European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

19/01/2023

Dr Marta Martos Rodríguez
Dr Paraskevi Panagopoulou

ADRENOCORTICAL TUMORS IN CHILDREN AND ADOLESCENTS

Moderation: Dr Calogero Virgone

Funded by the European Union's EU4Health Programme

SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

COI declaration

Disclosures

I *DO NOT* HAVE ANY RELATIONSHIPS WITH COMMERCIAL INTERESTS TO DISCLOSE.

I *DO NOT* INTEND TO REFERENCE UNLABELED OR UNAPPROVED USES OF DRUGS OR PRODUCTS IN MY PRESENTATION.

Background

- Pediatric ACTs are rare and potentially aggressive endocrine malignancies
- Associated with **Li-Fraumeni** syndrome (50-65%), Beckwith-Wiedemann, MEN 1
- 0.2% of all childhood cancer
- 0.2 new cases per 1 million children per year
  * Southern Brazil (TP53 pathogenic variant Arg337His)
- Male:Female = 1:2
- Two peaks of incidence
  * < 3 years
  * Adolescence

Classification

Adrenocortical adenoma (ACA)	Adrenocortical carcinoma (ACC)
20%	80%
Benign	Highly malignant
Excellent prognosis	5 year survival 20-80%

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Poor outcome

- Age > 4 years
- Tumor size
- Cushing syndrome at diagnosis
- Incomplete resection
- Higher stage

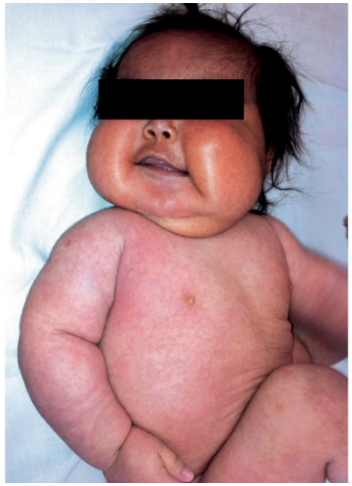
Clinical prognostic factors in pediatric adrenocortical tumors: A meta-analysis

Elisa Zambaiti[1] | Miriam Duci[1] | Federica De Corti[1] | Piergiorgio Gamba[1] | Patrizia Dall'Igna[2] | Filippo Ghidini[1] | Calogero Virgone[1]

Initial tumour assessment

- High variability of signs/symptoms
  - * Abdominal pain/mass effect
  - * Fatigue
  - * Cushing syndrome (15-40%)
  - * Virilization (80%) / Feminization (7%)
  - * Hyperaldosteronism (1-4%)

<10% **NON-FUNCTIONAL** tumors (older children and adolescents)



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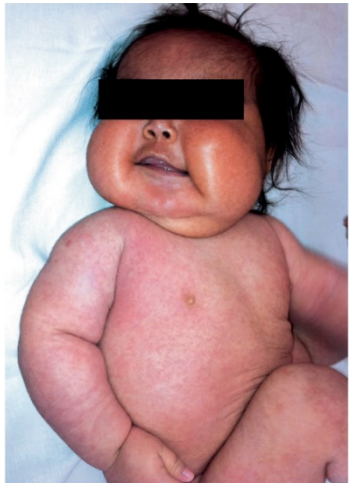
AVOID BIOPSY

Worse prognosis



Diagnosis

- **Hormonal assessment**: ACTH, cortisol, 17-OHP, androstenedione, DHEA-S, testosterone, estradiol, renin and aldosterone
- Pelvic and abdominal **ULTRASOUND** with doppler
- Pelvic/abdominal **MRI** or CT scan

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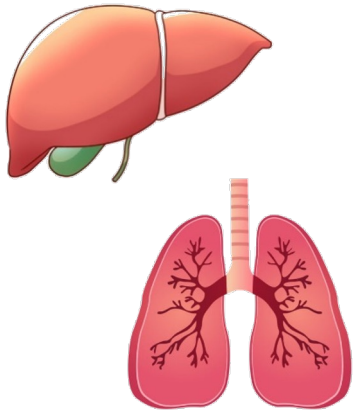
Distant metastases

- **Chest CT scan**
- PET-scan / PET-MRI
- Brain MRI



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- **Hormonal assessment**: ACTH, cortisol, 17-OHP, androstenedione, DHEA-S, testosterone, estradiol, renin and aldosterone
- Pelvic and abdominal **ULTRASOUND** with doppler
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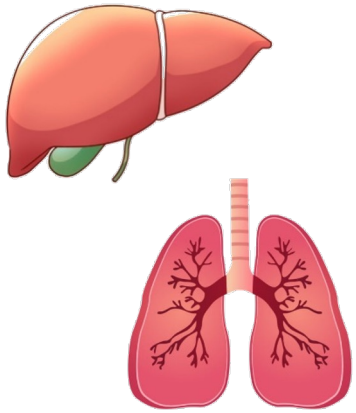
Genetic counseling

Endocrinologist evaluation

Distant metastases

- **Chest CT scan**
- PET-scan / PET-MRI
- Brain MRI



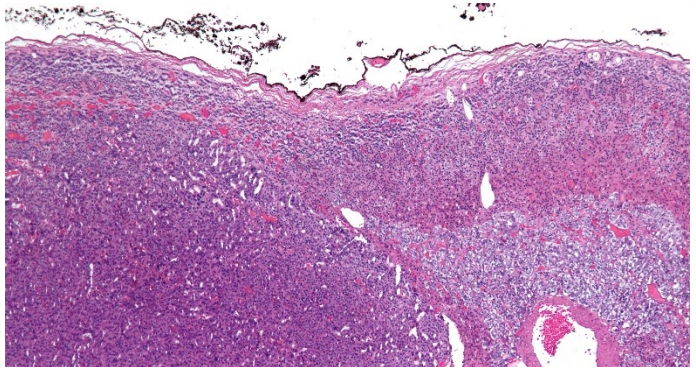
Histopathological evaluation

- Mandatory for diagnosis confirmation
- Pathologist with experience in pediatric tumors

Frozen sample

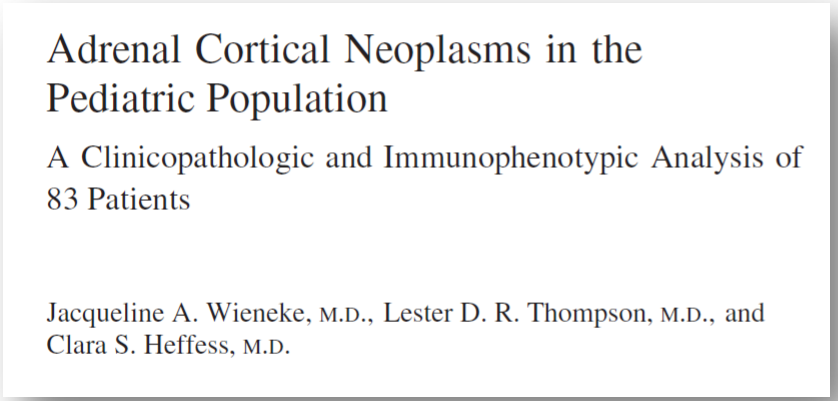
Blood sample

Biological studies



- Histology and genic expression profile **different to adult's tumors**
- Difficult to differentiate BENIGN from MALIGNANT

Wieneke index



Adrenal Cortical Neoplasms in the Pediatric Population

A Clinicopathologic and Immunophenotypic Analysis of 83 Patients

Jacqueline A. Wieneke, M.D., Lester D. R. Thompson, M.D., and Clara S. Heffess, M.D.

TABLE 8. *Proposed criteria for malignancy of adrenal cortical neoplasms in pediatric patients*

Macroscopic and microscopic criteria for malignancy of adrenal cortical neoplasms in pediatric patients
Tumor weight of >400 g
Tumor size >10.5 cm
Extension into periadrenal soft tissues and/or adjacent organs
Invasion into vena cava
Venous invasion
Capsular invasion
Presence of tumor necrosis
>15 mitoses per 20 HPF
Presence of atypical mitotic figures

HPF, high-power field (400×).

9 histological criteria

- ≤ 2 → BENIGN
- 3 → INDETERMINATE
- > 3 → MALIGNANT

5-item microscopic score

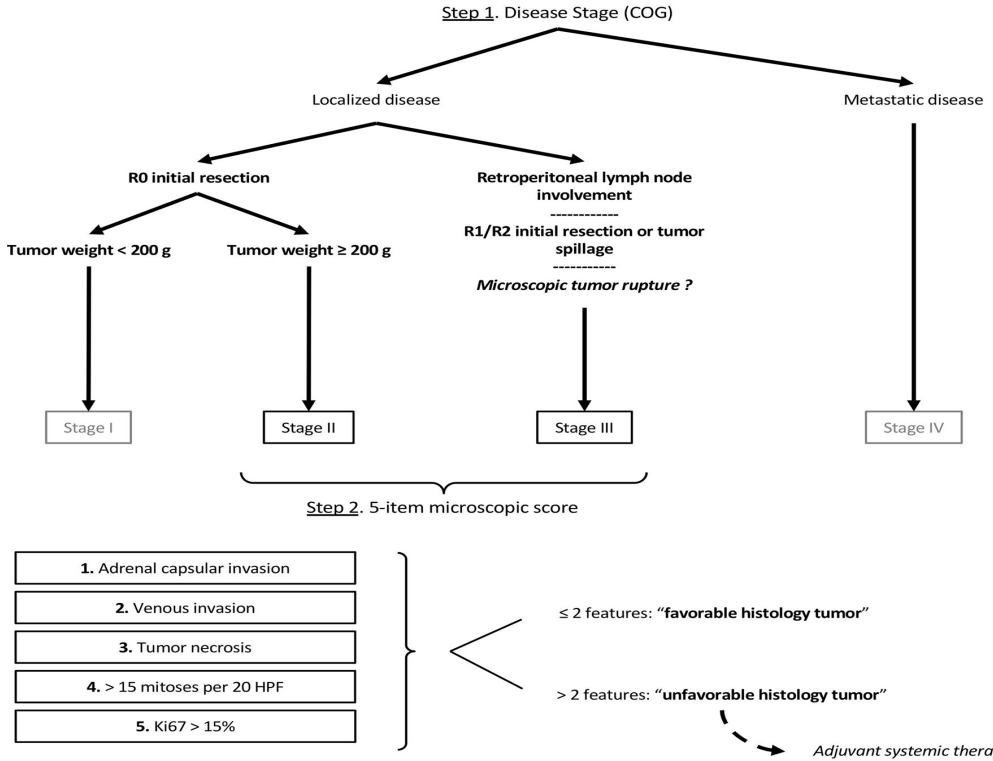
Modern Pathology (2019) 32:546–559
https://doi.org/10.1038/s41379-018-0174-8

USCAP

ARTICLE

Revisiting the role of the pathological grading in pediatric adrenal cortical tumors: results from a national cohort study with pathological review

Cécile Picard[1] · Daniel Orbach[2] · Matthieu Carton[3] · Laurence Brugieres[4] · Karine Renaudin[5] · Sébastien Aubert[6] · Dominique Berrebi[7] · Louise Galmiche[8] · Fanny Dujardin[9] · Pierre Leblond[10] · Cécile Thomas-Teinturier[11,12] · Frédérique Dijoud[1]



Staging system - COG

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

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LOCAL / SURGICAL TREATMENT

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Treatment - SURGERY

Complete tumor resection is a major prognostic factor

Surgery is the basis of treatment for localized ACT

Tumor rupture (pre or intraoperatively) → ↑ risk of locoregional recurrence (almost fatal outcome)

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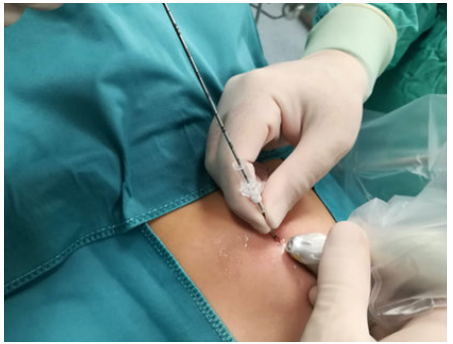
AVOID BIOPSY!

Limited to

- Non-secreting tumors
- Metastatic disease
- Unresectable primary tumor

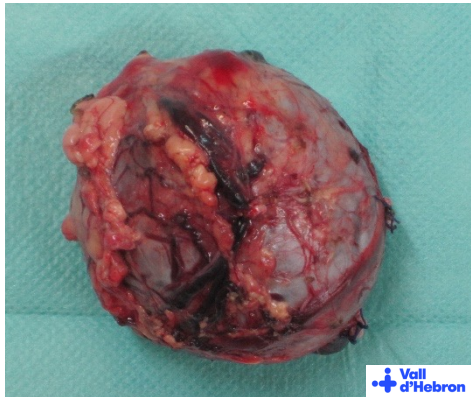


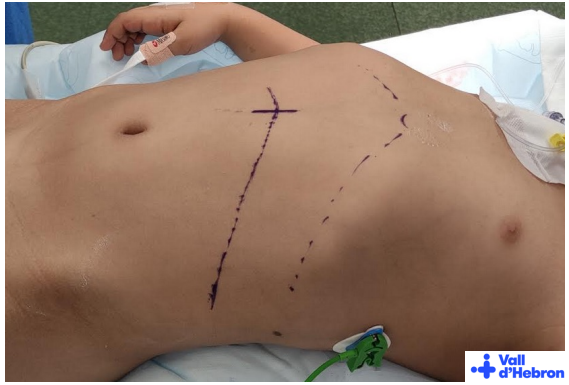
Posterior approach

Treatment - SURGERY

PRIMARY TUMOR

- Experienced surgeons
- Complete en-bloc resection
- Up to 20% of tumor rupture at initial excision (friable tumor)



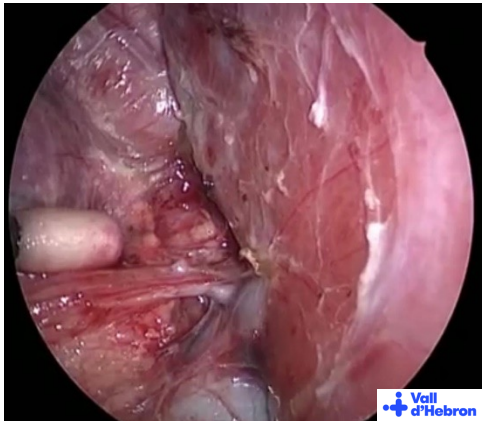


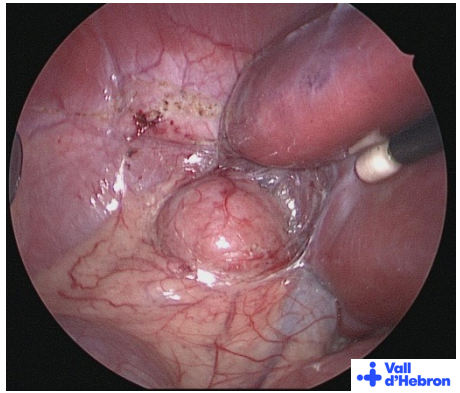
- **<u>Transverse</u>** or midline laparotomy
- Nephrectomy is accepted to ensure free margins
- Thrombosis of vena cava – ECMO?

Treatment - SURGERY

Minimally invasive resection of adrenal masses in infants and children: results of a European multi-center survey

Francesco Fascetti-Leon[1] · Giovanni Scotton[1] · Luca Pio[2] · Raimundo Beltrà[3] · Paolo Caione[4] · Ciro Esposito[5] · Girolamo Mattioli[6] · Amulya K. Saxena[7] · Sabine Sarnaki[2] · Piergiorgio Gamba[1]





- Small non-infiltrating, non-metastatic tumors (ACA)
- Strongly discouraged if malignancy is suspected
- Tertiary care centers and surgeons experienced in oncologic and adrenal surgery

> 200 cm3

Suspicious nodal involvement

Local invasion

Open laparotomy

Treatment - SURGERY

REGIONAL LYMPH NODES

- All suspicious or enlarged lymph nodes
- Systematic biopsy of the regional nodes
- Suspicious or proven ACC → Routine locoregional lymphadenectomy (periadrenal and renal hilum)
- No systematic RPLND is advised (controversial)

Treatment - SURGERY

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- All suspicious or enlarged lymph nodes
- Systematic biopsy of the regional nodes
- Suspicious or proven ACC → Routine locoregional lymphadenectomy (periadrenal and renal hilum)
- No systematic RPLND is advised

METASTASES

- Aggressive approach (complete surgery + chemotherapy + mitotane) if clearance is feasible and good clinical condition
- Timing and indication should be discussed within **MDT**

Case Report

- 15-month-old girl
- Referred for VIRILIZATION
- Family history:
  * Aunt (paternal line): Breast cancer at age 31
  * Father's cousin: ACC at 1 year of age
  * Paternal uncle: Lung cancer at 60 years of age
  * Paternal aunt: Breast cancer at 27 years old
- Study of predisposition syndromes:

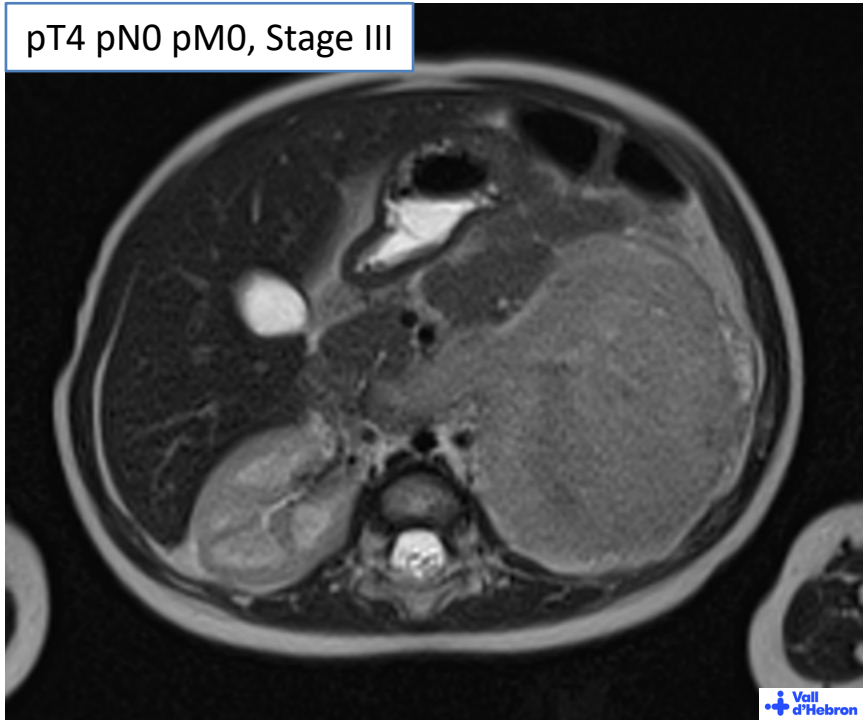
Diagnosis **Li Fraumeni syndrome**

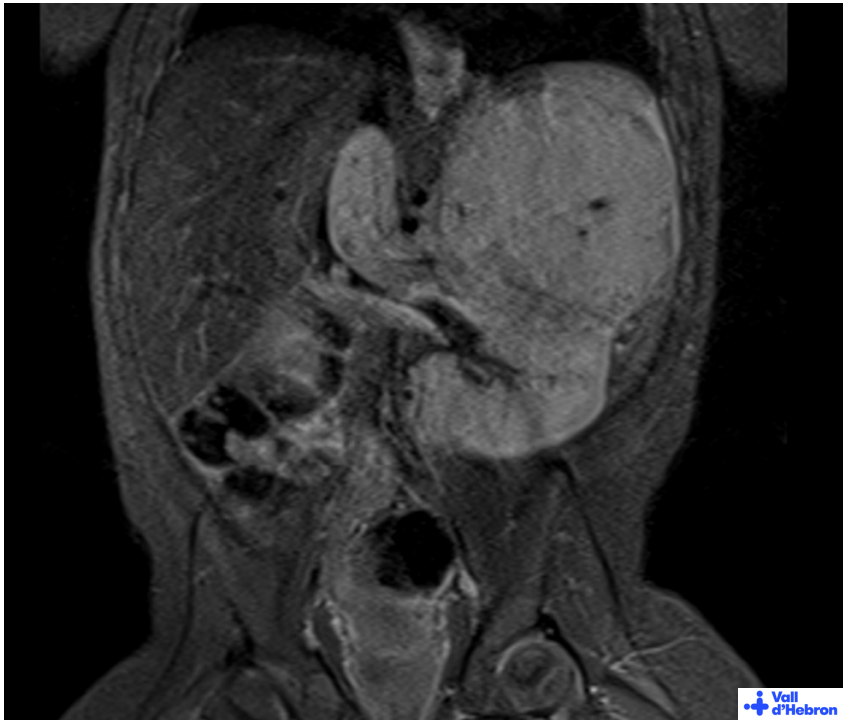
(germline heterozygous mutation, variant c. 1010G>A (p.Arg337His)

Case Report

AT DIAGNOSIS

pT4 pN0 pM0, Stage III



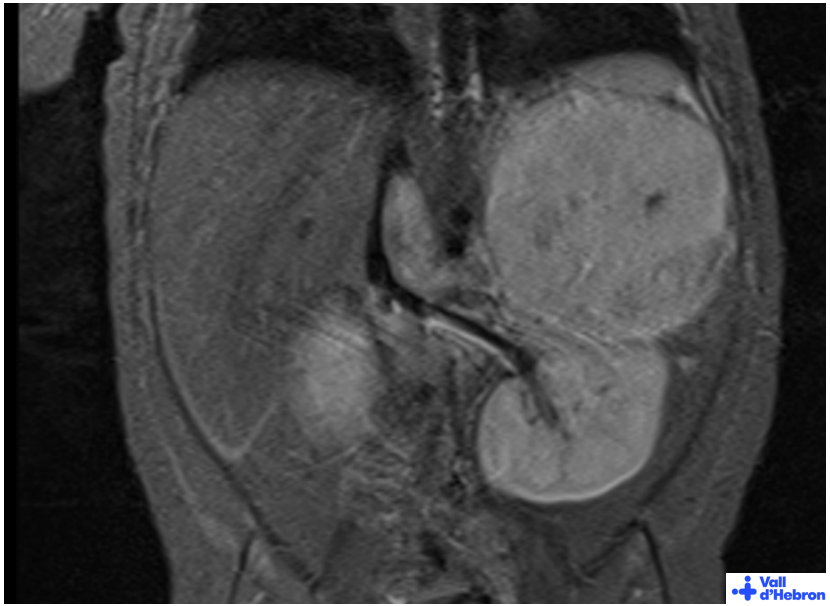


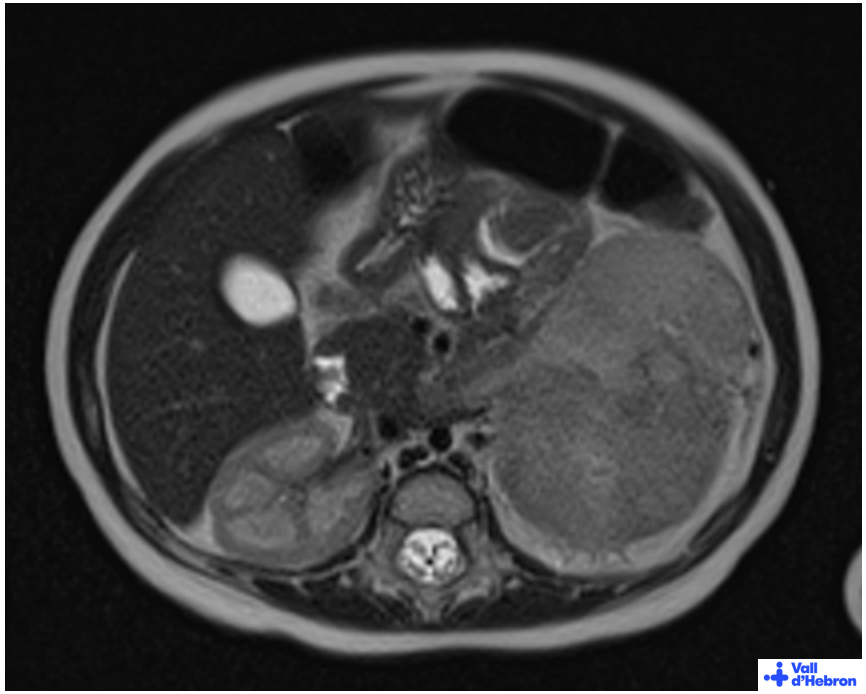
Case Report

COG ARAR0332

Evaluation after 2 cycles of

Cisplatine, Adriamicine and Mitotane

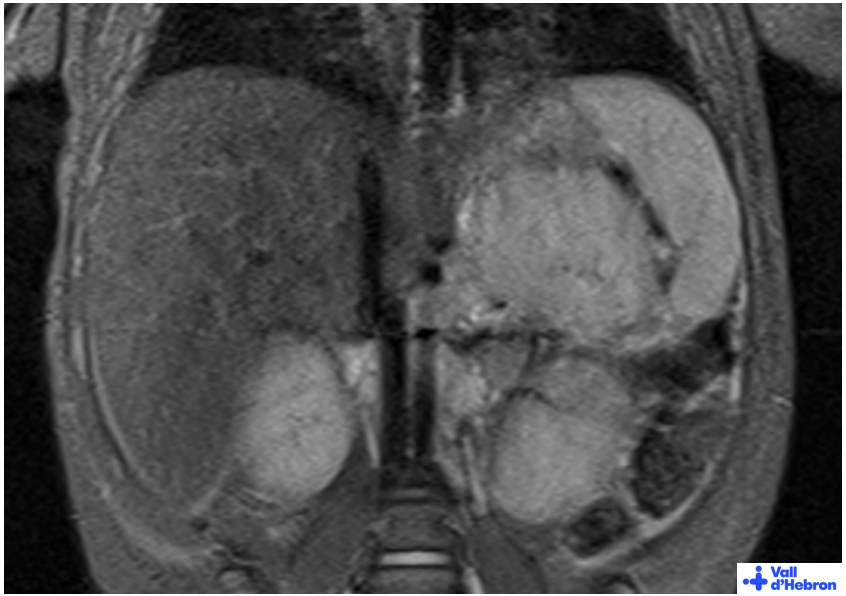


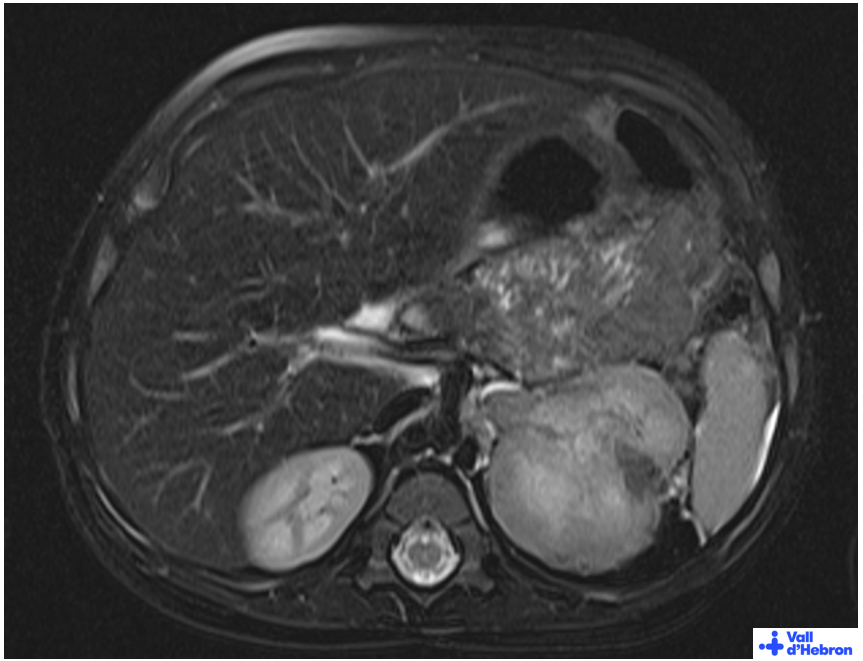


Case Report

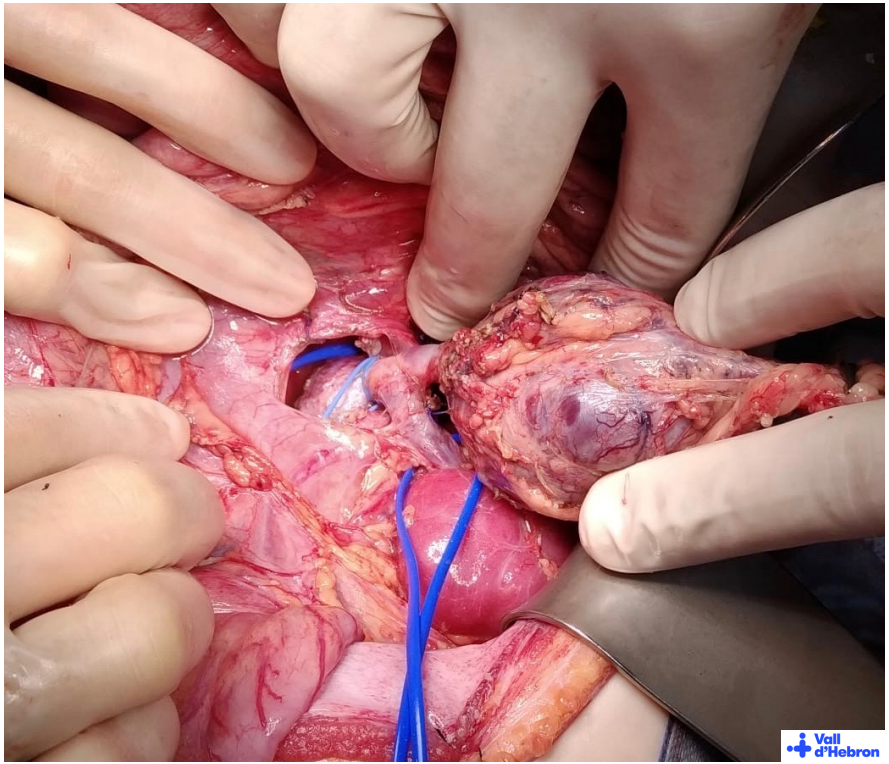
COG ARAR0332

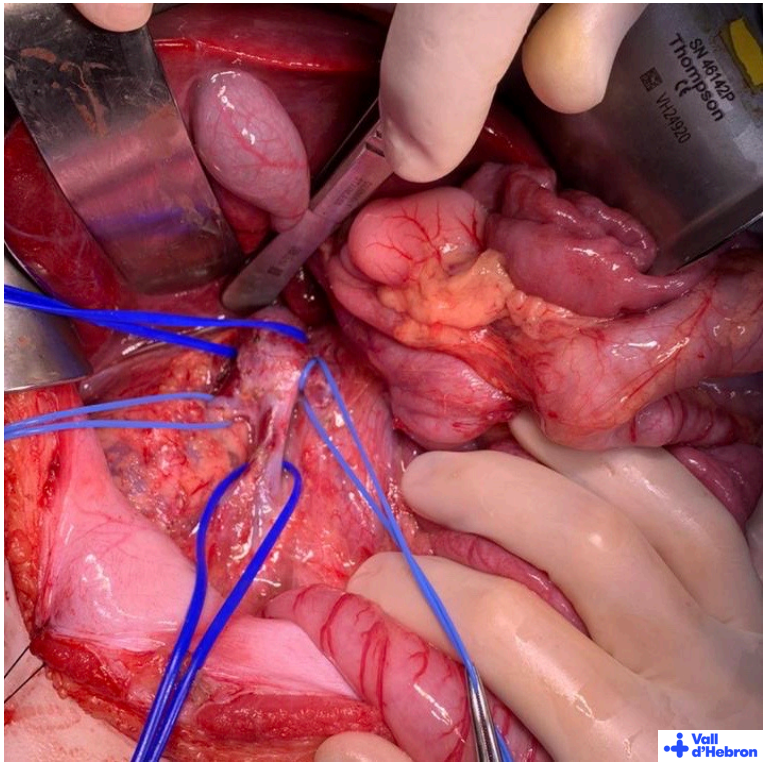
Evaluation after 5 cycles





Case Report

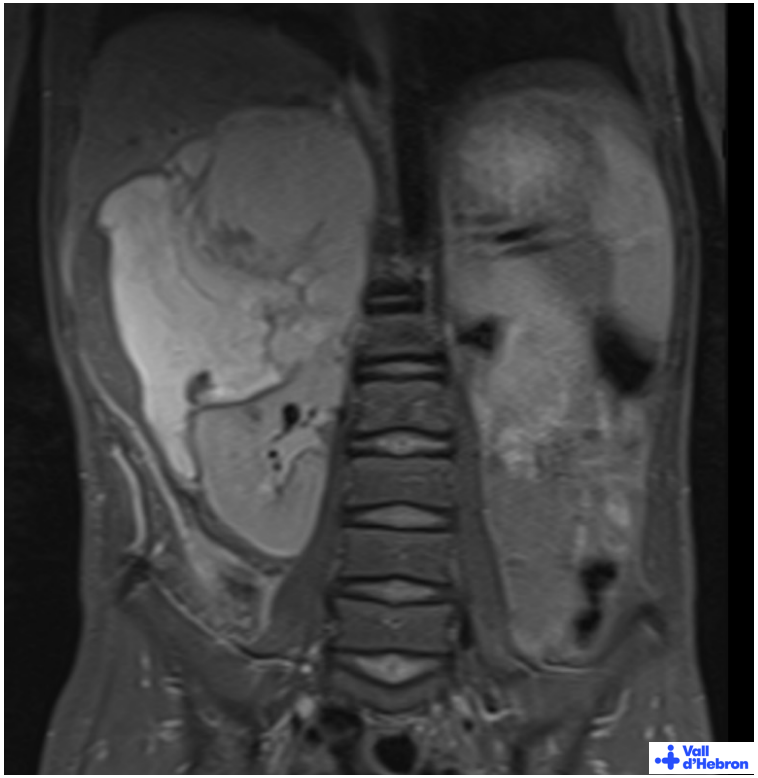


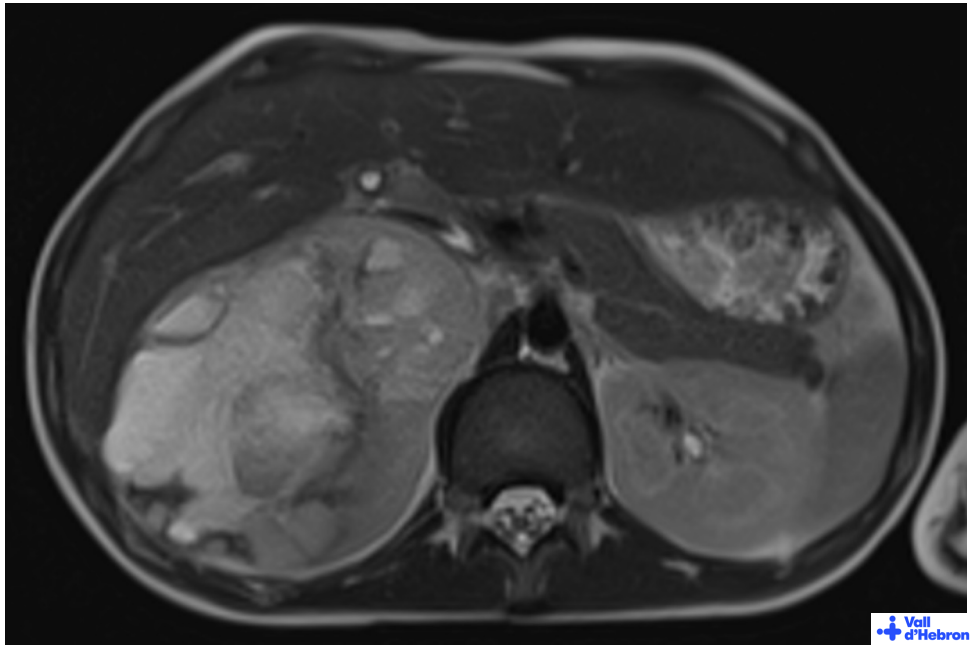


Case Report

- 9 year-old boy
- Referred from another county for ADRENOCORTICAL CARCINOMA
  * R2 resection. Tumoral rupture. → Stage III
- Palpable mass in right hypochondrium, subcostal transverse laparotomy, tumor implant at abdominal drain scar

Case Report

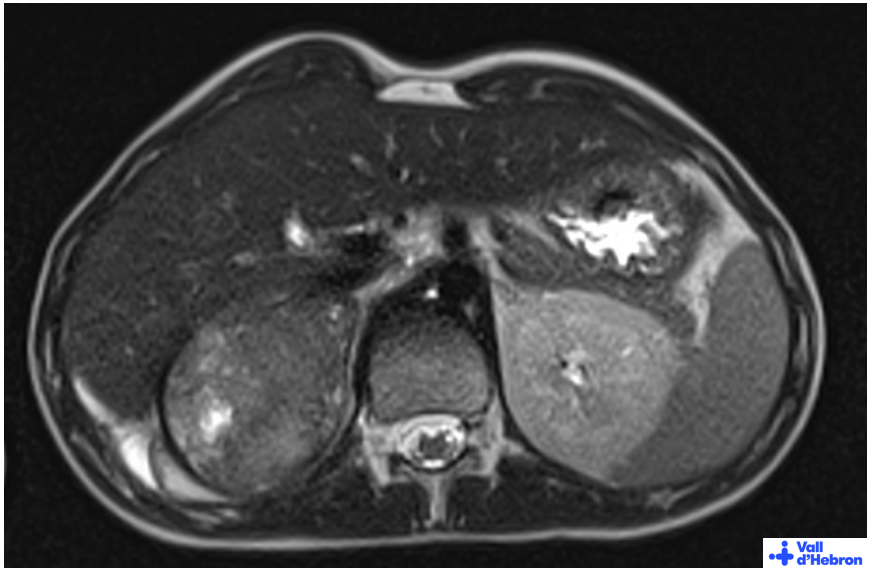


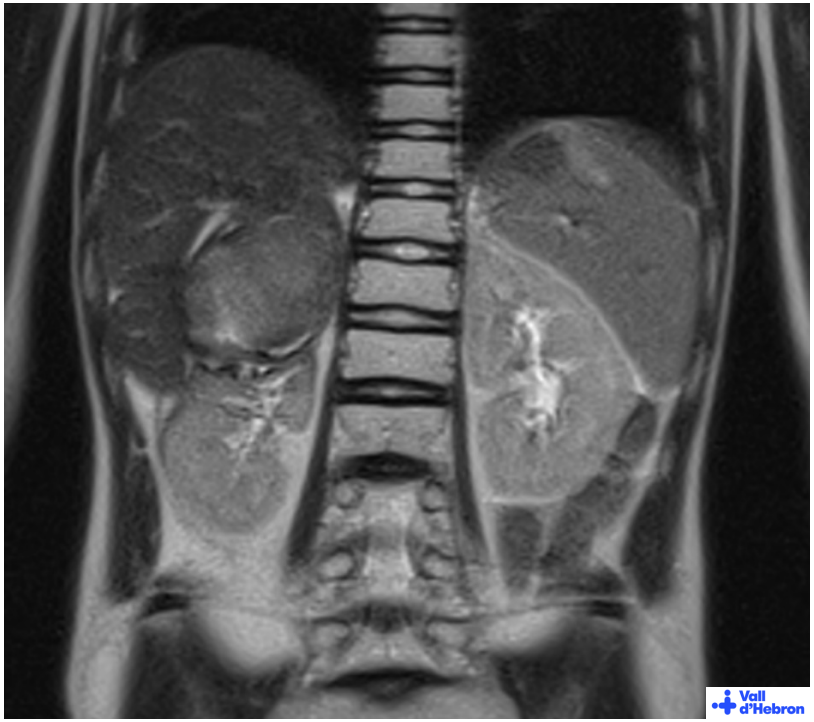


Case Report

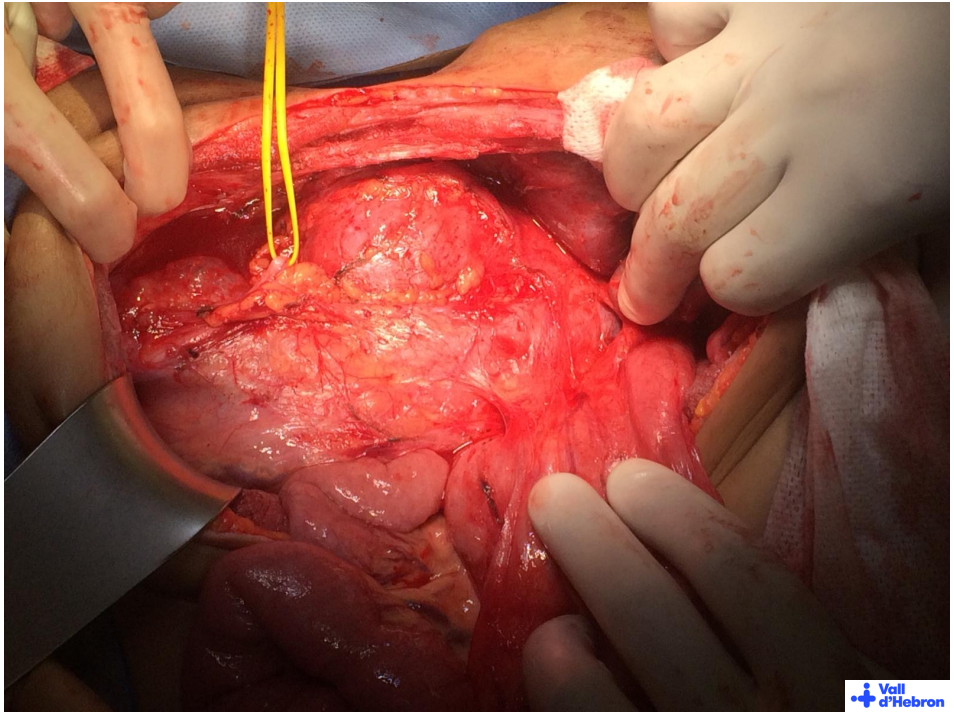
COG ARAR0332

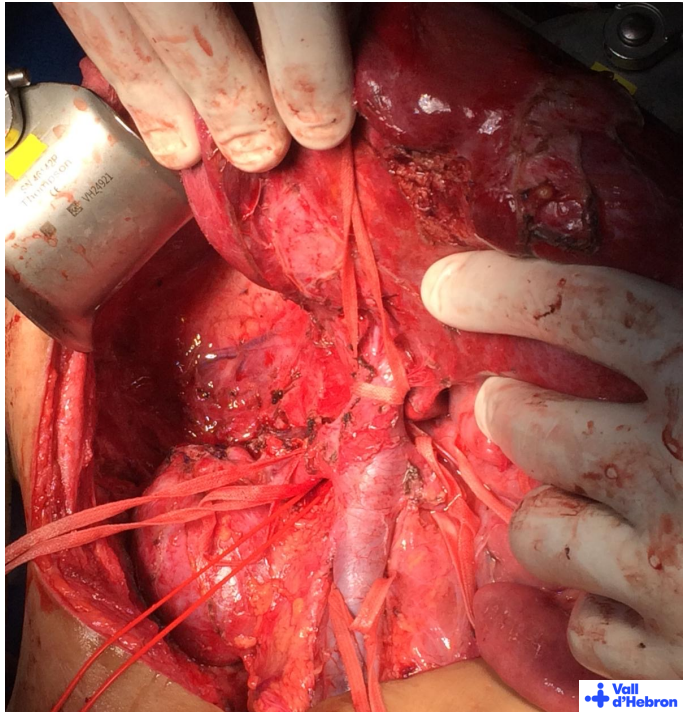
- 5 cycles of Cisplatine, Adriamicine and Mitotane





Case Report





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SYSTEMIC / MEDICAL TREATMENT

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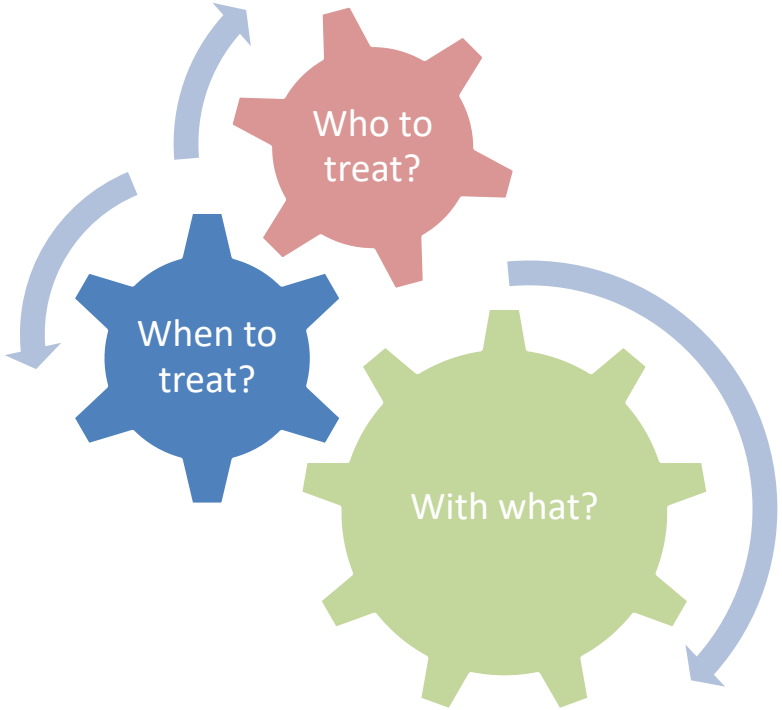
Medical therapy



3 questions

1. Who to treat?
2. When to treat?
3. With what?

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1. WHO TO TREAT?

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Chemotherapy - Who to treat

- **Stage I:** all resectable lesions should have **upfront surgical resection** (aim for complete, avoid spillage). NO need for systemic therapy.

  [Level III; Grade A]

- **All other stages**: Some form of chemotherapy is recommended either **before** surgical excision, **after** or **both**.

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2. WHEN TO TREAT?

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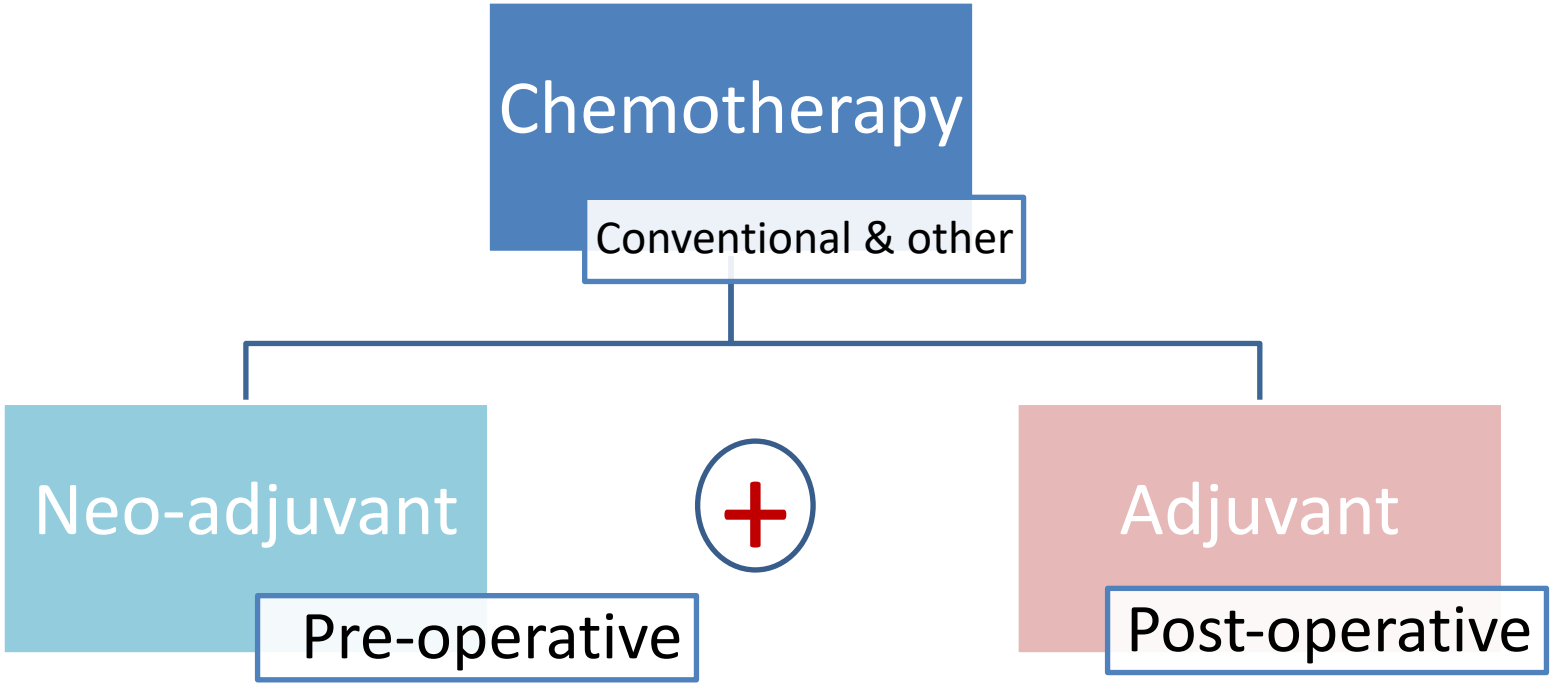
When to treat?



Chemotherapy – When to treat?

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Neo adjuvant (pre-op) conventional chemotherapy

(+ mitotane and delayed surgical excision) should be considered for patients with:

1. Unresectable (Stage III) and/or metastatic (Stage IV) tumours with regular monitoring according to RECIST criteria [Level IV; Grade C]
2. Large tumours with local invasion/regional nodes involvement
3. Large tumours with high risk of intraoperative rupture [Level III; Grade A]

- 2-4 cycles of neoadjuvant chemotherapy with CED or NN1/NN2 then
- Complete **delayed resection** of the primary tumor and combined or delayed resection of metastatic site(s) if possible, depending on response to neo-adjuvant treatment.

Chemotherapy – When to treat?

Adjuvant (post-op) conventional chemotherapy

should be considered in case of advanced-stage ACC or incomplete tumor resection

[Level IV; Grade B]

- **Adjuvant chemotherapy + mitotane** is proposed for **Stage III** isolated malignant ACC, tumor rupture, in children >4 years or in non-normalization of hormonal markers

BUT [Level IV; Grade C]

- **Adjuvant chemotherapy** is debatable is children <4 years with isolated capsular tumor rupture + histologically proven ACC (discuss in MDT)

[Level IV; Grade C]

Metastases (Stage IV)

- For metastatic cases, an aggressive approach combining **neoadjuvant** and **adjuvant** chemotherapy **plus mitotane** with **aggressive (complete) surgery**, is recommended and should aim to clear the primary tumor and metastatic sites as much as possible.

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3. WITH WHAT TO TREAT?

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Chemotherapy – With what?

- ACC: generally resistant to chemotherapy
- Regimens derive from standard treatments used in adults

First-line (conventional chemo) recommended regimens are:

- **CED** (cisplatin- doxorubicin-etoposide)
- **NN1/NN2** (vincristine-ifosfamide-doxorubicin and carboplatin-etoposide)

[Level IV; Grade B]

Second-line or salvage therapies: There is **no consensus,** they should be considered on an individual basis, supplemented with **genetic analysis of molecular targets**

[Level IV; Grade C]

Chemotherapy – With what?

- **+ MITOTANE** : cytostatic agent usually added to standard chemotherapy
- **Stage II** & some **Stage III** (with spillage): **mitotane alone** is considered if several risk factors are associated:
  - unfavourable histology (5-item score or Wieneke score >3)
  - older age
  - hormonal secretion.

[Level IV; Grade C]

- **Stage III + IV:** in combination with conventional chemo

Conventional chemotherapy -1

- There is no evidence-based optimal chemotherapy established for children (as no prospective RCTs)

[Level III, grade C]

- The GPOH and the COG , investigated the use of standard chemotherapy.
- **IPACTR (CED)**
- **254 ACT patients**

(Michalkiewicz et al JCO, 2004)

VOLUME 22 · NUMBER 5 · MARCH 1 2004

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Clinical and Outcome Characteristics of Children With Adrenocortical Tumors: A Report From the International Pediatric Adrenocortical Tumor Registry

E. Michalkiewicz, R. Sandrini, B. Figueiredo, E.C.M. Miranda, E. Caran, A.G. Oliveira-Filho, R. Marques, M.A.D. Pianovski, L. Lacerda, L.M. Cristofani, J. Jenkins, C. Rodriguez-Galindo, and R.C. Ribeiro

IPACTR study (JCO, 2004)

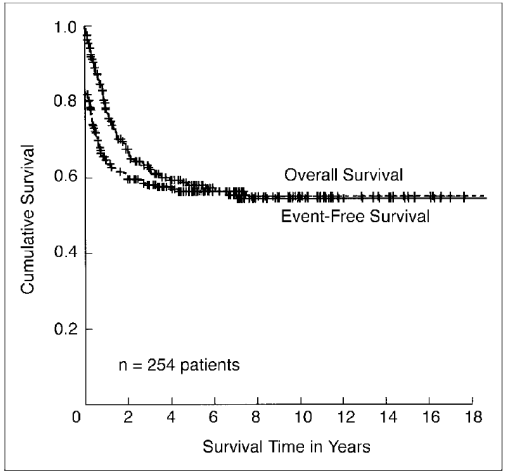


Fig 2. The probability of 5-year event-free survival and survival estimates was 54.2% (95% CI, 48.2% to 60.2%) and 54.7% (95% CI, 48.7% to 60.7%), respectively.

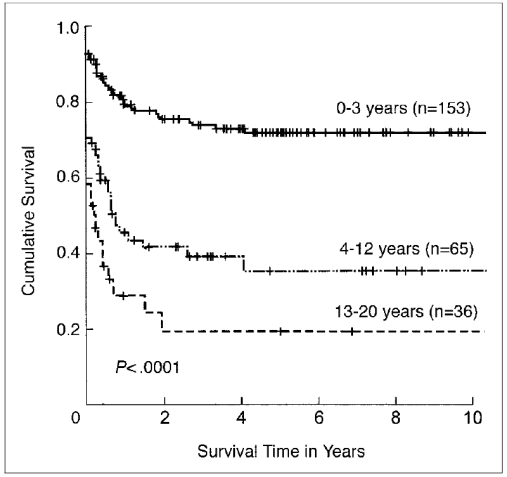


Fig 3. Probability of 5-year event-free survival according to age at the time of diagnosis in 254 patients with adrenocortical tumor.

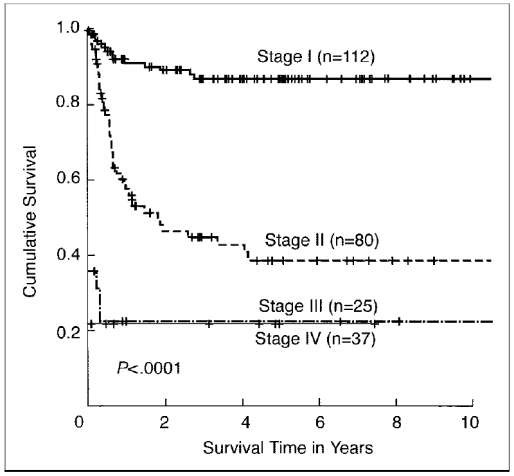


Fig 4. Probability of 5-year event-free survival according to disease stage at the time of diagnosis in 254 patients with adrenocortical tumor.

Conventional chemotherapy -CED

original reports

Treatment of Pediatric Adrenocortical Carcinoma With Surgery, Retroperitoneal Lymph Node Dissection, and Chemotherapy: The Children's Oncology Group ARARO332 Protocol

Carlos Rodriguez-Galindo, MD[1,2]; Mark D. Krailo, PhD[3,4]; Emilia M. Pinto, PhD[5]; Farzana Pashankar, MD[6]; Christopher B. Weldon, MD[7]; Li Huang, MS[3]; Eliana M. Caran, MD[8]; John Hicks, MD[9]; M. Beth McCarville, MD[10]; David Malkin, MD[11]; Jonathan D. Wasserman, MD, PhD[12]; Antonio G. de Oliveira Filho, MD[13]; Michael P. LaQuaglia, MD[14]; Deborah A. Ward, PharmD[15]; Gerard Zambetti, PhD[5]; Maria J. Mastellaro, MD[16]; Alberto S. Pappo, MD[1]; and Raul C. Ribeiro, MD[1]

Rodrigues-Galindo et al, J Clin Oncol 2021; 39:2463.

- ARAR0332 protocol:
- Study by COG & Brazilian hospitals

Aim:

1. To describe the outcome of Stage I ACC treated with adrenalectomy alone
2. To describe the outcome of Stage II ACC (completely resected >200 cc or >100 g) treated with adrenalectomy and retroperitoneal lymph node dissection; and
3. To describe the outcome of Stage III or IV ACC treated with **cisplatin-based chemo + mitotane (i.e. to evaluate the impact on unresectable and metastatic disease).**

COG-ARAR0332 protocol -STRATEGY

TABLE 1. Stage and Treatment Administered in ARAR0332

Stage	Definition	Treatment
I	Completely resected, small tumors (< 100 g and < 200 cm^3) with normal postoperative hormone levels	Surgery
II	Completely resected, large tumors (≥ 100 g or ≥ 200 cm^3) with normal postoperative hormone levels	Surgery plus RPLND
III	Unresectable, gross, or microscopic residual disease Tumor spillage patients with stage I and II tumors who fail to normalize hormone levels after surgery Patients with retroperitoneal lymph node involvement	Surgery plus RPLND Cisplatin, etoposide, and doxorubicin × 8 cycles Mitotane × 8 months
IV	Presence of distant metastases	Surgery plus RPLND Cisplatin, etoposide, and doxorubicin × 8 cycles Mitotane × 8 months

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

COG-ARAR0332 protocol - RESULTS

	5-year EFS	5-year OS
• Stages I (24 patients)	86.2%	95.2%
• Stage II (15 patients)	53.3%	78.8%
• Stage III (24 patients)	81%	94.7%
• Stage IV (14 patients)	7.1%	15.6%

On univariate analysis:

- age, stage, virilization, Cushing syndrome or hypertension, germline TP53 status, and presence of a **somatic ATRX mutation** were associated with outcome.

On multivariable analysis:

- only **stage** and **age** were significantly associated with outcome.

COG-ARAR0332 protocol - CONCLUSIONS

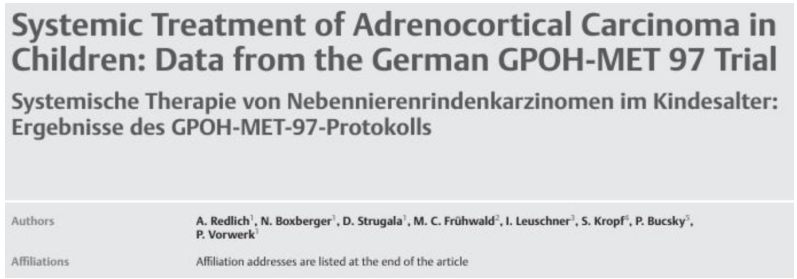
- Stage I : excellent outcome with surgery.
- Stage II: inferior outcome despite **retroperitoneal lymph node dissection**.
- Stage III : excellent outcome combining **surgery and chemotherapy**.
- Stage IV : are older and have a poor outcome

*****New treatments should be explored for this high-risk group. *****

COG-ARAR0332 protocol - CONCLUSIONS

- The **combination of mitotane** and **chemotherapy** as prescribed in ARAR0332 resulted in significant **toxicity.**
- **Up to 1/3** of patients with advanced disease could **not** complete the scheduled treatment.
- Other groups from Europe (TREP, FRACTURE) have used the **same** drugs in slightly **different regimens** but with **similar** results.

German POH-MET 97 trial



Systemic Treatment of Adrenocortical Carcinoma in Children: Data from the German GPOH-MET 97 Trial

Systemische Therapie von Nebennierenrindenkarzinomen im Kindesalter: Ergebnisse des GPOH-MET-97-Protokolls

Authors: A. Redlich[1], N. Boxberger[1], D. Strugala[1], M. C. Frühwald[2], I. Leuschner[3], S. Kropf[4], P. Bucsky[5], P. Vorwerk[1]

Affiliations: Affiliation addresses are listed at the end of the article

Redlich et al, Klin Padiatr 2012; 224:366

They used 2 different **alternating** courses **ALSO** combined with **mitotane**:

- one with **vincristine, ifosfamide and doxorubicin** (**NN1**), and the
- second with **carboplatin and etoposide** (**NN2**).

Compared to historical controls, EFS and OS were

- stage II (44% and 70%)
- stage III (25% and 75%)
- stage IV (36% and 51%)

were better, without severe A/E, but maybe there is a confounding factor.

Conclusions:

1. Duration of mitotane >6 months and levels >14 mg/l -- significantly better survival.
2. Local relapse was associated with worse prognosis compared to distant mets only.

Outcome for Pediatric Adreno-Cortical Tumors Is Best Predicted by the COG Stage and Five-Item Microscopic Score—Report from the German MET Studies

Michaela Kuhlen [1,*], Marina Kunstreich [1,2], Stefan A. Wudy [3], Paul-Martin Holterhus [4], Lienhard Lessel [2], Dominik T. Schneider [5], Ines B. Brecht [6], Denis M. Schewe [2], Guido Seitz [7], Christoph Roecken [8], Christian Vokuhl [9], Pascal D. Johann [1], Michael C. Frühwald [1], Peter Vorwerk [2] and Antje Redlich [2]

- Risk prediction, retrospectively assigned to the COG stages and the five-item score.
- 01/ 1997- 12/ 2021: 161 patients with ACT
- ACA n = 51, ACx n = 19, ACC n = 91)
- Median age = 4.3 years (range: 0.1–17.8)
- Lymph node and distant metastases in 10.7% and 18.9% of the ACC/ACx.
- Mean follow-up = 4.5 years (range of 0–16.7).
- 3-year (OS) and EFS (EFS) rates were 65.5% and 50.6%.

Outcome for Pediatric Adreno-Cortical Tumors Is Best Predicted by the COG Stage and Five-Item Microscopic Score—Report from the German MET Studies

Michaela Kuhlen [1,*], Marina Kunstreich [1,2], Stefan A. Wudy [3], Paul-Martin Holterhus [4], Lienhard Lessel [2] Dominik T. Schneider [5], Ines B. Brecht [6], Denis M. Schewe [2], Guido Seitz [7], Christoph Roecken [8], Christian Vokuhl [9], Pascal D. Johann [1], Michael C. Frühwald [1], Peter Vorwerk [2] and Antje Redlich [2]

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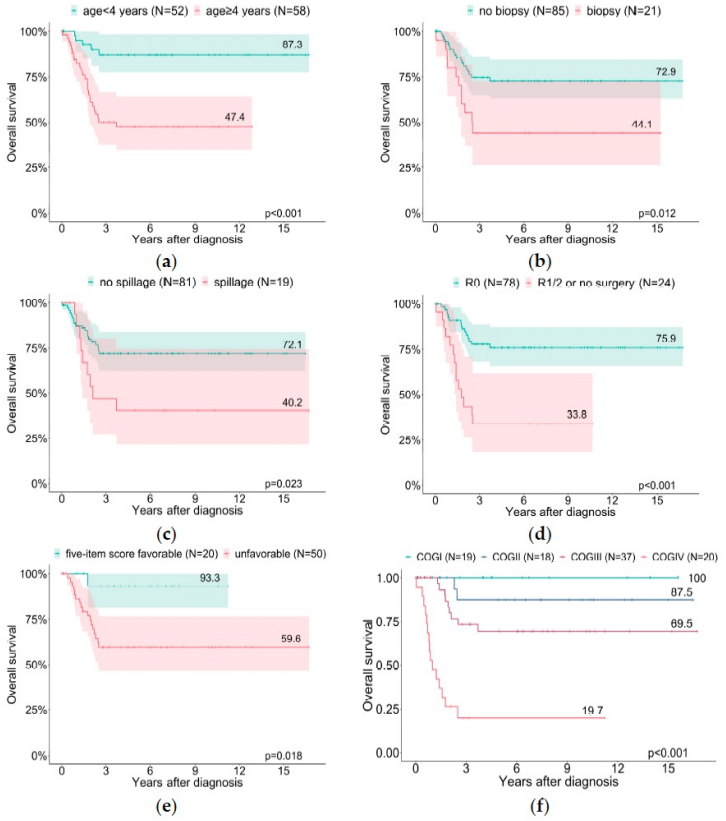
- **Univariate**: > 4 years, with initial biopsy, tumor spillage, incomplete tumor resection , unfavorable histology, COG stages III/IV impaired OS
- **Multivariate**: COG stages III/IV and an unfavorable five-item score: independent negative prognostic factors for EFS and OS.
- **Conclusions**: Age defines the clinical presentation and prognosis in pediatric ACTs. Outcome is best predicted by the COG stage and five-item score.



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DETAILS OF CHEMOTHERAPY

Co-funded by the European Union's Health Programme

SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

CHEMOTHERAPY REGIMENS-1

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.**

Duration: 6 to 8 cycles (limited data)

CHEMOTHERAPY REGIMENS-1

- **Hydration protocol**
- Cisplatin at these doses may be poorly tolerated digestively, esp. in adolescents.
- Highly emetogenic: **intensive anti-emetic** treatment needed
- **Besides the discomfort felt and the risk of dehydration, this digestive intolerance can make it difficult to take mitotane orally.**
- Mitotane levels may be lower than expected, due to digestive intolerance leading to vomiting mitotane.
- (We have to take this into account before any modification of the mitotane dose! and therefore not to increase it systematically, especially due to variable but very long half-life of mitotane).
- **G-CSF** is recommended in case of neutropenia.

CHEMOTHERAPY REGIMENS-2

GOPH – MET 97

- **NN1 regimen**

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

- **NN2 regimen**

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

Given every 21 days
Duration: 4 to 8 cycles
(limited data)

GPOH-MET therapy stratification

ACC:

- ***Stage I, II, stage III*** *completely resected, no LN metastases (****T3, N0, M0****)*

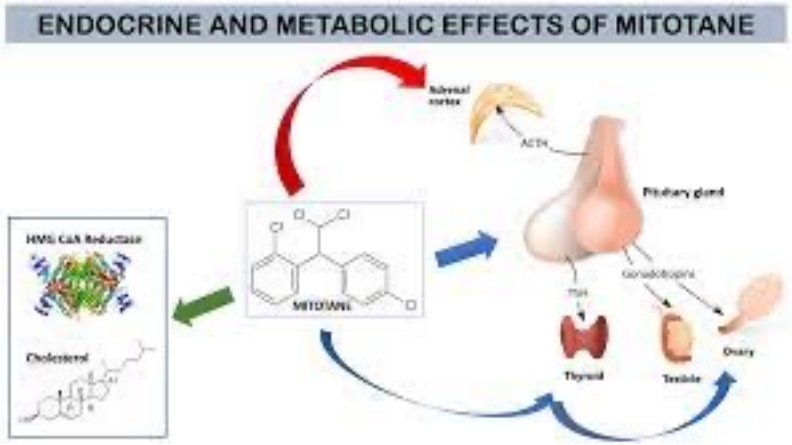
  → Watch-and-wait

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

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

- ***Stage IV***

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



MITOTANE

Co-funded by the European Union's Health Programme

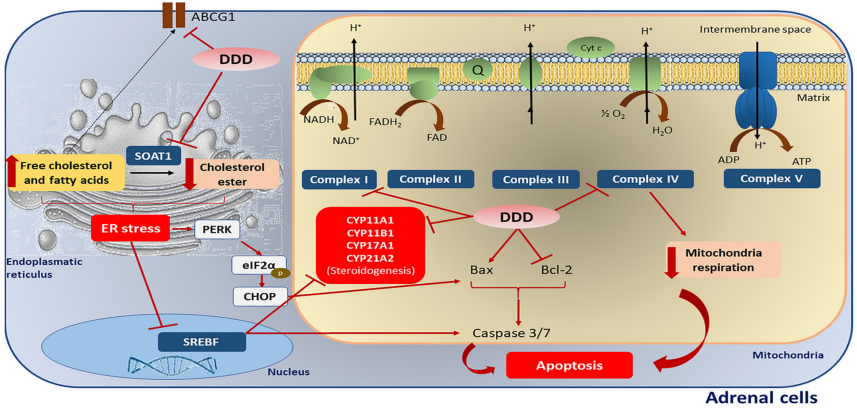
Mitotane

- 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.
- It is an inhibitor of mitochondrial cortisol synthesis by inhibiting 11-ß hydroxylation and cleavage of the cholesterol chain.
- The **only specific and targeted therapy** available for these tumors
- Systemic treatment with **mitotane with or without chemotherapy** is indicated for inoperable or metastatic tumours, although the impact on OS has not been demonstrated for all study groups.

Mitotane

- Available as: breakable tablets 500 mg (Lysodren®) [Level IV; Grade A]
- Long half-life: up to 150 days!!!
- It is stored in tissues with a high lipid concentration and then released.

Pharmacological profile and effects of mitotane in ACC



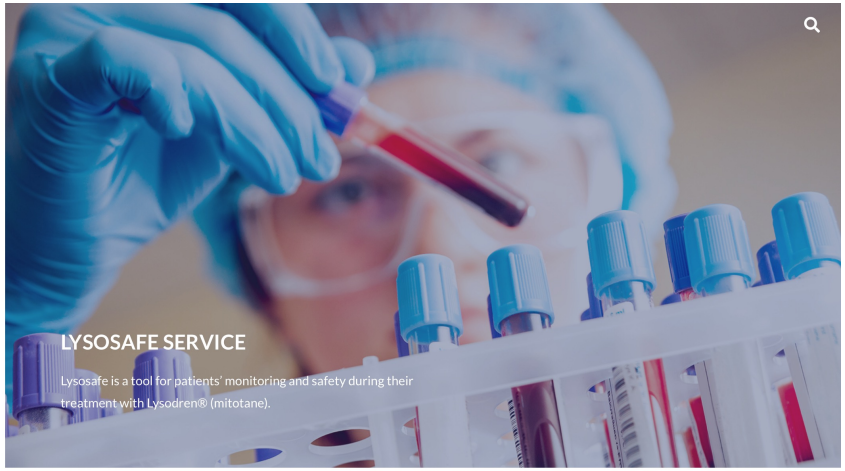
Brit J Clinical Pharma, Volume: 87, Issue: 7, Pages: 2698-2710, First published: 31 December 2020, DOI: (10.1111/bcp.14721)

Mitotane

- Treatment should
  - start 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]
- Dose should be **increased every 4 days** depending on digestive tolerance and urgency of tumor control to reach **target dose in 15 days** [Level IV; Grade B]

Mitotane

- **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** b/c of rapid increase in plasma levels.
- Once the **target dose reached** (may take several months), mitotane **levels** should be monitored, **q 2 weeks**, as the concentrations may increase even though the dose of mitotane has not change.
- Once **blood level has stabilized** for **4 to 6 weeks**, monitoring can be once **monthly** or more frequently in case of significant S/E.
- Monitoring is difficult and not available in all centres or in all European countries.
- Dosage is monitored using **Lysosafe**, which is available to all physicians applying mitotane (www.lysosafe.com).



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https://www.hra-pharma-rare-diseases.com/lysosafe-service

HRA Pharma

LYSOSAFE

Terms of use

a. LYSOSAFE Service is a free of charge mitotane plasma level testing service associated with the use of LYSODREN in patients with advanced Adrenal Cortical Carcinoma. LYSOSAFE allows the LYSOSAFE contact to frequently perform mitotane plasma level assays during LYSODREN treatment. Each sample result is validated by the LYSOSAFE assay manager. A specific certified result report is sent to the LYSOSAFE contact by email/fax and regular mail.

b. Access to LYSOSAFE ONLINE will enable the LYSOSAFE contact to have a complete historical overview of the mitotane plasma level results of their patient(s). However, the sample result mentioned on the specific certified result report should be considered as the validated and thus correct result.

c. Each LYSOSAFE contact registered for LYSOSAFE ONLINE will have access to the results of the patient(s) he/she recieves the specific result report for.

Mitotane - Levels

- Mitotane **level >14 mg/L is necessary for maximum effectiveness**

Target: 14 - 20 mg/L

BUT neurotoxicity (drowsiness, dizziness, tremor, ataxia, and encephalopathy) appears with levels above 20 mg/L [Level IV; Grade B]

- German experience: levels up to **30 mg/L** can be safely maintained.
- An effective serum level is **obtained in 2 to 3 months.**

Mitotane - Duration

- **Duration** of treatment:
  - not defined
  - very variable depending on the cooperative groups
  - should start with the **first cycle of chemotherapy** and
  - **continue for 1 to 3 years** depending on tolerance and compliance.
- German GPOH strategy: 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, only periods with effective therapeutic plasma levels should be considered as **effective treatment time**.

Mitotane - efficacy

- Pharmacokinetics of mitotane and the ability to maintain "effective" blood levels (> 14 mg/L) for an extended period have a direct impact on tumor response in adults

(Haak HR, *Br J Cancer*. 1994;69(5):947-951,

Dickstein G, *JCEM*. 1998;83(9):3100-3103)

- Same in the pediatric setting (as shown by the GPOH group).

Mitotane- efficacy (adults)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma

Massimo Terzolo, M.D., Alberto Angeli, M.D., Martin Fassnacht, M.D.,

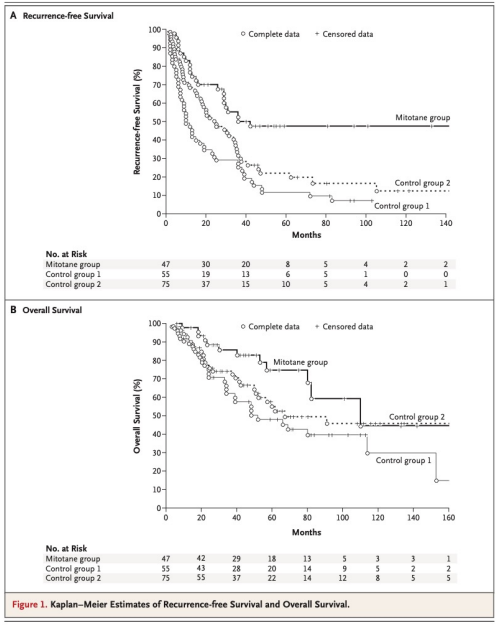


Figure 1. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.

- Retrospective analysis of 177 adults with stage I and II ACC with initial complete tumor resection.
- **47 patients** received **mitotane**, the other patients serving as a control group
- They showed: **adjuvant treatment with mitotane improved EFS** (50% Vs. 15%).
- Median treatment duration : 29 months (6 -164 m)
- 21 patients treated for >4 years

(Terzolo M, et al. *NEJM*. 2007;356:2372)

Mitotane - efficacy

In this study:

- S/E: 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, therefore the recommendation is **NOT to** offer this treatment systematically after complete removal of a localized tumor.

In children: literature data very limited.

- A French retrospective series showed that the response rate to mitotane was:

  30% in 20 treated patients and increased to

  50% in patients with mitotane **blood levels > 14 mg/L.**

(Teinturier C, et al. *Med Pediatr Oncol*. 1999;32:106)

Mitotane - efficacy

- The data from the German group on “serum level guided mitotane therapy” were also encouraging as they demonstrated a **significant survival benefit.**
- Patients with advanced disease :
  - ~ 20-30% had objective tumor responses, with mitotane alone
  - ~ 75% had hormonal responses.
- However, responses are transient and **effect on prolonged survival is uncertain.**
- Mitotane is sometimes administered for inoperable tumours to induce regression, BUT with **NO significant improvement of survival**

Mitotane - efficacy

Overall:

- Some authors consider 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.
- Some authors found better OS in children treated with mitotane alone when used for >6 months.
- Although there are limited data about the use of mitotane in children, it should be always considered in first-line treatment, alone or in association with chemotherapy.

Mitotane - toxicity

- Treatment with mitotane is **complicated** to handle with a difficult balance between efficacy and toxicity
- Factors limiting the dose of mitotane (DLT):
  - **Gastrointestinal A/E** (nausea, vomiting, diarrhoea, abdominal pain) and
  - **Neurological A/E** (tremor, drowsiness, lethargy, ataxia, depression, dizziness)
- **A/E** may be responsible for **poor compliance** with treatment.

Mitotane - toxicity

ATTENTION!!!

- **Endocrinologist input: is essential** b/c of endocrine disorders related to the relative adrenal insufficiency following surgical excision of primary tumor and/or induced by mitotane a few days after treatment start.
- A suitably experienced endocrinologist will address the management of substitution therapy and ALSO will help the parents and the child to tolerate A/E. [Level IV; Grade A]

Mitotane - toxicity

So, patients on Mitotane require systematic supplementation with:

- **hydrocortisone** (often high doses, around 20-30 mg/m^2/d) and
- **fludrocortisone**

b/c it induces **adrenal insufficiency after 2 to 3 weeks**.

- They also require measurement of urinary free cortisol and ACTH for optimal hormonal substitution. [Level IV; Grade A]

NB: higher than normal doses of mineralocoticoid and glucocorticoid therapy are required due to an increased serum steroid-binding capacity during mitotane therapy

Endocrine-Related Cancer | M Kuhlen *et al.* | 29:9 | 545-

RESEARCH

Key factors for effective mitotane therapy in children with adrenocortical carcinoma

Michaela Kuhlen[1], Pascal Mier[2], Marina Kunstreich[2], Lienhard Lessel[2], Dominik Schneider[3], Ines Brecht[4], Denis M Schewe[2], Michael C Frühwald[1], Peter Vorwerk[2] and Antje Redlich[2]

- 43 patients (median age: 7.5 yrs (range: 0.2–17.8); 29 F)
- Median follow-up of 2.2 yrs (range: 0.04–12.71).
- 3-year OS=44.9% &
- 3-year PFS = 28.5%

Endocrine-Related Cancer | M Kuhlen *et al.* | **29**:9 | **545**–555

RESEARCH

Key factors for effective mitotane therapy in children with adrenocortical carcinoma

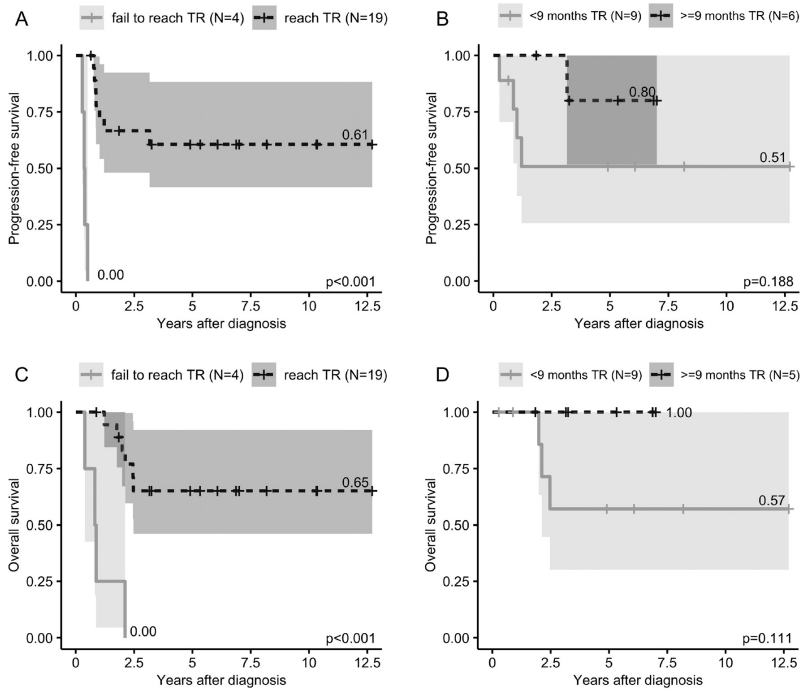
- 11/43: received mitotane as **neoadjuvant treatment** and 4/11 reached partial remission (PR).
- 27/43: received mitotane combined with chemotherapy in an **adjuvant** setting resulting in PR of measurable target lesions in 5/13 patients.
- **Metastatic disease, duration** of mitotane treatment **<9 months**, and **NOT achieving drug target range (TR)** were **negative** prognostic factors for PFS and OS.

Endocrine-Related Cancer | M Kuhlen *et al.* | 29:9 | 545–555

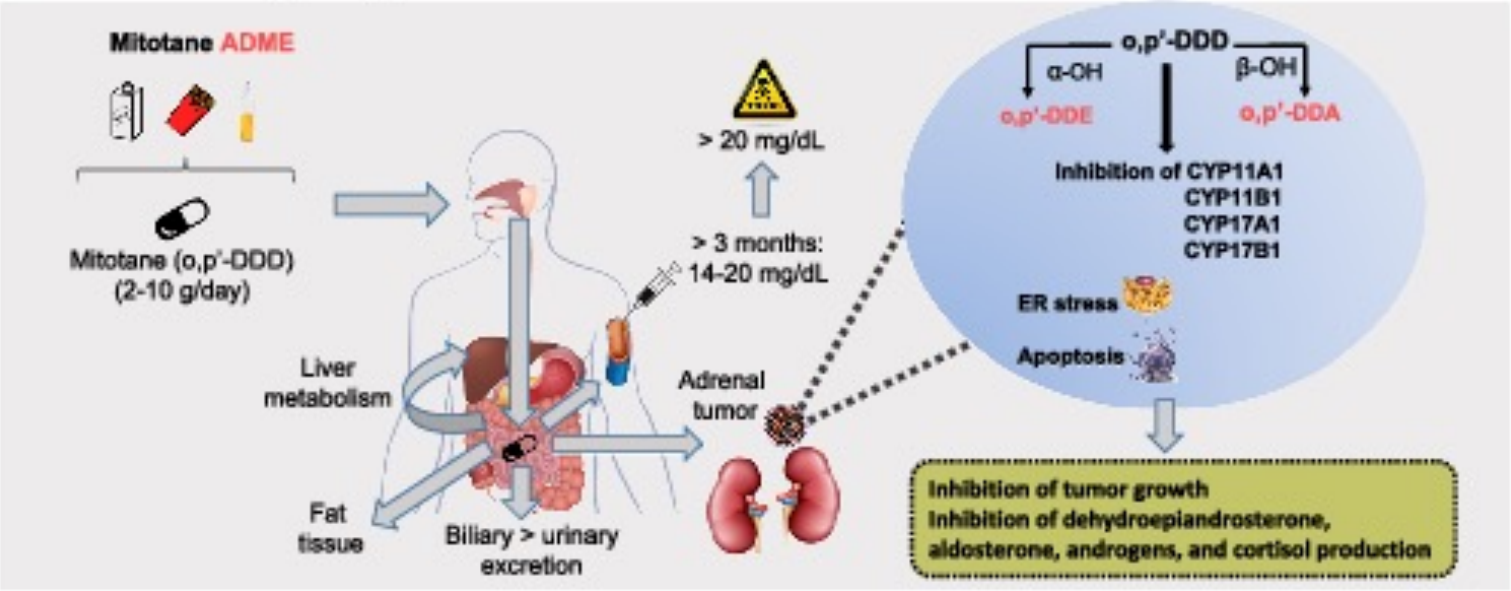
RESEARCH

Key factors for effective mitotane therapy in children with adrenocortical carcinoma

- The risk of progression decreased by 10.4% for each month of mitotane TX.
- **Re-treatment** with mitotane after first-line treatment proved **ineffective**.
- **Improving the efficacy of mitotane, including appropriate indications, needs to be evaluated in prospective RCT.**

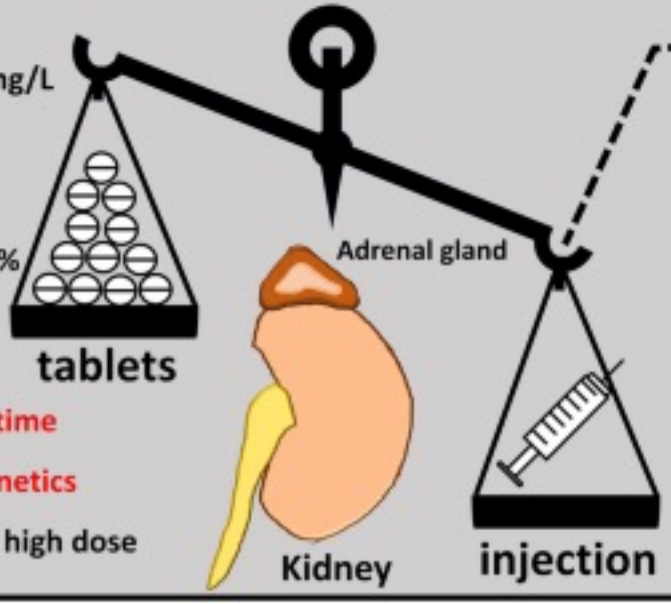


Pharmacological profile and effects of mitotane in adrenocortical carcinoma



Mitotane: Oral vs Injectable: potential advantages

- Poor water solubility: 0.1 mg/L
- High LogP: 6
- High daily dose: 4-6 g/day
- Poor bioavailability: 35-40 %



- Long plasma equilibration time
- Unpredictable pharmacokinetics
- Adverse effects because of high dose

Mitotane Injection: Will it be a Better Alternative?

- Reduction in administered dose/frequency
- 100 % bioavailability
- First pass effect/extra hepatic metabolism will be avoided
- Better control over pharmacokinetics
- Reduction in inter/intra individual variability
- Shorter plasma equilibration time
- Reduction in adverse effects

Radiotherapy

- Role of radiotherapy: uncertain (ACCs usually radio-resistant).
- Limited data on efficacy (mostly used only as salvage therapy).
- **Adults**: locoregional RT, including brachytherapy for liver metastases may improve EFS but not OS.
- RT should be **avoided** as much as possible in **Li-Fraumeni** syndrome (potential mutagenic effect) [Level IV; Grade B]
- RT should be discussed for some refractory stage III ACC (R2, unresectable tumors), stage IV or relapsed tumor. [Level IV; Grade C]

Radiotherapy

Radiotherapy for pediatric adrenocortical carcinoma – Review of the literature

Verena Wiegering [a,b,1,*], Maria Riedmeier [a,1], Lester D.R. Thompson [c], Calogero Virgone [d], Antje Redlich [e], Michaela Kuhlen [f], Melis Gultekin [g], Bilgehan Yalcin [h], Boris Decarolis [i], Christoph Härtel [a,b], Paul-Gerhardt Schlegel [a,b], Martin Fassnacht [b,j], Beate Timmermann [k]

- Final decision should be taken case by case after **MDT** discussion.

  [Level IV; Grade C]

- There is **no consensus** on the optimal dose and volume of radiotherapy.

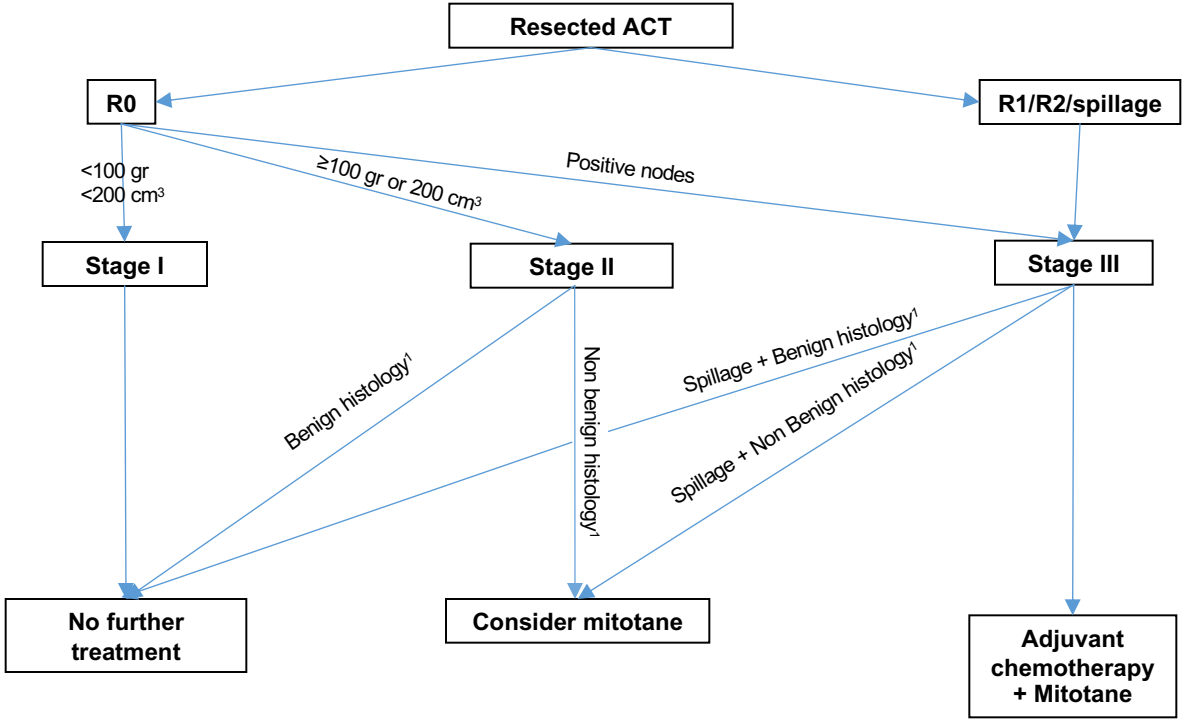
  [Level IV; Grade C]

- Recommended dose:

  45 Gy on tumor bed and **peri-aortic regional nodes**

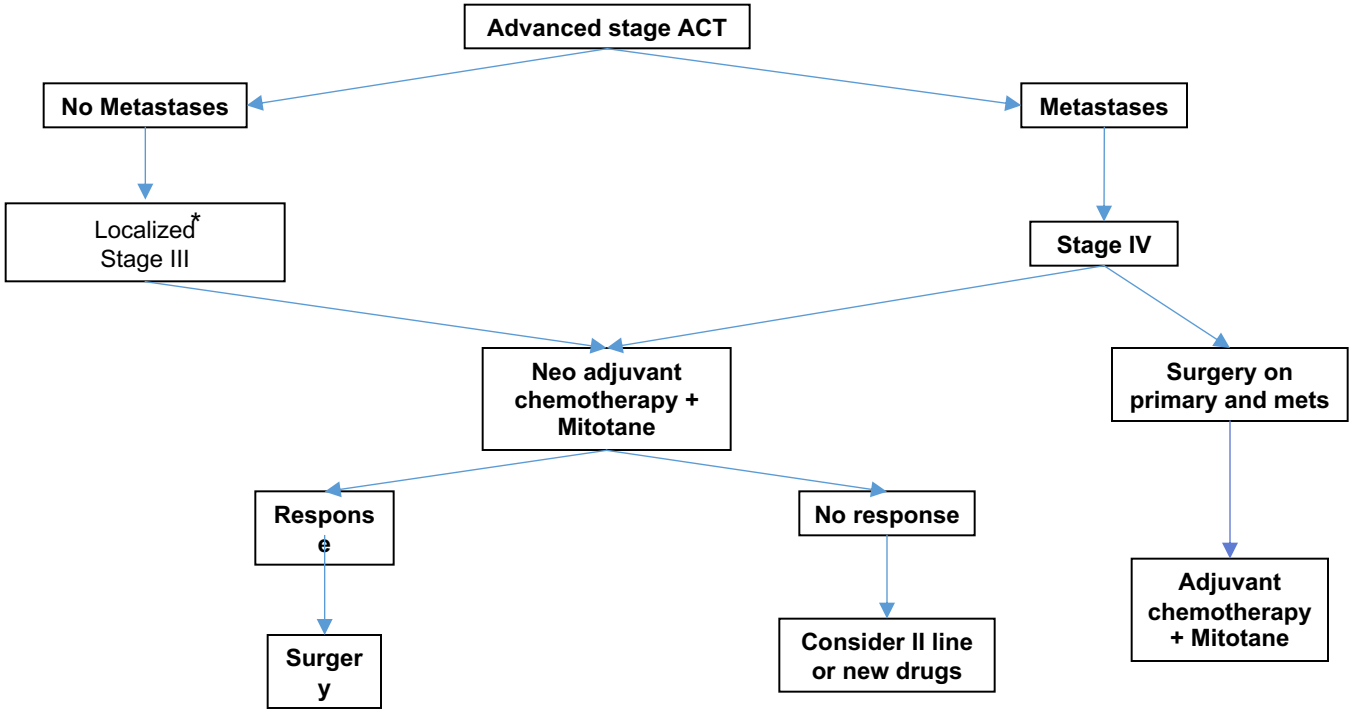
  & boost of 5 - 15 Gy on tumor bed depending on margins of resection/presence of residual tumor. [Level IV; Grade C]

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



[1] according to Wieneke or 5-item score or clinical risk factors (age, secretion)

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



*unresectable tumors or large pre-surgical stage III (hormones +, nodes +)

No specific second-line treatment is defined.

RELAPSED ACC

Co-funded by the European Union's Health Programme

Local relapses

- Local relapses should be treated aggressively, as these are almost invariably fatal.
- **Complete surgical clearance** of any visible tumor is recommended whenever feasible.
- **Adjuvant treatment with mitotane for at least 2 years** is recommended, **in combination with second-line chemotherapy** or other standard regimen could be considered case by case.
- Enrolment in prospective trials is also advised

[Level V; Grade B]

Local relapses

- For unresectable relapses, **adjuvant chemotherapy & mitotane** or **second-line chemotherapy & mitotane** should be administered: → in **case of response, surgery** could be considered.
- **Radiation therapy** should be discussed in both cases within MDT, taking 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 (**conventional chemo & mitotane or other regimens & mitotane**) & **radiation therapy** should be attempted.
- Alternatively, **enrolment in phase I-II trial** (if available) should be considered.

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Network Paediatric Cancer (ERN PaedCan)

OTHER RECOMMENDATIONS

Co-funded by the European Union's Health Programme

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GENETIC CONSIDERATIONS

- **Genetic counselling** is mandatory and 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 cancer predisposition genetic conditions** (Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome and other overgrowth syndromes).

[Level IV; Grade A]

LONG TERM FOLLOW-UP RECOMMENDATIONS - 1

Unfavourable clinical and/or histological risk factors (advanced stages, >4 years of age and/or unfavourable histology) should undergo **clinical, hormonal and imaging** evaluation:

- **Every 3 months in years 1 and 2**
- **Every 4 months in year 3**
- **Every 6 months in year 4**
- **Once in year 5**

(Level IV; Grade B)

LONG TERM FOLLOW-UP RECOMMENDATIONS -2

Favourable 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**
- **Every 6 months in years 3, 4 and 5**

(Level IV; Grade B)

LONG TERM FOLLOW-UP RECOMMENDATIONS -3

For patients harbouring a **germline *TP53* variant** or **with a definite diagnosis of Li–Fraumeni syndrome**, long-term follow-up for other tumours is also highly recommended

(Level IV; Grade A)

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

(Frebourg et al. and Kratz et al)

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SURVIVAL

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SURVIVAL

The overall 5-year survival for children with ACTs depends on the stage and histology and it is:

- >80% for patients with small localized resected ACT

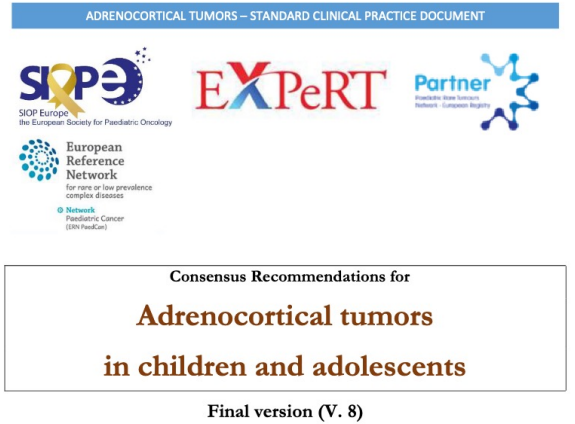
But …

- <20% for patients with metastatic ACC (10-33% of all cases).

Conclusions

- All the above recommendations have been incorporated in a document that contains the guidelines on Diagnosis and Treatment of ACT.

- These have also been published in a special issue of PBC, together with a set of guidelines concerning other rare tumours.


ADRENOCORTICAL TUMORS – STANDARD CLINICAL PRACTICE DOCUMENT

SIOPE
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EXPeRT

Partner

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

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.

EXPeRT

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- Ferrari et al. Facing the challenges of very rare tumors of pediatric age: The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) background, goals, and achievements
- Orbach et al. The European Paediatric Rare Tumours Network - European Registry (PARTNER) project for very rare tumors in children
- Bisogno G et al. Pleuropulmonary blastoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations
- Bien E et al. Pancreatoblastoma in children: EXPeRT/PARTNER diagnostic and therapeutic recommendations
- Schneider D et al. Consensus recommendations from the EXPeRT/PARTNER groups for the diagnosis and therapy of sex cord stromal tumors in children and adolescents
- Stachowicz-Stencel T et al. Thymoma and thymic carcinoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations
- Ben-Ami T et al. Nasopharyngeal carcinoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations
- Virgone C et al. Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations
- Surun A et al. Salivary gland carcinoma in children and adolescents: The EXPeRT/PARTNER diagnosis and treatment recommendations
- Ferrari A et al. Cutaneous melanoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations

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Pediatric Blood & Cancer

SUPPLEMENT ARTICLE

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

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Conclusions

- The European PARTN-ER project has led to a consensus strategy regarding the treatment of children and adolescents with ACC, which is available for use.

- The prognostic stratification based on histology remains controversial and, consequently, the post-surgical treatment of Stage II and some Stage III tumors

- The use of Mitotane (+/-) chemotherapy for advanced stages may be frustrating and new strategies are needed.