European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

"Synchronous tumours: the chemotherapy challenge for the modern oncologist"

February 17th 2021

Emma Seaford & Meriel Jenney

ERN PaedCan – Young SIOPE webinar series

"Most challenging cases in paediatric oncology"

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Presentation at a young age

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Presentation

- 5 month old girl presented April 2012
- Squint, 3 weeks worsening right eye proptosis

Past history

- Nil of note
- Normal growth and development
- No family history of cancer

Examination

- Right sided proptosis
- No lymphadenopathy
- No other significant findings

Bloods

- Mild anaemia
- WCC, platelet count, renal and liver function normal
- Tumour markers normal

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Imaging revealed a retro-orbital mass

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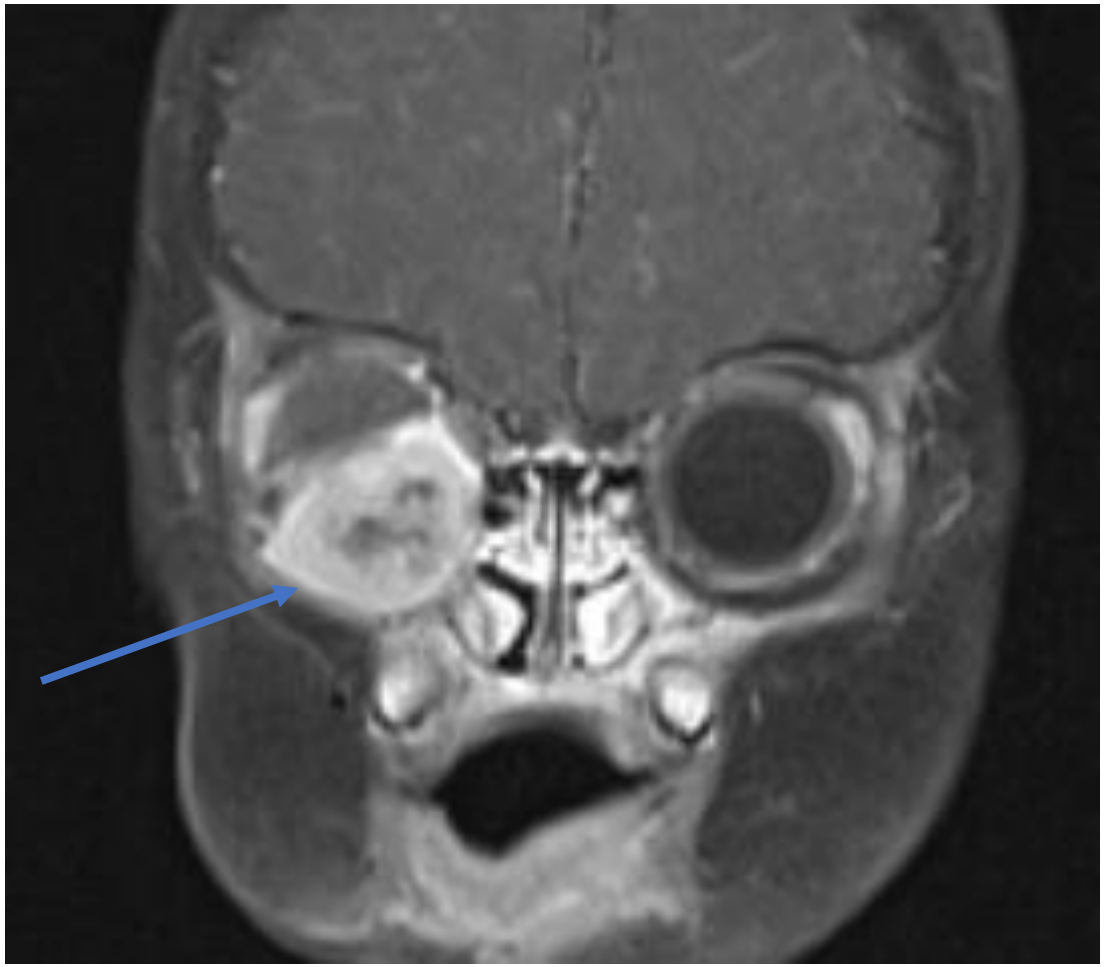

1.9 x 2.4 x 2.3cm mass in inferior aspect of right orbit

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An unexpected finding on imaging

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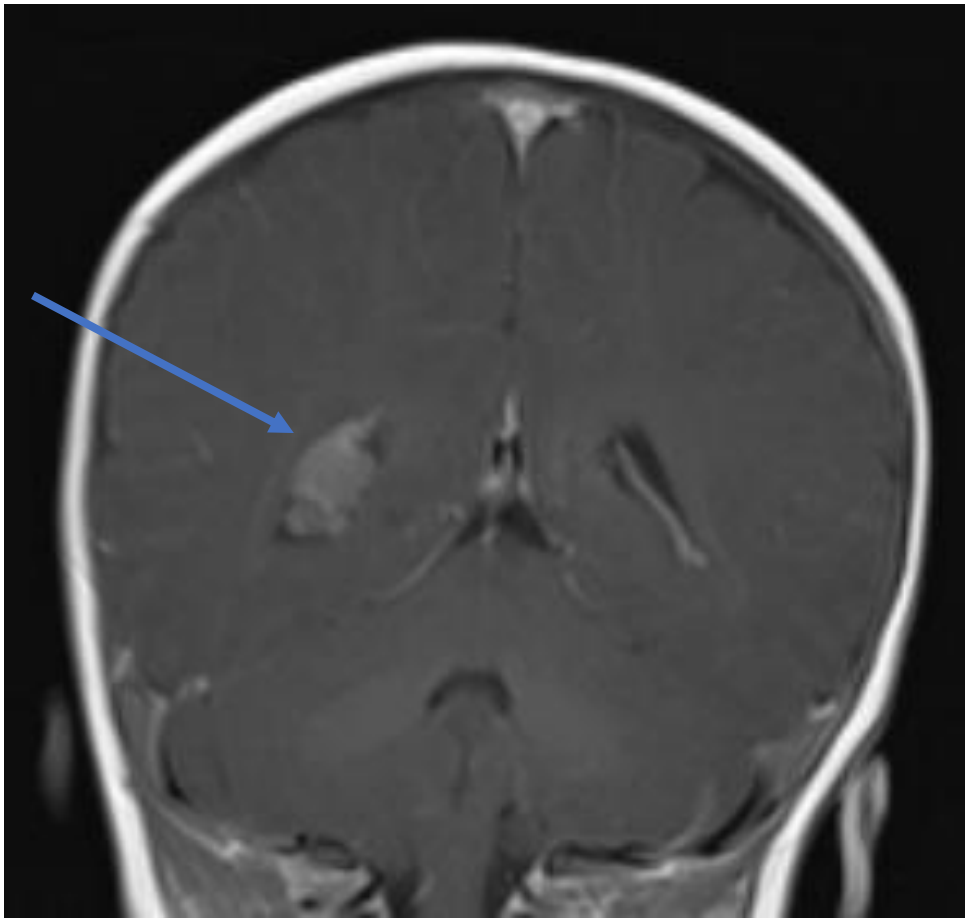
A further mass noted within the occipital horn of the right lateral ventricle 1.5 x 1.7 x 1.2cm



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What was the unexpected choroid plexus lesion?

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- Choroid plexus lesion ?metastasis ?second primary
- Biopsy retro-orbital lesion confirmed sarcoma
- Decision made to proceed with surgical resection of choroid plexus lesion

"Whilst possible for the choroid plexus lesion to be a metastasis from sarcoma, it is difficult to be confident in this age group and important to ascertain that we are dealing with a single pathology"

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Two distinct entities

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	Retro-orbital lesion	Choroid plexus lesion
Histopathology	Interlacing fascicles of spindle cells with densely eosinophilic cytoplasm	Poorly differentiated, polygonal or round cells predominantly in sheets, papillary pattern focally
Immunohistochemistry		
• Desmin, Myogenin, MyoD1	+	-
• INI1/BAF47	+	+
• SMA	-	
• Pancytokeratin	-	+
• S100	-	+
• NB84		+
• CD99	-	-
Conclusion	**Spindle cell variant of rhabdomyosarcoma, embryonal subtype**	**Choroid plexus carcinoma**

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Why did she have synchronous tumours?

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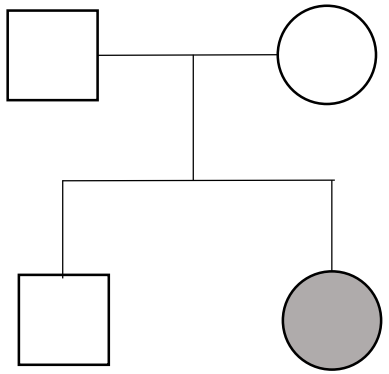
- Diagnosed with synchronous tumours at young age
- Both tumours types are those typically associated with predisposition syndromes
- Genetics testing and referral
- Significant family implications



No significant family history of cancer

The fact she has synchronous tumours is almost certainly indicative of a **cancer predisposition syndrome**, such as Li Fraumeni syndrome

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Synchronous tumours in infant <6 months

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Diagnosis
Spindle cell embryonal rhabdomyosarcoma

Staging
- Localised: Bone scan and bone marrow sampling revealed no metastatic disease

Diagnosis
Choroid plexus carcinoma

Staging
- Localised: MRI head and spine and CSF sampling revealed no metastatic disease

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Synchronous tumours in infant <6 months

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Diagnosis

Spindle cell embryonal rhabdomyosarcoma

Staging

- Localised: Bone scan and bone marrow sampling revealed no metastatic disease
- Standard risk, subgroup C: favourable pathology, favourable site, N0

Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	A	Favourable	I	Any	N0	Favourable
Standard Risk	B	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High Risk	E	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable*	I, II, III	Any	N0	Any
Very High Risk	H	Unfavourable	I, II, III	Any	N1	Any

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Synchronous tumours in infant <6 months

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Diagnosis
Spindle cell embryonal rhabdomyosarcoma

Staging
- Localised: Bone scan and bone marrow sampling revealed no metastatic disease
- Standard risk, subgroup C: favourable pathology, favourable site, N0

Prognosis
OS 70-75%

Diagnosis
Choroid plexus carcinoma

Staging
- Localised: MRI head and spine and CSF sampling revealed no metastatic disease
- Gross total resection, no residual

Prognosis
OS 50%

?

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Local and systemic therapy for both tumours

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Surgery

- Gross total resection choroid plexus carcinoma
- No role for surgery in retro-orbital rhabdomyosarcoma

Chemotherapy

- Bespoke!

+/- Radiotherapy

- No indication for choroid plexus carcinoma in view of age and GTR
- Dependent on response to treatment for rhabdomyosarcoma
- Prefer to avoid in view of age and possible underlying condition

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Chemotherapy dilemma

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Aim: Treatment of both tumour types using optimum chemotherapy

EpSSG RMS 2005, treatment group C

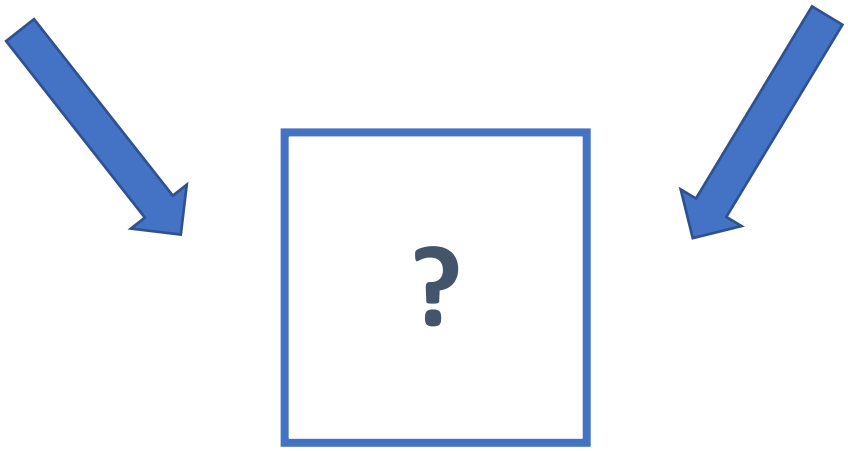
9 cycles of IVA given every 21 days

- Ifosfamide
- Vincristine
- Actinomycin-D

CPT-SIOP-2000

Established CPC to be responsive to:

- Etoposide
- Vincristine
- Carboplatin or cyclophosphamide (superior agent not determined)



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Chemotherapy dilemma

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Network Paediatric Cancer (ERN PaedCan)

Aim: Treatment of both tumour types using optimum chemotherapy

EpSSG RMS 2005, treatment group C

9 cycles of IVA given every 21 days

- Ifosfamide
- Vincristine
- Actinomycin-D

CPT-SIOP-2000, 6 cycles every 28 days

Established CPC to be responsive to:

- Etoposide
- Vincristine
- Carboplatin or cyclophosphamide

Objectives:

- **Incorporate 9 cycles of ifosfamide/cyclophosphamide**
- **Include vincristine weekly for first 7 weeks then every cycle**
- **Include actinomycin D**
- **Alternate with cycles containing etoposide and carboplatin**

Alternating: IVA / V-CyCE / IVE

IVA	V-CyCE	IVE
- **I**fosfamide	- **V**incristine	- **I**fosfamide
- **V**incristine	- **Cy**clophos	- **V**incristine
- **A**ctinomycin-D	- **C**arboplatin	- **E**toposide
	- **E**toposide	

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Chemotherapy dilemma

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Cycle	Wk	Chemo
1	1	IVA(Do*)
	2	V
	3	V
2	4	V-CyCE
	5	V
	6	V
3	7	IVE
4	10	IVA
5	13	V-CyCE
6	16	IVE
7	19	IVA
8	22	V-CyCE
9	25	IVE

- **IVA according to EpSSG RMS 2005**
- **CyCE according to EpSSG NRSTS 2005**
- **IVE according to SIOP MMT95 (2 doses ifosfamide only)**

Mg/kg dosing appropriate for age and weight (<10kg, <12 mnths)

Chemotherapy	Prescribed Dose/kg	Cumulative Dose
Cyclophosphamide (Cy)	73.5mg/kg/cycle x3	220.5mg/kg
Vincristine (V)	0.05mg/kg/cycle x13	0.65mg/kg
Actinomycin-D (A)	0.05mg/kg/cycle x3	0.15mg/kg
Etoposide (E)	16.5mg/kg/cycle x3	49.5mg/kg
Doxorubicin (Do)	1.5mg/kg/cycle x1	1.5mg/kg
Ifosfamide (I)	100mg/kg/cycle x6	600mg/kg
Carboplatin (C)	Dosed according to GFR	

**started treatment urgently due to rapidly progressing proptosis, brain lesion initially thought to be metastatic RMS*

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Progress on treatment

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Treatment

- Tolerated chemotherapy well
- Single septic episode requiring line change

Re-assessment

- Good partial response
- Significant residual mass 1.7 x 2.1 x 1.4 cm

Genetics

- Li Fraumeni syndrome confirmed
- Heterozygous for pathogenic *TP53* mutation c524G>A
- Rare autosomal dominant inherited genetic condition
- Significantly increased lifetime risk of cancer
- Most frequently sarcoma, breast, brain, adrenocortical

Radiotherapy?

- Local therapy critical in RMS
- Surgery not usually utilised in primary orbital RMS
- Evidence of increased risk of radiation-induced cancer in Li Fraumeni syndrome
- Advised to consider alternative therapies to minimise or avoid radiotherapy use where possible

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Progress on treatment

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Treatment

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Radiotherapy

- Decision was made to give radiotherapy
- 36 Gy delivered to whole orbit plus boost to original tumour volume with a margin to total dose of 50.4 Gy
- Tolerated well

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Long-term toxicities were minimal

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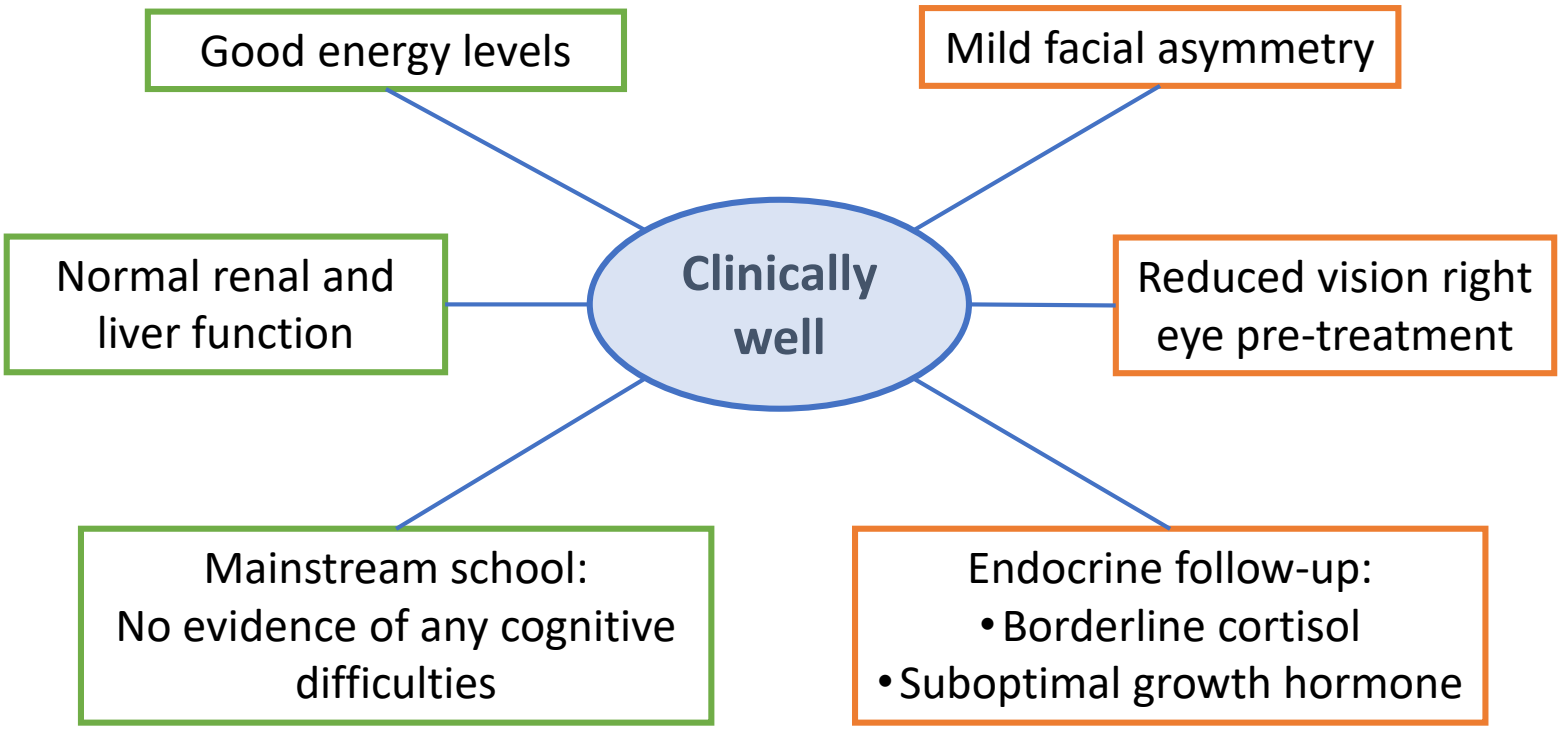

Regular MRI scans showed no evidence of recurrence
No specific imaging performed with regard to underlying Li Fraumeni syndrome

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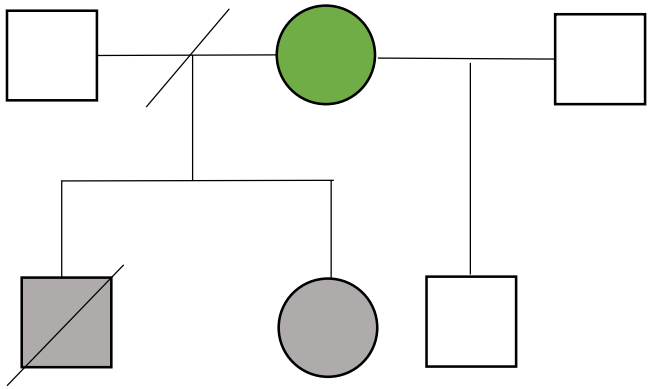
Difficult family events

- Older brother diagnosed with grade III anaplastic ganglioglioma
- Rapid genetic testing confirmed familial pathogenic *TP53* mutation
- Treated with radiotherapy and temozolomide, relapsed within 2 months



- Parents offered genetic testing
  - Mum did not have *TP53* mutation
  - Dad declined testing
- Possible that one of parents is gonadal mosaic or that dad has mutation

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Re-presentation 8 years post-end of treatment

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Rapidly growing mass arising from right side of palate

Underwent biopsy and staging

Diagnosed with **localised sarcoma with malignant osteogenic differentiation** of right maxilla (within margin of radiotherapy field)

On-going treatment with chemotherapy and radical surgery

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Discussion

- Which **chemotherapy** regime would likely give the best chance of cure from both tumours for this patient?
- Was the balance of risks and benefits, both immediate and in the longer-term, in favour of giving or avoiding **radiotherapy** in this situation?
- What are the **long-term** implications of giving this chemotherapy and radiotherapy at such a young age?
- Should regular **screening** for further malignancies have been offered as part of the follow-up in view of the underlying Li Fraumeni syndrome?

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Take home messages

- Comprehensive understanding of the rationale for treatment protocols and contribution of each drug is critical in complex decision-making
- Very low threshold to undertake genetic testing for tumours presenting at young age or simultaneously as may impact significantly on treatment decisions
- Treatment decisions can be very complex
  - Frequently there is no 'right' or 'wrong' treatment decision, just a careful balance of risks, supported by open and honest conversations with the family and consensus within the multi-disciplinary team

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Thank you for your attention

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Back-up slides

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Questions for Polls

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QUESTION 1 (after slide 2)

What would be your top three differential diagnoses?

- Leukaemia
- Langerhans cell histiocytosis
- Retinoblastoma
- Rhabdomyosarcoma
- Neuroblastoma

QUESTION 2 (after slide 11)

Which chemotherapy would you have given in this case?

- According to RMS protocol/guideline
- According to CPC protocol/guideline
- Combination of chemotherapy agents in individualised protocol

QUESTION 3 (after slide 14)

Would you have given radiotherapy in this case?

- Yes - ideally external beam radiotherapy
- Yes - ideally proton beam therapy
- No

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Screening recommendations for people with Li Fraumeni syndrome

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Children (birth to age 18 years)
General assessment • Complete physical examination every 3–4 months, including blood pressure, anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), Cushingoid appearance, signs of virilization (pubic hair, axillary moisture, adult body odor, androgenic hair loss, clitoromegaly, or penile growth), and full neurologic assessment • Prompt assessment with primary care physician for any medical concerns
ACC • US of abdomen and pelvis every 3–4 months • In case of unsatisfactory US, blood tests[a,b] may be performed every 3–4 months: total testosterone, dehydroepiandrosterone sulfate, and androstenedione
Brain tumor • Annual brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality)
Soft tissue and bone sarcoma • Annual WBMRI

Adults
General assessment • Complete physical examination every 6 months • Prompt assessment with primary care physician for any medical concerns
Breast cancer • Breast awareness (age 18 years onward) • Clinical breast examination twice a year (age 20 years onward) • Annual breast MRI screening[c] (ages 20–75) • Consider risk-reducing bilateral mastectomy
Brain tumor (age 18 years onward) • Annual brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal)
Soft tissue and bone sarcoma (age 18 years onward) • Annual WBMRI[c] • US of abdomen and pelvis every 12 months
Gastrointestinal cancer (age 25 years onward) • Upper endoscopy and colonoscopy every 2–5 years
Melanoma (age 18 years onward) • Annual dermatologic examination

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Screening recommendations for people with Li Fraumeni syndrome

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Table 1 Agreed surveillance recommendations for *TP53* carriers

Tumour	Screening recommendation
ACC	Abdominal USS 3–4 monthly birth:18 years Biochemistry (17 OH-progesterone, total testosterone, DHEAS, androstenedione) should only be performed where there is an unsatisfactory USS.
Breast cancer (women only)	Annual dedicated MRI from age 20–70 years Consider risk-reducing mastectomy from age 20 years
Brain tumour	Annual dedicated brain MRI from birth (first MRI with contrast)*
Sarcoma	Annual WB-MRI† from birth*
Haematological	Routine FBC are not indicated due to lack of evidence that these detect haematological malignancy at an early stage.
Colon	Colonoscopy only indicated when family history of colorectal cancer or polyposis‡; consider investigation for, possibly coinherited, causes if strong family history of colorectal cancer or polyposis The presence of microcytic anaemia should prompt investigation for a gastrointestinal tract malignancy (routine FBC not advised).
Gastric	Recommend *Helicobacter pylori* testing and eradication if required Endoscopy not indicated due to lack of evidence
Skin	Annual dermatology review from 18 years (general practitioner or dermatology) General advice on use of high protection factor sunscreen and covering up in sun
Physical examination	Full physical examination 3–4 monthly in children (including blood pressure, anthropometric measurements, signs of virilisation and neurological exam) Routine physical examination not recommended in adults; advise detailed discussion of 'red flag' symptoms and low threshold for fast track referral of persistent or unusual symptoms
Other	Recommend detailed discussion of red flag symptoms in both children and adults and provide information on relevant resources. Discuss importance of making positive lifestyle choices (eg, not smoking, eating a healthy diet, limiting alcohol consumption, sun protection, keeping physically active and providing appropriate resources).

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IVA weeks 1,10 and 19

(Use IVA RMS pre-printed charts for prescribing. No Mesna dose reduction for age or weight)

DAY	IFOSFAMIDE	VINCRISTINE	ACTINOMYCIN D
1	100 mg/kg (3g/m^2)	0.05mg/kg (1.5mg/m^2)	0.05mg/kg (1.5mg/m^2)
2	100 mg/kg (3g/m^2)		
Cum. dose per cycle	**200 mg/kg (6g/m^2)**	**0.05mg/kg (1.5mg/m^2)**	**0.05mg/kg (1.5mg/m^2)**
Cum dose for all 3 cycles	**600 mg/kg (18g/m^2)**	**0.15mg/kg (4.5mg/m^2)**	**0.15mg/kg (4.5mg/m^2)**
Notes	Give IV over 3 hours in sodium chloride 0.9% with Mesna and hydration (Ifosfamide fluid volume- <2000- 4000mg in 50ml, >4000mg in 100ml)	Max 2mg. Give as IV bolus in 3ml sodium chloride 0.9%	Max 2mg. Give as IV bolus

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CyCE weeks 4, 13 and 22

Additional Vincristine: weekly weeks 4, 5, and 6 @ 0.05mg.kg

Carboplatin dosing: to be prescribed according to dosing and adjusted if GFR reduced as per protocol/consultant advice

DAY	CYCLOPHOSPHAMIDE	CARBOPLATIN	ETOPOSIDE	VINCRISTINE
1	14.7mg/kg (440mg/m^2)	According to GFR (see NRSTS protocol)	3.3mg/kg (100mg/m^2)	0.05mg/kg (1.5mg/m^2)
2	14.7 mg/kg (440mg/m^2)		3.3mg/kg (100mg/m^2)	
3	14.7 mg/kg (440mg/m^2)		3.3mg/kg (100mg/m^2)	
4	14.7 mg/kg (440mg/m^2)		3.3mg/kg (100mg/m^2)	
5	14.7 mg/kg (440mg/m^2)		3.3mg/kg (100mg/m^2)	
Cum dose per cycle	**73.5 mg/kg (22 0.5mg/m^2)**	-	**16.5mg/kg (500mg/m^2)**	**0.05mg/kg (1.5mg/m^2)**
Cum dose for all 3 cycles	**220.5 mg/kg (661.5mg/m^2)**	-	**49.5mg/kg (1500mg/m^2)**	**0.15mg/kg (4.5mg/m^2)**
Notes	Give IV over 1 hour in sodium chloride 0.9% with mesna and hydration. Minimum volume = 20ml in a syringe	Give IV over 1 hour in glucose 5%	Give IV over 1 hour in sodium chloride 0.9% (max conc. 0.3mg/ml)	Give as IV bolus in 3ml sodium chloride 0.9%

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IVE weeks 7, 16 and 25

IVE modifications to MMT95 protocol: Ifosfamide for 2 days, rather than 3. Applying principles of mg/kg dosing as in RMS and NRSTS (as these are more recent protocols).

DAY	IFOSFAMIDE	VINCRISTINE	ETOPOSIDE
1	100mg/kg (3g/m^2)	0.05mg/kg (1.5mg/m^2)	5mg/kg (150mg/m^2)
2	100mg/kg (3g/m^2)		5mg/kg (150mg/m^2)
3			5mg/kg (150mg/m^2)
Cum dose per cycle	**200mg/kg(6g/m^2)**	**0.05mg/kg (1.5mg/m^2)**	**15mg/kg (450mg/m^2)**
Cum dose for all 3 cycles	**600mg/kg(18g/m^2)**	**0.15mg/kg (4.5mg/m^2)**	**45mg/kg (1350mg/m^2)**
Notes	Give IV over 3 hours in sodium chloride 0.9% with Mesna and hydration (Ifosfamide fluid volume- <2000-4000mg in 50ml, >4000mg in 100ml)	Max 2mg. Give as IV bolus in 3ml sodium chloride 0.9%	Give IV over 2 hours in sodium chloride 0.9% (max concentration 0.3mg/ml)