European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

September 14th 2022

*María Pérez-Torres Lobato*

# "Precocious puberty and adrenal mass in an infant with family history of early-onset cancer. What´s the diagnosis and what´s next"

*Invited expert: Christian Kratz*

*Moderation: Teresa de Rojas*

Co-funded by the European Union's Health Programme

# COI declaration

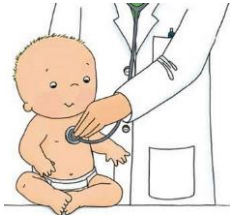
- None

# Case presentation

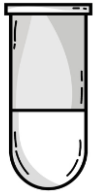
*(August 2019)*

**12-month-old Spanish girl with a 3-week history of pubic hair development and adult body odor**

- No remarkable medical/surgical history



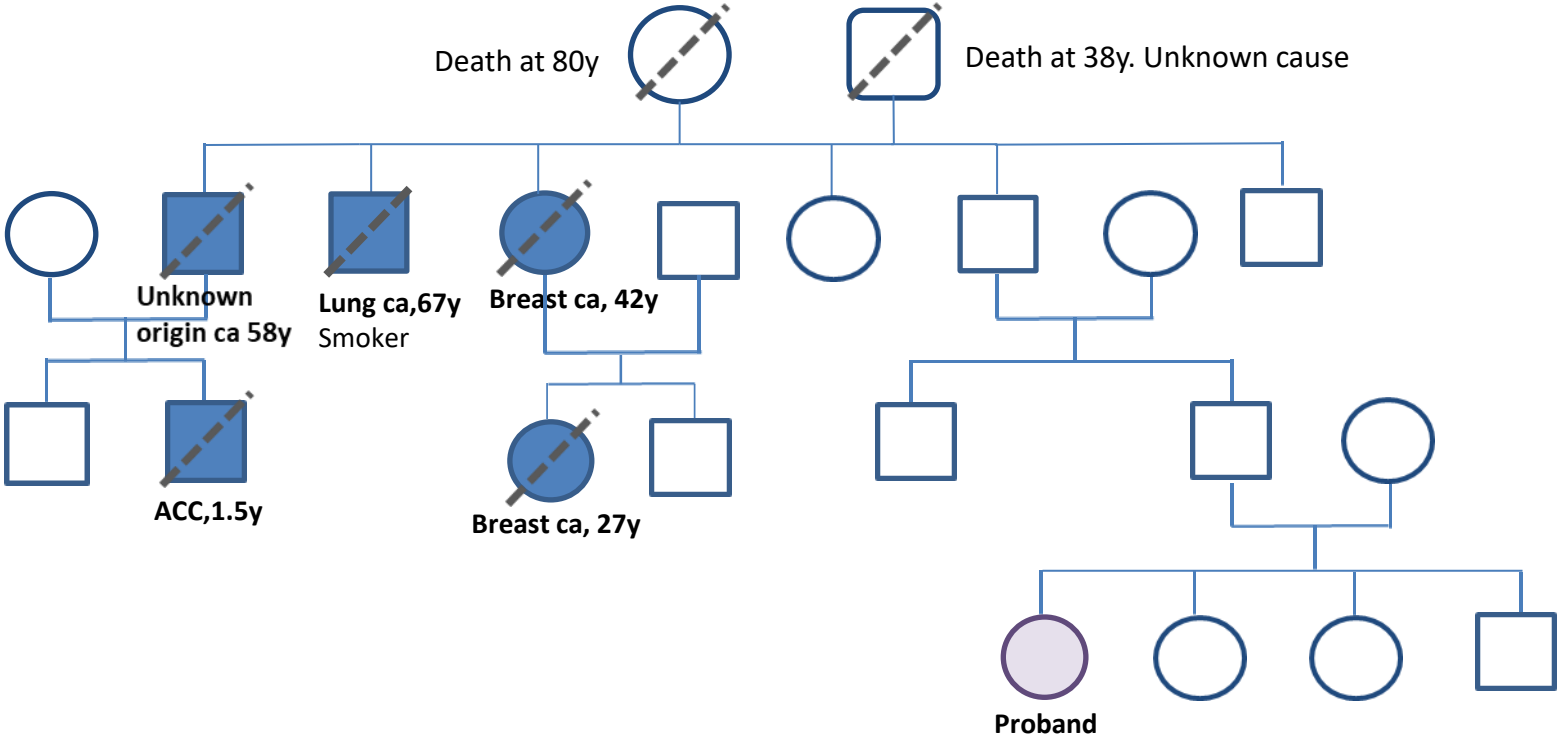
- BP 97-67 mmHg (p>99).
- Cushingoid facies. Pubarche (*Tanner stage P2S1* ). Clitoromegaly (*Prader stage 1-2*).
- Rest of the exam normal.



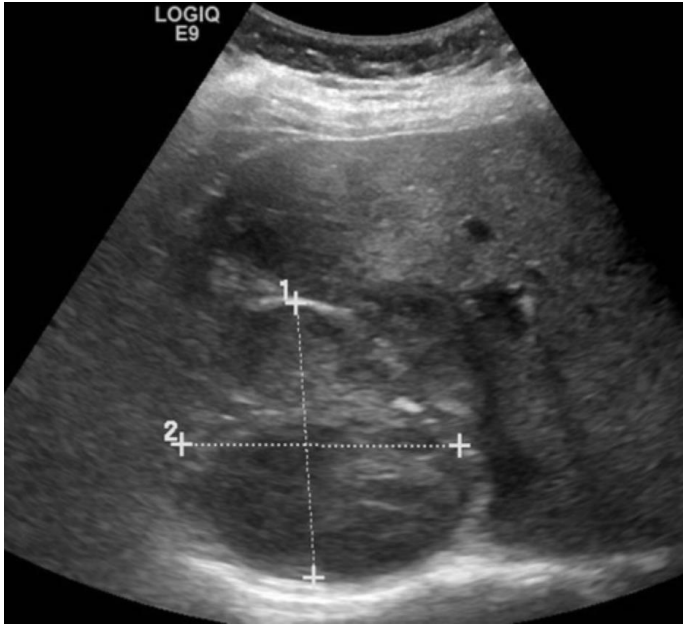
↑ Dihydro-epiandrosterone sulfate *(1601.49 µg/dL)* 17-OH-progesterone *(16 ng/mL),* androstendione *(12 ng/ml)* and testosterone *(314 ng/ml).*

↑ Morning and night cortisol serum levels *(34-35 ug/dL).* 24h urine catecholamines: normal

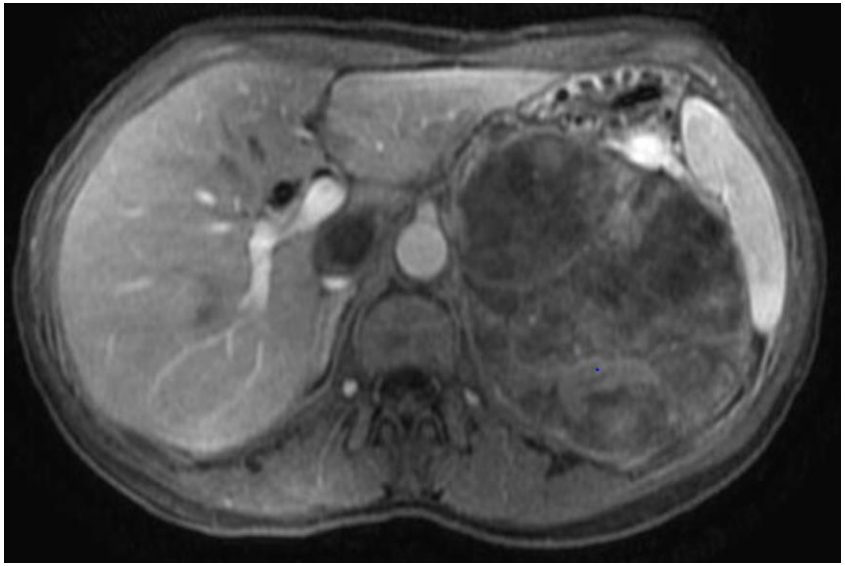
# Family history



## Abdominal ultrasound

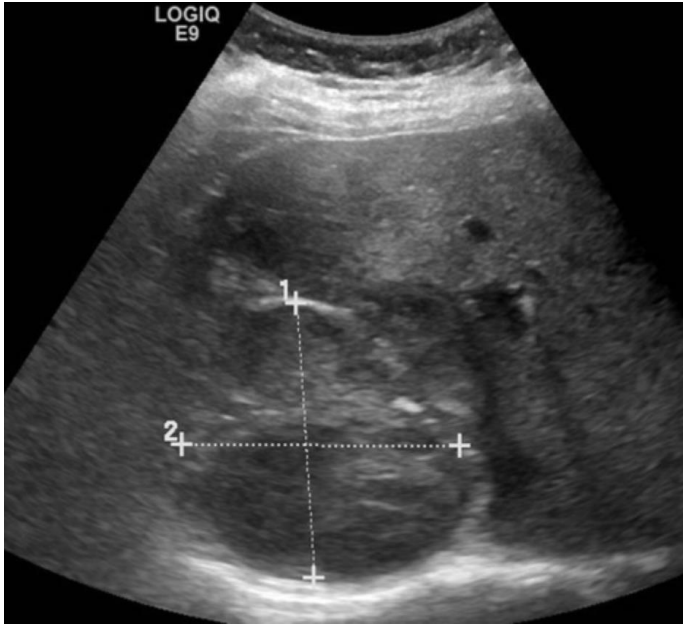



## Abdominal MRI

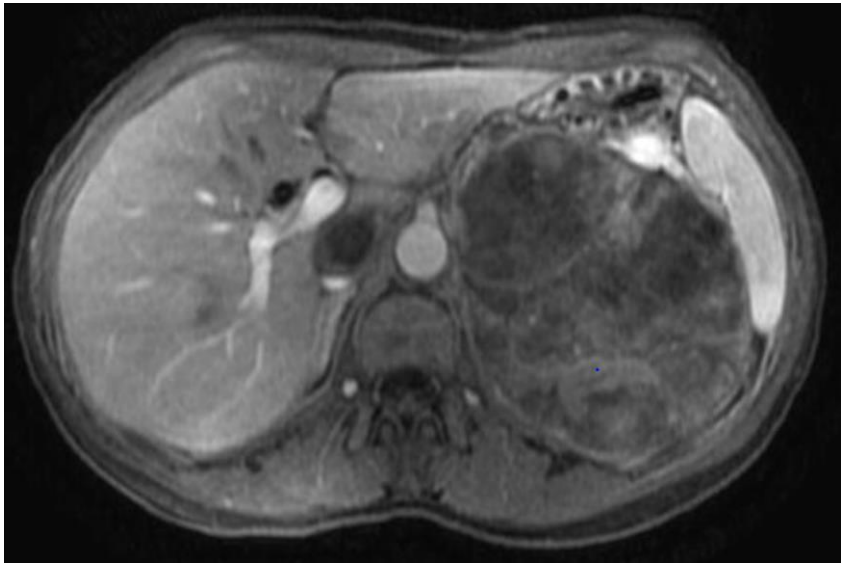


*Solid hypoechoic lesion of 70x55x60 mm in size in the **left suprarenal region** without calcification or cystic component, with **signs of renal and suprarenal vein invasion** and thrombosis of the inferior vena cava.*

## Abdominal ultrasound




## Abdominal MRI



**Chest CT, PET-CT**: ruled out disseminated disease

# Question 1

**What is the most probable diagnosis?**

a) Neuroblastoma

b) Adrenocortical adenoma

c) Adrenocortical carcinoma

d) Pheocromocytoma

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**c) Adrenocortical carcinoma**

~~d) Pheocromocytoma~~

# Adrenocortical carcinoma (ACC)

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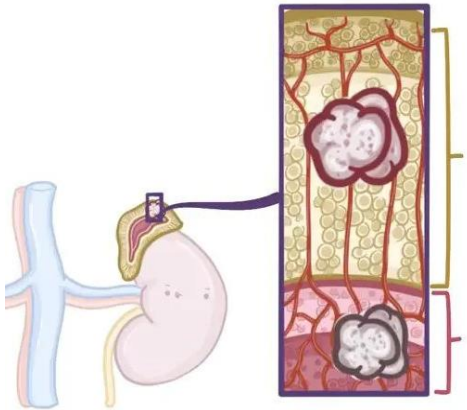
Network Paediatric Cancer (ERN PaedCan)

- 0.2% of all childhood cancer cases.
- **Male/female** ratio: 1/2.
- **Biphasic age** distribution: <3 years and adolescence.
- Almost universally **functioning tumors** (+++ androgens>glucocorticoids).
- **Diagnosis:** bio-clinical presentation + hormonal secretion + radiology.




Sexual hormones, mineralocorticoids, glucocorticoids secretion (**Adrenocortical tumors** )

Catecholamines secretion (**pheocromocytoma, neuroblastoma…**)

***Radiology:*** *large size (>3cm), heterogeneous, irregularly-shaped, hemorrhage, necrosis, vascular invasion*

Dall'Igna P, Virgone C, De Salvo GL, et al. Adrenocortical tumors in Italian children: analysis of clinical characteristics and P53 status. Data from the national registries. J Pediatr Surg. 2014;49(9):1367-1371.

CHILDREN'S ONCOLOGY GROUP

ARAR0332

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for rare or low prevalence complex diseases
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**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 |

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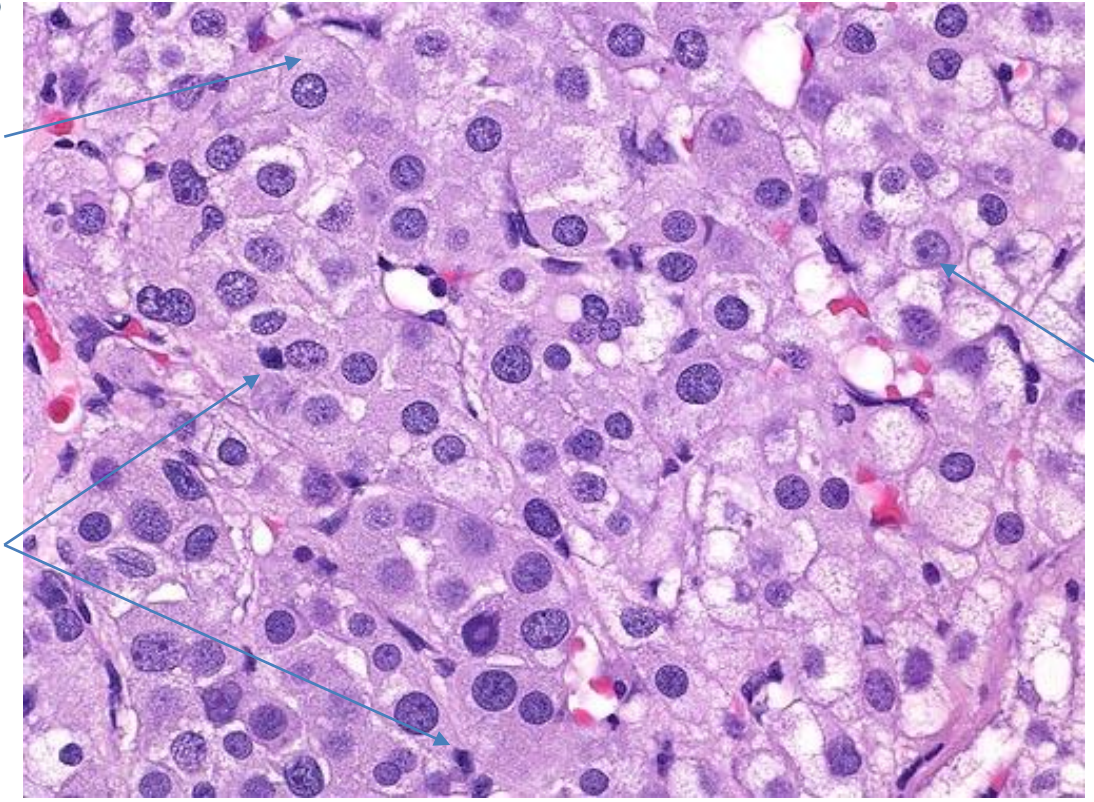


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Biopsy (via posterior approach) *confirmed* diagnosis of Adrenocortical Carcinoma (ACC)

# Question 2

**Is the biopsy always mandatory to confirm diagnosis of ACC?**

a) Yes

b) No

# Question 2

**Is the biopsy always mandatory to confirm diagnosis of ACC?**

~~a) Yes~~

**b) No**

Version Date: August 30, 2006

European Reference Network
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Network Paediatric Cancer (ERN PaedCan)
CureSearch Children's Oncology Group

# CHILDREN'S ONCOLOGY GROUP

## ARAR0332

## Treatment of Adrenocortical Tumors with Surgery plus Lymph Node Dissection and Multiagent Chemotherapy

**Stage III and IV→ diagnostic confirmation by biopsy of the primary tumor or metastasis required** *(percutaneous or open routes as indicated)*

Obsolete according to **EXPeRT/PARTNER recommendations (2021)**

Consensus Recommendations for

# Adrenocortical tumors in children and adolescents

Final version (V. 8)

## BIOPSY INDICATIONS

**Non-secreting tumors AND metastatic disease/unresectable primary tumor**

**AND atypical presentation** *[Level IV, grade B]* via posterior approach.

➡ *Mandatory after tumor resection*

**Risk of tumor rupture and tumor shedding!!**

Virgone C, Roganovic J, Vorwerk P, et al. Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations. Pediatr Blood Cancer. 2021;68(4):e29025.

# Question 3

**Would you consider genetic testing in this patient?**

a) Yes, I would do genetic tests, but the evidence base is limited.
b) Yes, I would strongly recommend genetic testing.
c) No, I would only recommend it if first degree relatives had also cancer.
d) No, I would only recommend it if there was family history of sarcoma or brain tumor.

# Question 3

**Would you consider genetic testing in this patient?**

~~a) Yes, I would do genetic tests, but the evidence base is limited.~~

**b) Yes, I would strongly recommend genetic testing.**

~~c) No, I would only recommend it if first degree relatives had also cancer.~~

~~d) No, I would only recommend it if there was family history of sarcoma or brain tumor.~~

Consensus Recommendations for

# Adrenocortical tumors in children and adolescents

Final version (V. 8)

Genetic counselling **should be offered to all patients affected by adrenocortical tumors and to their families** *[Level IV; Grade A].*

# Hereditary cancer risk assessment

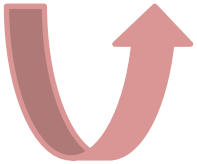
- **Suspicious family features.**
- Rare tumors commonly associated with cancer predisposition.
- Bilateral or multifocal tumors.
- Cancer diagnosis at a younger than expected age.
- Multiple synchronous or metachronous tumors, second tumors.
- Dismorphic features/ additional conditions (e.g., axillary freckling) indicative of an underlying syndrome.
- Unexpected/excesive toxicity to oncological treatments.
- Comorbilities (e.g immunodeficiency, short stature...).

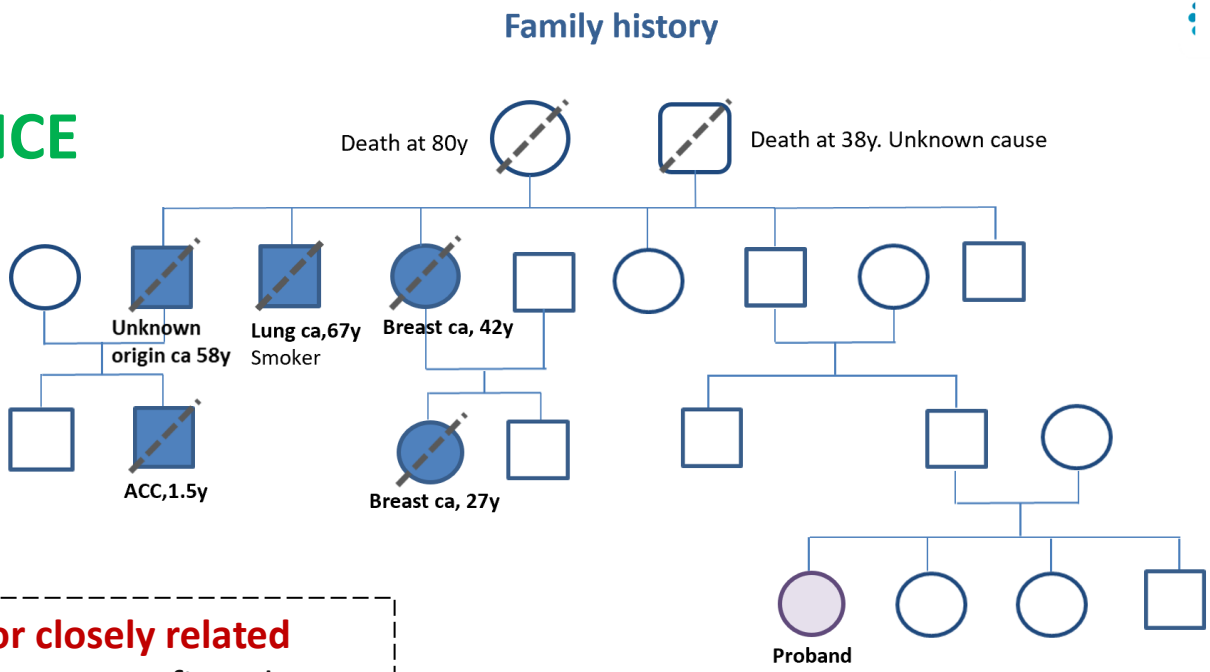
Knapke S. Hereditary cancer risk assessment in a pediatric oncology follow-up clinic. *Pediatr Blood Cancer* 2012

Kuhlen M. Cancer suscepitibility syndromes in children in the area pf broad clinical use of massive parallel sequencing. *Eur J Pediatr* 2015

Early Performance Testing

# CANCER SURVEILLANCE IMPROVES SURVIVAL






**(a) Familial clustering of the same or closely related cancers**, **(b)** cancer diagnoses in two or more first-degree relatives, **(c) tumor patterns associated with a specific cancer predisposition syndrome**, **(d)** exceptional young age at diagnosis, **(e)** sibling with childhood cancer, and **(f)** consanguineous parents.

Fam Cancer. 2021 Oct;20(4):257-262. doi: 10.1007/s10689-021-00233-5. Epub 2021 Mar 2.

**Effective identification of cancer predisposition syndromes in children with cancer employing a questionnaire**

Miriam Schwermer [1], Astrid Behnert [1], Beate Dörgeloh [1], Tim Ripperger [2], Christian P Kratz [3]

# Question 4

**Which underlying genetic condition would you think of in this patient?**

a) Lynch syndrome

b) Beckwith-Wiedemann Syndrome

c) Li Fraumeni syndrome

d) Multiple Endocrine Neoplasia type 1 (MEN1)

# Question 4

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~~b) Beckwith-Wiedemann Syndrome~~

**c) Li Fraumeni syndrome**

~~d) Multiple Endocrine Neoplasia type 1 (MEN1)~~

# Cancer patients who should be tested for germline disease-causing *TP53*[a]

| | |
|---|---|
| Recommendation 1 | All patients who meet the modified 'Chompret Criteria' should be tested for germline *TP53* variants:<br>• *Familial presentation*: proband with a *TP53* core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma) before 46 years AND at least one first- or second-degree relative with a core tumour before 56 years; *or*<br>• *Multiple primitive tumours*: proband with multiple tumours, including 2 *TP53* core tumours, the first of which occurred before 46 years, irrespective of family history; *or*<br>• *Rare tumours*: patient with adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; *or*<br>• *Very early-onset breast cancer*: Breast cancer before 31 years, irrespective of family history |
| Recommendation 2 | Children and adolescents should be tested for germline *TP53* variants if presenting with:<br>• Hypodiploid acute lymphoblastic leukaemia (ALL); *or*<br>• Otherwise unexplained *sonic hedgehog*-driven medulloblastoma; *or*<br>• Jaw osteosarcoma |

## Li Fraumeni syndrome (LFS)

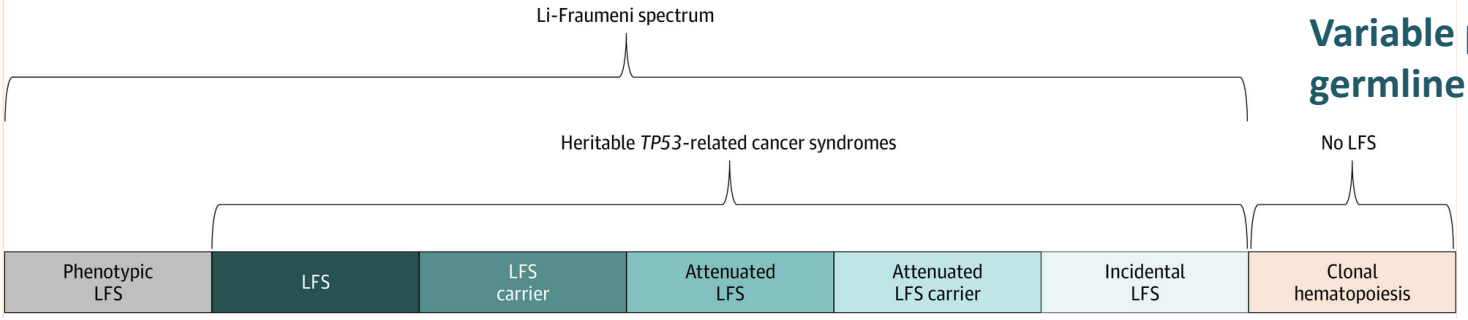
- **Cancer predisposition syndrome**.
- Inherited **autosomal dominant disorder**.
- Germline mutations in the **tumor suppressor protein P53** (17p13 chromosome).

**Guidelines for the Li–Fraumeni and heritable *TP53*-related cancer syndromes**

Thierry Frebourg[1] · Svetlana Bajalica Lagercrantz[2] · Carla Oliveira[3] · Rita Magenheim[4] · D. Gareth Evans[5] · The European Reference Network GENTURIS

# ACC and LFS

- **ACC: often the presenting malignancy for LFS.**
- Risk for multiple **other cancers** (brain/breast ca, sarcoma, leukemia…).
- **~50–80%** of children diagnosed **with ACC have LFS**.
- **% TP53 germline mutations** in ACC **decreases with age** (<10% adulthood).




**Variable penetrance of germline TP53 variants**


Petr EJ, Else T. Adrenocortical carcinoma (ACC): When and why should we consider germline testing? Presse Med. 2018 Jul-Aug;47( 2):119-25.
Kratz CP, Freycon C, Maxwell KN, et al. Analysis of the Li-Fraumeni Spectrum Based on an International Germline TP53 Variant Data Set: An International Agency for Research on Cancer TP53 Database Analysis. JAMA Oncol. 2021;7(12):1800-5.

# NM_000546.6(TP53):c.1010G>A (p.Arg337His)

**NM_000546.6(TP53):c.1010G>A (p.Arg337His)**

| | |
|---|---|
| **Allele ID:** | 27418 |
| **Variant type:** | single nucleotide variant |
| **Variant length:** | 1 bp |
| **Cytogenetic location:** | 17p13.1 |
| **Genomic location:** | 17: 7670699 (GRCh38) GRCh38 UCSC |
| | 17: 7574017 (GRCh37) GRCh37 UCSC |

**HGVS:**

| Nucleotide | Protein | Molecular consequence |
|---|---|---|
| NM_000546.6:c.1010G>A MANE SELECT | NP_000537.3:p.Arg337His | missense |
| NM_001126112.3:c.1010G>A | NP_001119584.1:p.Arg337His | missense |
| NM_001126113.3:c.*29G>A | | 3 prime UTR |

... more HGVS

**Protein change:** R337H, R205H, R298H, R178H

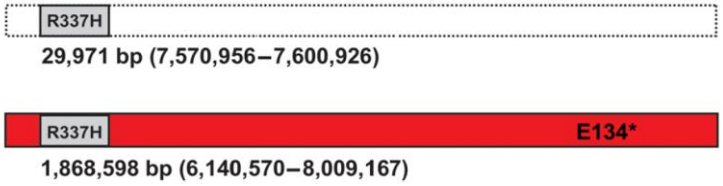
***Associated with***

- Variable penetrance*
- Founder effect

CANCER

## XAF1 as a modifier of p53 function and cancer susceptibility

X-linked inhibitor of apoptosis-associated factor 1




Extended haplotype (*TP53*-R337H + *XAF1*-E134*): higher incidence of cancer.

0.3% of the population from Southern Brazil

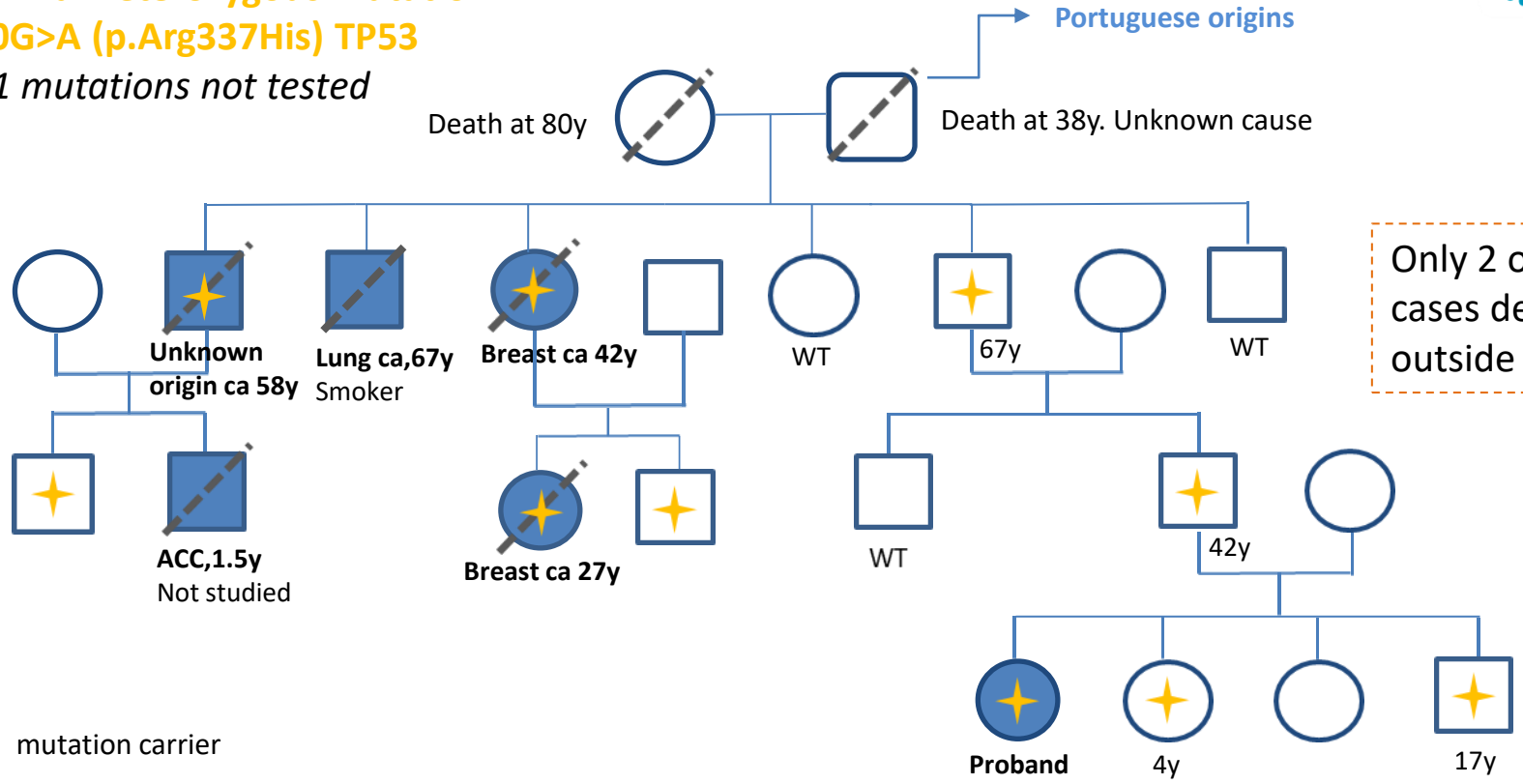
Pinto *et al.*, *Sci. Adv.* 2020; **6** : eaba3231 24 June 2020

Chromosome 17p13

## Germinal heterozygous mutation 1010G>A (p.Arg337His) TP53

*XAF1 mutations not tested*

# Family history




Only 2 other cases detected outside Brazil

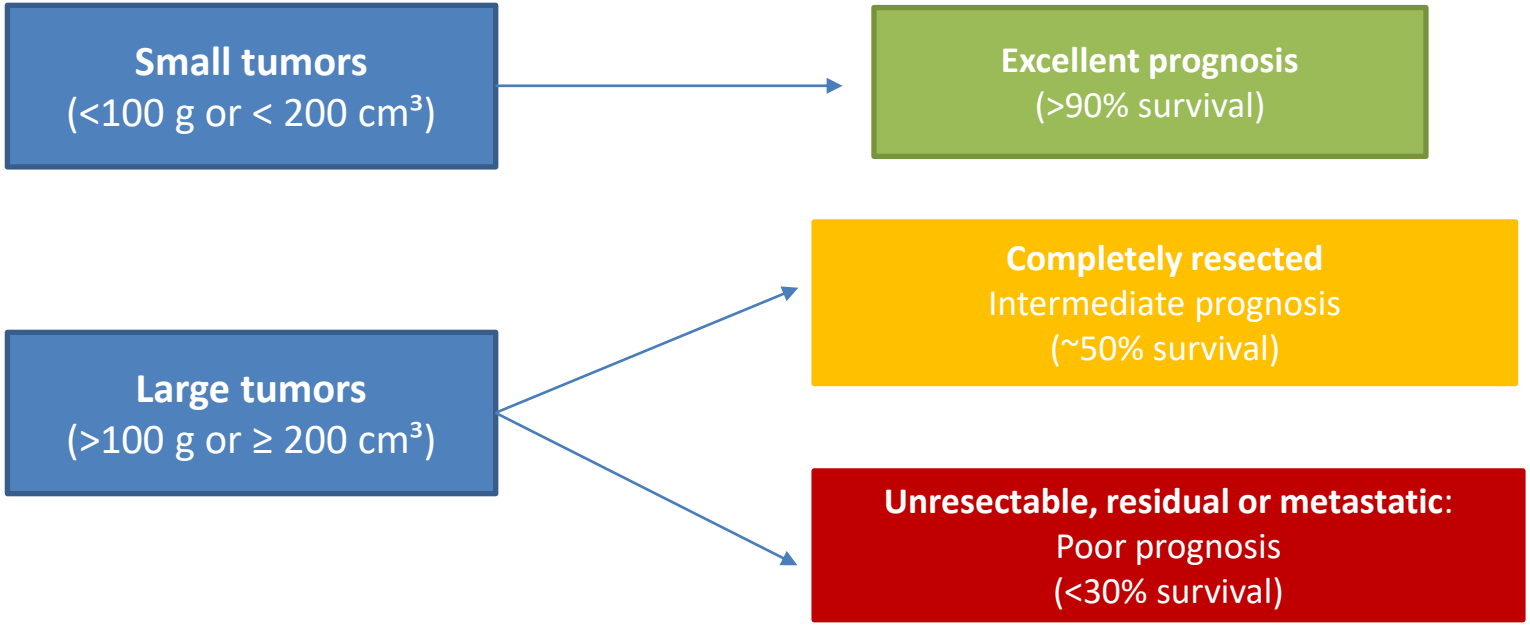
mutation carrier

**WT** wild type

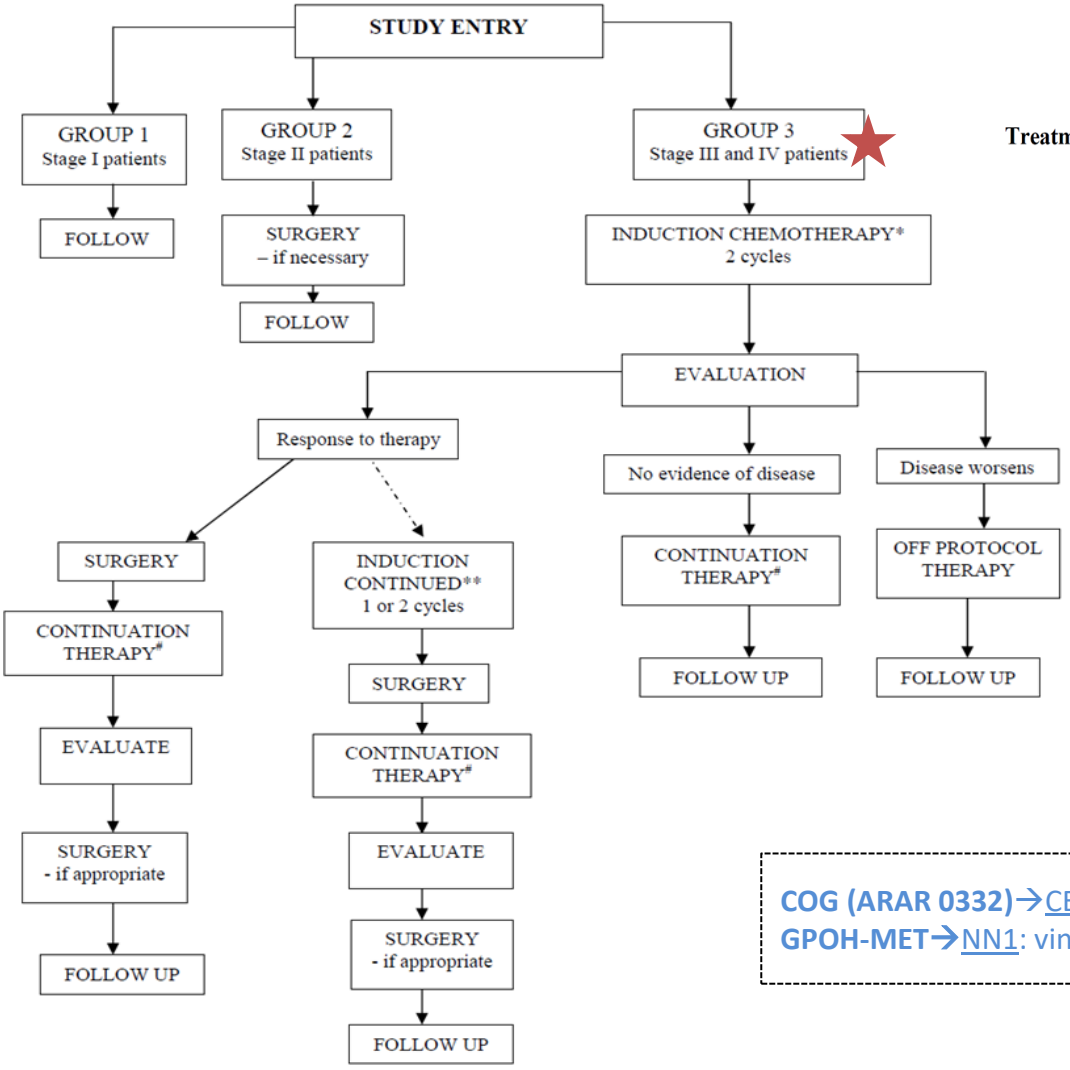
Paskulin DD, Giacomazzi J, Achatz MI, et al. Ancestry of the Brazilian TP53 c.1010G>A (p.Arg337His, R337H) Founder Mutation: Clues from Haplotyping of Short Tandem Repeats on Chromosome 17p. PLoS One. 2015;10(11):e0143262.

# Surgery: cornerstone of treatment

- Complete resection is key
- Avoid surgical spill




Michalkiewicz E, Sandrini R, Figueiredo B, et al. Clinical and outcome characteristics of childrenwith adrenocortical tumours: a report from the International Pediatric Adrenocortical Tumour Registry. *Jclin Oncol*. 2004;22(5):838-45.




**CHILDREN'S ONCOLOGY GROUP**

**ARAR0332**

**Treatment of Adrenocortical Tumors with Surgery plus Lymph Node Dissection and Multiagent Chemotherapy**

Consensus Recommendations for

Adrenocortical tumors

in children and adolescents

## Stage III/IV:

- 2 to 4 cycles of chemotherapy (CED, NN1/2) before extended surgery and regional lymph node dissection.
- Adjuvant chemotherapy for a total of 6-8 cycles + mitotane.

**COG (ARAR 0332)→**CED: cisplatin, etoposide and doxorubicin
**GPOH-MET→**NN1: vincristine, ifosfamide, adriamycin/NN2: carboplatin, etoposide

# Mitotane [1,1-dichloro-2- (0-chlorophynyl) -2 (p-chlorophenyl) -ethane, or O'p'DDD]

- **Synthetic insecticide derivative**.
- Inhibitor of **mitochondrial cortisol synthesis** (11ß hydroxylation).
- **Duration of treatment**: variable depending on the cooperative groups (1-**2y**).
- **Side effects:** gastrointestinal and neurological.

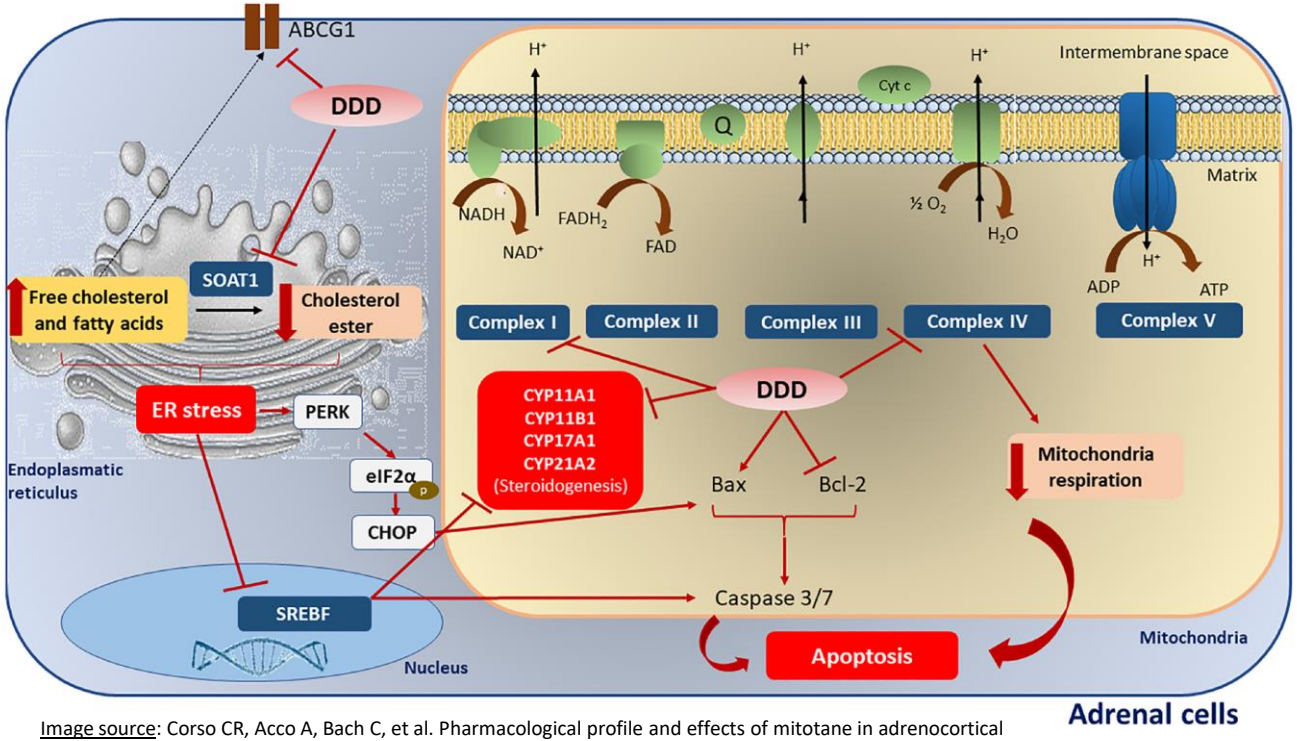
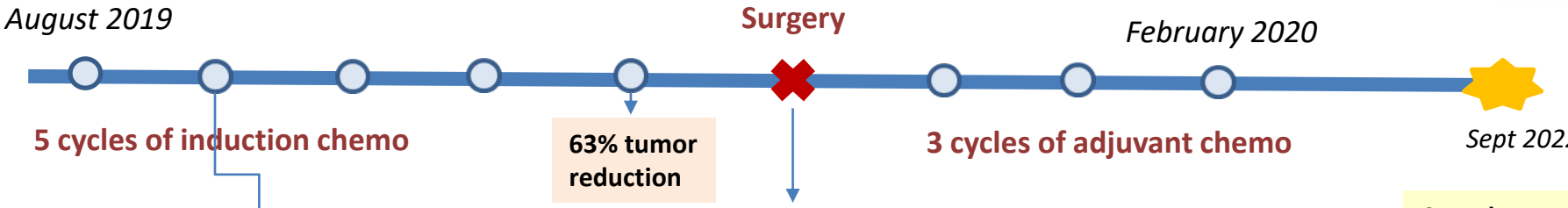



Image source: Corso CR, Acco A, Bach C, et al. Pharmacological profile and effects of mitotane in adrenocortical carcinoma. Br J Clin Pharmacol. 2021 Jul;87(7):2698-2710

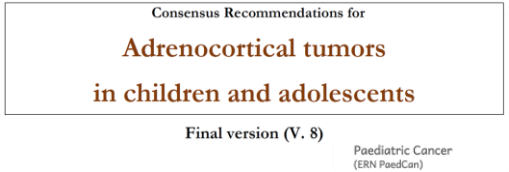



| DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Mitotane | | | | | | | |
| Cisplatin | | | | | | | |
| Etoposide | | | | | | | |
| Doxorubicin | | | | | | | |
| G-CSF | | | | | | | |

Day 21

x 8 cycles

# Long-term follow up




**ACC with unfavourable clinical and/or histological risk factors**

**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
- Yearly in year 5

*Altered steroid hormones found at diagnosis remain as the best hormonal markers of relapse*

**Li Fraumeni (< 18y)**

**Brain tumor**

- Annual brain MRI

**Soft tissue and bone sarcoma**

- Annual whole-body MRI

*(*) Clinical exam and abdominal US every 6 months.*

Kratz CP, Achatz MI, Brugières L, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res. 2017;23(11):38-45.
Frebourg T, Bajalica Lagercrantz S, et al.European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet. 2020;28(10):1379-86.

# DISCUSSION

# Take home messages

1. **Genetic counselling to** all patients affected by **ACC and families**.
2. **Patients with hereditary cancer benefit from ca surveillance** → importance of <u>early testing</u>.
3. **ACC** often is the **presenting malignancy for LFS**.
4. **>50%** children diagnosed **with ACC** have **LFS**.
5. **Surgery**: cornerstone of treatment.
6. **Avoid initial tumor biopsy** if typical presentation of ACC (risk of **tumor spillage**).