Consensus Recommendations for

Adrenocortical tumors in children and adolescents

Final version (V. 8)

The Partner Project:

PARTN-ER aims to create a European Registry dedicated to children and adolescents with very rare tumors (VRT) linking existing national registries and to provide a registry for those countries not already having a registry for VRT in place. The European Registry will be an essential part of the activity of the VRT subnetwork part of the ERN PaedCan. The possibility to link the registry with a virtual consultation system and the elaboration of diagnostic/treatment recommendations will create a platform that can be easily accessed by EU Health care providers. The increasing expertise in VRT based on the data collected in the European registry will increase the capacity to provide international consultation and define standard of treatment recommendations. This will ultimately result in improved patients' care and reduce currently existing inequalities in cancer outcome across EU member states.

Conflicts of interest: The authors have no conflicts of interest to disclose.

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Funding source: This publication is part of the project PARTNER (ERN-PAEDCAN Partner Paediatric Rare Tumours Network – European Registry) which has received funding from the European Union's Health Programme (2014-2020) (3rd Health Programme Call: HP-PJ-06-2016: Rare diseases - support for New Registries. CHAFEA Grant Nr: 777336)

Co-funded by
the Health Programme
of the European Union

Summary:

Pediatric very rare tumors (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical of pediatric age, while other more commonly arise during adulthood and only rarely develop in children. Using the definition *any solid malignancy or borderline tumor characterised by an annual incidence < 2/million children <18 years old and/or not already considered in other clinical trials* the European Cooperative Study group for Pediatric Rare Tumors (*EXPeRT*) has initially identified a number of pediatric VRT[1]. Due to the low number of patients, it is very difficult – or even impossible - to conduct clinical trials on them, and this makes it hard to arrive to evidence-based treatment guidelines. As a consequence, the treatment of patient with VRT is often individualized.

Background:

Adrenocortical tumors (ACTs) are rare in childhood, representing 0.2% of all pediatric tumors with an incidence of 0.2 new cases per 1 million children per year. The distinction between large benign adenoma (ACA) and adrenocortical carcinoma (ACC) may be difficult, and the optimal treatment tricky. A complete surgical resection provides the best chance of cure, and in case of ACC is a prerequisite of cure. However, it is not always possible. The role and the efficacy of the adjuvant medical therapy are still controversial. The various staging systems for ACTs adopted in the pediatric population do not facilitate comparative studies, and the prognostic factors adopted for adults often lack sensitivity and specificity. Even histologic criteria of malignancy are not completely shared by pathologists, inter-individual concordance is limited, and therefore, a sharp demarcation between benign and malignant lesions, even after surgery, has not yet been identified, making it difficult to better delineate patients who potentially need perioperative therapy.

Objective: To establish internationally recognized recommendations for the diagnosis and treatment of children and adolescents with ACT (WP6 – "Standard of care recommendations for children with VRT"). This constitutes one of the deliverables of PARTN-ER project (ERN-PAEDCAN Partner Paediatric Rare Tumours Network – European Registry), Co-funded by the Health Programme of the EU.

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1. METHODOLOGY

According to Consensus conference Standard Operating Procedure methodology the grade of evidence can be classified from Grade I to V[2].

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System [1])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Table I. Grading scale.

Using the definition of any solid malignancy or borderline tumor characterized by an annual incidence < 2/million children <18 years old, the European Cooperative Study group for Pediatric Rare Tumors (*EXPeRT*) has identified several pediatric very rare tumors (VRT) and rare sarcomas. The ExPO-r-Net was a 3-year project that endeavoured to build a European Reference Network (ERN) for Paediatric Oncology and reduce the current inequalities in childhood cancer survival and healthcare capabilities in different EU Member States by launching guidelines for VRT graded according to the ESMO scale, based on the evidence collected from published series, case reports (grade III) and personal expertise. To develop consensual recommendations, *EXPeRT* members designed the following procedure: - First, identified the tumor of interest on the basis of its relevance, then designated two coordinators for each VRT on the basis of their expertise (data analysis, publications, and personal experience). Coordinators have to search through the medical literature and select all relevant papers, propose a series of recommendations in the form of a first draft, identify the main diagnostic and therapeutic problems for the designated VRT. The first draft circulate along with the relevant publications to all member of *EXPeRT*, and the subsequent edited drafts are validated with external experts identified by the coordinators on the basis of their recognized experience. *EXPeRT* members recognized that due to the rarity of this tumor, no evidence of grade I or II levels of evidence exists in ACTs (i.e. results from at least one randomized controlled trial). Only few prospective or comparative cohort studies have been published on ACTs

(level III of evidence, Table I). Therefore, recommendations for this VRT must mainly be developed based on evidence collected from published retrospective series (level IV), case reports (level V) and personal expertise (level V)[3]. The "strength" of recommendations will be categorized by additional grading (Grade A to E).

NB: These recommendations may change over time according to new data available. Local clinicians remain responsible for the care of the patient. The *EXPeRT*/PARTN-ER members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with *EXPeRT* members of these groups via the expert website: ***https://vrt.cineca.it***. The final document including recommendations will be available on PARTN-ER website.

2. BACKGROUND

Pediatric ACTs are rare but potentially aggressive endocrine malignancies. They are frequently associated with Li-Fraumeni syndrome, a familial cancer predisposition disorder caused by germline pathogenic variant in the tumor suppressor gene *TP53*. ACTs account for approximately 0.2% of all childhood cancer cases, with the incidence approximately 0.2 new cases per 1 million children per year[4]. The incidence may vary remarkably worldwide and is particularly high in southern Brazil[5,6]. The male/female ratio is 1/2 and the age incidence curve during childhood is characterized by two peaks, the first under 3 years and the second during adolescence[4–6]. The higher incidence observed in the Brazilian population has been linked to a specific pathogenic variant of *TP53* gene (unique founder *TP53* pathogenic variant Arg337His) which leads to the onset of ACC limited to the pediatric age[5,7,8]. The frequency of this pathogenic variant is about 0.3% in the general population of Paraná[5]. Also, onsets of choroid plexus carcinoma, osteosarcoma, breast cancer, and stomach cancer have been reported in Arg337His carriers[9]. In about 40% of these families, Li–Fraumeni-like phenotype has been observed (breast and brain tumors being the most frequent cancers).

ACTs comprise benign adenoma (ACA) and highly malignant adrenocortical carcinoma (ACC), of which the pathogenesis is not completely understood. Only about 20% of pediatric 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 Wienecke index has been reported to show a stronger prognostic predictive value compared to other histologic prognostic scores used in adults[4,5,9,10]. Nevertheless, the prognostic stratification of pediatric ACTs is still challenging due to their rarity, variable presentation, and difficulty in histologic definition. Overall, the 5-year survival for children with ACTs depends on the stage and histology. It may vary from more than 80% for patients with small localized resected ACT to less than 20% for patients with metastatic ACC (10-33% of all cases)[4,11,12].

At diagnosis, all ACAsand most ACCs occurring in children are localized and can be completely resected; therefore, a microscopically complete resection is considered to be a major predictor for good prognosis and should always be the ultimate therapeutic goal. Of note, tumor spillage should be avoided wherever possible, even if only at the microscopic level e.g. caused by fine needle biopsy. Various clinical features have been reported to be associated with poor outcome; however, they may vary between studies. Age > 4 years, tumor size, presence of Cushing syndrome at diagnosis, incomplete resection and higher stage have more commonly been reported as adverse prognostic factors. In addition, it has been almost universally observed that children aged less than 4 years have a better outcome than adolescents. This may be explained in the light of the observation that distant metastases and non-secreting tumors have been observed more frequently in adolescents than in children[10]. Although tumor size is assessed with different units of measurements by different authors (diameter, volume, or weight), most authors consider large tumor size as an adverse prognostic factor. 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. A recent work published by the European group (*EXPeRT*) tried to define "high risk" tumors based on the presence of one of the following features: age at diagnosis, volume more than 200 cm^3, Cushing syndrome, initial biopsy (open or tru-cut), surgical excision with microscopic residuals or spillage (R1) or macroscopic residuals (R2), regional lymph node involvement, histologic vascular invasion, and distant metastases at diagnosis[13,14]. 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 stage II or III after surgery, in which a benign or malignant course is almost unpredictable.

3. RECOMMENDATIONS

3.1 INITIAL TUMOR ASSESSMENT

The clinical features of ACTs can vary widely from abdominal pain and fatigue to hormonal symptoms. Most ACTs are functional and secrete excessive androgens/oestrogens and/or glucocorticoids that lead to clinical symptoms such as virilization/feminization or Cushing syndrome. Therefore, ACTs should be suspected when there is a radiological evidence of an adrenal mass associated to signs of virilization/feminization and/or cushingoid features and/or hypertension. Symptoms are easier to notice if the tumor is secreting the hormone usually found in the opposite sex. Therefore, the analysis of the steroid hormones in the urine and plasma allows for valid clinical diagnosis in most cases. The most frequent diagnostic problem relates to the circumstance that ACTs have not been considered preoperatively. In rare cases, diagnosis could be challenging in the absence of hormonal secretion: non-functional tumors (<10%) tend to occur in older children and adolescents. However, the possibility of a neuroblastoma, particularly in young children, and of a pheochromocytoma should be investigated and excluded by analysis of urine and plasma catecholamines and their metabolites. The negativity of the MIBG scan is another argument to evoke this diagnosis. Some patients are asymptomatic, and ACT is diagnosed within the group of incidentally discovered adrenal masses (incidentalomas).

The group recommends avoiding any open or fine needle biopsy for histological confirmation of an ACT, which is suspected based on clinical, radiographic and laboratory investigations. This recommendation is based on evidence that initial biopsy may be a predictor of survival, associated with a poorer outcome, as shown by the German prospective series[15]. Accordingly, in the series presented by Picard et *al* [13], among three stage III patients in which percutaneous biopsy was the sole cause of tumor 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

recognized that preoperative and postoperative spillage may worsen the prognosis[16,17], although in adults initial biopsy does not affect survival.

Despite the low number of patients concerned, these findings demonstrate that an initial tumor biopsy should be avoided whenever possible out of caution (both percutaneous and, by extension, open tru-cut biopsies) in pediatric ACTs, especially when the tumor is associated with hormonal secretion [Level IV; Grade B]. Therefore, diagnosis should be evoked on clinical symptoms, radiographic assessment and laboratory investigations (analysis of steroid hormones) and confirmed histologically after the upfront tumor resection.

Staging investigations include:

a. Primary tumor and loco-regional tumor extension

All ACTs must be evaluated by a **pelvic and abdominal ultrasound (US) with doppler**, preferably pelvic/abdominal magnetic resonance imaging (**MRI**) or if not possible computed tomography (**CT**) scan [Level IV; Grade B]. It is recommended to exclusively use MRI in those cases with a family history characterized by early onset of tumors (breast cancer, soft tissue sarcoma, ACT), which may lead to an immediate suspicion of a cancer predisposing syndrome (e.g., Li-Fraumeni syndrome), in order to limit/avoid irradiation in these patients [Level IV; Grade B]. The imaging finding should be discussed in a multidisciplinary team (MDT) meeting (including at least the following disciplines: pediatric oncology, endocrinology, pathology, radiology, surgery, +/- adult oncology if needed) in order to evaluate the possible local invasion and the regional nodes involvement. This is of primary importance for planning the surgical excision of the primary tumor or the choice of preoperative chemotherapy followed by delayed resection [Level IV; Grade A].

b. Distant metastases

Considering that the most common sites of metastatic disease in pediatric ACC are liver and lungs, staging investigations should be primarily focused on these sites to confirm or exclude the presence of the metastatic disease:

- **Chest CT scan** is necessary to identify or exclude possible lung metastases 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** to identify unusual sites of metastatic disease should be considered individually according to present symptoms and signs; caution should be made for patients with Li-Fraumeni syndrome or suspicion for whom radiation exposure should be limited (in these patients a whole body-MRI can be considered) [Level IV; Grade B];
- **Bone CT scan** (in the absence of PET scan) should be limited to cases where the clinical suspicion of bone metastasis is present [Level IV; Grade B];]; or whole body MRI [Level V; Grade C]
- **Brain MRI** should be performed when cerebral metastases are clinically suspected [Level IV; Grade B] or in cases with suspicious/proven Li-Fraumeni syndrome.

c. Additional assessments

- It is reasonable to propose a genetic counselling preoperatively, but it could be delayed after surgical treatment if there is no high clinical suspicion of cancer predisposition disorder [Level IV; Grade A].
- Cardiac ultrasound in case of vascular and diaphragmatic involvement seems useful [Level IV; Grade B].
- Hormonal assessment:

  All children with suspected ACT should be initially evaluated by a pediatric endocrinologist

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 levels of adrenal hormones at diagnosis, a regular monitoring of hormonal levels is recommended during the follow-up [Level IV; Grade A].

It is recommended to start a hormonal replacement therapy postoperatively in all patients with hypercortisolism: hydrocortisone 50-100 mg/m^2/d 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[3,18].

Hormonal assessment should include[3] [Level IV; Grade B]:

- Glucocorticoid excess:
  - Dexamethasone suppression test
  - Free 24-hours cortisoluria (with creatininuria)
  - Basal Adrenocorticotropin hormone (ACTH) (plasma)
- Sex steroids and steroid precursors excess:
  - Dehydroepiandrosterone sulfate (DHEA-S) (serum)
  - 17-OH-Progesterone (serum)
  - (Delta-4-) Androstenedione (serum)
  - Testosterone (in both sex) (serum)
  - 17-beta-Estradiol (in both sex) (serum)
  - 11-Deoxycortisol
  - Estrone (E1) and Estradiol (E2)
- Mineralocorticoid excess:
  - Aldosterone
  - Natremia, Kalemia (plasma), Natriuresis
- Aldosterone/renin ratio (in patients with hypertension and/or hypokalemia
- Urinary metanephrines and catecholamines
  -)

- If case of chemotherapy, classic biologic screening (i.e., hematological, hepatic and renal function) and specific pre-treatment evaluation depending on chemotherapeutic agents are required (audiometry, cardiac) [Level V; Grade A].

Diagnosis of ACT is frequently associated with Li-Fraumeni syndrome.

Most ACTs are functional and secrete excessive androgens/oestrogens and/or glucocorticoids. Therefore, main symptoms are an **adrenal mass associated to endocrine signs** (virilization/feminization and/or cushingoid features and/or hypertension). Rarely, abdominal pain and fatigue may be the only symptoms.

Initial tumor and regional node assessment should include:

- **Complete clinical examination** including systematic evaluation by pediatric endocrinologist [Level IV; Grade A];
- **Pelvic and abdominal ultrasound with doppler** [Level IV; Grade B];
- **Pelvic and abdominal MRI** (or **CT scan** if MRI is not available); MRI should be preferred in case of suspicion of a cancer predisposing syndrome [Level IV; Grade B];
- **Chest CT scan** in case of suspicion of malignancy [Level IV; Grade A];
- **PET-scan or PET-MRI** depending on present symptoms [Level IV; Grade B];
- **Bone CT scan** (if no PET) only if clinical suspicion of bone metastasis [Level IV; Grade B]; or whole body MRI [Level V; Grade C]
- **Brain MRI** in cases if clinical suspicion of cerebral metastasis [Level IV; Grade B] or when suspicious/proven Li-Fraumeni syndrome.

Additional investigations should include:

- **Hormonal assessment** as described above [Level IV; Grade B];
- **Cardiac ultrasound** in case of vascular and diaphragmatic involvement [Level IV; Grade B];
- **Genetic counselling** preoperatively (or postoperatively if no high clinical suspicion of cancer predisposition disorder) [Level IV; Grade A].
- In case of chemotherapy: classic biologic screening (i.e., hematological, hepatic and renal function) and specific pre-treatment evaluation depending on chemotherapeutic agents [Level V; Grade A].

3.2 DIAGNOSIS

In most cases, clinical diagnosis can be established based on typical tumor site, hormone profile and exclusion of other tumors in differential diagnosis (especially neuroblastoma in young children). However, final histopathological evaluation is mandatory after tumor resection to allow for confirmation of diagnosis and histological stratification of ACT. Histology should especially distinguish ACT from other adrenal neoplasm [Level IV; Grade A].

Nevertheless, the decision on immediate surgical resection should be re-evaluated in large tumors with a high risk of intraoperative rupture. In these, a preoperative chemotherapy (including mitotane) based on clinical diagnosis followed by delayed resection should be the preferred strategy. The most important risk factor standing above all is completeness of resection and avoidance of spillage at diagnosis. In very large tumors and those with locoregional metastases, spillage also has to be avoided, which plead for preoperative chemotherapy in typical clinical and biological presentation, without any biopsy.

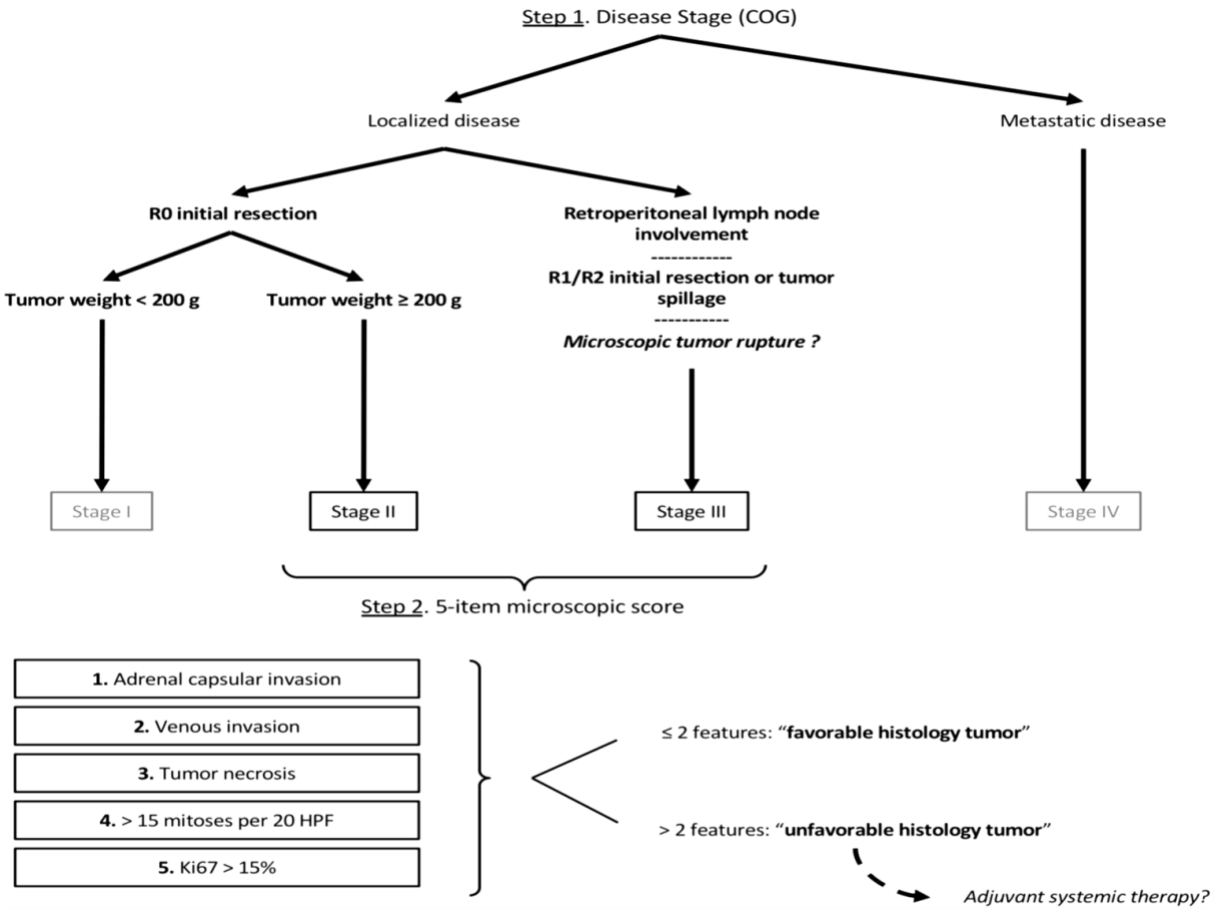
A revision of the histological slides from a pathologist with proven experience in pediatric tumors and especially in ACTs is highly recommended [Level IV; Grade B]. It is strongly recommended to store a frozen tumor sample and a blood sample on EDTA in a tumor bank for possible subsequent biological studies, including genetics [Level III; grade A].

Differentiating benign from malignant ACT is often difficult, and adult scores (Weiss, Hough, Van Slooten, etc...) have been demonstrated to be poorly predictive especially in younger children. Dehner and Hill[5,9,19,20] hypothesized that pediatric 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. Weiss scoring system seems poorly reliable for pediatric ACTs. Later, **Wieneke index** (first described in 2003)[5,9] has been reported to have a prognostic value that is more reliable compared to other histologic

prognostic scores used in adults[4,9,10]. This index classifies ACTs in 3 prognostic groups (benign, malignant, and of undetermined malignant potential) on the basis of the number of present pathologic criteria (tumor size, tumor weight, extension into periadrenal soft tissues and/or adjacent organs, vena cava invasion, capsular invasion, necrosis, mitotic rate/atypical mitoses, vascular invasion) (≤2, benign; 3, undetermined malignant potential; ≥4, malignant). Although it is widely recognized, the paucity of cases a pediatric pathologist may encounter and the number of criteria to be considered may make the Wieneke pathological stratification poorly defined and observer-dependant. Moreover, this index incorporates items which cannot be evaluated in case of biopsy (venous involvement, adjacent organ extension). More recently, Picard and al.[10] described **a 5-item microscopic score** (Figure 1) based on the evaluation of adrenal capsular invasion, venous invasion, tumor necrosis, mitoses > 15/20 high power fields and Ki67 index > 15%. ACTs with 2 or less features should be considered to show a "favourable histology", and those with more than 2 features an "unfavourable histology". They postulated that the use of this 5-item score could be of interest to stratify tumors with favourable versus unfavourable histology, especially for localized ACTs, with the possibility to limit the use of systemic treatment to the latter group, in the light of the lower risk of disease progression among tumors with favourable histology.

The absence of well-defined pathological prognostic system in pediatric age may hinder therapeutic stratification, especially for patients with large tumors or with incomplete resection (R1 [incomplete tumor resection] or spillage), as R1 or R2 status constitutes the strongest unfavourable risk factor. Though not validated, the use of a pediatric prognostic score (**Wieneke or 5-item score**) to enable stratification of these patients, should be introduced also in consideration of the fact that systemic therapy shows important limits in terms of toxicity and efficacy [Level IV; Grade B]. On this basis, the importance of a MDT discussion to better define the biology of the disease and the central review of the histology are of vital importance [Level IV, Grade A].

Figure 1. Five-item microscopic score role (Picard et al. 2019)[10]



Histological diagnosis

Histology after tumor resection is **mandatory** for ACT diagnosis, even if clinical diagnosis can be established based on typical tumor site, hormone profile and exclusion of other tumors as differential diagnosis [Level IV; Grade A].

Revision of the histological slides from a pathologist with proven experience in pediatric tumors and especially in ACTs is highly recommended [Level IV; Grade B].

Frozen tumor sample and a blood sample on EDTA could be stored in a tumor bank for possible subsequent biological studies, including genetic studies [Level III; grade A].

Pathologic staging should be incorporated in the final report: **Wieneke** [Level IV; Grade B] and/or **5-items microscopic score** [Level V; Grade B], in order to stratify tumors between favourable and unfavourable histology and thus guide systemic therapy decision.

3.3 STAGING SYSTEM

Most widely used staging systems in pediatric age have been proposed by Sandrini[21], and has been later modified. This is a post-surgical staging system, which relies on the possibility and the quality of resection, tumor size, regional nodes involvement and presence of metastatic disease. Thus, it is only in part transferrable to a neoadjuvant strategy. The COG system (Table II) has been adopted by the French VRT FRACTURE Group and, with some modifications, by the Italian TREP project. It is recommended to use the **COG system** to allow national and international referral, comparison of data, and a proper pediatric stratification [Level III; Grade C].

Table II. COG ACT Staging System for adrenal tumors

Stage	Definition
I	R0 (complete histological resection) and small localized tumors (< 100 gr or < 200 cm^3) with normalization of hormone levels after surgery
II	R0 and large localized tumors (≥ 100 gr or ≥ 200 cm^3) with normalization of hormone levels after surgery
III	Unresectable tumors or gross/macroscopic residual disease; Tumor spillage (pre- or intra-operatively); Failure to normalize hormone levels after exclusive surgery; Retroperitoneal lymph nodes involvement.
IV	Distant metastases

Staging should follow the **COG system** [Level III; Grade C].

3.4 TREATMENT

General considerations:

- MDT is mandatory at diagnosis and during therapy [Level IV; Grade A].
- Patients/families should be proposed the enrolment in a prospective trial if available, and data collection in national or international databases [Level IV; Grade B].

a. Surgery

The anesthetic management of patients with hypercortisolism at diagnosis or during hormone supplementation due to the adrenal insufficiency associated with mitotane must be carried out in

collaboration with the pediatric endocrinology team. The risk of acute adrenal decompensation at the time of surgical tumor removal should be considered.

Different series, although with a limited number of patients, have shown that complete tumor resection is a major prognostic factor [Level III; Grade A]. Therefore, **complete surgery** constitutes the cornerstone of cure for children with localized ACT. Tumor rupture, pre- or intra-operatively, has been associated with a worse prognosis and almost fatal outcome. As already mentioned, initial biopsy should be strongly discouraged in all patients as it is considered as a violation of the capsule resulting in an upstaging up to stage IV, turning a potentially curable tumor into a fatal disease [Level III, grade E]. Therefore, it should be limited only to children with non-secreting tumors and metastatic disease and/or unresectable primary tumor [Level IV, grade B]. In such situations, biopsy is not required if the clinical presentation and endocrinological assessment are typical and diagnostic [Level IV, grade B]. If biopsy is performed, it should preferentially be performed by a posterior approach to avoid any risk of peritoneal spillage [level III; Grade B]. In case of metastatic disease, a biopsy of a metastatic site could also be preferred. In case of localized ACT without hormonal secretion (and MIBG scan negative), physicians should preferentially perform an immediate adrenal resection without any previous biopsy [Level IV; Grade B]. The surgical planning in all patients with localized disease should aim for a microscopically complete resection: in this light, an accurate preoperative radiological evaluation of the adrenal mass and the regional nodes status should be performed [Level III; Grade A].

Primary tumor

Surgical resection of ACT should be performed only by surgeons experienced in adrenal and oncological surgery aiming at a complete en-bloc resection Upfront en-bloc resection is the treatment of choice in all cases in which a complete removal of the primary tumor is deemed feasible, considering that surgery alone may, in most cases, cure the patient [Level III; Grade A].

ACTs are particularly friable tumors. The incidence of intraoperative tumor ruptures has been evaluated in pediatric series at 20% at the time of the initial excision, and more than 40% in the case of surgery on a locoregional recurrence[12,21]. The rupture is responsible for tumor spread in the peritoneal cavity, increasing the risk of loco-regional recurrence, with dismal outcome[10,12,13]. The preferred surgical approach should be an open approach through a right or left transverse abdominal incision or a midline laparotomy in case of exceptionally huge masses[22] [Level IV; Grade B]. The tumor should be removed without rupture and a systematic regional node sampling should always be performed [Level V; 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 tumor cannot be separated from the kidney with tumor free margins [Level IV; Grade B]. The presence of a thrombosis of the vena cava (COG stage III) does not necessarily categorize the tumor as inoperable although it complicates the surgical procedure, because of the risk of tumor embolism during the manipulation of the vena cava and the increased risk of intraoperative tumor rupture. A surgical approach under cover of an extra-corporeal circulation must be considered and is justified by the prognostic importance of the quality of the resection[4,23] [Level IV; Grade B].

Recently, a minimally invasive approach (both laparoscopic and robotic minimally invasive surgery (MIS) to ACA has been discussed for infants and pre-school children with small non-infiltrating, non-metastatic tumors, showing similar results both in terms of rate of complications and oncological outcome in some studies[24–29]. However, in case of suspected ACC, a surgical procedure offering the maximum of surgical-oncological safety should always be preferred. In particular, tumors 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]. MIS is strongly discouraged when malignancy is suspected (large tumor size > 5 cm, presence of nodes enlargement, vena cava infiltration…) [Level III, Grade E]. Therefore,

minimally invasive techniques in the surgical management of ACT are not recommended and could only be considered in early childhood, but their use should be limited to: a) small localized tumors likely to be benign without invasion of surrounding structures and nodal involvement at pre-operative imaging; and b) tertiary care centers and surgeons experienced in oncologic and adrenal surgery [Level IV; Grade D].

After surgery, the examinations must nevertheless very precisely look for the presence of a residual tumor mass requiring its removal if it remains present after surgery or after medical therapy.

Regional lymph nodes

The involvement of regional lymph nodes has been reported to be present in up to 30% of children with ACC. All suspicious or enlarged lymph nodes detected on pre-operative imaging or intra-operatively should be removed[3]. For suspicious or proven ACC, routine locoregional lymphadenectomy should be considered and therefore include (as a minimum) the periadrenal and renal hilum nodes. A sampling of regional nodes is recommended in all cases:

- All enlarged lymph nodes detected at radiology or intra-operatively should be removed [Level III; Grade A].
- A systematic biopsy of the regional nodes should be performed if they are not found suspicious pre- or intra-operatively [Level IV; Grade C].

On the other hand, a complete retroperitoneal lymph nodes dissection (RPLND) has not been demonstrated effective on EFS and OS: the only protocol which investigated the systematic role of RPLND (ARAR0332 protocol from the COG) in localized ACTs did not find any outcome improvement[30] but the median total number of removed lymph nodes was limited (4) [Level III; Grade E].

Metastases

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

Surgery

No biopsy should be performed before surgery [Level III; Grade E], unless rare exceptions (i.e., non-secreting tumors and metastatic disease and/or unresectable primary tumor and atypical presentation [Level IV, grade B]) and via a posterior approach.

The **anesthetic management** of patients with hypercortisolism must be carried out in collaboration with the pediatric endocrinology team, including post-surgical hydrocortisone substitution at stress levels.

For localized ACT:

- In case of typical bio-clinical presentation with hormonal secretion, **upfront complete surgery with en-bloc resection** is recommended [Level III; Grade A].
- In case of non-secreting tumor (and MIBG scan negative), immediate adrenal resection without any previous biopsy should also be performed [Level IV; Grade B].
- An **open approach** through a right or left transverse abdominal incision or a midline laparotomy in case of exceptionally huge masses should be preferred [Level IV; Grade B].
- Involvement of surrounding structures (kidney, vena cava, periadrenal fat) does not contra-indicate upfront surgery, but may make necessary wide excision, including nephrectomy if the tumor cannot be separated from the kidney with tumor free margins [Level IV; Grade B], or an extra-corporeal circulation in case of thrombosis of the vena cava [Level IV; Grade B].
- **Mini-invasive surgery is strongly discouraged** when malignancy is suspected [Level III, Grade E]. Its use should only be considered by experiment surgeons, case by case, for younger children

with small localized tumors likely to be benign without invasion of surrounding structures and nodal involvement at pre-operative imaging [Level IV; Grade D].
- For suspicious or proven ACC, **routine locoregional lymphadenectomy** should be considered and including the periadrenal and renal hilum nodes, all suspicious lymph nodes on preoperative imaging or intraoperatively [Level III; Grade A], and a systematic sampling of regional nodes if they are not found suspicious pre- or intra-operatively [Level IV; Grade C]. Yet, systematic RPLND is not recommended [Level III; Grade E].

For metastatic ACT

Surgery of metastatic sites should be considered for patients in good clinical condition and when a reasonable clearance of metastatic sites is deemed feasible [Level IV; Grade C].
Timing of surgery of the primary tumor and metastatic sites, and the use of neo-adjuvant or adjuvant chemotherapy combined with mitotane should be discussed case by case within MDT.

b. Medical therapy

Chemotherapy regimen used in patients with advanced stage ACT or relapsed ACT derives from the standard treatments used in adults. A cisplatin-based combination, usually incorporating doxorubicin and etoposide (CED), is most commonly used. Although limited data are available about the use of mitotane (Lysodren©) in pediatric age, this cytostatic agent is usually added to standard chemotherapy.

Standard chemotherapy

Due to the lack of prospective clinical randomized trials, there is no evidence-based optimal chemotherapy established for children to date [Level III, grade C]. The COG, together with Brazilian hospitals, investigated the use of standard chemotherapy (CED) in the above-mentioned ARAR0332 protocol[30]. One of the aims of this protocol was to evaluate the impact of mitotane and cisplatin-based chemotherapy for unresectable and metastatic disease (Table III)[7,12]. The

combination of mitotane and chemotherapy used in the protocol resulted in 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[4,13]. The GPOH-MET 97 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 historical 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 in the discussion, they underlined the possibility of existing confounding factors[15,31]. Details regarding chemotherapy can be found in Chapter 8 (PARTN-ER proposal) and Appendix.

Table III. The COG ARAR0332 protocol strategy

Treatment on the COG ARAR0332 protocol.

Stage	Treatment
Stage I	Surgery alone
Stage II	Surgery RPLN dissection
Stage III	Mitotane CDDP/ETO/DOX Surgery + RPLN dissection
Stage IV	Mitotane CDDP/ETO/DOX Surgery + RPLN dissection

Abbreviations: RPLN, retroperitoneal lymph node; CDDP, cisplatin; ETO, etoposide; DOX, doxorubicin.

As a consensus, neoadjuvant chemotherapy including mitotane should be considered in patients with primarily inoperable and/or metastatic tumors [Level IV; Grade A]. In some cases described, systemic therapy is effective with regard to reduction of tumor volume according to RECIST criteria[13,21]. However, as ACC could be refractory to medical therapy, surgical procedures should not be delayed when tumor resection is feasible [Level III; Grade A].

Adjuvant therapy should be considered in advanced-stage ACC or in case of incomplete tumor resection [Level IV; Grade B].

The first-line regimen is CED, considering the results aforementioned in adults and children, or NN1/NN2 according to the GPOH strategy[3,32,33] [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, best also supplemented with genetic analysis of molecular targets [Level IV; Grade C]. In adult advanced ACC, some interesting schedules including streptozocin and gemcitabine-capecitabine in combination with mitotane have been reported[34] [Level IV; Grade C].

Mitotane

Systemic treatment with mitotane with or without chemotherapy is certainly indicated in the case of inoperable or metastatic tumors, although the impact on OS has not been demonstrated for all study groups. However, in the GPOH strategy, the use of mitotane improved OS from 0.15 to 0.6. It should be noted that mitotane constitutes the only specific and targeted therapy in these tumors available to date.

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 acts as an inhibitor of mitochondrial cortisol synthesis by inhibiting 11ß hydroxylation and cleavage of the cholesterol chain. Its cytolytic effect comes from activation in o, p-DDA and o, p-DDE. Mitotane has a long half-life, up to 150 days; it is stored in tissues with a high lipid concentration and then released. It is available as breakable tablets of 500 mg under the brand name Lysodren®. Objective tumor responses have been observed in patients with advanced disease in approximately 20-30%, using mitotane alone[35] and hormonal responses in 75% of cases. However, these responses are often transient and the effect on prolonged survival

is uncertain. Mitotane is sometimes administered in case of an inoperable tumor to induce tumor regression, however without significant improvement of the survival. The duration of treatment is not defined and is very variable depending on the cooperative groups. 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 tumor response[36,37], also in the pediatric setting, as demonstrated by the GPOH study group. A study by Terzolo *et al.* allowed retrospective analysis of 177 adult patients with stage I and II ACC who benefited from the initial complete tumor resection[38]. In this cohort, 47 patients had received mitotane, the other patients serving as a control group. The authors demonstrated that adjuvant treatment with mitotane improved EFS (50% versus approximately 15%). The median duration of treatment was 29 months (range 6 to 164 months), and 21 patients had been treated for more than 4 years. The side effects of treatment were grade 1 or 2, and the dose had to be reduced in 13% of the patients. The results of this study argued for prolonged use of mitotane, but the impact on OS was much less obvious, prompting the FRACTURE committee not to offer this treatment systematically after complete removal of a localized tumor. In children, the literature data are very limited. In the French retrospective series, the response rate to mitotane was 30% in 20 treated patients[11] and increased to 50% in patients with mitotane blood levels > 14 mg/L. Factors limiting the dose of mitotane were mainly gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain) and neurological (tremor, drowsiness, lethargy, ataxia, depression, dizziness) side effects. These adverse effects may be responsible for poor compliance with treatment. This treatment remains complicated to use and must be administered in collaboration with a suitably experienced team [Level IV; Grade A]. The data from the German study group on serum level guided mitotane therapy are encouraging as they demonstrate 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 [Level III,

Grade B]. Regular monitoring is essential, as side effects may potentially result from overdosage. Monitoring plasma levels may be difficult and is not always available in all centers or in all European countries. Some authors[39] considered the use of mitotane as adjuvant therapy controversial in children with stage I and II ACC, but indicated in stage III and IV ACC in association with CED, as previously reported in adults. Some authors found better OS in children treated with mitotane alone when used for longer than 6 months[15]. Although limited data about the use of mitotane in children exist, it should be always considered in first-line treatment, alone or in association with chemotherapy.

Collaboration with an endocrinologist is essential, particularly for the management of endocrine disorders related to relative adrenal insufficiency following surgical excision of the primary tumor [Level IV; Grade A] and/or induced by mitotane a few days after the initiation of treatment. In addition, significant collaboration with a pediatric endocrinologist is also recommended throughout the duration of treatment with mitotane (substitute opotherapy) [Level IV; Grade A].

In principle, the management recommendations for mitotane are as follows:

- Mitotane-Lysodren® cp 500 mg breakable [Level IV; Grade A];
- The treatment is difficult to handle with a precarious balance between efficacy and toxicity, requiring a consultation of an endocrinologist accustomed to the management of the substitution therapy and in order to help the parents and the child to tolerate side effects [Level IV; Grade A];
- Treatment should be initiated with doses 1.5 g/m²/day, then increased progressively to reach 4 g/m²/day. The total daily dose should be divided into 2 or 3 doses depending on the patient's convenience. Tablets should be taken with a glass of water during meals rich in fat or with a fatty substance [Level IV; Grade B];
- Dosing should be increased every 4 days depending on digestive tolerance and the urgency of tumor control to reach the target dose in 15 days [Level IV; Grade B];

- Plasma mitotane concentrations must be monitored after each dose adjustment until the optimal maintenance dose is reached, being particularly vigilant at the level of 10 mg/L and upper because a rapid increase in plasma levels may be observed. The dosages can be monitored using Lysosafe, which is available to all physicians applying mitotane (www.lysosafe.com). Once the target dose has been reached which may take several months, mitotane plasma levels should be monitored regularly, every 2 weeks, as the concentrations may increase even though the dose of mitotane administered has not been changed. Once the blood level has stabilized for 4 to 6 weeks, monitoring can be once monthly [Level IV; Grade B] or more frequently in case of significant side effects.
- A serum level greater than 14 mg/L is necessary for maximum effectiveness; neurotoxicity (drowsiness, dizziness, tremor, ataxia, and encephalopathy) appears for levels above 20 mg/L [Level IV; Grade B]. In the German experience levels up to 30 mg/L can be safely maintained. An effective serum level is obtained in 2 to 3 months.
- Systematic supplementation with hydrocortisone (often high doses, around 20-30 $mg/m^2/d$) and fludrocortisone is required, since the treatment induces adrenal insufficiency after 2 to 3 weeks. Measurement of urinary free cortisol and ACTH is recommended for optimal hormonal substitution [Level IV; Grade A].

Duration of therapy

There are no data about the optimal duration of therapy. CED is usually scheduled in 6 to 8 cycles. Mitotane should be started with the first cycle of chemotherapy and continued for 1 to 2 years depending on tolerance and compliance; in the German GPOH strategy this treatment is delivered for 3 years for stages IV. The proposed duration of 2 years best covers the maximum period of relapse risk [Level IV; Grade C]. However, it should be noted that only periods with effective therapeutic plasma levels should be considered as effective treatment time.

Medical therapy

Neoadjuvant conventional chemotherapy + mitotane should be considered in patients with unresectable and/or metastatic tumors [Level IV; Grade A].

When tumor resection is deemed feasible, surgery should not be delayed even if systemic therapy may be effective in some cases with regard to reduction of tumor volume [Level III; Grade A].

Adjuvant therapy should be considered in case of advanced-stage ACC or incomplete tumor resection [Level IV; Grade B].

Chemotherapy

The first-line recommended regimen is **CED** (cisplatin- doxorubicin-etoposide) or **NN1/NN2** (vincristine-ifosfamide-doxorubicin and carboplatin-etoposide) [Level IV; Grade B], with 6 or 8 cycles of chemotherapy.

There is **no consensus for second-line or salvage therapies**, they should be considered on an individual basis, supplemented with genetic analysis of molecular targets if available [Level IV; Grade C].

Mitotane

Management of mitotane should be done in **collaboration with a suitably experienced team** because of the difficulty to obtain and maintain an effective blood level with correct efficacy/toxicity balance [Level IV; Grade A].

Collaboration with an endocrinologist is required because of the relative adrenal insufficiency following surgical excision of the primary tumor [Level IV; Grade A], and during the treatment with mitotane [Level IV; Grade A].

The use of **mitotane alone** as adjuvant therapy in children with **stage II ACC** is **controversial**, but should always be **considered in stage III and in IV ACC, in association with chemotherapy**.

Mitotane-Lysodren® cp 500 mg breakable should be used [Level IV; Grade A].

Treatment should be **initiated at 1.5 g/m²/day**, then increased progressively every 3 days **up to 4 g/m²/day**, divided in 2 or 3 doses per day; tablets should be taken with a glass of water and a fatty substance [Level IV; Grade B].

Factors limiting the dose of mitotane are mainly **gastrointestinal** (nausea, vomiting, diarrhoea, abdominal pain) and **neurological** (tremor, drowsiness, lethargy, ataxia, depression, dizziness) **side effects**.

Regular plasma concentration monitoring is essential [Level IV; Grade B]:

- after each dose adjustment until the optimal maintenance dose is reached,
- then regularly as the concentrations may increase even in the absence of dose change.
- once the blood level has stabilized for 4 to 6 weeks, monitoring can be once monthly.

Therapeutic plasma level target should be **between 14 and 20 mg/L** (20-30 mg/L according to the German experience) [Level III, Grade B].

An effective serum level is obtained in 2 to 3 months. It is then necessary to lower the doses regularly (up to 1-2 g/d) in order to avoid toxicity due to the accumulation of the drug in fatty tissues and release [Level IV; Grade B].

Systematic supplementation with hydrocortisone and fludrocortisone is required, with monitoring of urinary free cortisol and ACTH [Level IV; Grade A].

There is **no consensus about the duration** of mitotane therapy.

It should be started with the first cycle of chemotherapy and continued for at least **2 years** (taking into account the only periods with effective therapeutic plasma levels) depending on tolerance and compliance [Level IV; Grade C].

c. Radiotherapy

The role of external radiotherapy is uncertain, since ACCs are usually radio-resistant neoplasms. In adult's experience, locoregional radiotherapy, including brachytherapy in case of liver metastases may improve EFS but not OS[40]. Due to its potential mutagenic effect, radiotherapy should be avoided as much as possible in patients with a diagnosis of Li-Fraumeni syndrome [Level IV; Grade B]. Limited data exist on efficacy of radiotherapy and it has been mostly used only as salvage therapy[15].

Radiation therapy should be discussed to some refractory stage III ACC (R2, unresectable tumors), stage IV or relapsed tumors. 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 tumor bed and the peri-aortic regional nodes + boost of 5 - 15 Gy on the tumor bed depending on the margins of resection / the presence of residual tumor[41] [Level IV; Grade C].

Radiotherapy

Because of the radioresistance of ACC, the role of external radiotherapy is uncertain.

Radiotherapy is discouraged in patients with the diagnosis of **Li-Fraumeni** syndrome [Level IV; Grade B].

Radiation therapy could be discussed in case of **some stage III ACC (R2, unresectable tumors), stage IV and relapsed tumors** [Level IV; Grade C].

There is no consensus on the optimal dose and volume of radiotherapy; the dose recommended on the tumor bed and the peri-aortic regional nodes is **45 Gy**, with **boost of 5-15 Gy** on the tumor bed depending on the quality of resection [Level IV; Grade C].

d. Focal therapy to metastatic sites

Few data exist on the role of focal therapy (cryoablation, thermal ablation…) for metastatic sites in pediatric ACC and could be discussed case by case [Level IV; Grade C].

e. Overall strategy

Localized ACT (Stages I-II-some III)

The treatment of choice is upfront surgery in case of resectable lesions. In the rare occurrence of an unresectable localized tumor, neo-adjuvant chemotherapy to reduce size and invasion may be attempted after MDT discussion (cf. infra) [Level IV; Grade B].

In case of stage III caused by isolated tumor rupture in a child older than 4 years or in case of non-normalization of hormonal markers, 6 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].

Unresectable (stage III) and metastatic (stage IV) ACC

The feasibility of a surgery of the primary tumor and metastatic sites can be discussed at diagnosis but will be impossible in most cases. Therefore, an up-front multiagent chemotherapy plus mitotane is recommended, with regular monitoring according to RECIST criteria and delayed tumor surgery. Considering the scarce response observed in these patients, 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 with mitotane [Level IV; Grade C]. The goal of the medical therapy is to obtain a significant tumor reduction to enable a complete excision of the tumor and propose focal therapies to metastatic sites. Two to 4 cycles of neoadjuvant chemotherapy with cisplatin, etoposide and doxorubicin (CED) or NN1/NN2, with 21 days apart, will therefore be carried out, followed by evaluation report concerning the primary tumor and metastatic sites. The surgical intervention depends on the imaging data and consists of the complete excision of the primary tumor if possible, and delayed excision of different metastatic sites if possible. In case of tumor response to neoadjuvant chemotherapy, the patient should receive 4 to 6 cycles of adjuvant chemotherapy (CED, NN1/NN2), for a total of 6 to 8 cycles.

Poorly responding ACC

The experience is very limited. MTD should be reset up to discuss mutilating large resections [Level IV; Grade C]. A different regimen could be tested, including second-line chemotherapy used in

adult population. Alternatively, enrolment in a prospective trial testing new regimens or target-therapies should be taken into consideration [Level V; Grade B].

Relapsed ACC

Survival is very poor for these patients. No specific second-line treatment is strongly supported by literature data[15,34]. In case of local relapses, repeated surgeries, local therapy (thermal ablation, hyper-fractionated RT …) and re-use of mitotane may prolong survival, but the use of second-line chemotherapy depending of the previous drugs used or enrolment in prospective trials is also advised [Level V; Grade B]. All therapies should be considered case by case and validatedduring MTD.

Overall strategy

Localized ACT (Stages I-II-some III)

Upfront surgery is highly recommended in case of resectable lesion [Level III; Grade A].

Neo-adjuvant chemotherapy may be considered in case of unresectable ACC [Level IV; Grade B].

Adjuvant chemotherapy + mitotane is proposed in case of stage III due to isolated malignant ACC tumor rupture in children older than 4 years or non-normalization of hormonal markers [Level IV; Grade C].

In case of isolated capsular tumor rupture in children less than 4 years with histologically proven ACC, the adjuvant treatment is of debate and should be discussed in MDT [Level IV; Grade C].

Unresectable (stage III) and metastatic (stage IV) ACC

An up-front multiagent chemotherapy + mitotane is recommended, with regular monitoring according to RECIST criteria and delayed tumor surgery [Level IV; Grade C]:

- 2-4 cycles of neoadjuvant chemotherapy with CED or NN1/NN2
- complete resection of the primary tumor and combined or delayed resection of metastatic site(s) if possible, depending on response to neo-adjuvant treatment
- 4-6 cycles of adjuvant chemotherapy in case of tumor response to neoadjuvant chemotherapy, for a total of 6 to 8 cycles, combined with mitotane.

Whenever possible, these patients could be offered to participate in an experimental protocol [Level IV; Grade C].

Poorly responding and metastatic/unresectable tumor ACC

MDT discussion should be reset up to discuss mutilating large resections [Level IV; Grade C].

Second-line chemotherapy used in adults could be tested [Level IV; Grade C]. Alternatively, enrolment in a prospective trial testing new regimens or target-therapies should be taken into consideration [Level V; Grade B].

Relapsed ACC

No specific second-line treatment is defined.

In case of local relapses, repeated surgeries and re-use of mitotane may be proposed [Level V; Grade B].

Second-line chemotherapy or enrolment in prospective trials is also advised [Level V; Grade B].

4. GENETIC CONSIDERATION

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 (Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome and other overgrowth syndromes) [Level IV; Grade A].

Genetic counselling proposal for patients with ACT is mandatory [Level IV; Grade A].

5. LONG TERM FOLLOW-UP RECOMMENDATIONS

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. and Kratz et al. (Level IV; Grade A).

Long term follow-up for patients with a diagnosis of Li-Fraumeni is highly recommended, and can include, as proposed by Frebourg *et al.*:

In children: - clinical examination and abdominal ultrasound every 6 months
- annual whole-body MRI and brain MRI

In adults: - annual clinical examination and whole-body MRI
- annual breast MRI in females from 20 until 65 years

- annual brain MRI until 50 years

[Level V; Grade A].

6. SPECIFIC CONSIDERATIONS FOR LHEAR COUNTRIES

In 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 an expert pediatric surgical oncology may limit the management, but it could be overcome through referral to local adult surgeons (for older children) or to foreign pediatric surgical centers. The main limitations could be the use of mitotane and the monitoring of its plasma levels.

7. MAIN OPEN QUESTIONS IN THE TREATMENT OF ACC

- Optimal clinical, radiographic and endocrinological assessment for clinical diagnosis prior to surgical therapy, aiming for avoidance to tumor biopsy and tumor spillage.
- Best prognostic stratification of patients according to the pathology and/or clinical features.
- Role of adjuvant/neo-adjuvant chemotherapy in case of isolated tumor rupture.
- Best chemotherapy regimen: CED or NN1/NN2.
- Indications, dosage and way to monitor mitotane therapy.
- Length of mitotane therapy.
- Role of exclusive mitotane in case of isolated tumor rupture.
- Treatment of poor responding, metastatic and relapsed ACC.
- Efficacy of new drugs for ACC.

8. ACC TREATMENT: THE PARTN-ER PROPOSAL

Even if many aspects of ACC treatment could not be fully supported by evidence-based medicine, EXPeRT/PARTN-ER groups propose an overall strategy in order to help physician to treat patients. This therapeutic strategy should nevertheless be debated locally by MDT (Figure 2).

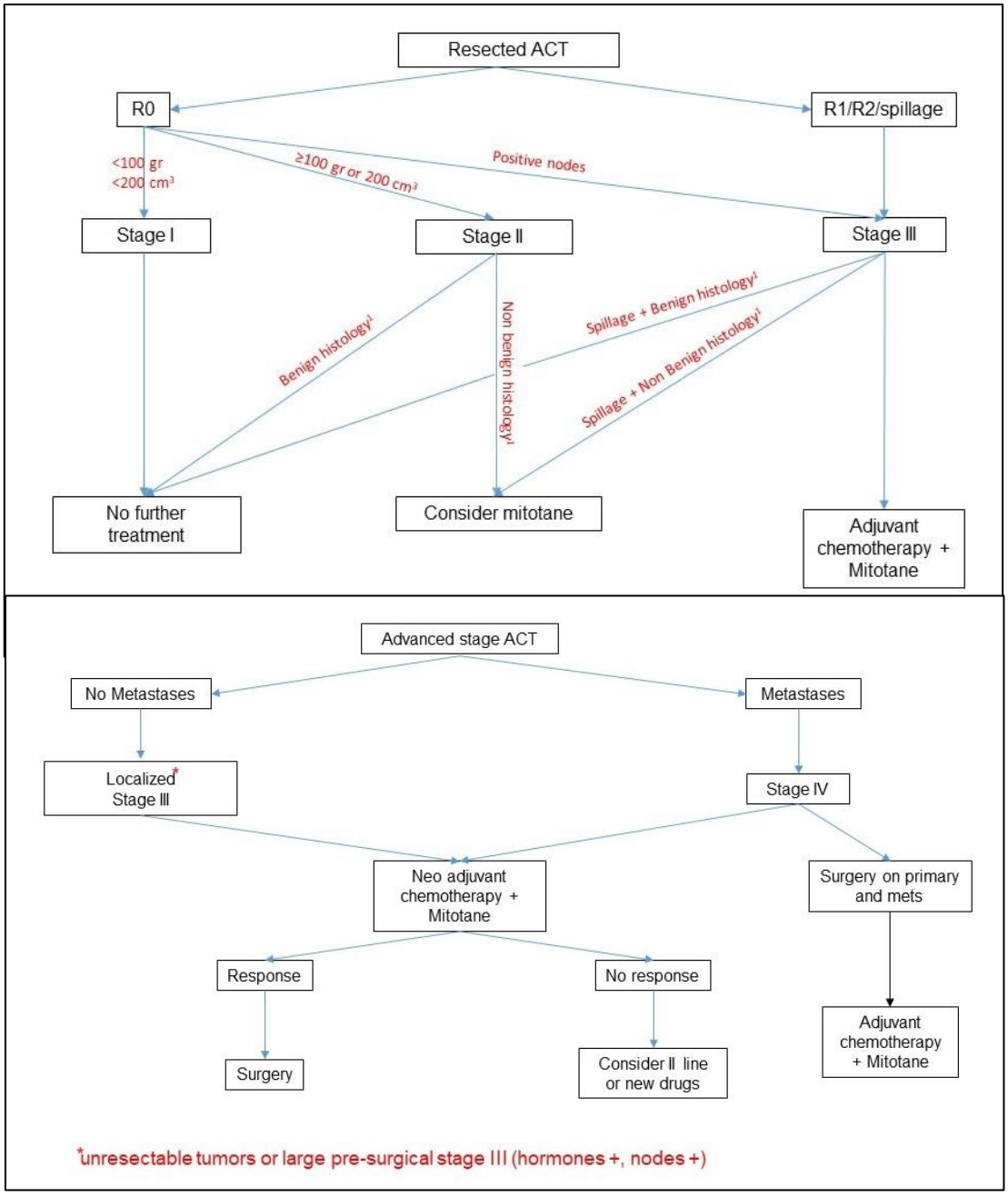


Figure 2. Therapy summary for adrenal carcinoma in children and adolescents according to COG stages.

Stage I:

No adjuvant treatment after surgery

Stage II:

Consider mitotane if several risk factors are present, i.e. unfavorable histology at 5-item score or Wieneke score ≥ 3, old age, and hormonal secretion

Stage III:

- *Unresectable tumors:*

Neo-adjuvant treatment (chemotherapy + mitotane) followed by surgery when feasible

- *Gross/macroscopic residual disease:*

Adjuvant therapy (chemotherapy + mitotane) followed by delayed surgery when feasible

- *Tumor spillage (pre- or intra-operatively):*

Consider mitotane if other risk factors are present, i.e. unfavorable histology at 5-item score or Wieneke score > 3, old age, hormonal secretion

- *Fail to normalize hormone levels after surgery:*

Consider mitotane or chemotherapy + mitotane

- *Retroperitoneal lymph nodes involvement:*

Chemotherapy + mitotane

Stage IV:

Neo-adjuvant therapy (chemotherapy + mitotane) followed by surgery when feasible.

Local relapses:

Local relapses should be treated aggressively, as these are almost invariably fatal. Surgery is recommended whenever feasible and should best be aimed to a complete surgical clearance of any visible tumor manifestations. Adjuvant treatment with mitotane for at least 2 years is recommended, a combination with chemotherapy or other standard regimen could be considered case by case. For unresectable relapses, adjuvant chemotherapy plus mitotane or second-line chemotherapy plus mitotane should be administered: in case of response, surgery could be considered. Radiation therapy should be discussed in both cases within MDT, taken into account the genetic context. However, unresectable relapses could also be chosen for palliative comfort care, considering the almost invariably fatal outcome.

Distant relapses:

As for stage IV at diagnosis, outcome for these patients is poor. Chemotherapy (chemotherapy + mitotane or other regimens combined with mitotane) and radiation therapy should be attempted, alternatively enrolment in phase I-II trial (if any available) should be considered.

APPENDIX 1. CHEMOTHERAPY REGIMENS AND FOLLOW UP

CED (cisplatin, etoposide and doxorubicin) regimen, 21-day cycles

- Cisplatin: 50 mg/m^2/day on D1 and D2, IV over 6 hours.
- Etoposide: 100 mg/m^2/day from D1 to D3, IV over 1.5 hours.
- Doxorubicin: 25 mg/m^2/day on D4 and D5, IV over 4 hours.

For children <10 kg or <12 months: dose reduction and calculation by body weight.

The **hydration protocol** associated with cisplatin is detailed in the Appendix. Cisplatin administered at these doses may be poorly tolerated digestively, especially in adolescents. It is recommended that anti-emetic treatment be implemented according to the protocol of each center. Besides the discomfort felt and the risk of dehydration, this digestive intolerance can make it difficult to take mitotane orally. Blood levels may then be lower than expected, due to digestive intolerance leading to vomiting mitotane. It is therefore imperative to take this into account before any modification of the dose of mitotane, and therefore not to increase it systematically, especially due to variable but very long half-life of mitotane. In addition, this association could result in neutropenia, and treatment with G-CSF is recommended.

GPOH-MET NN1 regimen

- Vincristine: 1.5 mg/m^2/day on D1 and D8 (max 2 mg)
- Ifosfamide: 1.0 g/m^2/day from D1 to D5 (with hydration and Uromitexan)
- Adriamycin: 35 mg/m^2/day on D2 and D4

GPOH-MET NN2 regimen

- Carboplatin: 125 mg/m^2/day from D1 to D5
- Etoposide: 100 mg/m^2/day from D1 to D5

GPOH-MET therapy stratification

ACC, Stage I, II, stage III completely resected, no lymph node metastases (T3 N0 M0)

→ Watch-and-wait

Stage III with lymph node metastases (T1-2, N1, M0)

→ 2 x NN1 + 2 x NN2 + Mitotane at therapeutic levels for 9 months

Stage IV

→ 4 x NN1 + 4 x NN2 + Mitotane at therapeutic levels for > 18 months

Chemotherapy toxicity monitoring

- Biological criteria before starting each cycle of chemotherapy:

o Polynuclear neutrophils > 750/mm^3, platelets > 75000/mm^3, in the ascending phase of hematological recovery,

o Creatinine clearance > 70 mL/min/1.73m^2, or cystatin C normal for age,

o Bilirubin <1.5N, ASAT and ALAT <2.5N.

- Audiogram every 2 cycles of platinum compounds.

- Cardiac ultrasound at least every 2 cycles of anthracycline. The shortening fraction (FR) must be greater than 28% and the ejection fraction (EF) of the left ventricle greater than 50% to the baseline.

Follow-up during chemotherapy (stage III and IV)

Tumor imaging must be performed post-operatively and then after 2 and 4 cycles of adjuvant chemotherapy.

Evaluation ideally must include the same examinations as at diagnosis:

- A thoraco-abdomino-pelvic CT or MRI in order to assess:

o the response to chemotherapy (tumor measurements in 3 dimensions),

o the operability of the primary tumor and metastases,

o vascular anatomical extension.

In case of a tumor response after first 2 cycles, it may be lawful to continue chemotherapy with 2 additional cycles in order to facilitate surgery.

- Other evaluation can be carried out during chemotherapy, depending on clinical course. Ultrasound or MRI imaging is preferable to X-ray or CT scan in these patients potentially having a *TP53* gene pathogenic variant. CT or abdominal ultrasound should be performed immediately after surgery, possibly accompanied by a PET-FDG scan to confirm complete remission. A thoraco-abdomino-pelvic CT scan or preferentially MRI should be performed at the end of adjuvant chemotherapy.

Assays for initially abnormal hormones should be performed every 2 cycles of chemotherapy. Hormone levels must be mainly repeated 8 to 10 days post-surgery, then at 1 month, then every 2 months for 2 years, every 3 months in the 3rd year, every 6 months up to 5 years in the absence of adjuvant treatment because their non-normalization or raise is a criterion of tumor persistence or recurrence and leads to the proposal a salvage treatment.

APPENDIX 2. CHEMOTHERAPY ADMINISTRATION SCHEME

CED (CDDP – ETOPOSIDE – DOXORUBICINE) course

Cisplatin: 50 mg/m² = _____ mg IV over 6 hours (in 100 mL/m² of 0.9% NaCl)
at D1 and D2

Pre-hydration and concomitant hydration (4 hours before and during Cisplatin):

1250 mL/m²/10 h	= _____ mL
(2.5% Glucose / 0.45 % NaCl)	
+ 20 mmol KCl / 1000 mL	= _____ mmol
+ 10 mmol $MgSO_4$ / 1000 mL	= _____ mmol
+ 12 g Mannitol / 1000 mL	= _____ g

Post-hydration (after Cisplatin):

1750 mL/m²/14 h	= _____ mL
(2.5% Glucose / 0.45 % NaCl)	
+ 20 mmol KCl / 1000 mL	= _____ mmol
+ 10 mmol $MgSO_4$ / 1000 mL	= _____ mmol

Doxorubicin: **25 mg/m² = _____ mg** IV over 4 hours (in 50mL of G5% or 0.9% NaCl)
at D4 and D5

Etoposide: 100 mg/m²/d = _____ mg/d IV over 1.5 hours (in 0,9% NaCl to obtain concentration < 0.4 mg/mL)
from D1 to D3

Diuresis monitoring

If diuresis <2/3 of the input, give Mannitol 20% 40 mL/m² IV over 30 minutes

NB: For children < 10 kg or < 12 months reduce dosage according to the age and body weight

GPOH-MET NN1 course

Vincristine: 1.5 mg/m² = _____ **mg** IV over 10 minutes (maximal dose 2.0 mg)
at D1 and D8

Ifosfamide: 1000 mg/m²/d = _____ **mg/d** IV over 1 hour (in 250 mL of 0.9% NaCl)
from D1 to D5

Hydration (15 minutes before, during, and 12 hours after the last dose of Ifosfamide):

2000 mL/m²/d	= _____ mL/d
(2.5% Glucose / 0.45 % NaCl)	
+ 20 mmol KCl / 1000 mL	= _____ mmol/d
+ 10 mmol $MgSO_4$ / 1000 mL	= _____ mmol/d

Uromitexan (continuous infusion, concomitant to hydratation):

1200 g/m²/d	= _____ g/d

Doxorubicin: **35 mg/m² =** _____ **mg** IV over 4 hours (in 50 mL of G5% or 0.9% NaCl)
at D2 and D4

Diuresis monitoring

If diuresis <2/3 of the input, give Furosemide 0.5 mg/kg IV over 10 minutes

GPOH-MET NN2 course

Etoposide: 100 mg/m²/d = _____ **mg/d** IV over 2 hours (in 0.9% NaCl to obtain concentration < 0.4 mg/mL)
from D1 to D5

Carboplatin: 125 mg/m²/d = _____ **mg/d** IV over 1 hour (in 100 mL of G5% or 0.9% NaCl)
from D1 to D5

NB: For children < 10 kg or < 12 months reduce dosage according to the age and body weight

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