

# Endocrine Care of Childhood Cancer Survivors:

## Approaches to Monitoring and Care

POGO AfterCare Education Day

June 14, 2024

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Jonathan Wasserman, MD, PhD

The Hospital for Sick Children, Toronto, Canada



# CASE 1

A 10 yo girl, is seen for an initial consult after moving from a different city where she completed therapy. Treated at age 6 for AT/RT.

## **XRT:**

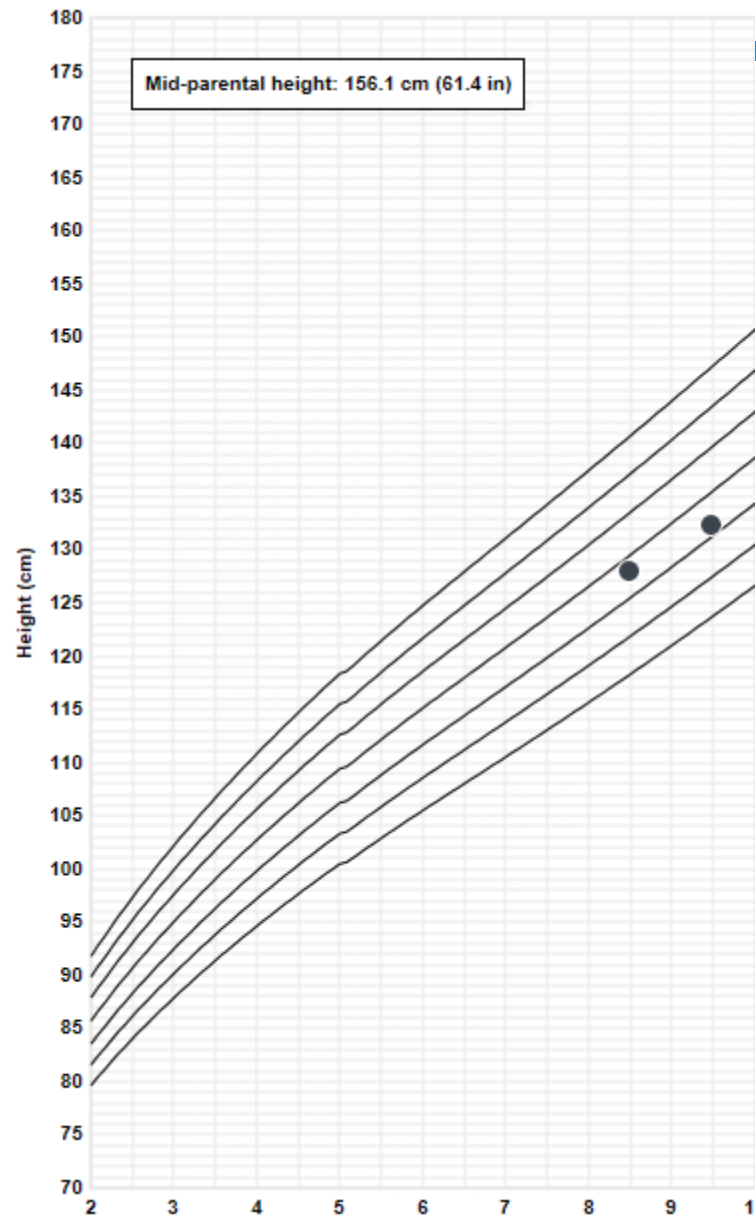
- 3600 cGy Craniospinal in 20 Fractions
- 1800 cGy Tumour bed boost in 10 Fractions
- 1440 cGy to Cervical and Thoracic spinal mets in 8 Fractions

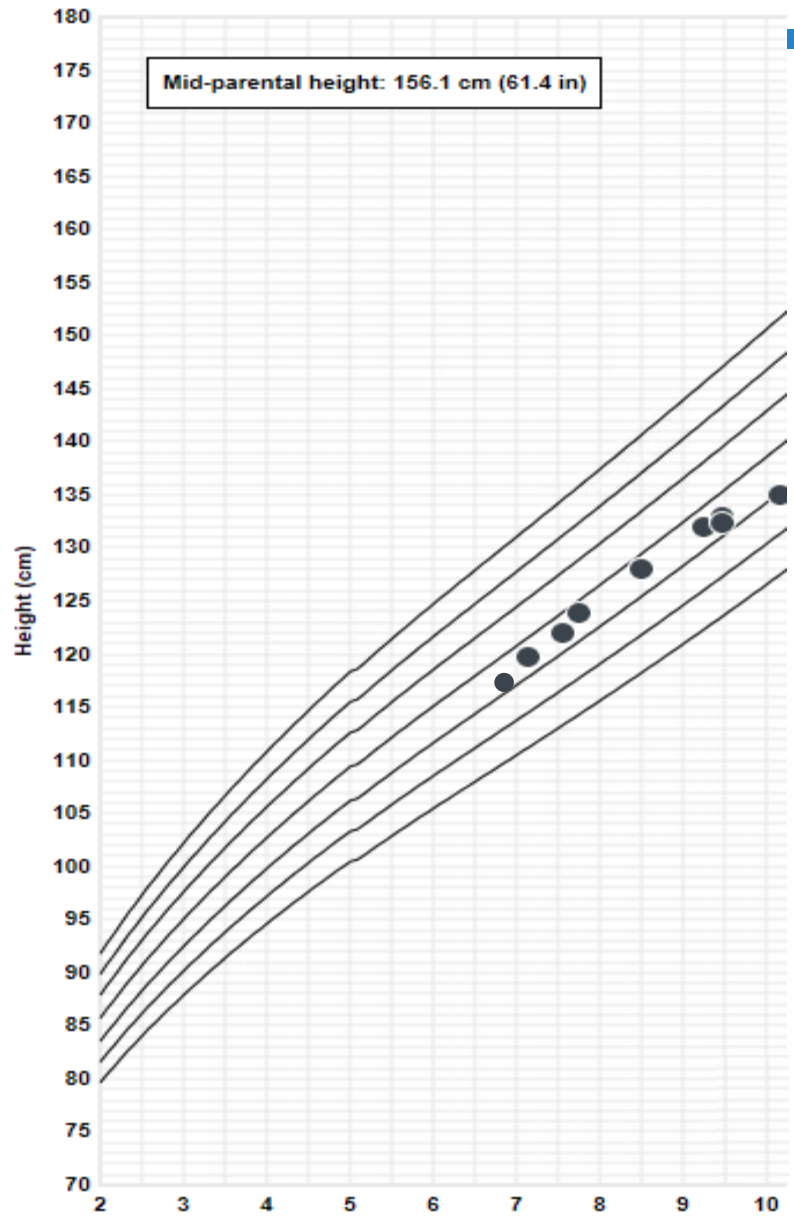
## **Chemotherapy (cumulative doses as per ACNS0333):**

- Cisplatin 210 mg/m<sup>2</sup>
  - Cyclophosphamide 7.2 mg/m<sup>2</sup>
  - HD Methotrexate 16 grams/m<sup>2</sup>
  - \*Thiotepa 1800 mg/m<sup>2</sup>
  - \*Carboplatin 510 mg/m<sup>2</sup>
  - VCR & VP-16
- Current height is at the 45<sup>th</sup> %ile
    - Mid-parental height is at the 30<sup>th</sup> %ile



**She Feels fine** **SickKids®**

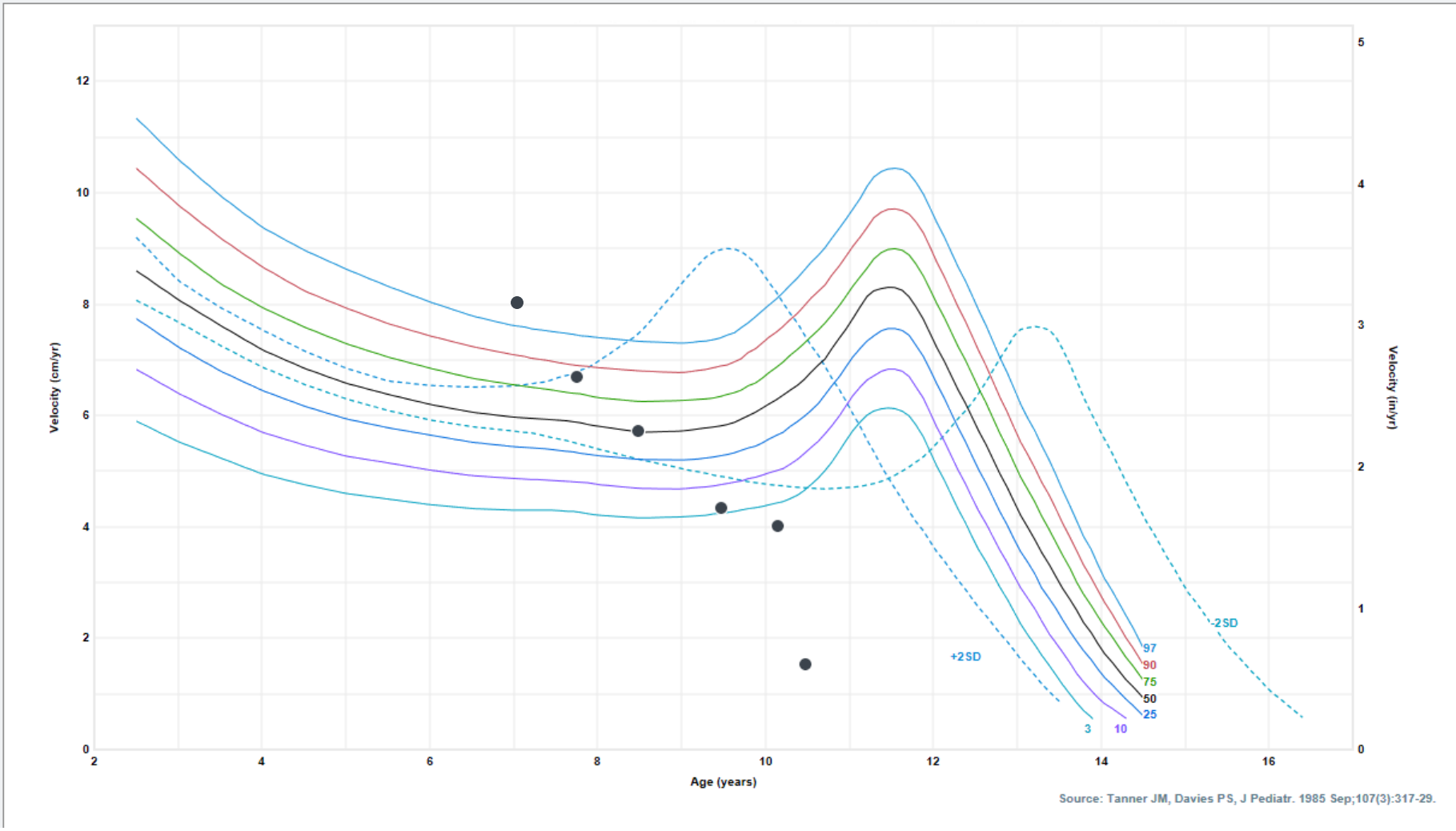




# Growth Velocity

Height Velocity-for-age Percentiles (Girls, 2.5 to 14.5 years)

100 %



Source: Tanner JM, Davies PS, J Pediatr. 1985 Sep;107(3):317-29.

# INITIAL “SURVEILLANCE” BLOODWORK

	Ref. Range	25/03/2019
<b>IGF-1</b>	67 - 407 ug/L	36
<b>TSH</b>	0.73 - 4.09 mIU/L	0.97
<b>Free T4</b>	10.0 - 17.6 pmol/L	9.6
<b>LH</b>	<4.3 IU/L	15.7
<b>FSH</b>	0.4 - 4.2 IU/L	53.3
<b>Estradiol</b>	<=239 pmol/L	<15
<b>Cortisol</b>	61 - 349 nmol/L	300

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- **GH Deficiency**
- **Central Hypothyroidism**
- **Premature ovarian insufficiency**

WHAT PROPORTION OF CHILDHOOD CANCER SURVIVORS (CCS)  
DEVELOP ENDOCRINOPATHIES OVER THEIR LIFETIME?

- a) 25%
- b) 40%
- c) 50%
- d) 65%
- e) 80%

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# OBJECTIVES

- Don't worry, I won't try to turn you into Endocrinologists
- I will try to convey the magnitude of endocrinopathies among childhood cancer survivors
- I will describe an exposure-based approach to monitoring for late-effects with a focus on a select few
- I will provide guidance regarding when to refer, and what to include

## WHAT IS THE SINGLE GREATEST EXPOSURE CONTRIBUTING TO SUBSEQUENT ENDOCRINOPATHY AMONG CCS?

- a) Alkylating chemotherapy
- b) Radiation treatment
- c) Hematopoietic Stem Cell Transplant
- d) Platinum-based chemotherapy
- e) Brain surgery

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## WHAT IS THE MOST PREVALENT ENDOCRINOPATHY AMONG CCS?

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- b) Infertility
- c) Adrenal Insufficiency (central)
- d) Gonadal failure
- e) Growth impairment

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# WHO COORDINATES ENDOCRINE CARE FOR SURVIVORS?

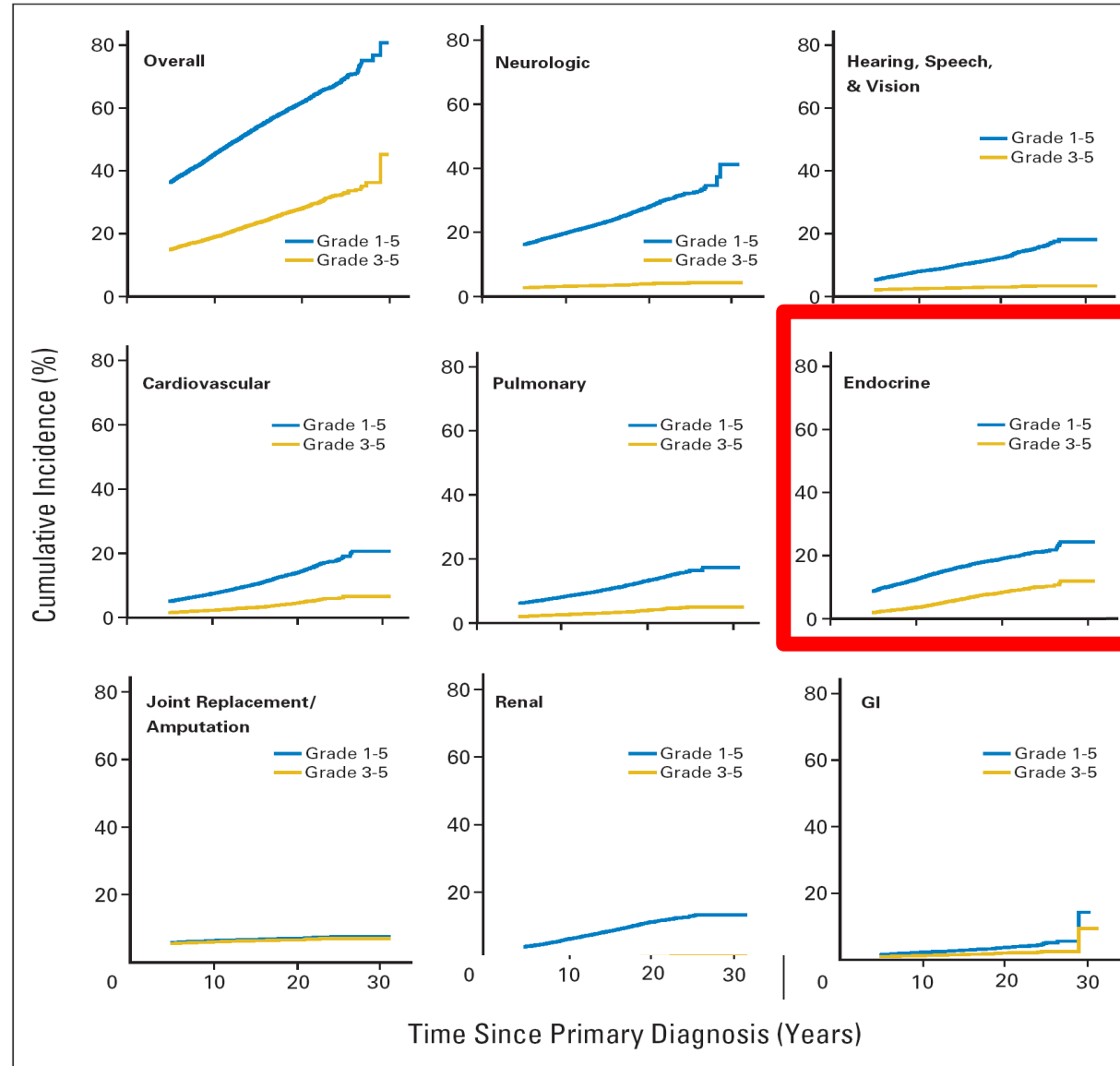
- a) Family Physicians
- b) Internists
- c) Oncologists
- d) Radiation Oncologists
- e) Pediatricians
- f) Endocrinologists
- g) I haven't got a clue!!

# WHO COORDINATES ENDOCRINE CARE FOR SURVIVORS?

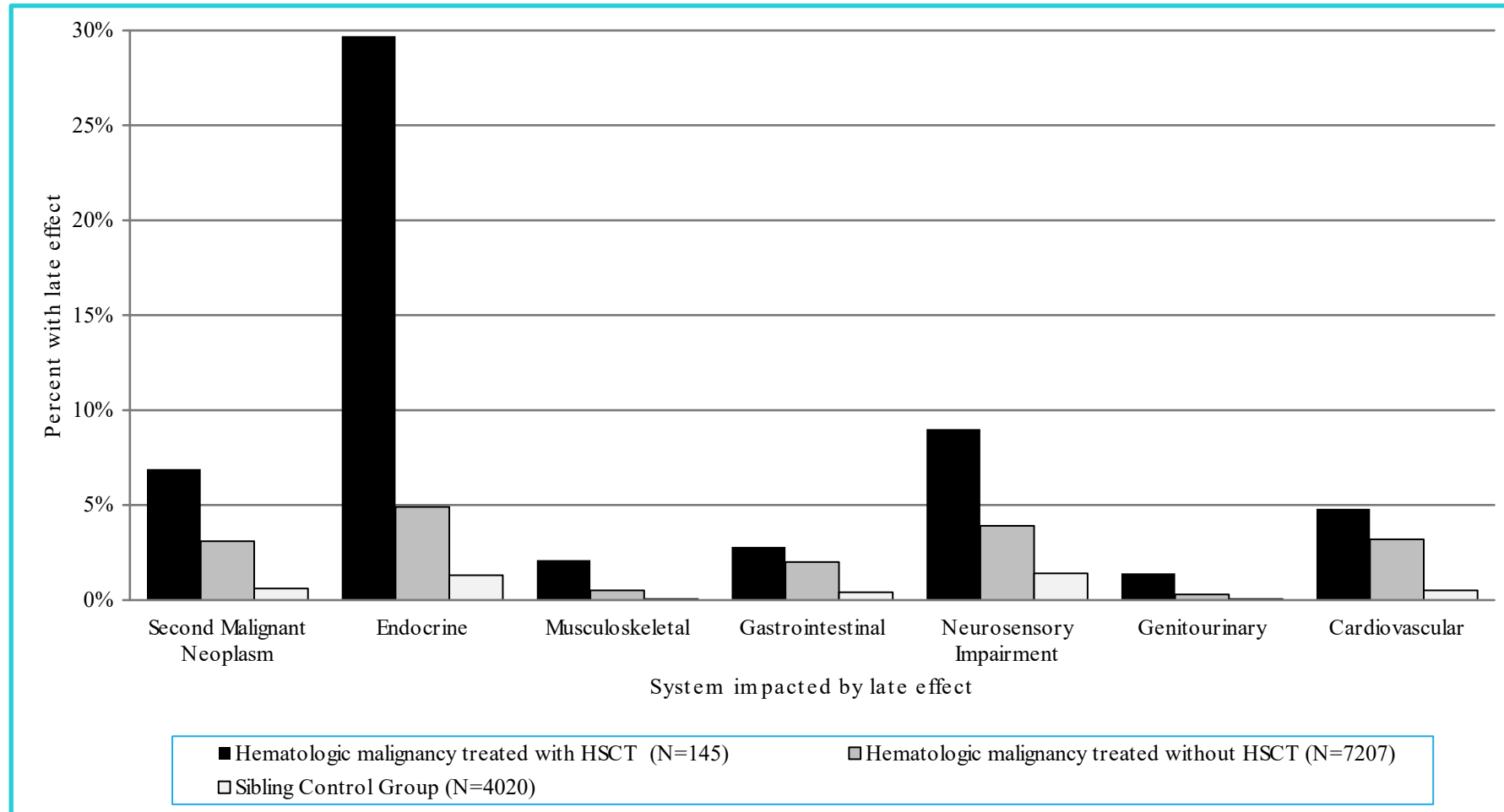
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# CHRONIC DISEASE OUTCOMES IN THE CCCCS

- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - life threatening or disabling
- 5 - death



# ENDOCRINOPATHIES ARE COMMON AMONG HSCT SURVIVORS



based on Armenian et al. 2011



EXPOSURES PREDICT EFFECTS



# WHAT INFLUENCES LATE EFFECTS?

- Age at Diagnosis
- Primary Tumour Type/Location
- Treatment modalities
  - Surgery
  - Chemotherapy
  - Radiation



- Complications of Cancer Therapy
  - Hydrocephalus
  - Bleeding
  - Infection (meningitis, etc.)
- Host environment/genetics

**Table 2.** Endocrine late effects of childhood cancer therapy: COG LTFUG

	GH deficiency	Hypothyroidism	Hyperthyroidism	Thyroid nodule/cancer	Central adrenal insufficiency	Precocious puberty	Hypogonadism	Infertility	Low bone mineral density	Obesity/hyperlipidemia	Metabolic syndrome	Hyperprolactinemia
Cranial irradiation <sup>1</sup>	+	+		+	+	+	+	+		+	+	+
Total body irradiation	+	+		+			+	+			+	
Target organ irradiation												
Thyroid <sup>2</sup>		+		+								
Gonadal <sup>3</sup>							+	+				
Alkylating agents												
Non-classical							+	+				
Alkylators							+	+				
Anthracyclines												
Heavy metals							+	+		+ Dyslipidemia		
Antimetabolites									+			
Antitumor antibiotics												
Corticosteroids									+			
Enzymes												
Plant alkaloids												
Epipodophyllotoxins												
Hematopoietic cell transplantation												
	PITUITARY/ THYROID						GONADAL		SKELETAL/METABOLIC			

<sup>1</sup> Cranial irradiation includes: cranial, orbital/eye, ear/infratemporal and nasopharyngeal.

<sup>2</sup> Thyroid irradiation includes: thyroid, neck, cervical spine, oropharyngeal, supraclavicular, mantle and mini mantle.

<sup>3</sup> Gonadal radiation includes: lumbosacral spine, abdomen and pelvis (females) and pelvis and testicular (males).

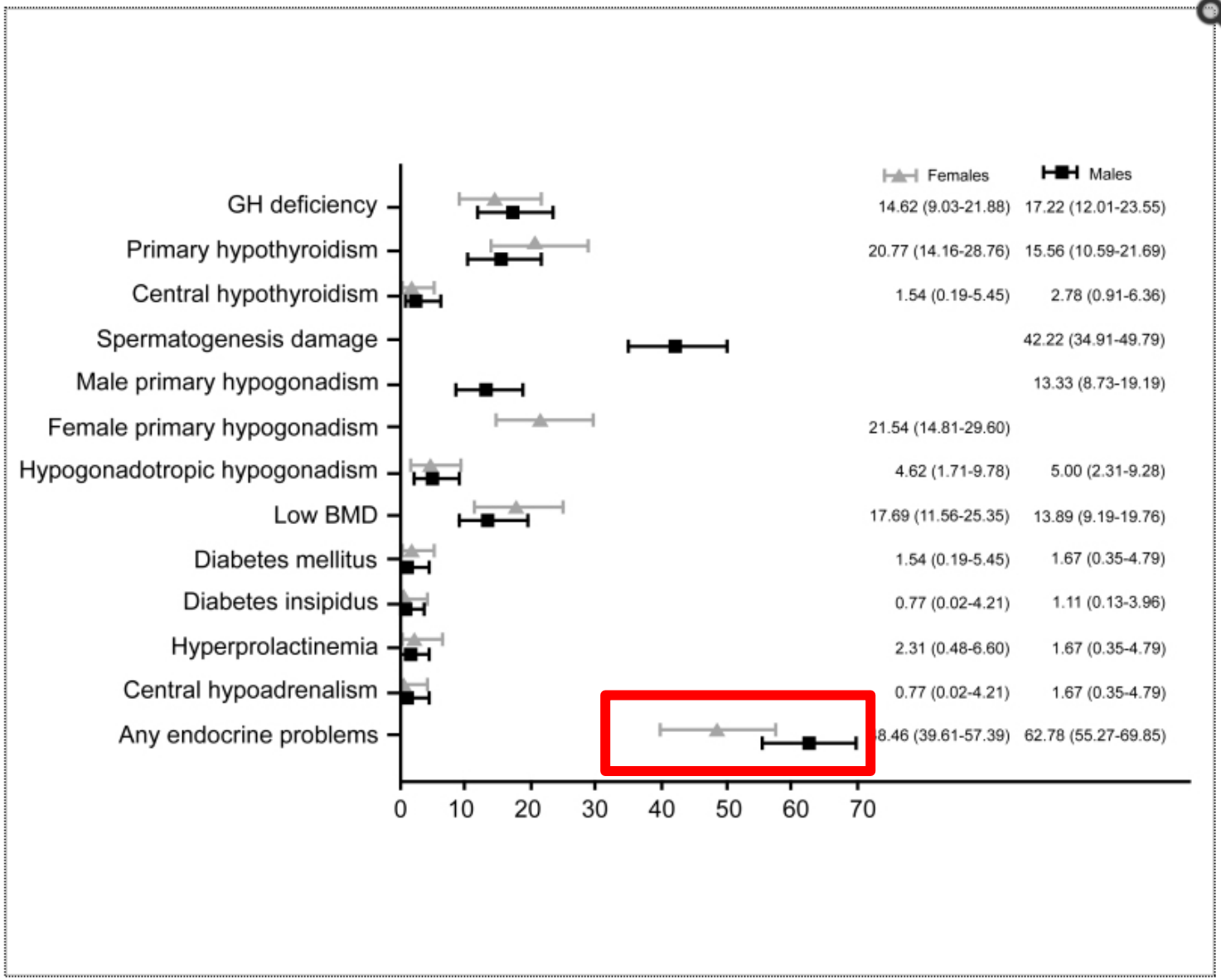


Figure 6. Prevalence of endocrine disorders at the last follow-up visit, by gender. Copyright © 2013, European Society of Endocrinology.

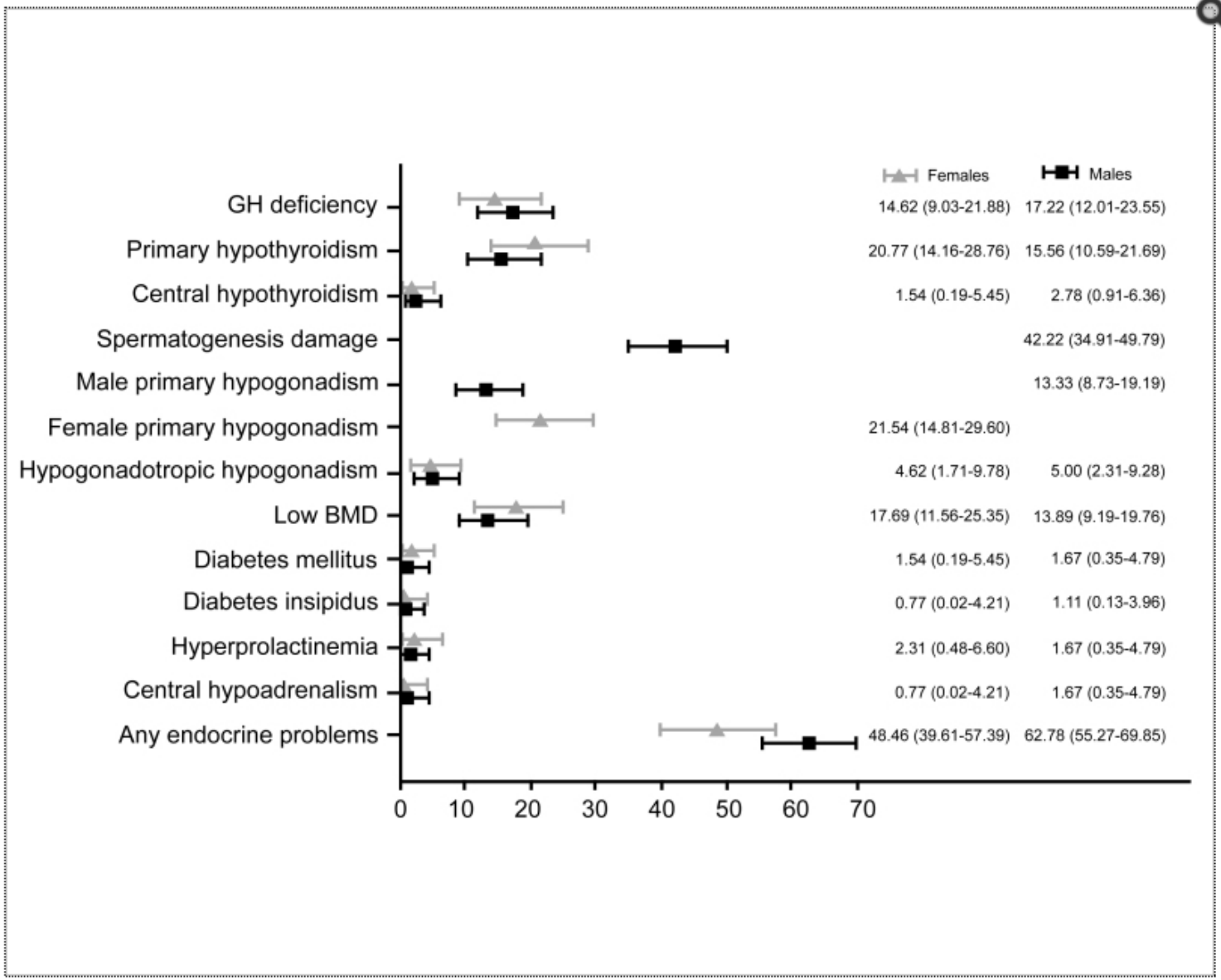
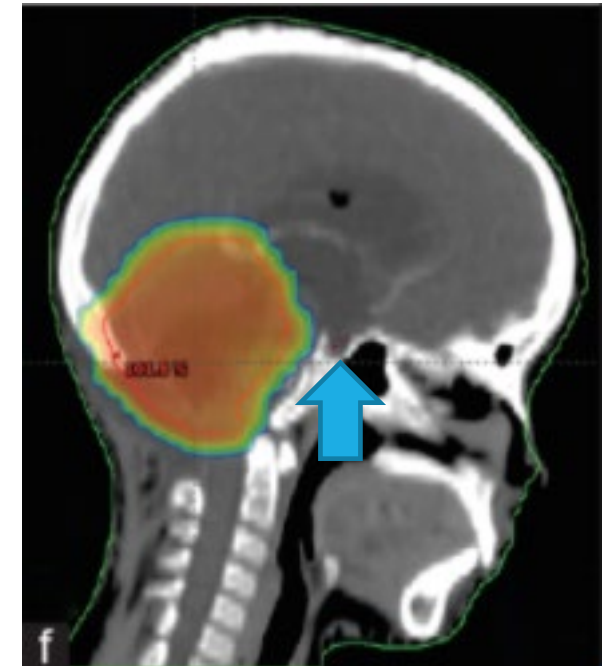
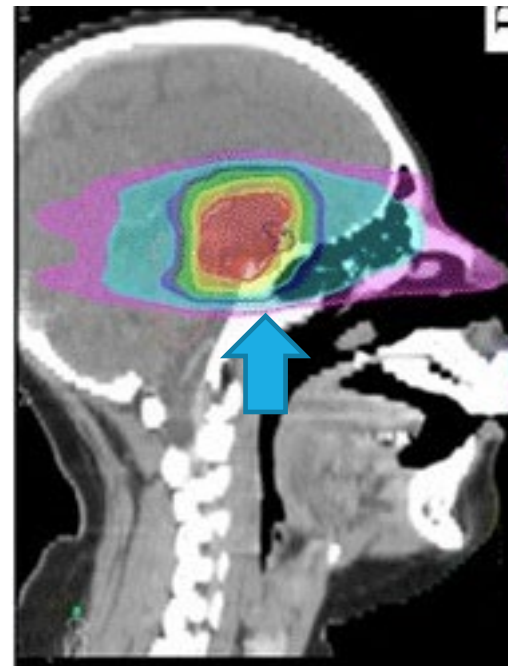


Figure 6. Prevalence of endocrine disorders at the last follow-up visit, by gender. Copyright © 2013, European Society of Endocrinology.

# PRIMARY RISKS FOR CANCER RELATED ENDOCRINOPATHY

- Radiation (dose? field?)
  - Cranial (Hypothalamus/Pituitary)
  - Craniospinal (HPA, vertebrae)
  - Neck (Thyroid)
  - Abdominal (Pancreas)
  - Pelvic (Gonads, Uterus)
- Alkylating Agents
- ?Corticosteroids





## **Hypothalamic–Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society\* Clinical Practice Guideline**

Charles A. Sklar,<sup>1</sup> Zoltan Antal,<sup>1,2</sup> Wassim Chemaitilly,<sup>3</sup> Laurie E. Cohen,<sup>4</sup>  
Cecilia Follin,<sup>5</sup> Lillian R. Meacham,<sup>6</sup> and M. Hassan Murad<sup>7</sup>

J Clin Endocrinol Metab, August 2018, 103(8):2761–2784

# CRANIAL RADIATION THERAPY

- Cell death at time of **attempted division** (hrs – yrs later)
- Cranial radiation (cumulative dose)

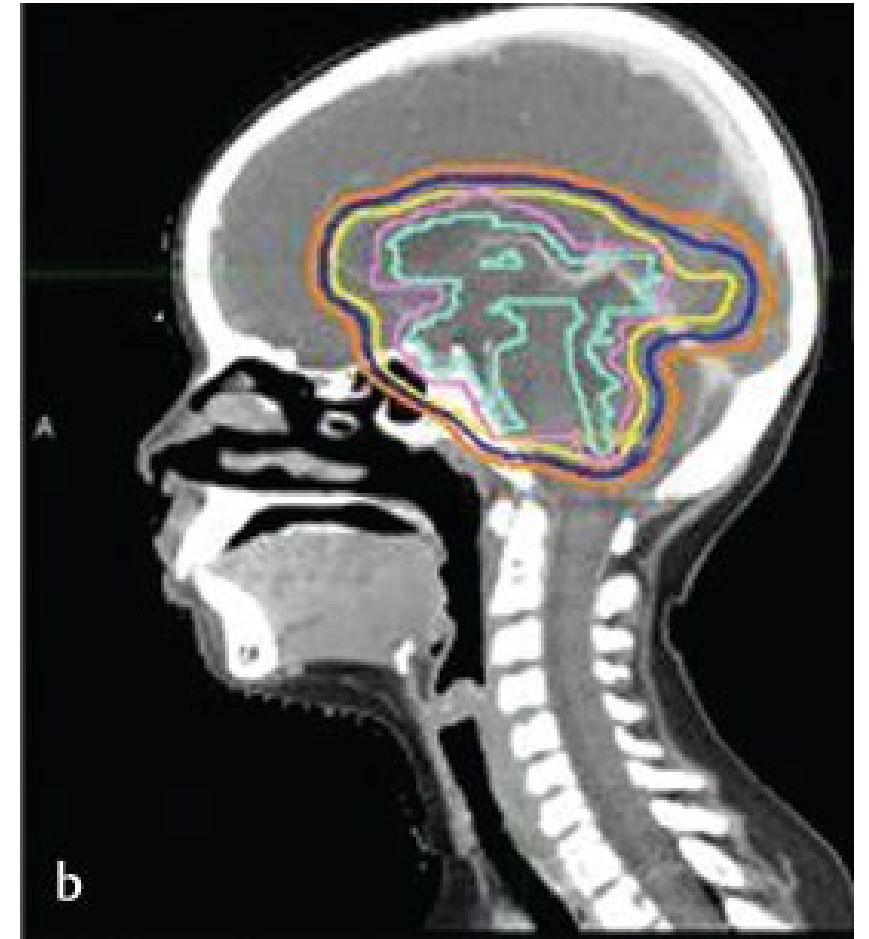
18 Gy

- Growth Hormone Deficiency
- Early Puberty

>30-40  
Gy

- Central Hypothyroidism
- Central Hypogonadism (Hypogonadotropic Hypogonadism)
- Adrenal Insufficiency (Central)

- Spinal radiation
  - Spinal shortening
  - Scatter to thyroid/ovaries/testicles



# ENDOCRINOPATHIES ARE RARELY PRESENT AT THE TIME OF BRAIN TUMOUR DIAGNOSIS

**Table 3.** Endocrine Disorders in All Patients (N = 718)

Endocrine Disorder	Prevalence, No. (%)	Present at Tumor Diagnosis, No. (%)*	Onset Year, Median (range)†	5-Year Cumulative Incidence, % (95% CI)
Any endocrine disorder	178 (24.8)	22 (3.1)	2.2 (0.01-10.2)	20.9 (15.6 to 26.7)
Hypothalamic-pituitary dysfunction	138 (19.2)	22 (3.1)	2.5 (0.01-10.2)	15.0 (9.8 to 21.2)
GH deficiency	90 (12.5)	2 (0.3)	2.5 (0.05-8.4)	11.1 (6.2 to 17.4)
TSH deficiency	66 (9.1)	7 (1.0)	2.8 (0.02-10.3)	7.2 (3.0 to 13.9)
ACTH deficiency	31 (4.3)	7 (1.0)	2.5 (0.01-7.0)	2.9 (0.4 to 10.6)
Precocious puberty‡	48 (12.2)	10 (1.4)	3.1 (0.1-8.8)	4.0 (0.9 to 11.1)
LH/FSH deficiency§	20 (4.2)	1 (0.1)	4.5 (0.2-9.5)	1.7 (0.0 to 11.1)
ADH deficiency	19 (2.6)	12 (1.7)	0.6 (0.01-10.2)	1.0 (0.0 to 11.2)
Thyroidal hypothyroidism	42 (5.8)	— (—)	1.9 (0.8-9.4)	5.4 (1.8 to 12.5)
Hypergonadotropic hypogonadism	29 (4.0)	— (—)	2.5 (0.6-9.2)	3.5 (0.6 to 10.8)

Abbreviations: ADH, antidiuretic hormone; ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.  
 \*Endocrine disorder already diagnosed at primary brain tumor diagnosis.  
 †Onset of endocrine disorder after primary brain tumor diagnosis.  
 ‡For this outcome, only CBTS who were age < 8 years (girls) and < 9 years (boys) at brain tumor diagnosis were included (n = 394).  
 §For this outcome, only CBTS who were age > 12 years (girls) and > 13 years (boys) at the last follow-up time point were included (n = 481).

Rarely present at diagnosis

# WHEN DOES ENDOCRINE DISEASE PRESENT?

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- Most endocrinopathies develop by 4-5 years after diagnosis
  - Window between diagnosis and AfterCare is peak of incident endocrinopathy
- Almost all present within 10 years

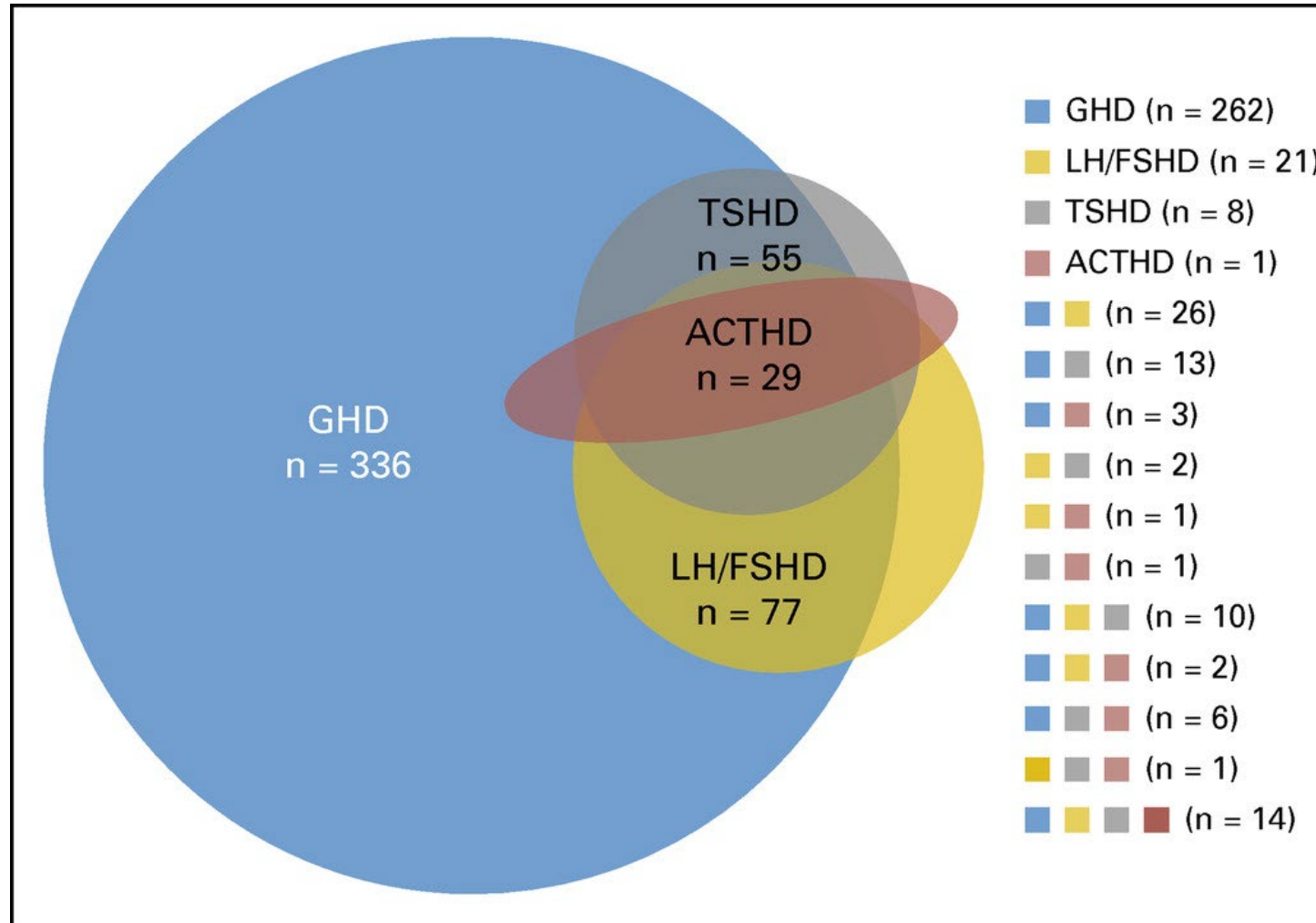
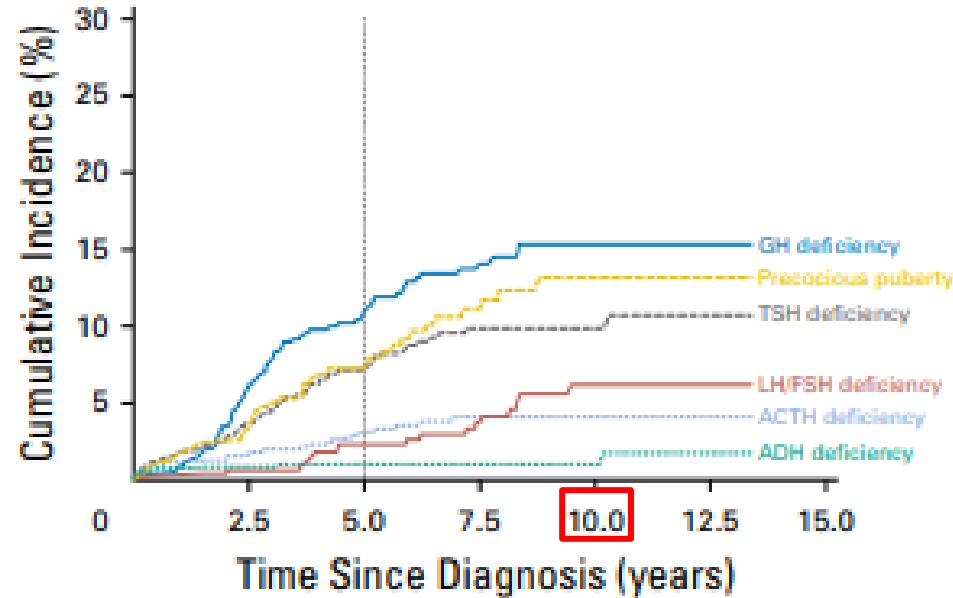


Fig 1. Overlap among anterior pituitary deficiencies after cranial radiotherapy. ACTHD, adrenocorticotrophic hormone deficiency; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; TSHD, thyroid-stimulating hormone deficiency. Reproduced with permission.<sup>3</sup> Copyright © 2015 American Society of Clinical Oncology.

# Radiation-Related Endocrinopathies Accrue For Years After Therapy



	No. at risk (No. experiencing failure)												
GH deficiency	716	(45)	648	(30)	420	(12)	247	(3)	114	(0)	19	(0)	0
TSH deficiency	711	(33)	660	(21)	437	(11)	263	(0)	124	(1)	21	(0)	0
ACTH deficiency	711	(19)	674	(8)	458	(4)	280	(0)	136	(0)	22	(0)	0
Precocious puberty	384	(23)	359	(13)	256	(9)	159	(3)	78	(0)	14	(0)	0
LH/FSH deficiency	480	(4)	468	(7)	357	(4)	241	(5)	131	(0)	25	(0)	0
ADH deficiency	707	(17)	677	(1)	466	(0)	291	(0)	143	(1)	21	(0)	0

## CASE 2\*

Referral:

“Please see this 16 year-old young woman, h/o brain tumour @ age 10, treated at CHEO, now moved to Toronto.”

Recently attended a Cancer Survivors’ group and is wondering whether she she needs Endocrine follow-up?”

\*courtesy of Stacey Urbach

# What's Wrong With This Picture?






## 1. Treatment Summary

1. Cancer Diagnosis
2. Chemotherapy – Agents and Doses
3. Radiation – Site and Dose
4. Surgery
5. Hematopoietic Stem Cell Transplant
  - Myeloablative regimen



## 2. Individualized Risk Profile

- 
- 10 year old girl
  - Average-risk medulloblastoma
    - Gross Total Resection
    - Chemotherapy:
      - Cyclophosphamide 16 g/m<sup>2</sup>
      - Cisplatin 600 mg/m<sup>2</sup>
      - Vincristine 31 mg/m<sup>2</sup>
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# ENDOCRINE LATE EFFECTS OF CANCER THERAPY

## Pituitary

- Growth
- Puberty/Fertility
- Thyroid (Central)
- Adrenal

## Peripheral/Systemic

- Thyroid
- Puberty/Fertility
- Pancreas (endocrine)
- Adipose Tissue
- Lipids
- Bone

# ENDOCRINE LATE EFFECTS OF CANCER THERAPY

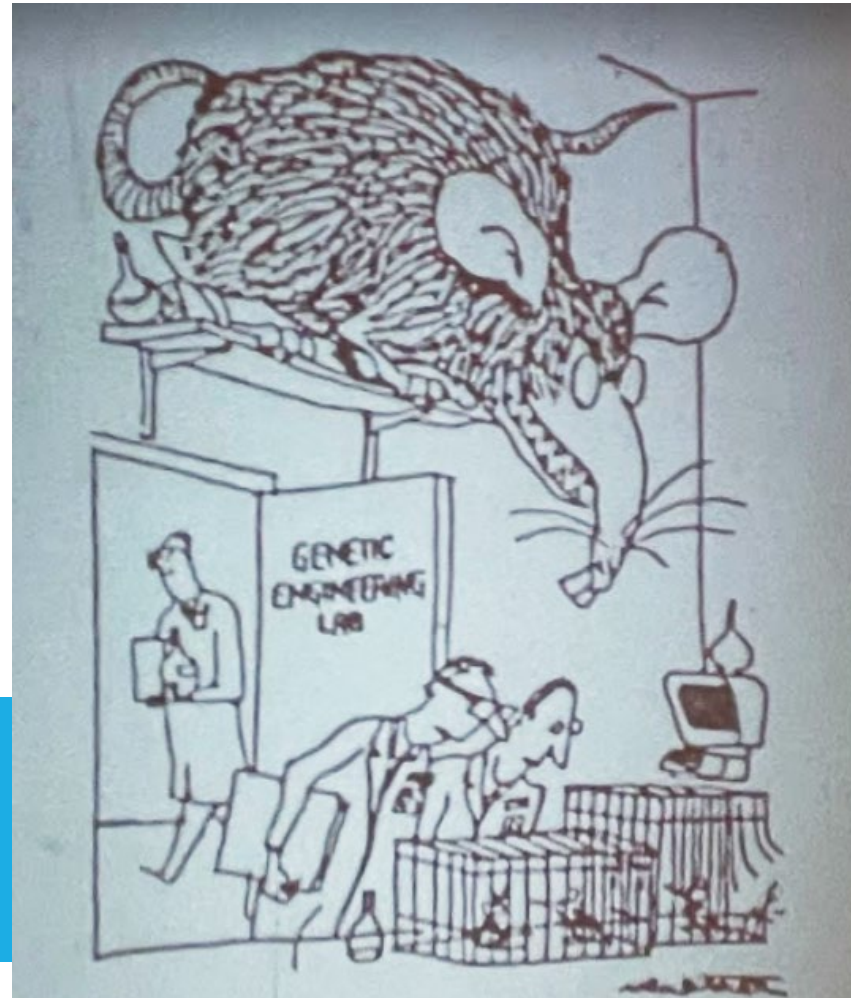
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## Peripheral/Systemic

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# GROWTH DISORDERS



"How disappointing ... they don't appear to have grown at all."

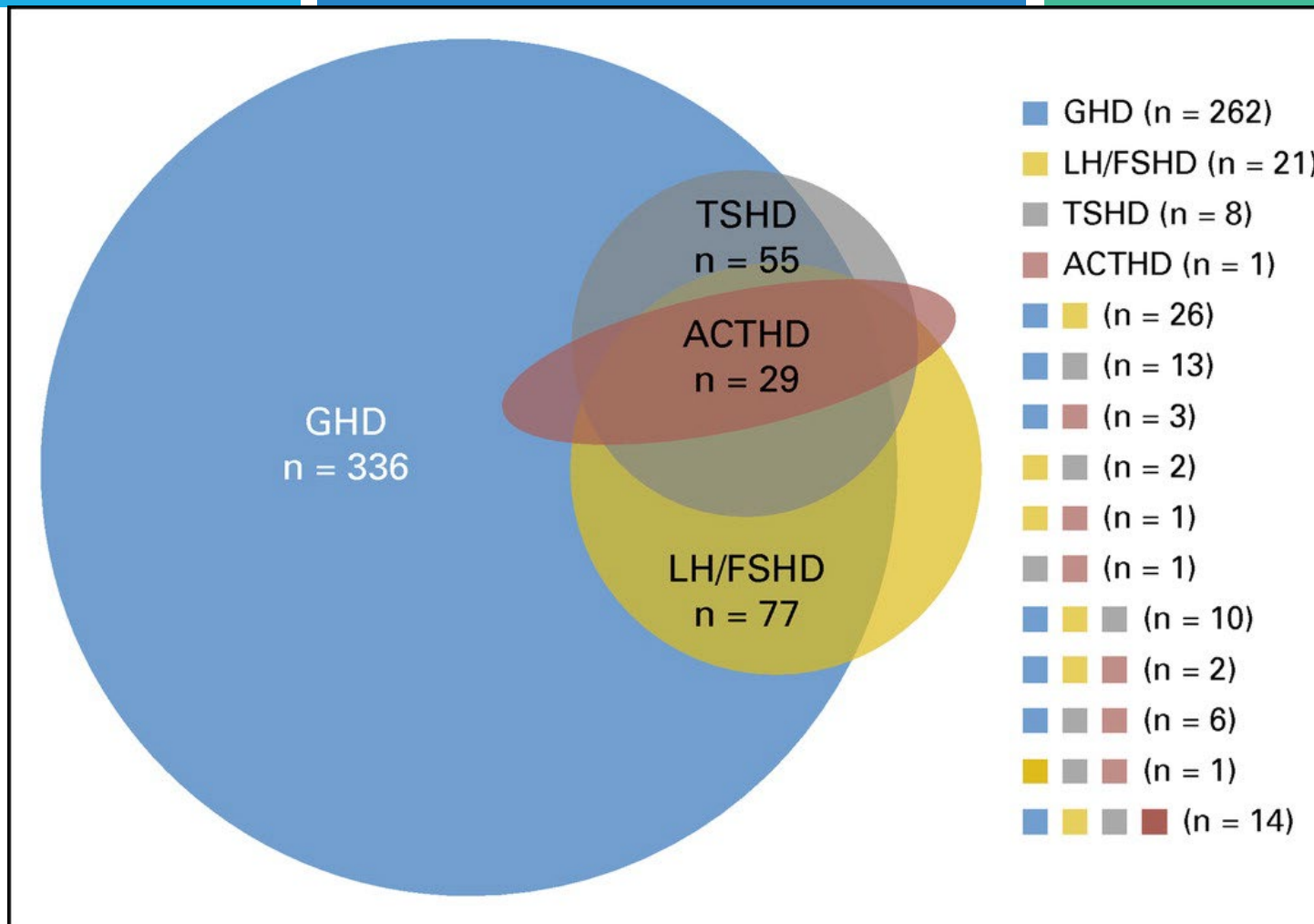
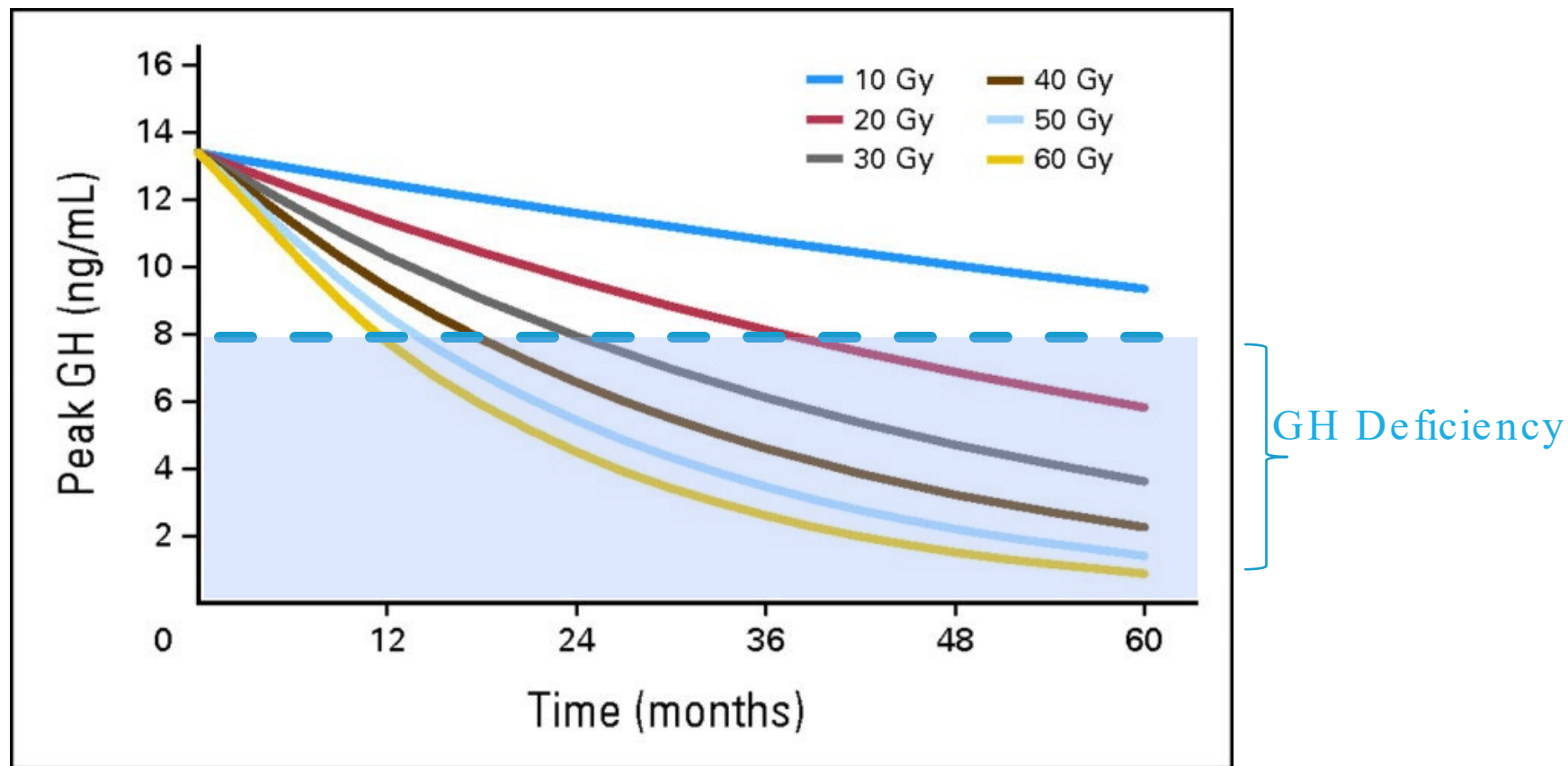


Fig 1. Overlap among anterior pituitary deficiencies after cranial radiotherapy. ACTHD, adrenocorticotrophic hormone deficiency; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; TSHD, thyroid-stimulating hormone deficiency. Reproduced with permission.<sup>3</sup> Copyright © 2015 American Society of Clinical Oncology.

# GH DEFICIENCY

- Short stature may not be apparent in acquired GHD, particularly with older onset.
- If possible, obtain pre-diagnosis growth data.
- Monitor for growth **deceleration** or **lack of growth spurt in puberty**
- Diagnostic “Gold Standard”: Dynamic GH testing.
- Treatment: SC rhGH is safe and effective, particularly if initiated when there is substantial remaining growth potential (don't wait!)

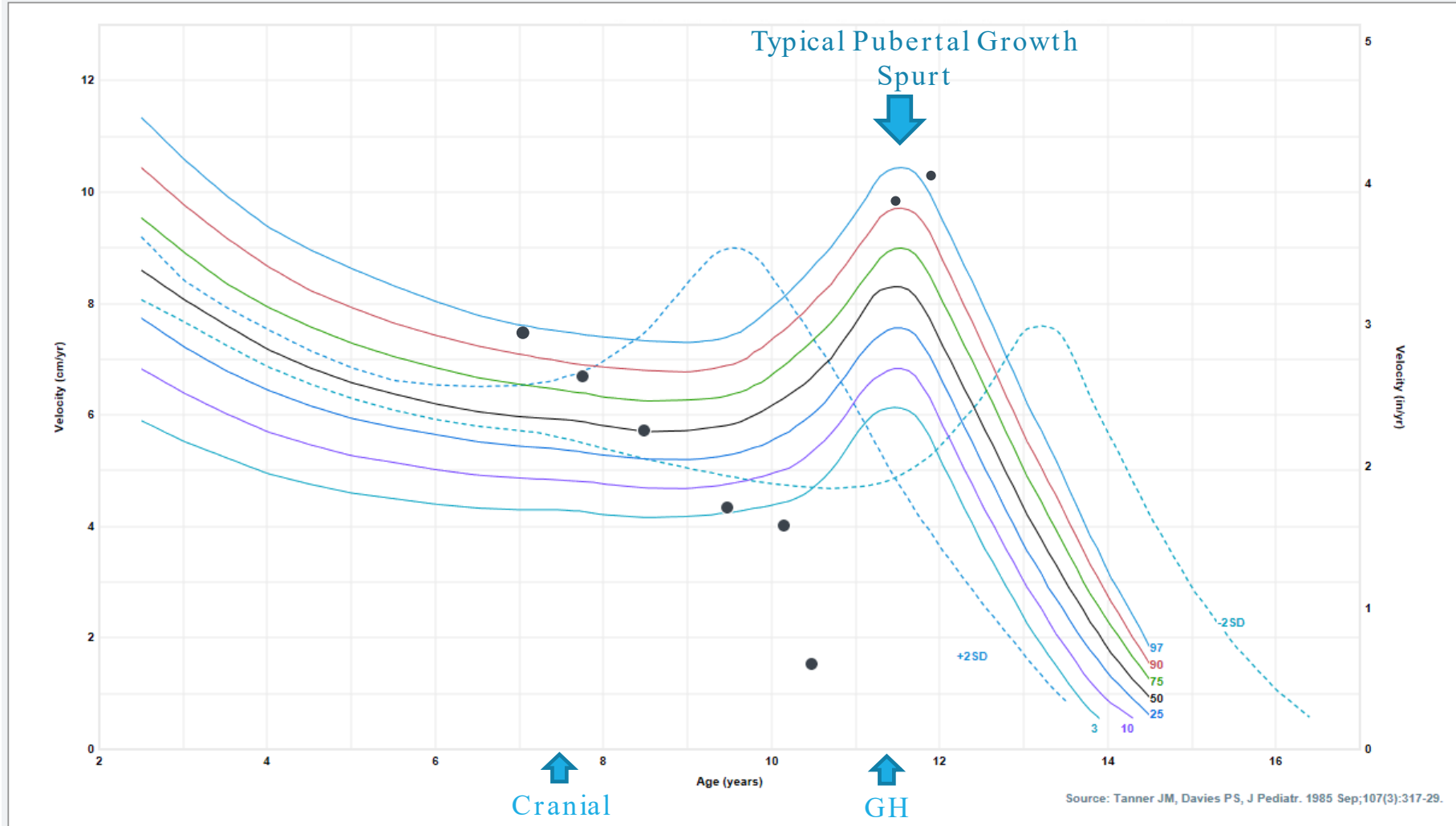
# GH DEFICIENCY IS TIME AND DOSE DEPENDENT AFTER XRT



# Growth Velocity


Height Velocity-for-age Percentiles (Girls, 2.5 to 14.5 years)

100 % 100 % Zoom In Zoom Out



Cranial Radiation

GH Replacement



..... But GH Deficiency isn't the only contributor to short stature  
after pediatric brain tumours

## A TALE OF TWO BOYS...

- Almost 13 year old male
  - Medulloblastoma diagnosed 1991 (age 4)
  - Average risk therapy
  - Referred to endocrine for poor growth rate
  - Height = 150.4 cm Weight = 45.2 kg
  - Testicular volume = 4ml
  - Bone age = 12 yrs 6 mnths (CA=12 yrs 11mnths)
- Almost 13 year old male
  - Medulloblastoma diagnosed 1991 (age 4)
  - Average risk therapy
  - Referred to endocrine for poor growth rate
  - Height = 150.4 cm Weight = 45.2 kg
  - Testicular volume = 15ml
  - Bone age = 16yrs (CA=12 yrs 11mnths)

## COMPARE THE CASES

- Almost 13 year old male
- Medulloblastoma diagnosed 1991 (age 4)
- Average risk therapy
- Referred to endocrine for poor growth rate
- Height = 150.4 cm Weight = 45.2 kg

- Testicular volume = 4ml
- Bone age = 12 yrs 6 mnths (CA=12 yrs 11mnths)

Rx Growth  
Hormone



Testicular/Breast Examination and Bone Age Assessment are **Essential** Components of Routine Assessment of Brain Tumour/HSCT Survivors

- Almost 13 year old male
- Medulloblastoma diagnosed 1991 (age 4)
- Average risk therapy
- Referred to endocrine for poor growth rate
- Height = 150.4 cm Weight = 45.2 kg

- Testicular volume = 15ml
- Bone age = 10 yrs (CA=12 yrs 11mnths)

**MISSED OPPORTUNITY**



# PUBERTAL ASSESSMENT IS MORE THAN PUBIC HAIR AND PERIODS



## ■ Girls

- Breast development is first sign of true puberty
- Onset between 8 and 13 yrs (mean 10.5 yrs)
- Peak growth velocity at onset of breast bud (T2)

## ■ Boys

- Testicular enlargement is first sign of true puberty  
(4ml = 2.5cm)
- Onset between 9.5 and 13.5 yrs (mean 11.5 yrs)
- Peak growth velocity later in puberty (10 – 12ml = 4cm)

# RAMIFICATIONS OF DISORDERS OF PUBERTAL TIMING

## Premature

- Psychosocial stigma
- Early epiphyseal closure → short stature

## Delayed/Absent

- Psychosocial stigma (esp ♂)
- Failure to attain adult body proportions
- Coronary A. Disease
- Bone mass accrual
- Uterine growth
- May portend future infertility

# CAUSES OF GROWTH COMPROMISE AMONG SURVIVORS

## Endocrine

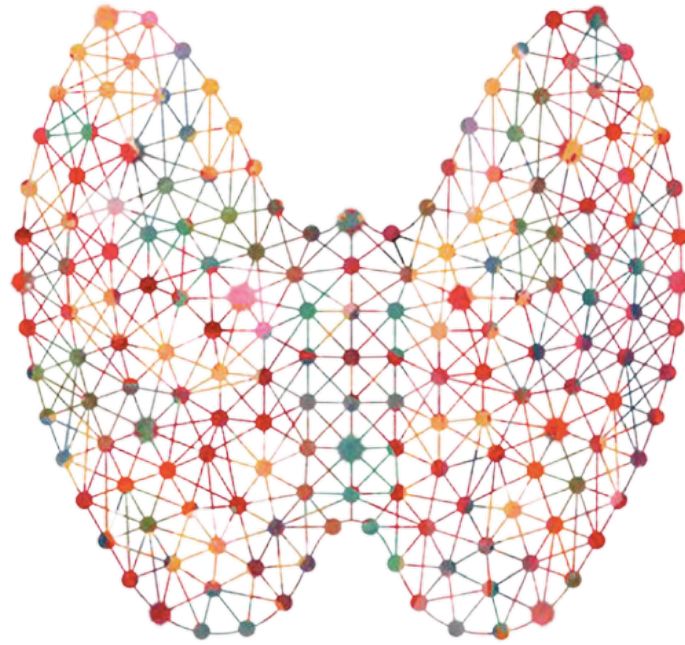
- Defects in GH secretion due to CI/CSI
- Early puberty (early epiphyseal closure)
- Hypothyroidism (untreated)

## Non-endocrine

- Direct radiotoxicity at Growth Plates (CSI)
- Chronic Illness
- Glucocorticoids
- Osteoporosis and Fractures (glucocorticoids, MTX)

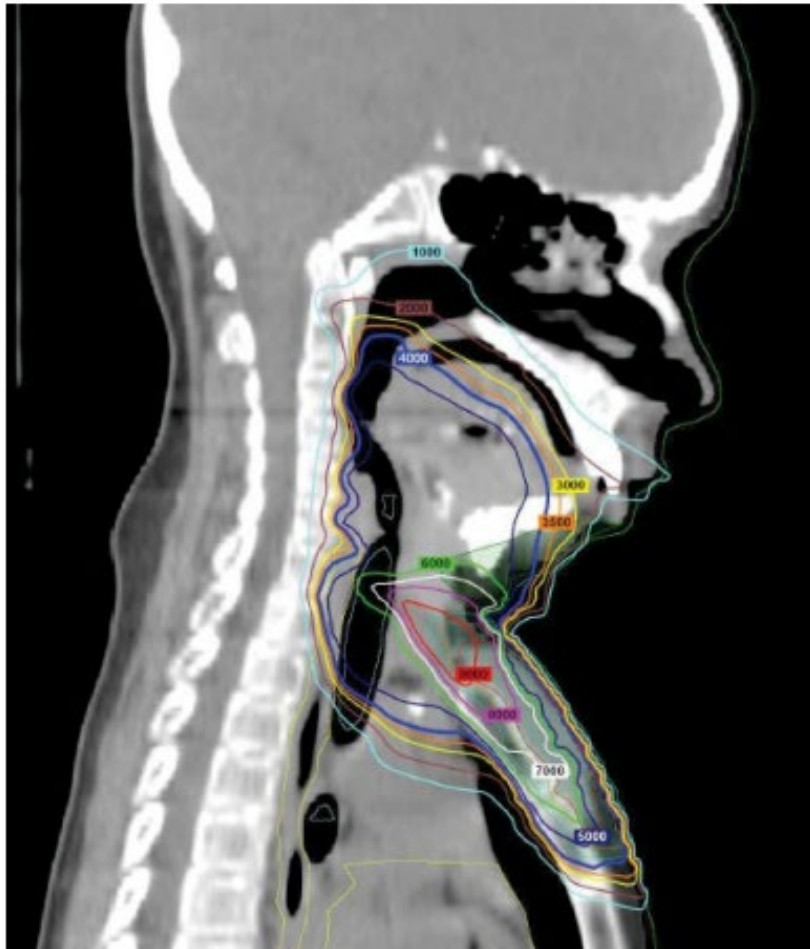
## WHAT CAN YOU DO?

1. Look at growth trajectory every 6-12 months
  - Use the Growth Velocity curves in EHR → you will see patterns much more clearly
2. Follow pubertal status → breast and testicular volume, not just pubic hair
3. If there are concerns, please refer. It helps to have Growth Chart, Bone Age and IGF-1 in addition to a Treatment Summary.



# THYROID DISEASE AMONG CANCER SURVIVORS

# RADIATION EXPOSURE AND THYROID DISEASE



- Mantle irradiation
- Cervical XRT
- Craniospinal XRT
- Total Body Irradiation
- Radionuclides ( $^{131}\text{I}$  MIBG)

# THYROID LATE EFFECTS

**Table 4** Therapy-related complications affecting the thyroid

Complication	Therapy-related risks	Relationship to time, dose to the thyroid when applicable, and available cumulative incidence data
Hypothyroidism	Radiotherapy to neck <sup>131</sup> I-labeled agents such as MIBG	Hodgkin's lymphoma survivors: cumulative incidence 28%, reaches 50% for doses >45 Gy over 20 years 40–80% within 2 years of exposure
Hyperthyroidism	Radiotherapy to neck	Doses >35 Gy, cumulative incidence 5% over 25 years
Autoimmune disease	HSCT	By transfer of abnormal clones of B- or T-cells from donor to host
Cancer	Radiotherapy to neck	Doses up to 20–29 Gy range. Cumulative incidence 18% Patients treated <10 years of age at higher risk Median latency exceeds 20 years

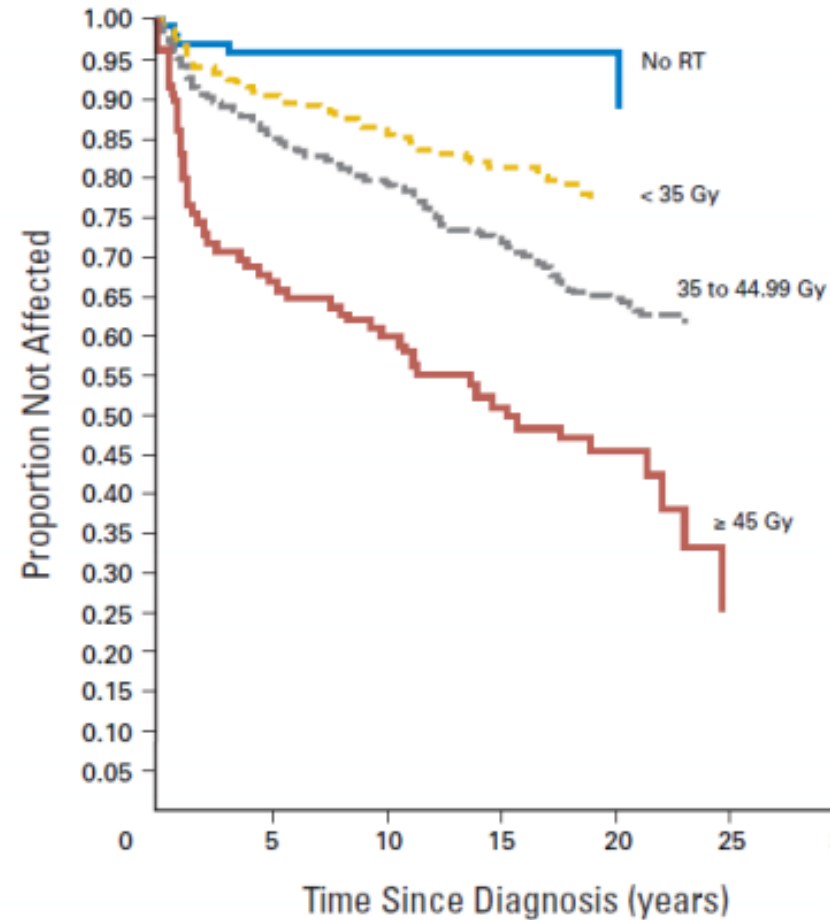
<sup>131</sup>I-MIBG, iodine-131-metaiodobenzylguanidine; HSCT, hematopoietic stem cell transplantation.



# HYPOTHYROIDISM

- May be:
  - Primary: Thyroid gland
  - Central: Hypothalamic/Pituitary
  - Both
- Exposures:
  - Craniospinal radiation for Brain Tumours
  - Neck/Mantle radiation for Hodgkin's Lymphoma
  - TBI prior to HSCT
  - (<sup>131</sup>I-MIBG)
- Dose and time dependent:

# PROBABILITY OF DEVELOPING HYPOTHYROIDISM ACCORDING TO RADIATION DOSE IN 5-YEAR SURVIVORS OF CHILDHOOD CANCER.



Pay attention to the axis

Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L: Abnormalities of the Thyroid in Survivors of Hodgkin's Disease: Data from the Childhood Cancer Survivor Study. J Clin Endo Metab 85 (9): 3227-3232, September 1, 2000

# PRIMARY HYPERTHYROIDISM

- Radiation is major risk factor
  - Thyroid dose > 35-40 Gy
  - ?Radiation effects on immune response? (unmask epitopes)
- 5% rate in large Hodgkin's Disease study
- Mean diagnosis 8 years after cancer diagnosis

# Risk Continues to Accrue Over Decades

## HYPOTHYroidism

## HYPERthyroidism

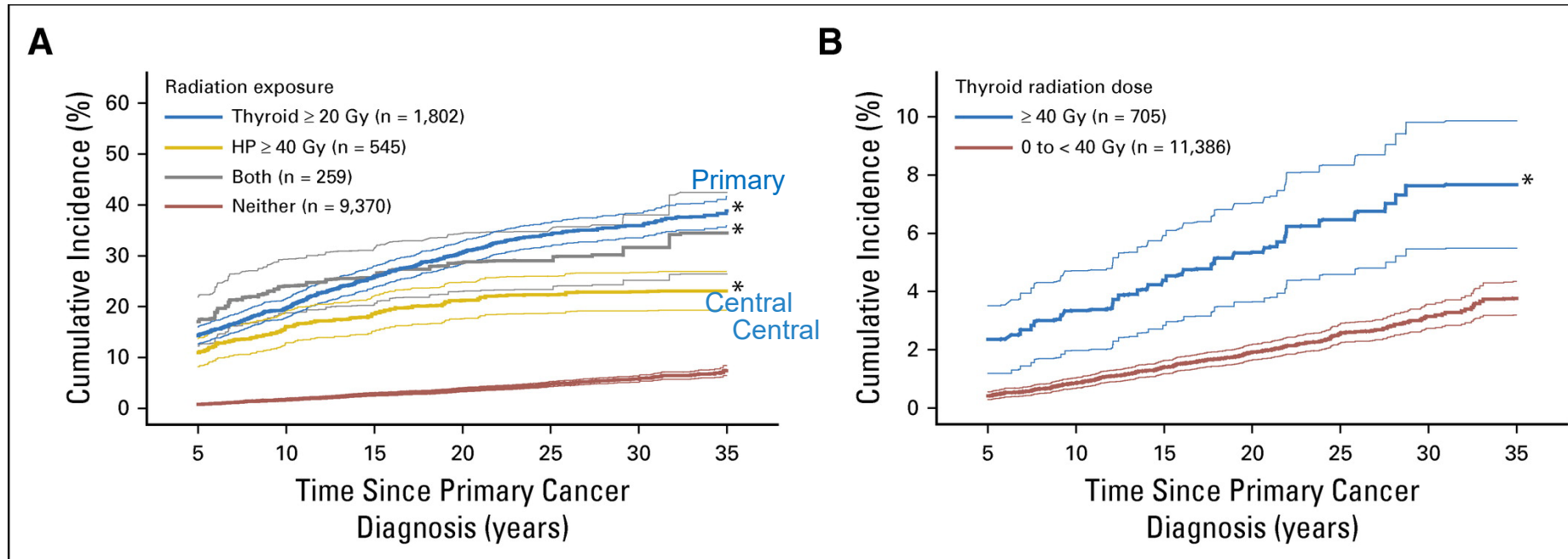


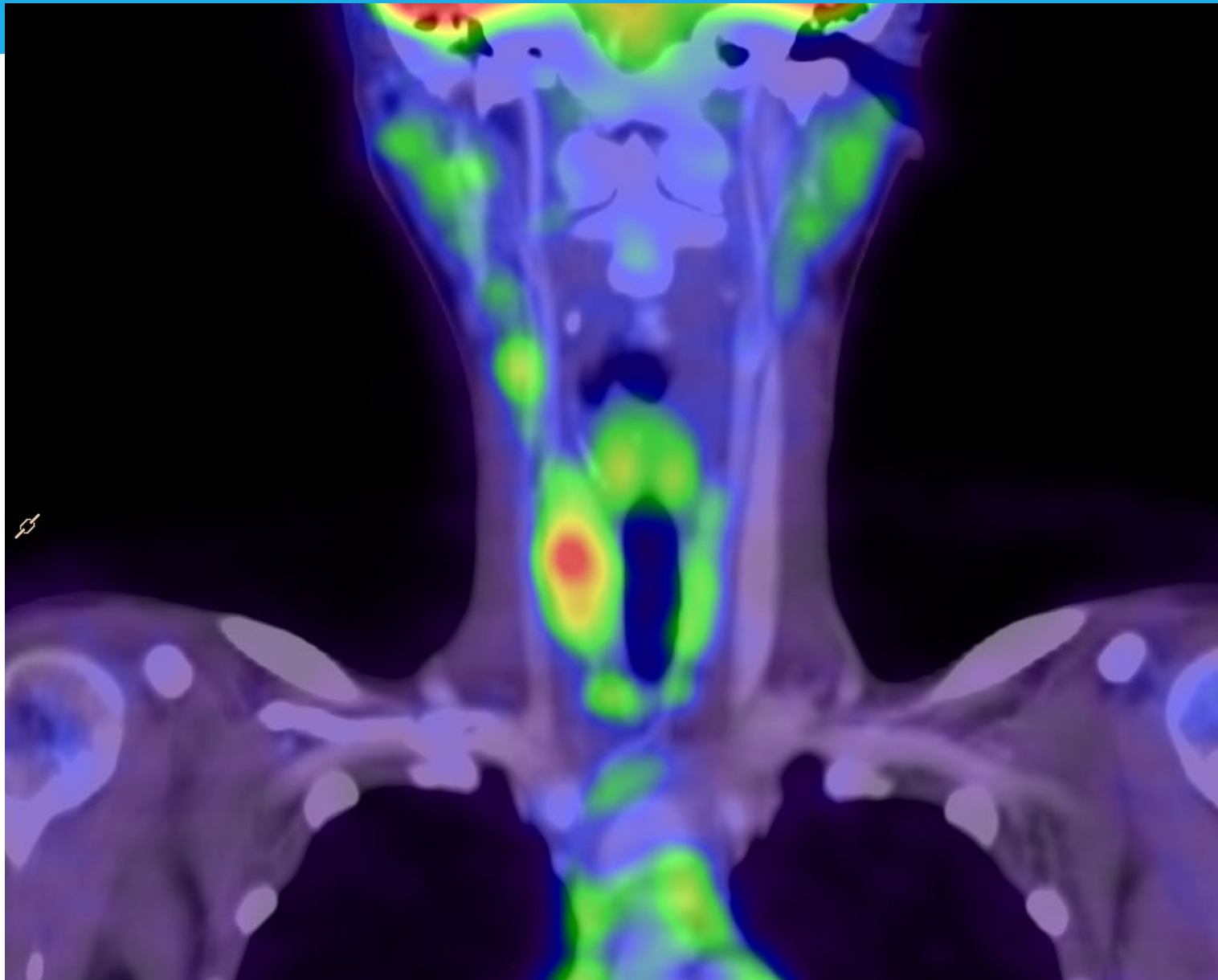
Fig 2. Cumulative incidence of thyroid disorders. (A) Underactive thyroid and (B) overactive thyroid in survivors stratified by treatment exposure. Thin lines represent 95% CIs. \* $P < .01$  for comparison versus the non-high-risk exposure group. HP, hypothalamic pituitary. Reproduced with permission.<sup>4</sup> Copyright © 2016 American Society of Clinical Oncology.

## CASE 4

- Almost 16 year old female
- Medulloblastoma diagnosed 1991(age 4)
- Treated with average risk therapy (surgery, chemo and radiation (35Gy)
- Referred to endocrine for irregular menstrual cycles
- TSH=1.53 (0.5-5) mIU/L
- Free T4=8.3 (10-21) pmol/L

What's going on?

AND THEN ...



**SickKids®**

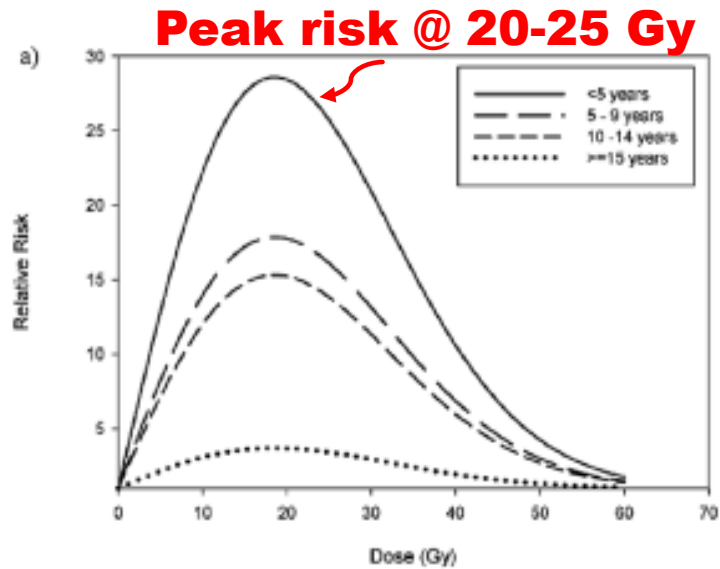
# THYROID CANCER AS A SECOND PRIMARY MALIGNANCY (SPM)

**Table 2. Standardized incidence ratios (SIR) of second and subsequent malignant neoplasms in the Childhood Cancer Survivor Study (CCSS) cohort**

Second/subsequent malignancy	SIR (95% CI)	Median time to occurrence (years)
All second/subsequent malignancies	6.4 (5.7–7.1)	11.7
Acute myeloid leukemia	7.9 (3.6–15.0)	6.1
Lymphoma	1.5 (0.80–2.6)	13.8
Central nervous system tumor	9.9 (6.9–13.63)	9.5
Breast cancer	16.2 (12.2–20.8)	15.7
Bone cancer	19.1 (12.7–27.7)	9.6
Soft tissue sarcoma	6.3 (4.3–8.9)	10.6
Thyroid cancer	11.3 (8.2–15.3)	13.3
Melanoma	4.0 (2.4–6.3)	14.6
All other cancers	4.0 (3.1–5.2)	13.9

Adapted with permission from Neglia *et al.* [45••].  
CI—confidence intervals; SIR—standardized incidence ratio.

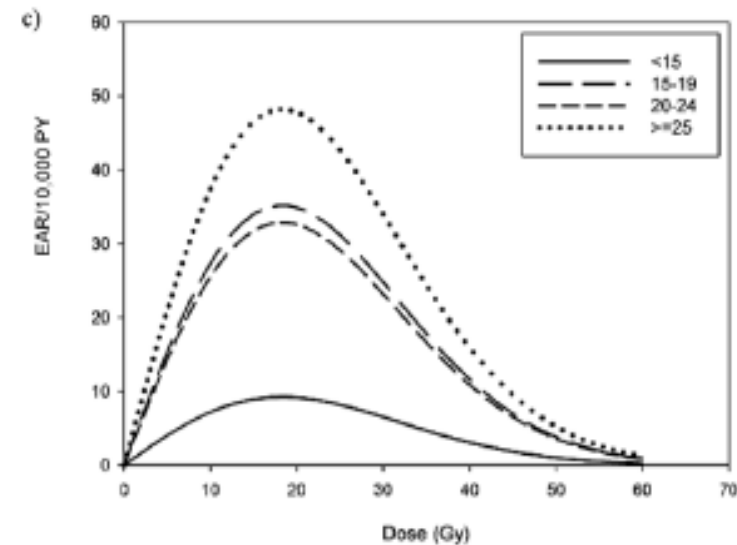
# SECONDARY THYROID MALIGNANCIES AFTER TREATMENT FOR CHILDHOOD CANCER



Age at treatment for primary malignancy



Younger children are more vulnerable

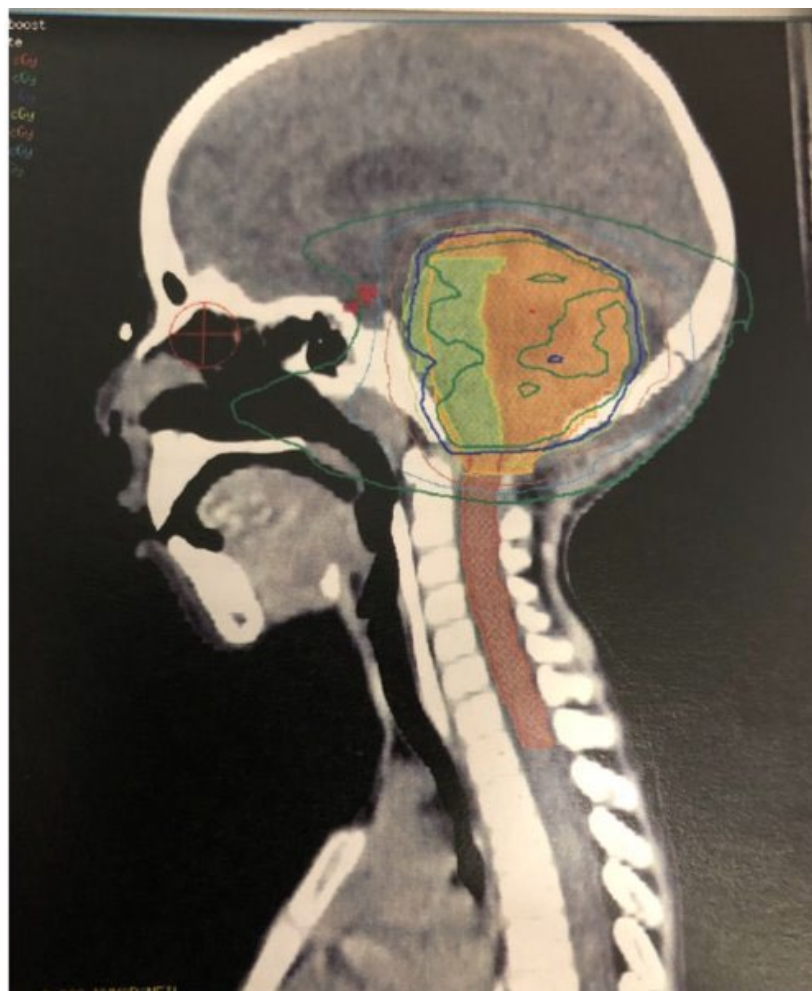


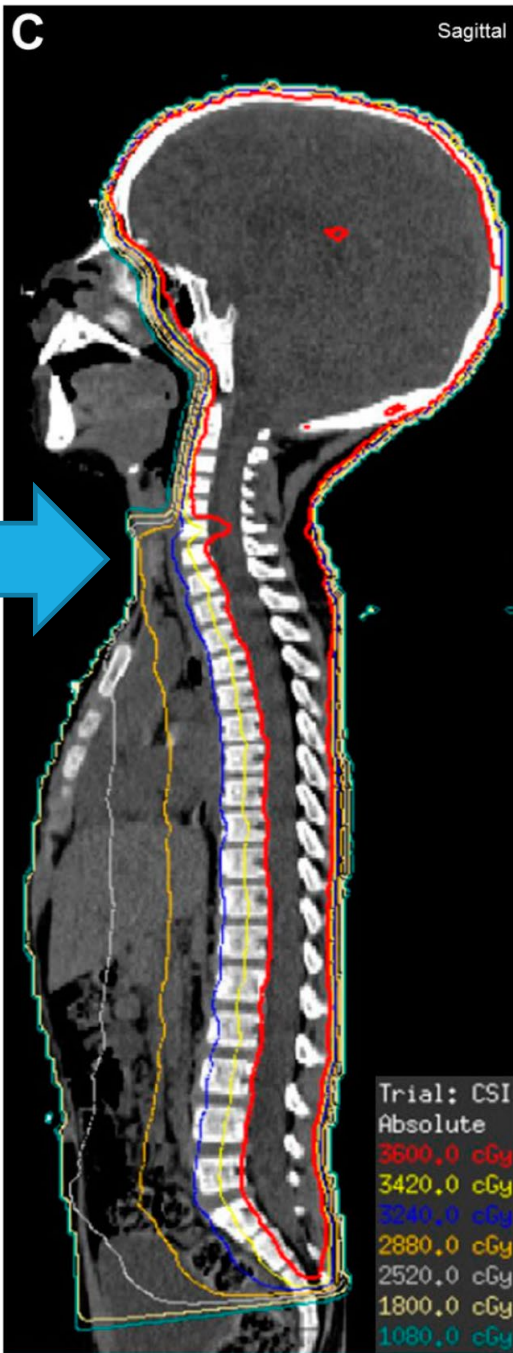
Time since initial radiation exposure



Risk continues to accrue for decades

# LOOK AT THE TREATMENT PLAN





## RECOMMENDATIONS (COG)

- Yearly TSH in any patients with spinal, chest or neck radiation (add Free T4 if CNS involved).
- Palpate the lower neck during routine physical examination
- If any thyroid nodules or cervical adenopathy, ultrasound and refer.
  - Routine neck ultrasound is controversial

# URBACH'S APPROACH TO THE MANAGEMENT OF CHILDHOOD CANCER SURVIVORS

- We are doing a good job curing cancer, but care of these patients is **lifelong**
  - Survivors of childhood cancer are numerous and the population is growing
- Understand who is at risk for endocrine complications of cancer therapy
  - Radiation
  - Alkylating agents
- Utilize exposure-based surveillance for Endocrine late effects
  - Treatment Summary
  - Individualized Risk Profile
- Follow growth and puberty closely in all patients
  - Keep growth chart during adolescence
  - Watch timing of onset of puberty
    - Males – testicular size/volume
    - Females – breast development
- Follow Thyroid Function and Exam



