised, completely resected ACT to less than 20% for patients with metastatic ACC (10–33% of all cases).[1,12,13]

Various clinical features have been reported to be associated with poor outcome; however, they vary between studies. Age >4 years, tumour size (>5 cm) and volume (>200 cm^3), presence of a Cushing syndrome at diagnosis, incomplete resection and higher stage have more commonly been reported as adverse prognostic factors.[14] Moreover, metastatic spread is universally considered as a highly unfavourable prognostic factor due to the fact that ACC is scarcely responsive to chemotherapy and/or radiotherapy (RT). In addition, it has been almost universally observed that children have a better outcome than adolescents. This may be explained by the observation that distant metastases and nonsecreting tumours may occur more frequently in adolescents than in children.[15] The European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) group tried to define 'high risk' tumours based on the presence of one of the following features: age at diagnosis, tumour volume more than 200 cm^3, presence of Cushing syndrome, initial biopsy (open or Tru-cut), surgical excision with microscopic residuals or spillage (R1) or macroscopic residuals (R2), regional lymph nodes involvement, histologic vascular invasion, and distant metastases at diagnosis.[16,17] Difficulties in stratifying patients prevent the identification of patients who may benefit from a systemic treatment after resection. This may be particularly frustrating in patients classified as Children's Oncology Group (COG) Stage II or III after surgery in which a benign or malignant course is almost unpredictable.

The aim of this study is to establish internationally recognised recommendations for the diagnosis and treatment of children (0–14 years) and adolescents (15–19 years) with ACT according to the Consensus Conference Standard Operating Procedure methodology with definition of levels of evidence (Levels I–V) and grades of recommendation (Grades A–E)[18,19] (Supporting Material S1).

2 | INITIAL ASSESSMENT

The initial assessment of paediatric ACT should be aimed first to exclude other tumours (especially neuroblastoma in young children, and pheochromocytoma in adolescents) and to avoid any kind of unnecessary biopsy. Clinical diagnosis can be established based on typical tumour site and hormone profile (see Table 1 for details): most tumours are functional and secrete excessive adrenocortical hormones leading to clinical symptoms (virilisation, feminisation or Cushing syndrome), even if symptoms sometimes could be weak. In rare cases, diagnosis could be challenging in the absence of hormonal secretion: non-functional tumours (<10%) tend to occur in older children and adolescents. Initial biopsy may be associated with a poorer outcome.[20] Accordingly, in the series presented by Picard et al.,[16] among three Stage III patients in which percutaneous biopsy was the only cause of tumour rupture, only one patient was disease-free after a follow-up of 25 months, although still on mitotane therapy, while other two patients died of disease. Moreover, it is traditionally recognised that preoperative and postoperative spillage may worsen the prognosis,[21,22] although in adults initial biopsy does not affect survival.[23] Therefore, in paediatric ACTs an initial tumour biopsy should be avoided whenever

TABLE 1 Recommended clinical investigations in paediatric adrenocortical tumours

Assessment	Eligible patients	Details	Comment
US (pelvic and abdominal)	All patients		(Level IV; Grade A)
Abdominal CT	All patients		(Level IV; Grade A)
Abdominal magnetic resonance imaging (MRI)/whole-body MRI	Family history characterised by early onset of tumours		(Level IV; Grade B)/(Level V; Grade C)
Chest CT	When the clinical and/or radiological suspicion of a malignant ACC is high		(Level IV; Grade A)
Positron emission tomography (PET) scan or PET MRI	When the clinical and/or radiological suspicion of a malignant ACC is high and individually according to present symptoms and signs		(Level IV; Grade B)
Bone CT	When the clinical suspicion of bone metastasis is present	In alternative of PET scan/MRI	(Level IV; Grade B)
Brain MRI	When cerebral metastases are clinically suspected or in cases with suspicious/proven Li–Fraumeni syndrome		(Level IV; Grade B)
Genetic counselling	All patients	Could be delayed after pathologic analysis if no high clinical suspicion	(Level IV; Grade A)
Cardiac ultrasound	In case of vascular and diaphragmatic tumour involvement		(Level IV; Grade B)
Hormonal assessment	All patients	Glucocorticoid excess (dexamethasone suppression test, free 24-hours cortisoluria, basal adrenocorticotropin hormone, salivary cortisol dosage) Sex steroids and steroid precursors excess (dehydroepiandrosterone sulfate, 17OH-progesterone, androstenedione, testosterone, 17-beta-estradiol, 11-deoxycortisol, estrone and estradiol) Mineralocorticoid excess (aldosterone, kalemia, aldosterone/renin ratio) Urinary catecholamines and metanephrines levels At diagnosis, and a regular monitoring of hormonal levels is recommended during the follow-up	(Level IV; Grade A)

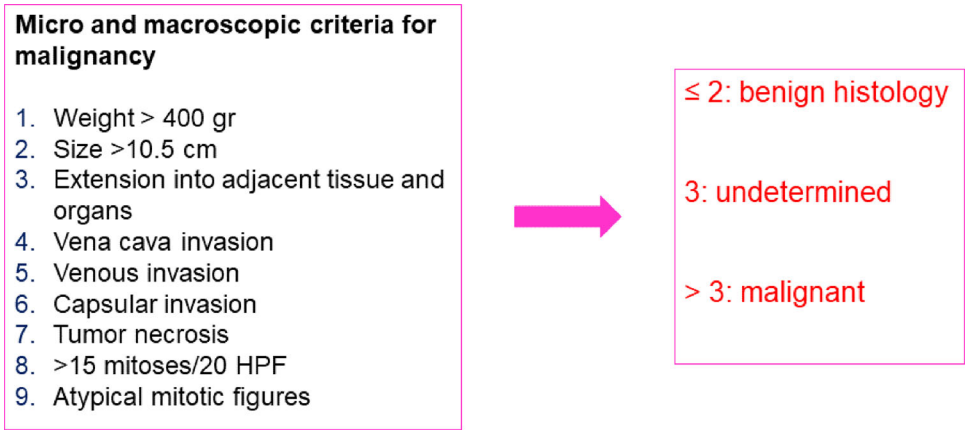

FIGURE 1 Wieneke Index stratification

possible out of caution (both percutaneous and, by extension, open Tru-cut biopsies), especially when the tumour is associated with hormonal secretion. It should be limited only to children with nonsecreting tumours and metastatic disease and unresectable primary tumour (Level IV; Grade B).

Final histopathological evaluation is mandatory after tumour resection for confirmation of diagnosis and histological stratification of ACT. Histology should especially distinguish ACT from other adrenal neoplasms (Level IV; Grade A). A revision of the histological slides from a pathologist with proven experience in paediatric tumours and especially in ACTs is highly recommended (Level IV; Grade B). It is strongly recommended to store a frozen tumour sample and a blood sample on EDTA in a tumour bank for possible subsequent biological studies, including genetics (Level III; Grade A). Differentiating benign from malignant ACT is often difficult, and adult scores (Weiss, Hough, Van Slooten) have been demonstrated to be poorly predictive especially in younger children.[3,24-27] Dehner and Hill[26,27] hypothesised that paediatric ACTs may arise from a cell resembling a phenotype of the foetal rather than the adult cortex. This may explain the mostly benign course of these neoplasms, despite the presence of impressively atypical microscopic features interpreted as a manifestation of biological regression rather than progression to a malignancy. The Wieneke Index (first described in 2003)[6] has been reported to have a prognostic value that is more reliable compared to other histologic prognostic scores used in adults.[1,7,11,12] Wieneke Index classifies ACTs in three prognostic groups (benign, malignant, and of undetermined malignant potential) on the basis of the number of present pathologic criteria (Figure 1). Although it is widely recognised, the paucity of cases a paediatric pathologist may encounter and the number of criteria to be considered may make the Wieneke pathological stratification poorly defined and observer-dependent. More recently, Picard and colleagues described a five-item microscopic score[15]: ACTs with two or less features should be considered to show a 'favourable histology', and those with more than two features an 'unfavourable histology' (Figure 2). This five-item score could be of interest to stratify tumours with favourable versus unfavourable histology, especially for localised ACTs, with the possibility to limit the use of systemic treatment to the former group, in the light of the lower risk of disease progression among tumours with favourable histology. The absence of well-defined pathological prognostic system in the paediatric age may hinder therapeutic stratification, especially for patients with large tumour volume or with incomplete resection (R1 [incomplete tumour resection] or spillage), as R1 or R2 status constitutes the strongest unfavourable risk factor. Though not validated, the use of a paediatric prognostic score (Wieneke or five-item score) to enable stratification of these patients should be introduced also in consideration of the fact that systemic therapy shows important limitations in terms of efficacy and toxicity (Level IV; Grade B). On this basis, the importance of a multidisciplinary team (MDT) discussion to better define the biology of the disease and the central review of the histology are of crucial importance (Level IV; Grade A).

The most widely used staging system in the paediatric age have been proposed by Sandrini et al.,[28] and has been later modified.[24] This postsurgical staging system relies on the possibility and the quality of resection, tumour size, regional nodal involvement, and presence of metastatic disease. Thus, it is only in part transferrable to a neoadjuvant strategy. The COG system (Table 2) has been adopted by the French very rare tumour (VRT) Groupe Français Des Tumeurs Rares de l'Enfant (FRACTURE) Group and, with some modifications, by the Italian TREP (Tumouri Rari in Età Pediatrica) project. It is recommended to use the COG system to allow national and international referral, comparison of data, and a proper paediatric stratification (Level III; Grade C).

3 | THERAPEUTIC RECOMMENDATIONS

3.1 | Surgery

Different series, although with a limited number of patients, have shown that complete tumour resection is a major prognostic factor (Level III; Grade A). Tumour rupture, pre- or intraoperatively, has been associated with a worse prognosis and almost fatal outcome. Initial tumour biopsy should be avoided whenever possible out of caution,

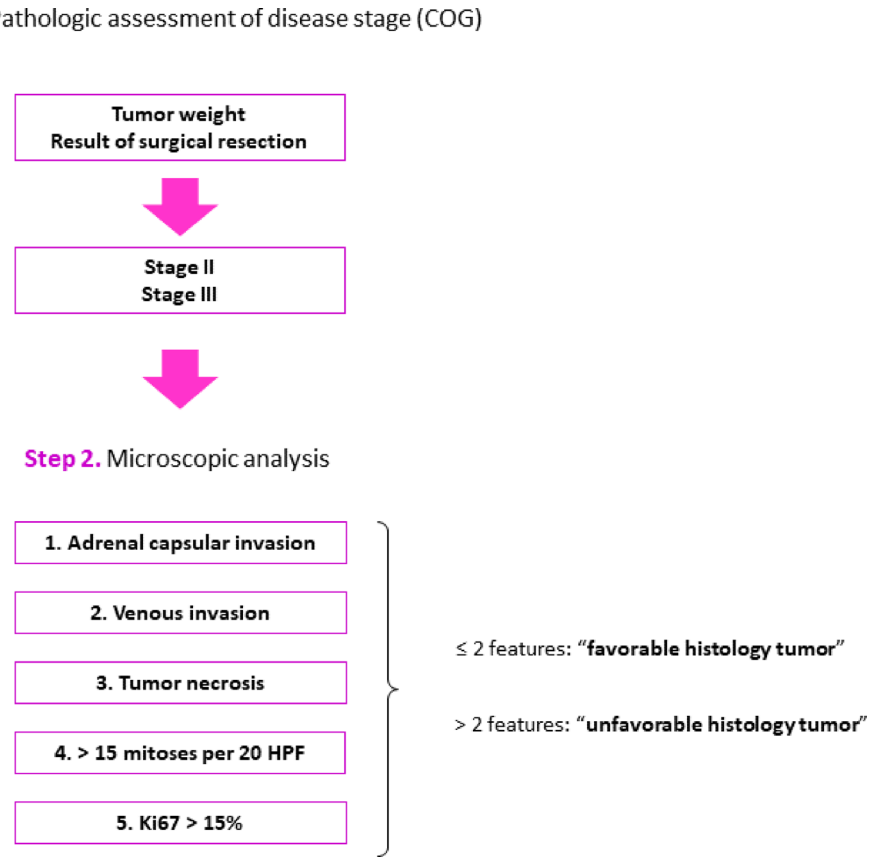

FIGURE 2 Five-item microscopic score stratification

TABLE 2 Children's Oncology Group (COG) staging system for adrenocortical tumours

Stage	Definition
I	R0 (complete histological resection) and small localised tumours (<100 g or <200 cm^3), with normalisation of hormone levels after surgery
II	R0 and large localised tumours (≥100 g or ≥200 cm^3), with normalisation of hormone levels after surgery
III	Unresectable tumours or gross/macroscopic residual disease; tumour spillage (pre- or intraoperatively); failure to normalise hormone levels after exclusive surgery; retroperitoneal lymph nodes involvement
IV	Distant metastases

although in adults it seems to not affect survival.[23] The incidence of intraoperative tumour ruptures has been evaluated in paediatric series at 20% at the time of the initial excision, and more than 40% in case of surgery on a locoregional recurrence.[13,28] Upfront en bloc resection is the treatment of choice in all cases in which a complete removal of the primary tumour is deemed feasible, considering that surgery alone may, in most cases, cure the patient (Level III; Grade A). All enlarged lymph nodes detected at radiology or intraoperatively should be removed (Level III; Grade A), or a systematic biopsy of the regional nodes should be performed if they are not found suspicious pre- or intraoperatively (Level IV; Grade B). On the other hand, a systematic complete retroperitoneal lymph node dissection (RPLND) has not been demonstrated effective on event-free survival (EFS) and overall survival (OS). The only protocol that investigated the systematic role of RPLND (ARAR0332 protocol from the COG) in localised stage II ACTs did not find any outcome improvement[29] but the median total of removed lymph nodes was limited (4) (Level III; Grade E).

The preferred surgical approach should be an open approach (Level IV; Grade B). Minimal invasive surgery is strongly discouraged when malignancy is suspected (Level III; Grade E). Therefore, minimally invasive techniques in the surgical management of ACT are not recommended, even when they are feasible,[30–34] and could only be considered in early childhood, but their use should be limited to (a) small-volume localised tumours likely to be benign without invasion of surrounding structures and nodal involvement at preoperative imaging; and (b) tertiary care centres and surgeons experienced in oncologic and adrenal surgery (Level IV; Grade D). In particular, tumours with a volume exceeding 200 cm^3 and/or suspicious regional nodal involvement

and/or signs of local invasion should always be resected using an open laparotomy, with no exceptions (Level IV; Grade B).

Local invasion, involving surrounding structures (kidney, vena cava, periadrenal fat) does not preclude the possibility to obtain a complete resection but sometimes requires wide en bloc resection; in particular, a nephrectomy is accepted when the tumour cannot be separated from the kidney with tumour-free margins (Level IV; Grade B). The presence of a thrombosis of the vena cava does not necessarily categorise the tumour as inoperable although it complicates the surgical procedure, because of the risk of tumour embolism during the manipulation of the vena cava and the increased risk of intraoperative tumour rupture. A surgical approach under support of an extracorporeal circulation must be considered and is justified by the prognostic importance of the quality of resection[1,35] (Level IV; Grade B).

For metastatic tumours, an aggressive approach combining complete surgical resection with neoadjuvant and adjuvant chemotherapy plus mitotane, is recommended and should be aimed to the clearance of the primary tumour and metastatic sites as much as possible. Surgery of metastatic sites should however be reserved for patients who are in good clinical conditions and when a reasonable clearance of metastatic sites is deemed feasible (Level IV; Grade C). Metastases may be either approached at the time of resection of the primary tumour or more frequently delayed to a second operation (Level IV; Grade C). Timing of surgery of the metastatic site should be discussed case by case and the use of adjuvant or neoadjuvant chemotherapy decided within MDT (Level IV; Grade B).

3.2 | Chemotherapy

Due to the lack of prospective clinical randomised trials, there is no evidence-based optimal chemotherapy established for children with ACC to date (Level III; Grade C). The COG investigated the use of standard chemotherapy (cisplatin–etoposide–doxorubicin [CED]) in the above-mentioned ARAR0332 protocol.[29] One of the aims of this protocol was to evaluate the impact of mitotane and cisplatin-based chemotherapy for unresectable and metastatic disease.[4,13] The combination of mitotane and chemotherapy resulted in the significant toxicity: up to one-third of patients with advanced disease could not complete the scheduled treatment. Other European groups (TREP, FRACTURE) have used the same drugs in slightly different regimens but with similar results.[1,16] The German GPOH-MET 97 (German Society for Pediatric Oncology and Hematology Malignant Endocrine Tumors Study) trial used two different alternating courses combined with mitotane: one with vincristine, ifosfamide and doxorubicin (NN1), and the second with carboplatin and etoposide (NN2). Compared to historic controls, outcome results in terms of EFS and OS for Stage II (43.9% and 70.0%, respectively), Stage III (25% and 75%, respectively), Stage IV (36% and 51%, respectively) were better, without severe adverse events, but the possibility of existing confounding factors was underlined.[20,36] Therefore, the first-line recommended regimen is CED or NN1/NN2 (vincristine, ifosfamide and doxorubicin/carboplatin and etoposide) according to the GPOH strategy (Supporting Material S2) (Level IV; Grade B).

As a consensus, neoadjuvant chemotherapy including mitotane should be considered in patients with primarily inoperable and/or metastatic tumours[37–39] (Level IV; Grade A). In some cases described, systemic therapy is effective with regard to reduction of tumour volume according to RECIST criteria[16,28,40] (Table 3). However, as ACC could be refractory to medical therapy, surgical procedures should not be delayed when tumour resection is feasible (Level III; Grade A). Adjuvant therapy should be considered in advanced stage ACC or in case of incomplete tumour resection (Level IV; Grade B).

Several second-line or salvage therapies have been used but without strong measurable effects on outcome and can be considered on an individual basis, preferably supplemented with genetic analysis of molecular targets[41–43] (Level IV; Grade C). In adult advanced ACC, some interesting schedules including streptozocin and gemcitabine–capecitabine in combination with mitotane have been reported[44] (Level IV; Grade C).

Mitotane (1,1-dichloro-2-(0-chlorophynyl)-2(p-chlorophenyl)-ethane, or O'p'-DDD) is a synthetic insecticide derivative that leads to necrosis of the cells of the adrenal cortex and inhibits the synthesis of steroid hormones. It constitutes the only specific and targeted therapy in ACCs available to date. Objective tumour responses have been observed in patients with advanced disease in approximately 20–30%, using mitotane alone,[45] and hormonal responses in 75% of cases. The pharmacokinetics of mitotane and the ability to maintain 'effective' blood levels (>14 mg/L) for an extended period appear to have a direct impact on tumour response,[46,47] also in the paediatric setting, as demonstrated by the GPOH study group. A study by Terzolo et al. allowed retrospective analysis of 177 adult patients with ACC Stages I and II who benefited from the initial complete tumour resection and in which an adjuvant treatment with mitotane improved EFS (50% vs. approximately 15%).[48] In the French paediatric retrospective series, the response rate to mitotane was 30% in 20 treated patients and increased to 50% in patients with mitotane blood levels >14 mg/L.[12] The data from the German study group on serum level-guided mitotane therapy are encouraging as they demonstrated a significant survival benefit. Therapeutic plasma level of mitotane ranging between 14 and 20 μg/ml is considered as target, but in the German group plasma levels between 20 and 30 mg/L are recommended[20] (Level III; Grade B). Some authors[49] considered the use of mitotane as adjuvant therapy controversial in children with ACC Stages I and II, but indicated in Stages III and IV in association with CED. Although limited data about the use of mitotane in children exist, it should be always considered in the first-line treatment, alone or in association with chemotherapy. This treatment remains complicated to use and must be administered in collaboration with an experienced team (Level IV; Grade A). Mitotane should be started with the first cycle of chemotherapy and continued for 1–2 years depending on tolerance and compliance; in the German GPOH strategy, this treatment is delivered for 3 years for Stage IV. The proposed duration of 2 years best covers the maximum period of relapse risk (Level IV; Grade C). However, it should be noted

TABLE 3 RECIST (response evaluation criteria in solid tumours) criteria

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis <10 mm
Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm
Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

that only periods with effective therapeutic plasma levels should be considered as effective treatment time. Management for mitotane administration is detailed in Supporting Material S3.

3.3 | Radiotherapy

The role of external RT is uncertain, as ACCs are radio-resistant neoplasms. In adult's experience, locoregional RT, including brachytherapy in case of liver metastases may improve EFS but not OS.[50] Due to its potential mutagenic effect, RT should be avoided as much as possible in patients harbouring a germline *TP53* variant or those with a diagnosis or clinical suspicion of Li–Fraumeni syndrome (Level IV; Grade B). Limited data exist on efficacy of RT and it has been mostly used only as salvage therapy.[20]

RT could be discussed for some refractory Stage III ACC (R2, unresectable tumours), Stage IV or relapsed tumours. However, final decision should be taken case by case after MDT discussion (Level IV; Grade C). No data exist on the optimal dose and volume of RT. The proposal is 45 Gy on the tumour bed and the para-aortic regional nodes plus boost of 5–15 Gy on the tumour bed depending on the margins of resection/the presence of residual tumour[51] (Level IV; Grade C).

4 | OVERALL STRATEGY PROPOSED BY THE EXPeRT MEMBERS (SUPPORTING MATERIAL S4)

4.1 | Specific considerations

MDT referral is mandatory at diagnosis and during therapy (Level IV; Grade A). All children with suspected ACT should be evaluated by a paediatric endocrinologist at onset in order to plan an extended preoperative hormonal assessment and to identify potential autonomous excess of sex hormones, glucocorticoids, mineralocorticoids and adrenocortical steroid hormone precursors. In addition, in all patients with high initial levels of adrenal hormones, a regular monitoring of hormonal levels is recommended during the follow-up (Level IV; Grade A).

The anaesthetic management of patients with hypercortisolism must be carried out in collaboration with the paediatric endocrinology team, including postsurgical hydrocortisone substitution at stress levels. It is recommended to start a hormonal replacement therapy postoperatively in all patients with hypercortisolism: hydrocortisone 50–100 mg/m^2/day intravenously for the first days (following the international recommendations in case of major surgical stress for patients with adrenal insufficiency), to be de-escalated orally, relating to the grade of suppression of the contralateral adrenal gland.[52]

Patients and families should be proposed the enrolment in a prospective trial if available and data collection in national or international databases (Level IV; Grade B).

Genetic counselling should be offered to all patients affected by ACT and to their families, in consideration of the rarity of these conditions and the possibility of underlying genetic conditions (germline *TP53* mutations, Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome and other overgrowth syndromes) (Level IV; Grade A).

In low health expenditure average rate (LHEAR) countries, the initial assessment and monitoring of the serum levels of hormones released by ACC is easily accessible. In some cases, the lack of a paediatric oncology surgical expert may limit the management, but it could be overcome through referral to local adult surgeons (for older children) or to foreign paediatric surgical centres. The main limitations could be the use of mitotane and the monitoring of its plasma levels.

4.2 | Localised ACT (Stages I–II resected, Stage III)

The treatment of choice is upfront surgery in case of resectable lesions (Figure 3). In the rare occurrence of an unresectable localised tumour, neoadjuvant chemotherapy and mitotane to reduce volume and invasion may be attempted after MDT discussion (Level IV; Grade B).

In case of Stage III caused by isolated tumour rupture in a child older than 4 years or in case of nonnormalisation of hormonal markers, six courses of adjuvant chemotherapy supplemented by mitotane are proposed (Level IV; Grade C). Young children (<4 years old) with an isolated capsular rupture as the only risk factor must be discussed in MDT in order to validate the need of an adjuvant treatment (Level IV; Grade C).

4.3 | Unresectable (Stage III) and metastatic (Stage IV) ACC

The feasibility of a surgery of the primary tumour and metastatic sites can be discussed at diagnosis but will be impossible in most cases (Figure 4). Therefore, an upfront multiagent chemotherapy plus mitotane is recommended, with regular monitoring according to

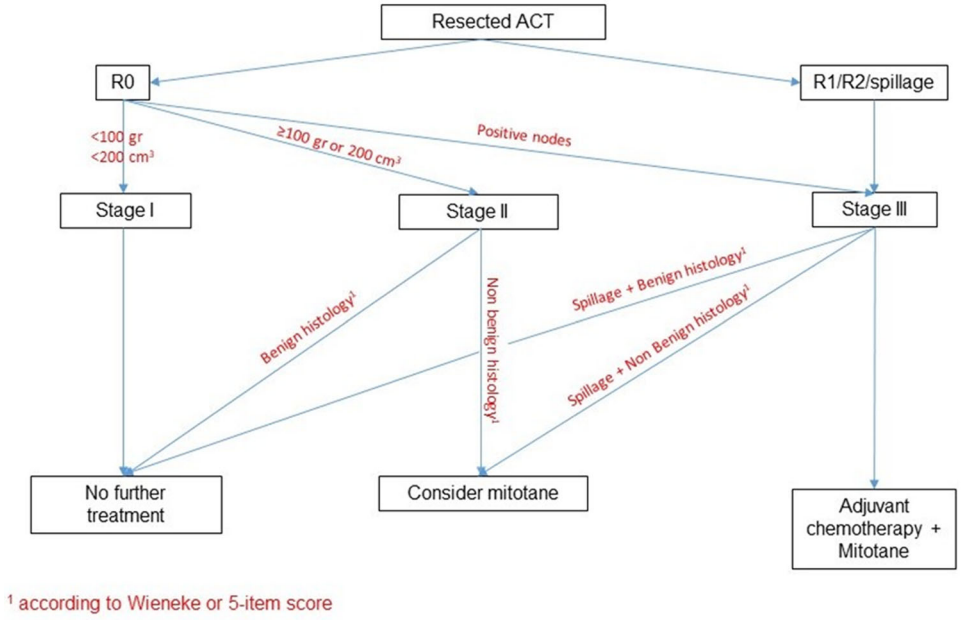

FIGURE 3 Therapy summary for localised adrenocortical tumours in children and adolescents according to Children's Oncology Group (COG) stages

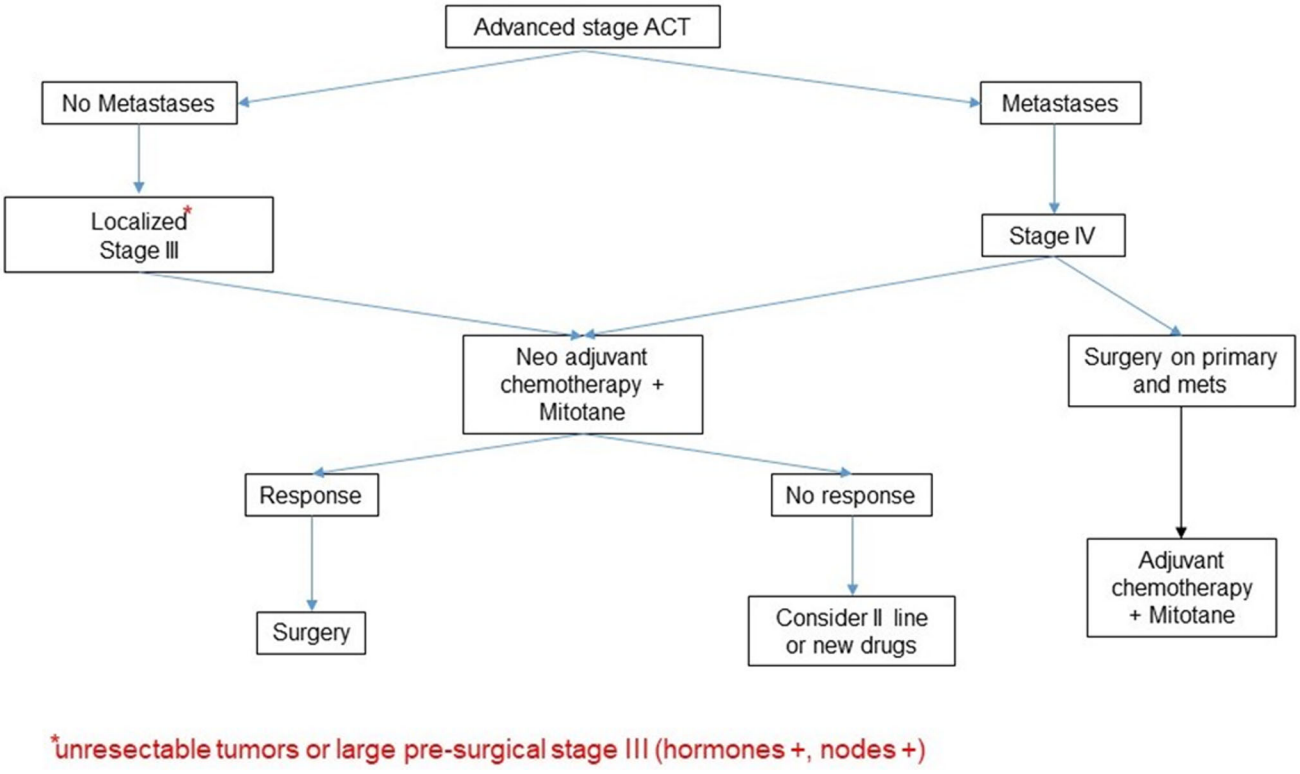

FIGURE 4 Therapy summary for unresectable adrenocortical tumours in children and adolescents according to Children's Oncology Group (COG) stages

RECIST criteria and delayed tumour surgery. Considering the scarce response observed in these patients, especially in the presence of distant metastasis, enrolment in a prospective trial testing new regimens or targeted therapies could also be taken into consideration (Level IV; Grade C); another option is to start with perioperative conventional chemotherapy and mitotane (Level IV; Grade C). The goal of pharmacotherapy is to obtain a significant tumour reduction to enable a complete tumour excision and propose local control to metastatic sites. Two to four cycles of neoadjuvant chemotherapy with CED or NN1/NN2, with 21-day intervals will therefore be carried out, followed by evaluation report concerning the primary tumour and metastatic sites. The surgical intervention depends on the imaging data and consists of the complete excision of the primary tumour if possible, and delayed excision of different metastatic sites whenever possible. In case of tumour response to neoadjuvant chemotherapy, the patient should receive four to six cycles of adjuvant chemotherapy (CED, NN1/NN2), for a total of six to eight cycles.

4.4 | Poorly responding advanced tumours

The experience is very limited. MTD should be re-setup to discuss mutilating large resections (Level IV; Grade C). A different regimen could be tested, including second-line chemotherapy used in adult population.[44] Alternatively, enrolment in a prospective trial testing new regimens or target therapies should be taken into consideration[41–43] (Level V; Grade B).

4.5 | Relapsed ACC

Survival is very poor for these patients. No specific second-line treatment is strongly supported by literature data.[20,44] In case of local relapses, repeated surgeries and reuse of mitotane may prolong survival, but the use of second-line chemotherapy depending on the previous drugs used or enrolment in prospective trials is also advised (Level V; Grade B).

5 | RECOMMENDATIONS FOR FOLLOW-UP

Patients with unfavourable clinical and/or histological risk factors (advanced stages, >4 years of age and/or unfavourable histology) should undergo a clinical, hormonal and imaging evaluation every 3 months in years 1 and 2. Clinical, imaging and hormonal studies may be delayed every 4 months in year 3, every 6 months in years 4 and yearly in year 5 (Level IV; Grade B).

Patients without unfavourable clinical and histological risk factors (low stages, favourable pathology) should undergo a clinical, imaging and hormonal evaluation every 4 months in years 1 and 2, and every 6 months in years 3, 4 and 5 (Level IV; Grade B).

For patients harbouring a germline *TP53* variant or with a diagnosis of Li–Fraumeni syndrome, long-term follow-up for other tumours is highly recommended, as proposed by Frebourg et al.[53] and Kratz et al.[54] (Level IV; Grade A).

5.1 | Some open questions remained

Optimal clinical, radiographic and endocrinological assessments for clinical diagnosis prior to surgical therapy, aiming to avoid tumour biopsy and tumour spillage; best prognostic stratification of patients according to the pathology and/or clinical features; role of adjuvant/neoadjuvant chemotherapy in case of isolated tumour rupture; best chemotherapy regimen: CED or NN1/NN2; best indications, dosage, length and monitoring of mitotane therapy; treatment of poor responding, metastatic and relapsed ACC and efficacy of new drugs for ACC.

All these questions underscore the constant focus on establishing closer international ties to overcome the disadvantage historically borne by children with VRT due to the rarity of their disease and the consequent shortage of clinical and biological information. It strongly suggests international alliances to increase ACC cases in the studies, and prospective studies and randomised clinical trials.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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