European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

November 17th 2021

Simona Zimová & Calogero Virgone

"Pseudopubertas Praecox and Tumour Rupture"

Chair: Sofia Castro

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Conflict of Interest

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Simona Zimová

No conflict of interest to declare

Calogero Virgone

No conflict of interest to declare

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Growth Chart

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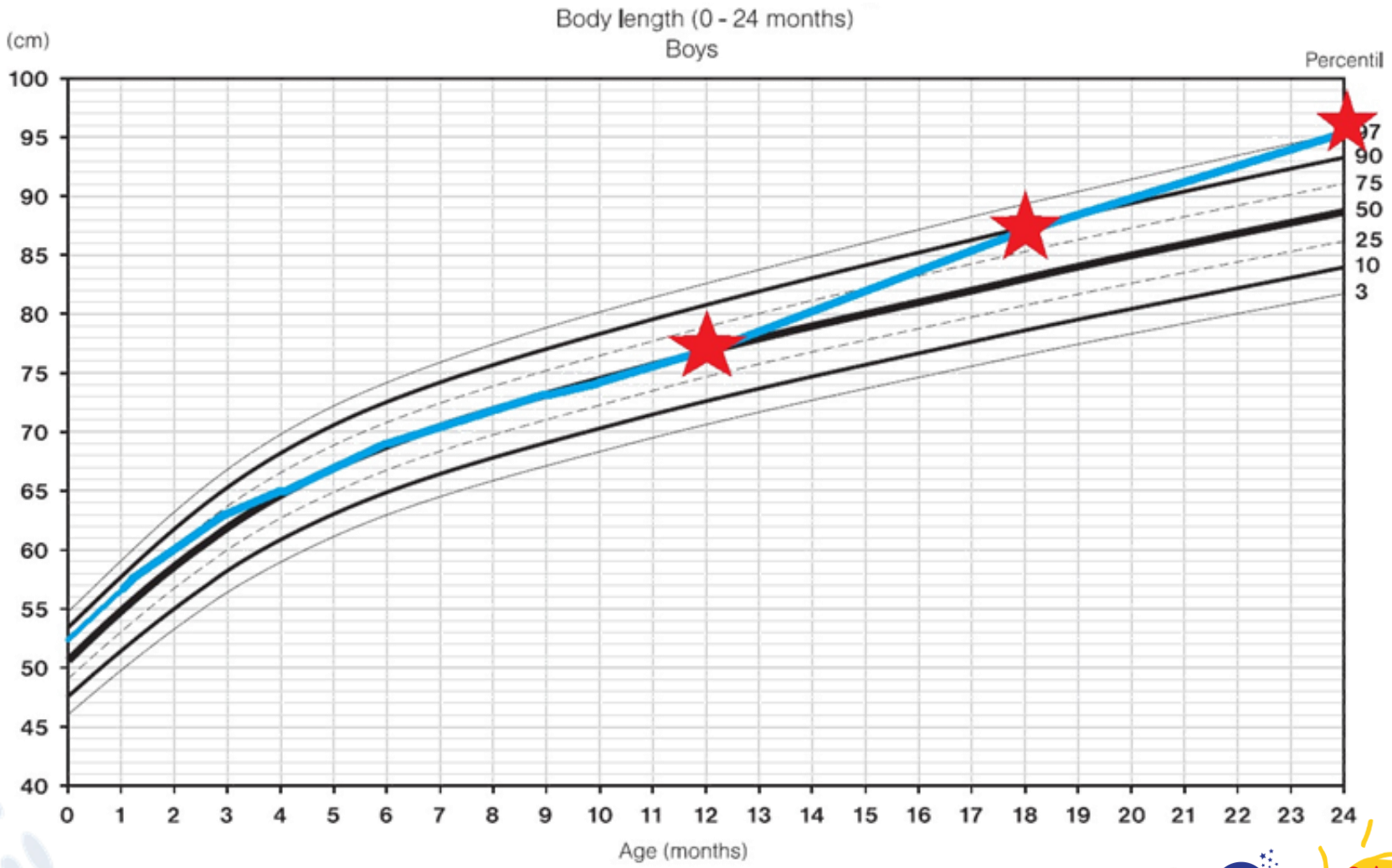

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Presentation

- Clinical finding (June 2020 – 2y1m ♂)
  - Growth chart: 50th p. → 97th p.
  - 5 months pubic hair growth
  - 1 month penis enlargement, testicles symmetrical, not enlarged
  - Irritability, aggressiveness, increased appetite, sweating
  - Bone age 5 y

- Lab finding

LDH	**48.16**	3.00-7.16	ukat/l
DHEAS	**>27.00**	0.01-0.53	umol/l
Testosterone	**4.62**	0.00-0.90	nmol/l
IGF-1	**177**	0-129	ug/l
Normal values: TSH, fT4, LH, FSH, cortisol			

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Q1

- What is the most probable tumour location based on this data?

a) CNS

b) Adrenal gland

c) Testes

d) Thyroid gland

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Q1

- In which organ would you expect the tumour based on the presented data?

~~a) CNS~~

b) Adrenal gland - peripheral precocious puberty

~~c) Testes~~ - Leydig cell tumour possible, but no asymmetry or enlargement

~~d) Thyroid gland~~

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MRI

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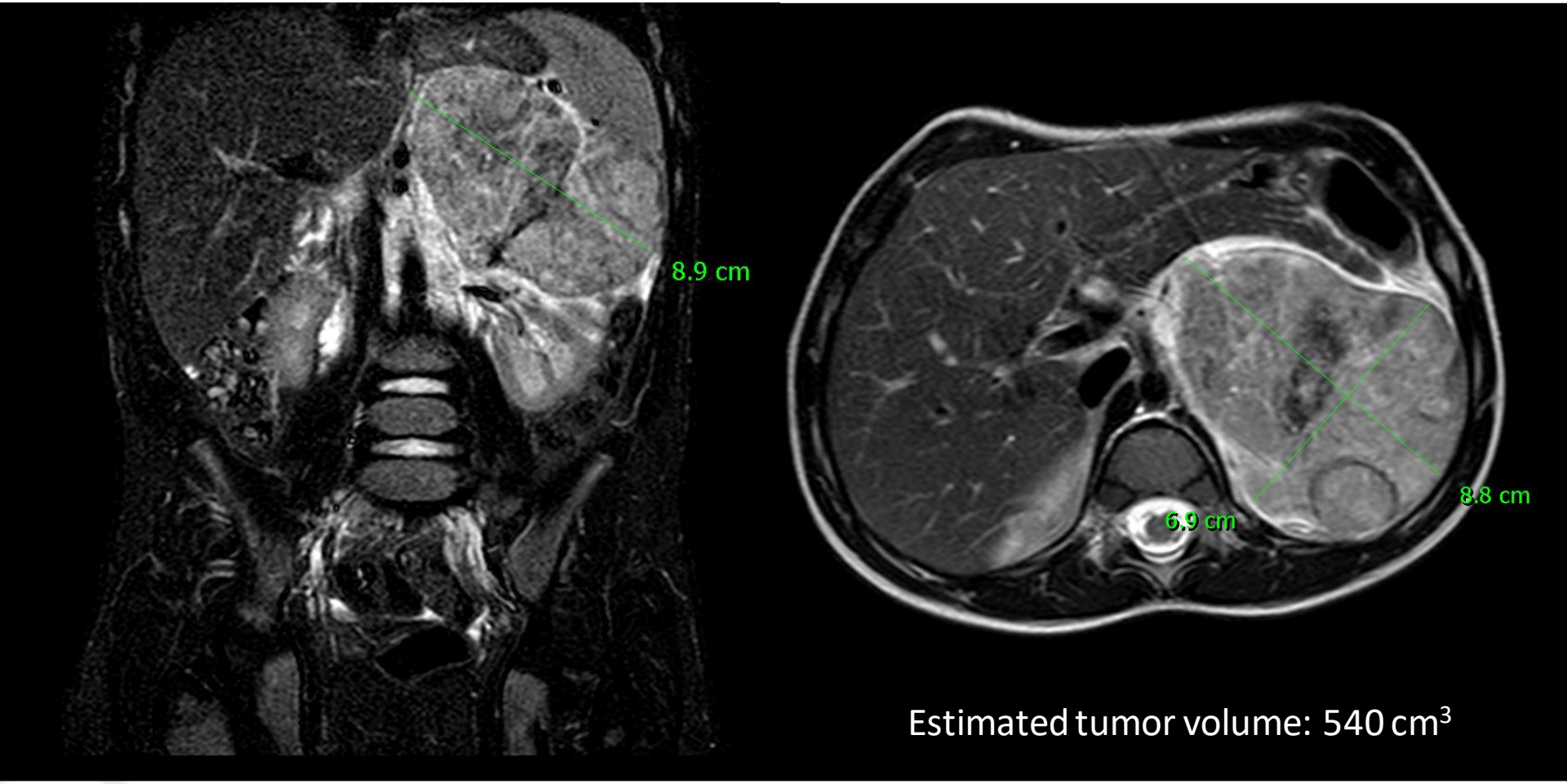

Estimated tumor volume: 540 cm^3

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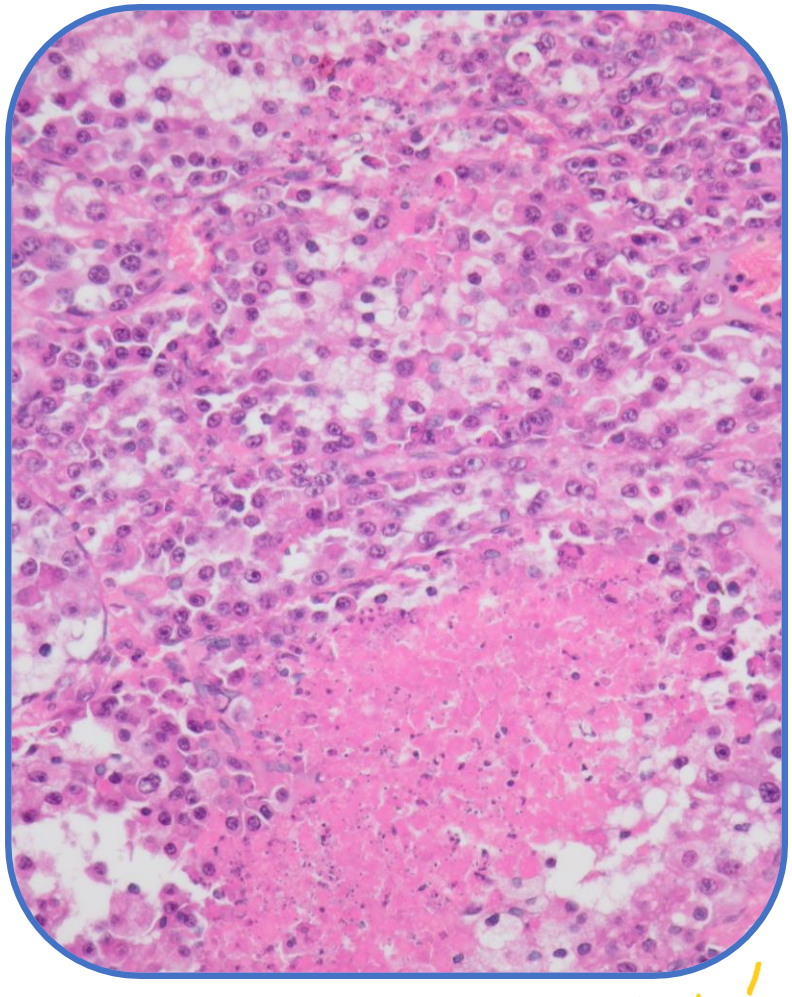
First Surgery

- Left adrenalectomy
  - Complicated with tumour rupture
  - Lavage of tumor bed
- Histology
  - 82x70x45 mm
  - Adrenocortical carcinoma
    - Mitoses, necrosis and calcifications, angioinvasion



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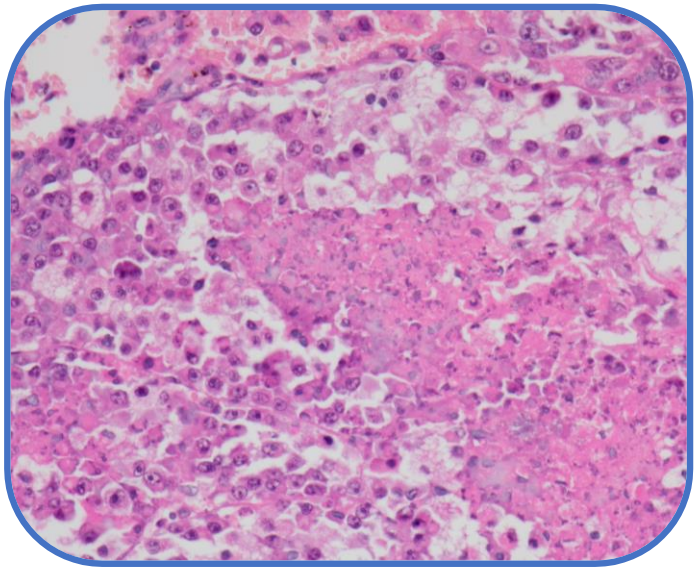
Histology

Wieneke score			
1	Tumor weight > 400 g	N/A (ETV 540 cm^3)	✓
2	Tumor size > 10.5 cm	No (max. 82 mm)	
3	Extension into periadrenal soft tissues and/or adjacent organs	No	
4	Invasion into the vena cava	No	
5	Venous invasion	Yes	✓
6	Capsular invasion	No	
7	Presence of tumor necrosis	Yes	✓
8	Mitotic count	High	✓
9	Presence of atypical mitotic figures	Yes	✓
4 out of 9 criteria = „malignant“ tumour			



Wieneke classifying factors	
<3	„benign“
3	„indeterminate“
>3	„malignant“

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Q2

- Which cancer predisposition syndrome would you look for in paediatric ACC?

a) Familial adenomatous polyposis

b) Li-Fraumeni syndrome

c) Neurofibromatosis type 1

d) Beckwith-Wiedemann syndrome

e) Fanconi anemia

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Q2

- Which cancer predisposition syndrome would you look for in paediatric ACC?

a) **Familial adenomatous polyposis**

b) **Li-Fraumeni syndrome** - in 50% of children with ACC

~~c) Neurofibromatosis type 1~~

d) **Beckwith-Wiedemann syndrome**

~~e) Fanconi anemia~~

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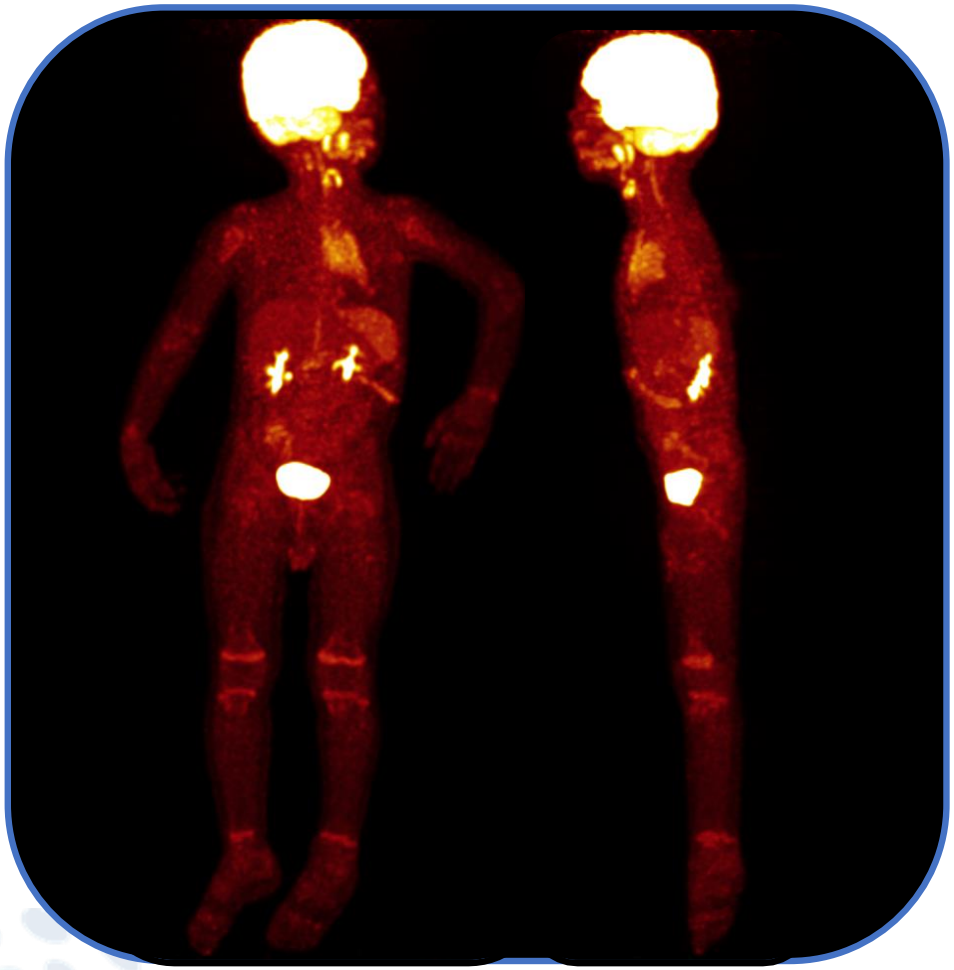
Initial Staging



TP53 mutation NEGATIVE
No cancer predisposition found

	Before	After		
LD	48.16	**5.62**	3.00-7.16	ukat/l
DHEAS	>27.0	**0.06**	0.01-0.53	umol/l
Testosterone	4.62	**<0.24**	0.00-0.90	nmol/l
IGF-1	177	**114**	0-129	ug/l

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Staging and Treatment

CureSearch
Children's Oncology Group

ARAR0332

Activated: September 18, 2006
Closed: May 28, 2013

Version Date: 08/03/10
Amendment: #2

CHILDREN'S ONCOLOGY GROUP

ARAR0332

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

- **STAGE I –**
  - Completely resected, small tumors (<100 g and <200 cm^3) with normal post-operative hormone levels
- **STAGE II –**
  - Completely resected, large tumors (≥100 g or ≥200 cm^3) with normal post-operative hormone levels
- **STAGE 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
- **STAGE IV –**
  - Presence of distant metastases

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Treatment Plan (stage III)

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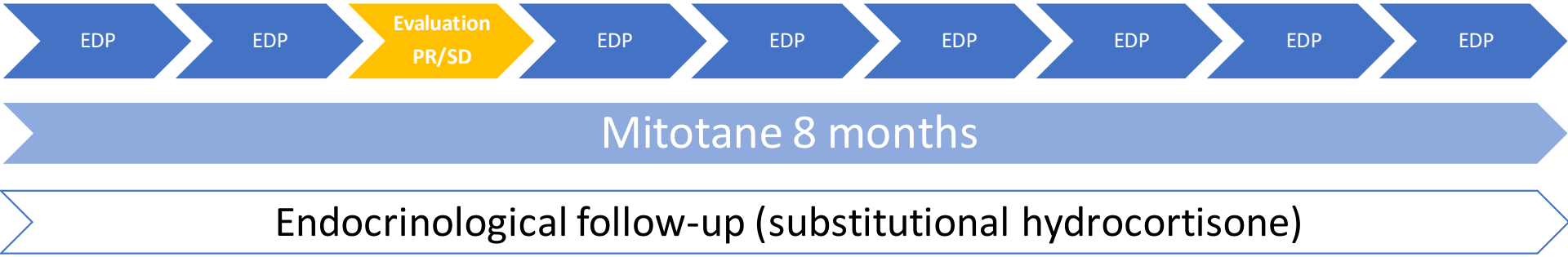
- 8 cycles of CTx + Mitotane daily
  - Cisplatin 50 mg/m^2 D1,2
  - Etoposide 100 mg/m^2 D1,2,3
  - Doxorubicin 25 mg/m^2 D4,5



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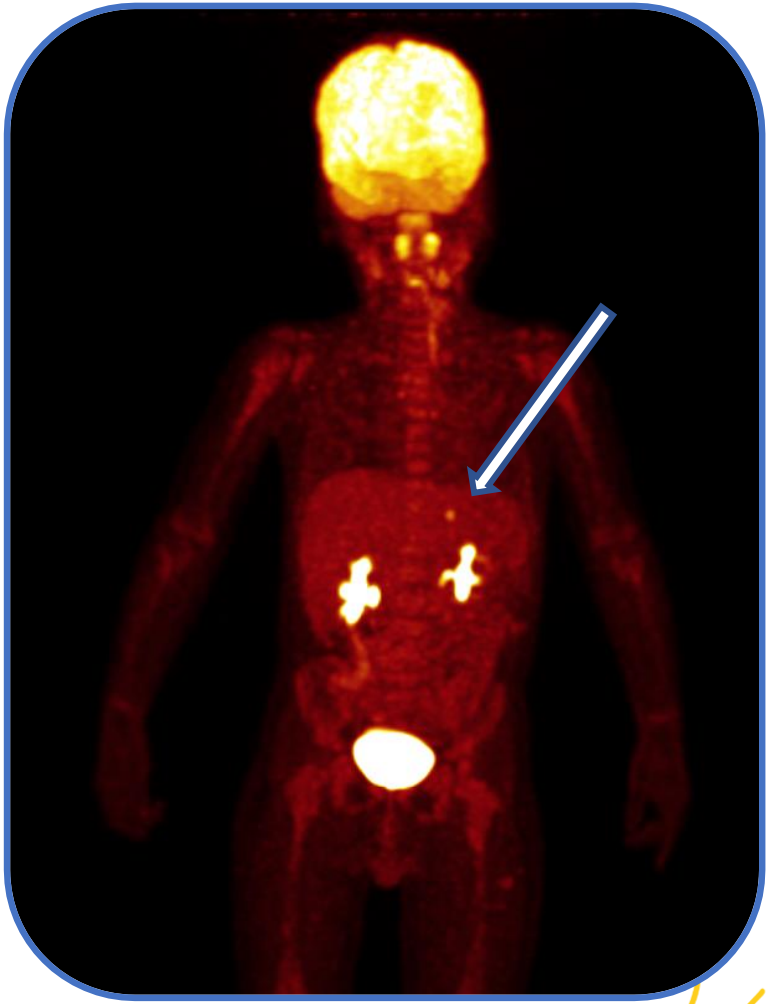
Evaluation

- MRI abdomen after 2nd cycle
  - No clear sign of tumour recurrence
- PET/MRI after 3rd cycle
  - Local recurrence?



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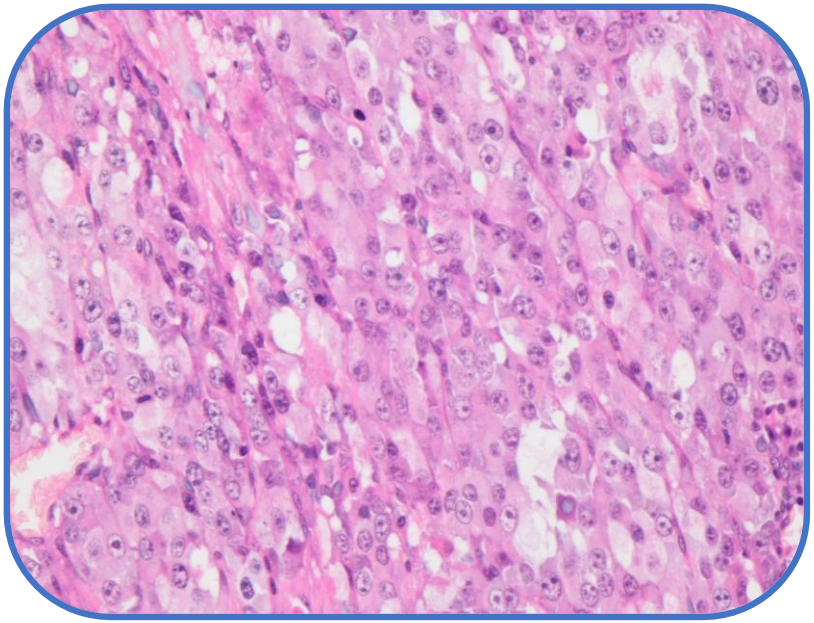
Second Surgery

- Complete resection of the nodule
- Histology
  - 10 mm
  - Confirmed adrenocortical carcinoma
- Exploration of the abdominal cavity – no other suspicious tissue

= 1st progression on treatment



Surgery rupture → PET/MRI clear → 2xEDP → MRI clear → 1xEDP → PET/MRI - relapse? → Surgical resection → PD on treatment

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Q3

- Which treatment modality would you use now?

a) Radiotherapy

b) Second line chemotherapy

c) Mitotane only & follow-up

d) Immunotherapy

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We did not know either…

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- St. Jude Children's Research Hospital: Carlos-Rodriguez Galindo and Raul Ribeiro
  - Reccommendations:
    - Follow with 2nd line CTx: **gemcitabine + capecitabine or 5-FU**
    - Keep Mitotane
    - Consider I-O
      - Pembrolizumab (PD-L1 expression?)
      - Cabozantinib
    - RT probably not

Clinical Trial > Endocr Relat Cancer. 2010 Apr 21;17(2):445-53. doi: 10.1677/ERC-09-0281. Print 2010 Jun.

Gemcitabine plus metronomic 5-fluorouracil or capecitabine as a second-/third-line chemotherapy in advanced adrenocortical carcinoma: a multicenter phase II study

Paola Sperone [1], Anna Ferrero, Fulvia Daffara, Adriano Priola, Barbara Zaggia, Marco Volante, Daniele Santini, Bruno Vincenzi, Giuseppe Badalamenti, Chiara Intrivici, Sabrina Del Buono, Silvia De Francia, Emmanouil Kalomirakis, Riccardo Ratti, Alberto Angeli, Luigi Dogliotti, Mauro Papotti, Massimo Terzolo, Alfredo Berruti

Affiliations + expand

PMID: 20410174 DOI: 10.1677/ERC-09-0281

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- INFORM registry
  - Somatic TP53 mutation: not druggable
  - Alternative lengthening of telemeres (borderline positive genomic signature): no drug target

intermediate
  - **MYC gain** (elevated expression): consider BETi/AURKi/CDK7&9i/HDACi

borderline
  - NTRK1 focal gain (w/o overexpression): consider NTRKi

borderline
  - BRD4 overexpression: consider BETi

low
  - MRAS overexpression: consider MEKi
  - BRCAness: consider PARPi

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Second line treatment

- Capecitabine + Gemcitabine
  - Capecitabine (oral)
  - Gemcitabine (i.v.) D1, D8
  - + Mitotane still daily
- Substitutional treatment with hydrocortisone

- Follow-up with MRI and PET/MRI
  - All clear until 10/2021 (12 months on 2nd line treatment)
  - 10/2021 gemcitabine withdrawn due to repeated neutropenias

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What's next?

How long should the patient be kept on capecitabine?

What to do in case of progression? If localised? If metastatic?

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Summary

- Adrenocortical carcinoma located in left adrenal gland – tumor spillage during adrenalectomy
- 1st (local) relapse/progression after 3 cycles of CTx

- 2nd line treatment Capecitabine + Gemcitabine + Mitotane for 1 year
- So far no 2nd relapse revealed

- INFORM study: no strong druggable target

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Take home message

- Adrenocortical carcinoma is one of the rare childhood tumours
- Usual presentation in childhood originates from excess of androgens
  - precocious pseudopuberty/virilisation
  - growth acceleration
- Li-Fraumeni syndrome in >50% children with ACC
- Testing for druggable targets is important in the background of non-established treatment in refractory/relapsing tumours

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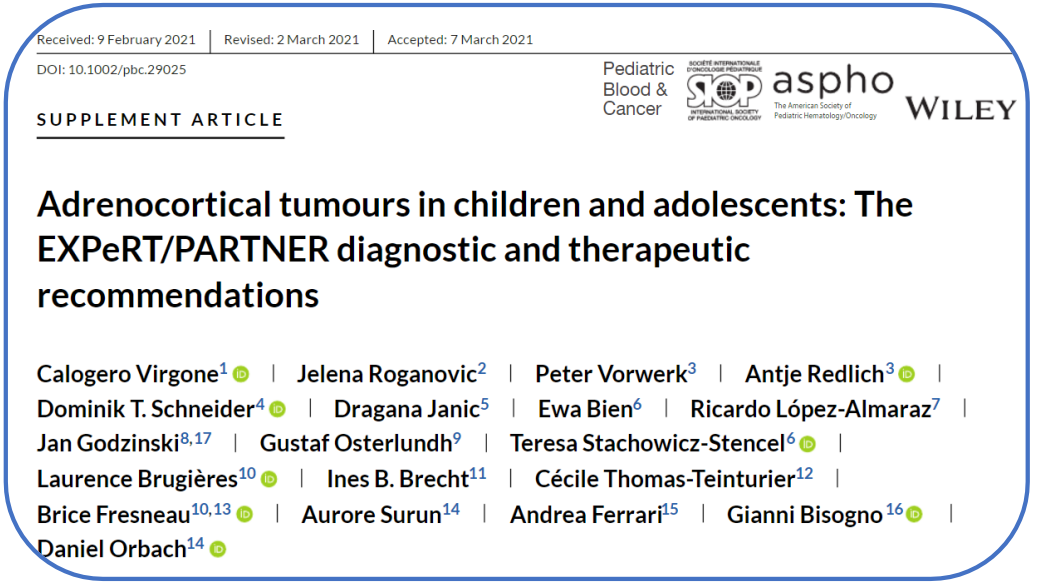
Take home message

- Guidelines were limited, but the situation is getting better



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Pediatric Blood & Cancer
SUPPLEMENT ARTICLE

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

Calogero Virgone[1] | Jelena Roganovic[2] | Peter Vorwerk[3] | Antje Redlich[3] | Dominik T. Schneider[4] | Dragana Janic[5] | Ewa Bien[6] | Ricardo López-Almaraz[7] | Jan Godzinski[8,17] | Gustaf Osterlundh[9] | Teresa Stachowicz-Stencel[6] | Laurence Brugières[10] | Ines B. Brecht[11] | Cécile Thomas-Teinturier[12] | Brice Fresneau[10,13] | Aurore Surun[14] | Andrea Ferrari[15] | Gianni Bisogno[16] | Daniel Orbach[14]