European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

18th May 2022

Anna Campello & Marjolijn Jongmans

"Adrenocortical carcinoma (ACC) with brain metastases in a child with Beckwith-Wiedemann syndrome"

Moderation: Sofia Castro

Co-funded by the European Union's Health Programme

SIOPE YOUNG

St. Anna Kinderkrebs Forschung

COI declaration

- Dr. Campello: Nothing to declare
- Dr. Jongmans: Nothing to declare

CLINICAL CASE

- Newborn with macroglossia, left ear crease and umbilical hernia
- Genetic Analysis: **mosaic LoM IC2** (chr 11p15.5)
  → **Beckwith-Wiedemann Syndrome (BWS)**

Molecular defect	Frequency of molecular defect	Mosaicism observed	Characteristic clinical features (compared with other molecular subgroups)
IC2 LOM	50%[48]	Yes[27,54,76,78,81]	• High frequency of exomphalos[11,14,17] • Low risk of Wilms tumour[14,58,149]

Box 2 | **Clinical features of Beckwith–Wiedemann spectrum**

Cardinal features (2 points per feature)

- ✓ Macroglossia
- Exomphalos
- Lateralized overgrowth
- Multifocal and/or bilateral Wilms tumour or nephroblastomatosis
- Hyperinsulinism (lasting >1 week and requiring escalated treatment)
- Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis

Suggestive features (1 point per feature)

- Birthweight >2 SDS above the mean
- Facial naevus simplex
- Polyhydramnios and/or placentomegaly
- ✓ Ear creases and/or pits
- Transient hypoglycaemia (lasting <1 week)
- Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma)
- Nephromegaly and/or hepatomegaly
- ✓ Umbilical hernia and/or diastasis recti

Brioude F et al, Nat. Rev. Endocrinol, 2018

CLINICAL CASE

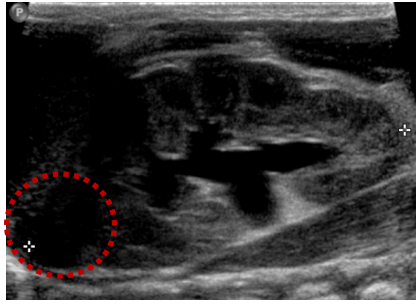
Diagnosis of BWS

Birth

2 m

Timeline

Abdominal US: left adrenal cyst (1 x 1 cm)



CLINICAL CASE

European Reference Network
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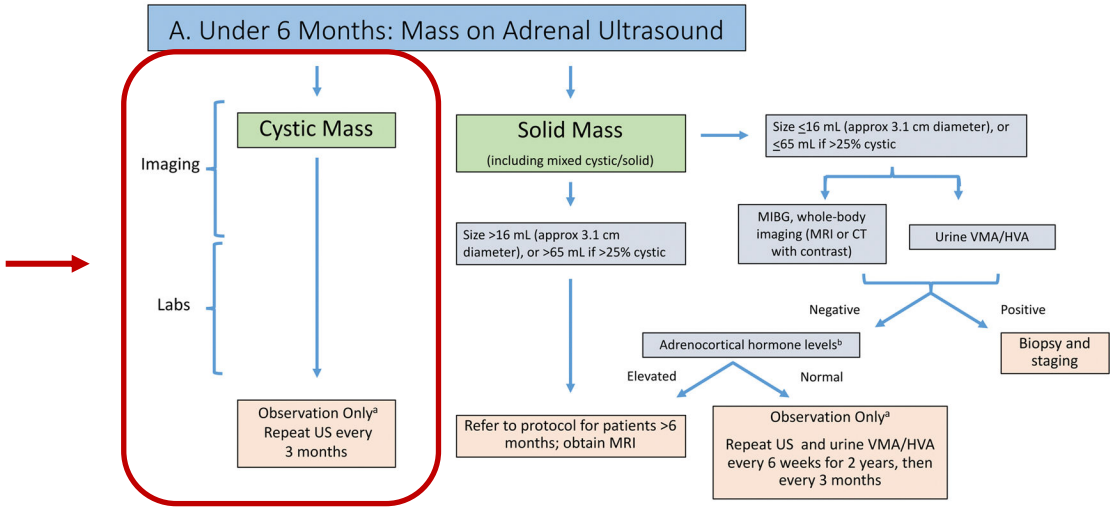
WILEY Pediatric Blood & Cancer | SIOP | aspho

Management of adrenal masses in patients with Beckwith–Wiedemann syndrome

Suzanne P. MacFarland[1] | Sogol Mostoufi-Moab[1,2] | Kristin Zelley[1] | Peter A. Mattei[2,3] | Lisa J. States[4] | Tricia R. Bhatti[2,5] | Kelly A. Duffy[6] | Garrett M. Brodeur[1,2] | Jennifer M. Kalish[2,6]



Tumour risk (% of patients)*	Tumour type for surveillance	Surveillance procedures	Timing
IC2 LOM			
• Overall risk (2.6%) • Hepatoblastoma (0.7%) • Rhabdomyosarcoma (0.5%) • Neuroblastoma (0.5%) • Thyroid cancer (0.3%) • Wilms tumour (0.2%) • Melanoma (0.1%)	Tumour incidence lower than other molecular subgroups; extremely variable tumour spectrum; only half of tumours arise in the abdomen	• No routine USS surveillance • Clinical assessment and USS in response to signs and/or symptoms or parental concerns	–

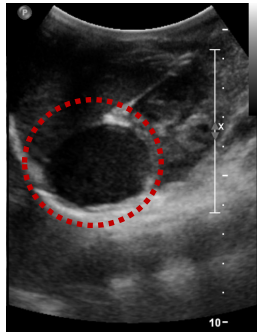
EXPERT CONSENSUS DOCUMENT

Clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement

McFarland S et al, Ped Blood Canc, 2017
Virgone C et al, Ped Blood Canc, 2021

CLINICAL CASE

Cyst size increase (3 x 3 cm)
↑ plasma metanephrines
and normetanephrine



Diagnosis of
BWS

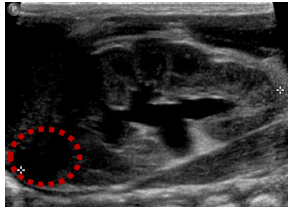
Birth

2 m

5 m

Timeline

Abdominal US:
left adrenal cyst
(1 x 1 cm)

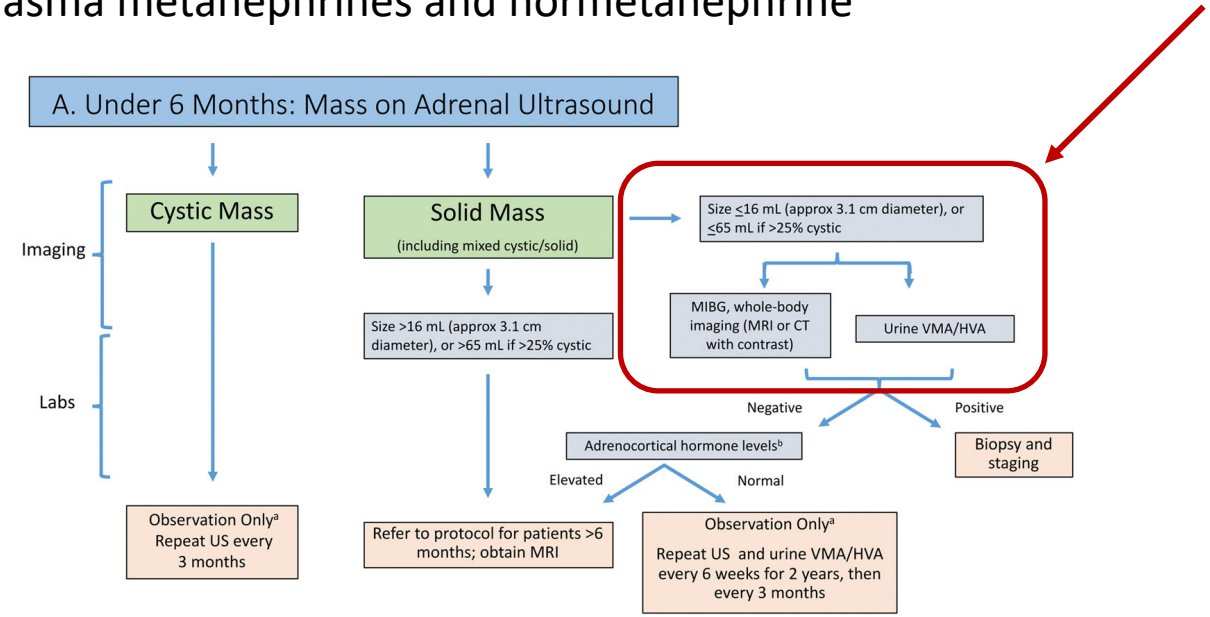


Q1: What would you do next?

1. Biopsy for histological confirmation
2. Abdominal CT
3. Abdominal MRI
4. ^{123}I-Meta-Iodobenzylguanidine (MIBG) Scintigraphy

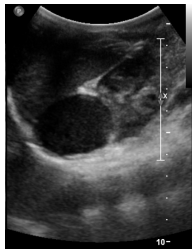
CLINICAL CASE

- 5-month-old: cyst size increase (3 x 3 cm) with vascular spots
- High levels of plasma metanephrines and normetanephrine



McFarland S et al, Ped Blood Canc, 2017

CLINICAL CASE



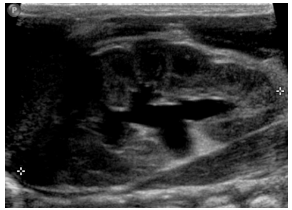
Diagnosis of BWS

Cyst size increase (3 x 3 cm)
↑ plasma metanephrines and normetanephrine

Birth — 2 m — 5 m — Timeline

Abdominal US: left adrenal cyst (1 x 1 cm)

MIBG scintigraphy: neg



Every 3 months:
- Abdominal US
- AFP levels
- Endocrinologic f.up

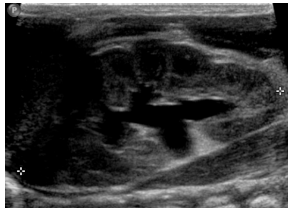
CLINICAL CASE

Birth

Diagnosis of BWS

2 m

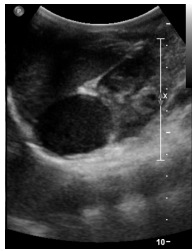
Abdominal US: left adrenal cyst (1 x 1 cm)



Cyst size increase (3 x 3 cm)
↑ plasma metanephrines and normetanephrine

5 m

MIBG scintigraphy: neg



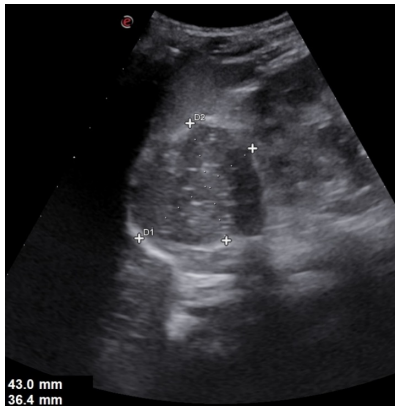
Timeline

Every 3 months:
- Abdominal US
- AFP levels
- Endocrinologic f.up

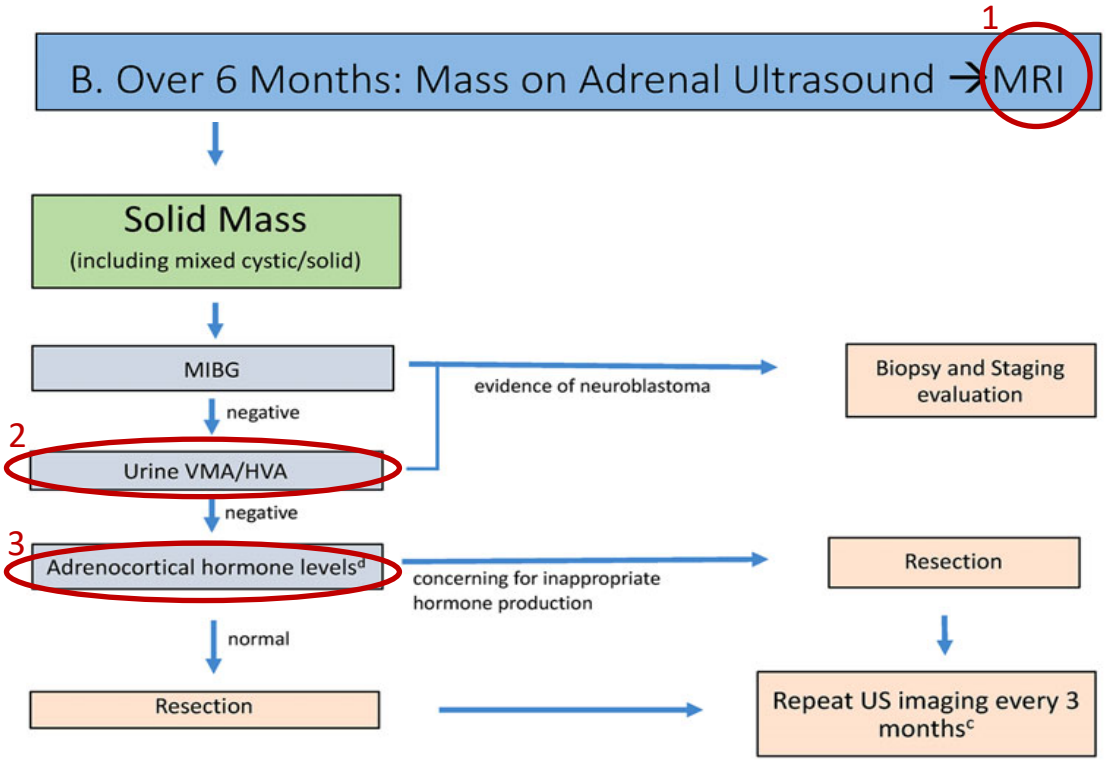
Precocious puberty
(pubic hair, enlarged testicles and penis)

3 y

Abdominal US: left adrenal cyst size increase + solid components

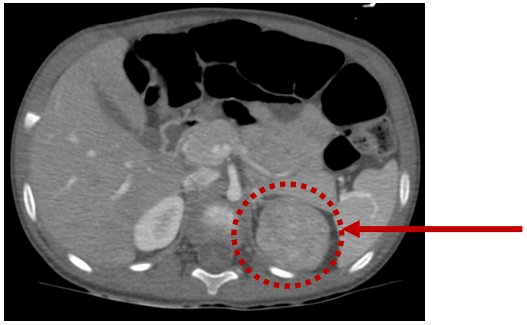


CLINICAL CASE



McFarland S et al, Ped Blood Canc, 2017

1. Thoraco-Abdominal CT scan: Left adrenal mass (4,5 x 3,6 x 3,8 cm)



2. Urine catecholamines, plasma metanephrines and normetanephrine: negative

3. ↑ plasma testosterone and dehydroepiandrosterone-sulfate (DHEAS)

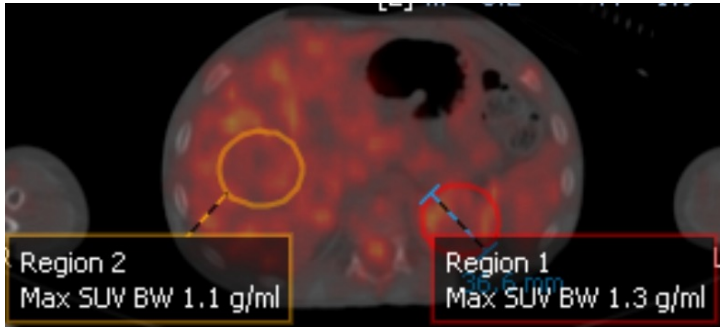
- DHEAS 1616 µg/L (47-194 µg/L)

Q2: What‘s the most likely diagnosis?

1. Neuroblastoma
2. Neuroendocrine Tumor
3. Adrenocortical Tumor
4. Pheochromocytoma

CLINICAL CASE

- Malignant adrenal tumor?
- PET scan: increased uptake (max SUV 1.3) of the adrenal mass; no other uptakes.



- Brain MRI...

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

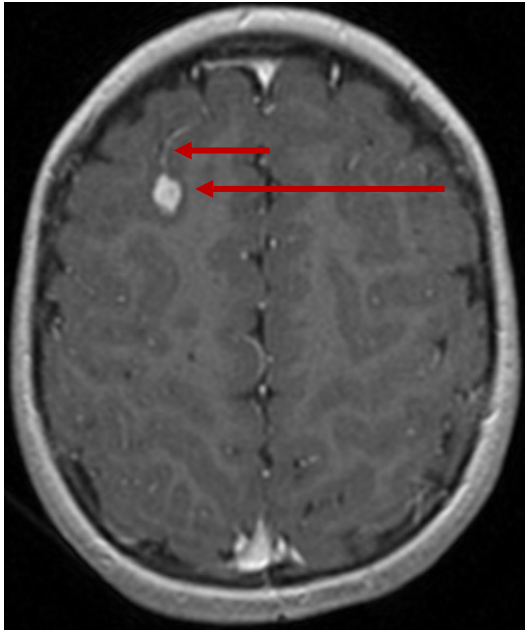
WILEY Pediatric Blood & Cancer · aspho

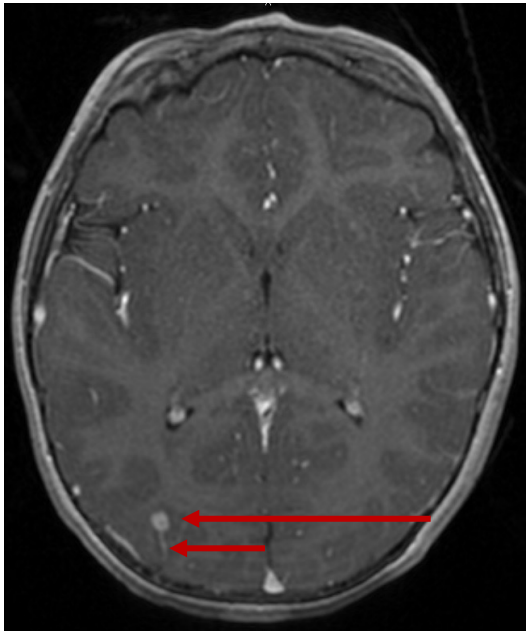
TABLE 1 Recommended clinical investigations in paediatric adrenocortical tumours

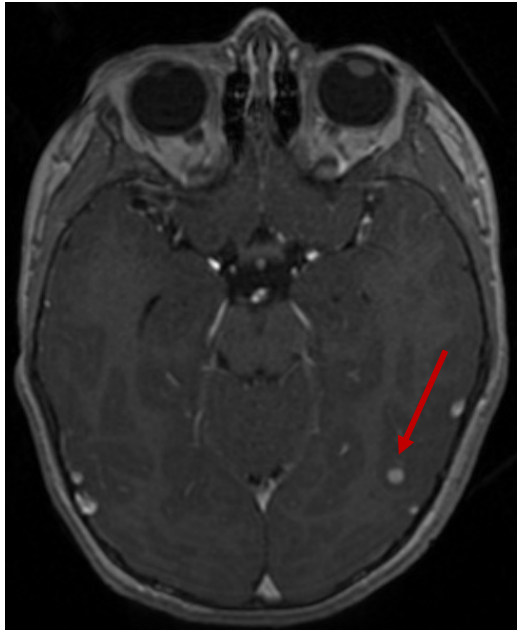
	Assessment	Eligible patients
✓	US (pelvic and abdominal)	All patients
✓	Abdominal CT	All patients
	Abdominal magnetic resonance imaging (MRI)/whole-body MRI	Family history characterised by early onset of tumours
✓	Chest CT	When the clinical and/or radiological suspicion of a malignant ACC is high
✓	Positron emission tomography (PET) scan or PET MRI	When the clinical and/or radiological suspicion of a malignant ACC is high and individually according to present symptoms and signs
	Bone CT	When the clinical suspicion of bone metastasis is present
✓	Brain MRI	When cerebral metastases are clinically suspected or in cases with suspicious/proven Li–Fraumeni syndrome

CLINICAL CASE

- Brain MRI

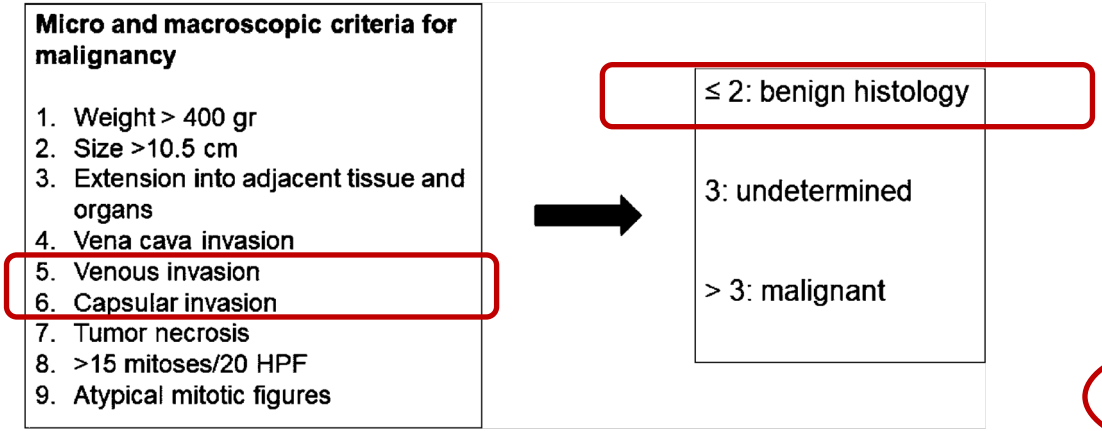






CLINICAL CASE

- Open Left adrenalectomy, complete resection without tumor rupture.
  - Normalization of DHEAS
- Histological Evaluation: Adrenocortical neoplasm, Wieneke score=2



Wieneke Index stratification

Brain lesions?

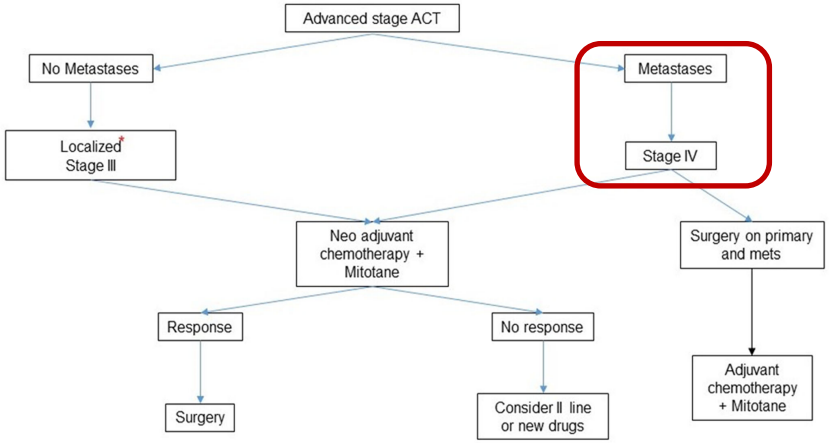
Virgone et al, Ped Blood Canc, 2021

Q3: What would you do?

1. Observation only
2. Biopsy for histological confirmation
3. Surgical removal of all the lesions

CLINICAL CASE

- Brain Biopsy → Histological Evaluation: **metastasis from adrenocortical carcinoma**
- Treatment: 6 cycles of CT (cisplatin, etoposide and doxorubicin) + mitotane
- NGS Assay:
  - CTNNB1 S45P
  - GNAS R201H



Disease evaluation at the end of the treatment:

- No local relapse
- Brain metastasis: Stable Disease

Brain surgery was considered not feasible

Virgone et al, Ped Blood Canc, 2021

Q4: Brain metastasis: what would you do?

1. Strict follow-up
2. Whole-Brain radiotherapy
3. Stereotactic radiosurgery
4. Other chemotherapy cycles
5. New drugs (TKi)

CLINICAL CASE

Current situation:

- Off therapy (+3 months from the end of treatments)
- Mitotane up to 2 years from diagnosis
- Follow up: every 3 months
  - Abdominal US
  - Brain MRI
  - Chest X-Ray
- **Radiosurgery** in case of an increase in size of one/more brain metastasis

FOCUS POINTS:

1. Wieneke score‘s prognostic value
2. Tumor surveillance strategies in children with BWS

(1) Wieneke score‘s prognostic value

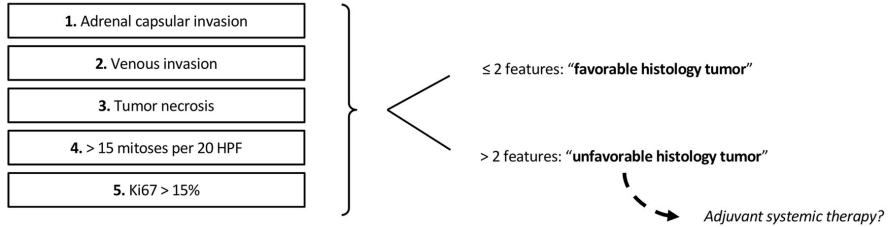
- Histological features are used to classify pediatric adrenocortical tumors (adenomas or carcinoma)
- The Wieneke score has shown to be **predictive of patient outcomes when score as “benign”** (< 3)
- A high proportion in the “**malignant**” subgroup (>3) have **benign outcomes**
- 5-item microscopic score (Picard et al.)

Wieneke Score

Micro and macroscopic criteria for malignancy

1. Weight > 400 gr
2. Size >10.5 cm
3. Extension into adjacent tissue and organs
4. Vena cava invasion
5. Venous invasion
6. Capsular invasion
7. Tumor necrosis
8. >15 mitoses/20 HPF
9. Atypical mitotic figures

Picard Score

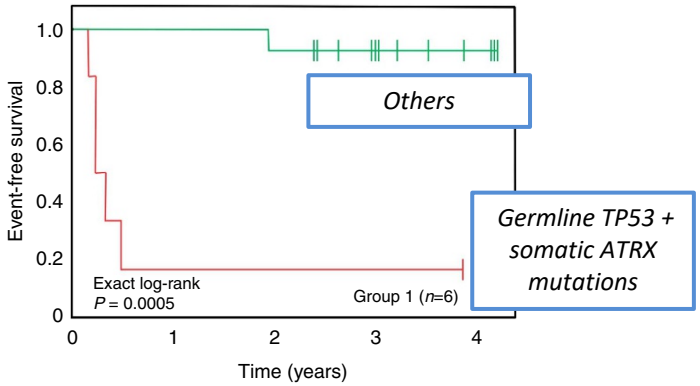


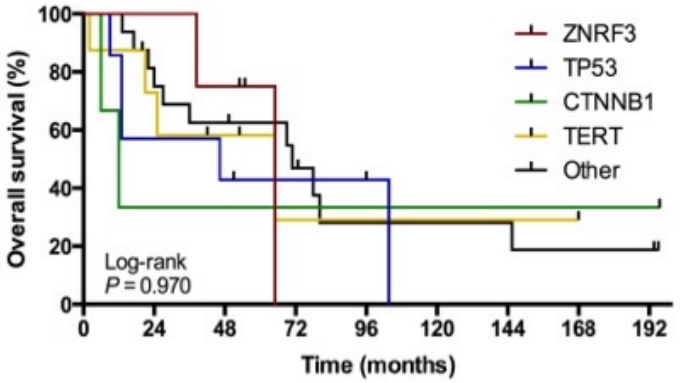
Picard C et al, Mod Pathol, 2019
Virgone et al, Ped Blood Canc, 2021

Future Direction

- Next-generation sequencing may open opportunities to improve the current tumor prognostic stratification
- Pediatric ACC with both **germline TP53 and somatic ATRX mutations** are associated with poor EFS
- Activating mutations in **CTNNB1 (WNT/β-catenin)** are common (better survival?)

Somatic Mutations in present case:
CTNNB1 S45P
GNAS R201H





Pinto E et al, Nat Comm, 2014
Juhnlin C et al, J Clin Endocrinol Metab, 2015

(2) Tumor surveillance strategies

Tumour risk (% of patients)*	Tumour type for surveillance	Surveillance procedures	Timing
IC2 LOM			
• Overall risk (2.6%) • Hepatoblastoma (0.7%) • Rhabdomyosarcoma (0.5%) • Neuroblastoma (0.5%) • Thyroid cancer (0.3%) • Wilms tumour (0.2%) • Melanoma (0.1%)	Tumour incidence lower than other molecular subgroups; extremely variable tumour spectrum; only half of tumours arise in the abdomen	• No routine USS surveillance • Clinical assessment and USS in response to signs and/or symptoms or parental concerns	–
IC1 GOM			
• Overall risk (28.1%) • Wilms tumour (24%) • Neuroblastoma (0.7%) • Pancreatoblastoma (0.7%)	Wilms tumour	Abdominal USS	Every 3 months from diagnosis until age 7 years
upd(11)pat			
• Overall risk (16%) • Wilms tumour (7.9%) • Hepatoblastoma (3.5%) • Neuroblastoma (1.4%) • Adrenocortical carcinoma (1.1%) • Phaeochromocytoma (0.8%) • Lymphoblastic leukaemia (0.5%) • Pancreatoblastoma (0.3%) • Hemangiotheloma (0.3%) • Rhabdomyosarcoma (0.3%)	• Wilms tumour • Hepatoblastoma • Adrenal tumours	Abdominal USS	Every 3 months from diagnosis until age 7 years
CDKN1C *mutation*			
• Overall risk (6.9%) • Wilms tumour (1.4%) • Neuroblastoma (4.2%) • Acute lymphoblastic leukaemia (1.4%)	Neuroblastoma	Abdominal USS	Every 3 months from diagnosis until age 7 years
Classical BWS with negative molecular tests			
• Overall risk (6.2%) • Wilms tumour (4.1%) • Neuroblastoma (0.6%) • Hepatoblastoma (0.3%) • Rhabdomyosarcoma (0.3%) • Adrenocortical carcinoma (0.3%)	Wilms tumour	Abdominal USS	Every 3 months from diagnosis until age 7 years

- Tumor types:
  - **Wilms tumor**
  - **Hepatoblastoma**
  - **Neuroblastoma**
  - **Rhabdomyosarcoma**
  - **Adrenocortical carcinoma**
- Screening is generally considered for a tumor risk >5% in Europe (>1% in the USA)
- In BWS, screening is stratified **according to the genotype** (not recommended for IC2 LOM)

Brioude F et al, Nat. Rev. Endocrinol, 2018

(2) Tumor surveillance strategies

- **Abdominal USS** for Wilms tumour screening.
- Doubtful benefits of **AFP screening** for hepatoblastoma
- **Adrenal carcinoma is rare in BWS**: there is no data on the utility of screening strategies
- Benign adrenal masses are frequent in BWS (cyst, adenoma..)

There should be a low threshold for investigation in response to symptoms or parental concern

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Management of adrenal masses in patients with Beckwith–Wiedemann syndrome

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Brioude F et al, Nat. Rev. Endocrinol, 2018
Lapunzina P, Am J Med Genet Semin Med Genet, 2005
MacFarland S et al, Ped Blood Canc, 2017

Q5: Tumor Surveillance in your Center

1. Abdominal US is performed in all the patients with BWS
2. Screening is stratified according to the genotype (IC2 LOM excluded)
3. Different surveillance protocol (CT/MRI/..)
4. I don‘t know

Expert Opinion

TAKE HOME MESSAGES

- Beckwith-Wiedemann is a known predisposing syndrome for adrenocortical carcinoma (ACC).
  - Think about it in case of an adrenal mass or a precocious puberty!
- The incidence of brain metastases in ACC is low; the correct management is still unknown.
- The biologic behavior of pediatric adrenocortical tumors is difficult to predict
- Histopathologic classification criteria have a limited role in guiding therapeutic decisions
  - Prognostic value of the Wieneke score
- Incorporating molecular data will maybe help stratify and improve outcomes in patients with ACC

BEDANKT!

Marjolijn Jongmans
Prinses Máxima Centrum

Grazie

Anna Campello
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