ENDO2019

E21. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer:

An Endocrine Society Clinical Practice Guideline

Read the guideline and associated resources by navigating to endocrine.org/CPGsurvivors

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Plenary Panel Members

Moderator:

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Panel:

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Disclosures

Hanneke M. van Santen, MD – Educational Fee: Pfizer BV and Ferring BV

Charles A. Sklar, MD – Honorarium: Sandoz Consultant: St. Jude Research Hospital

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Wassim Chemaitilly, MD – No conflicts to disclose

Laurie E. Cohen, MD – Honorarium: Scherer Clinical Communications (Novo Nordisk) Site PI: Versartis, Ascendis, Opko

Access Guideline and Other Resources

Guideline

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

Guideline Resource Page

endocrine.org/CPGsurvivors

Includes links to:

- Full published guideline
- Online patient resources
- Clinician Education
- Podcast
- Interview with the Guideline Writing Committee Chair
- Point of Care tool available in CPG Mobile App

Plenary Format

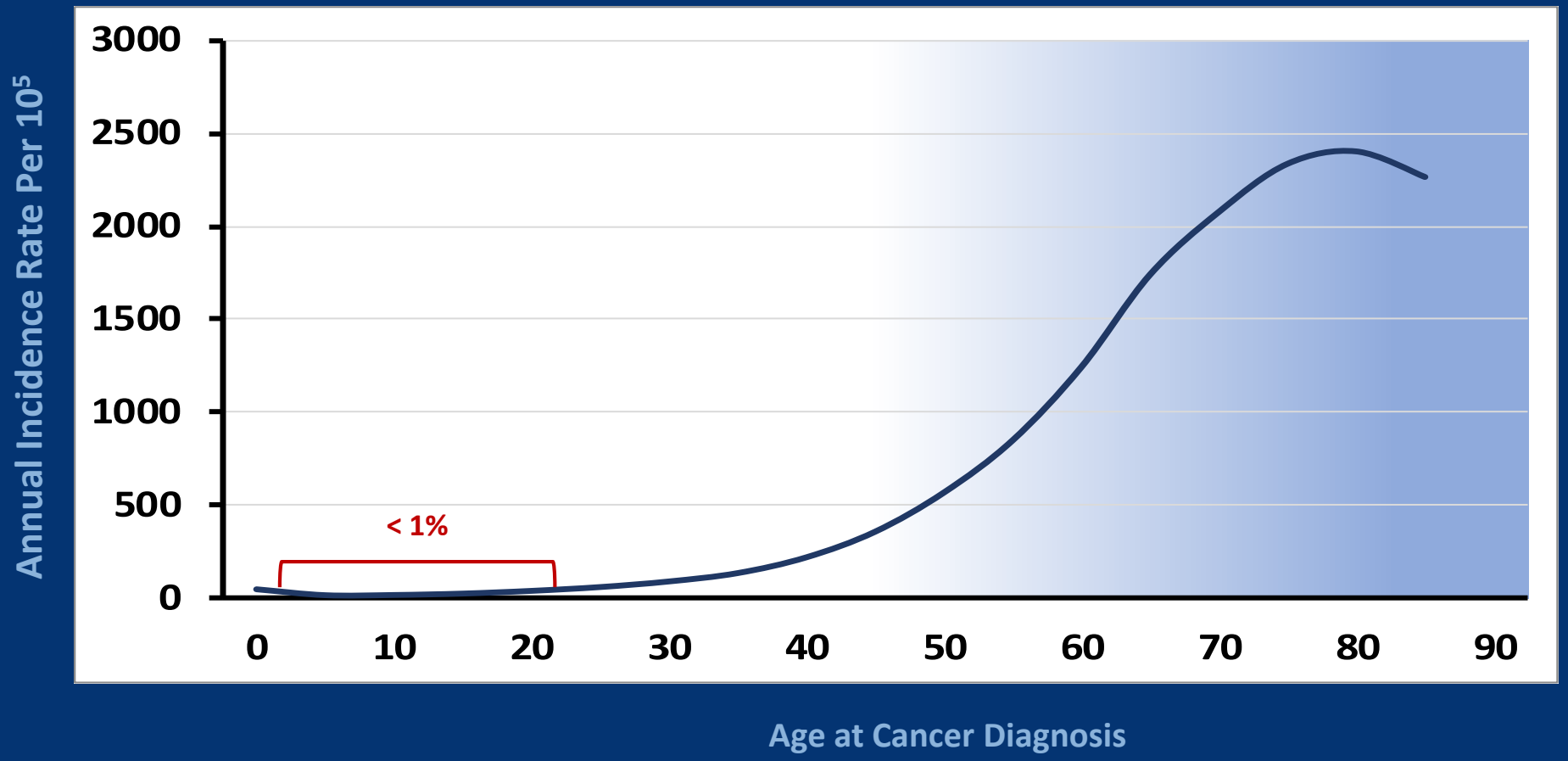
1. Overview of Childhood Cancer Survivorship (Dr. Sklar)
2. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer (Dr. van Santen)
3. Cases 1 – 3 (Panelists):
    a. Multiple choice question with audience response
    b. Panel discussion of case
    c. Relevant guideline recommendations
    d. Q&A related to case
        - *Audience may submit questions at any time during case*

Overview of Cancer Survivorship

Charles Sklar, MD

Director, Memorial Sloan Kettering Cancer Center, New York, NY

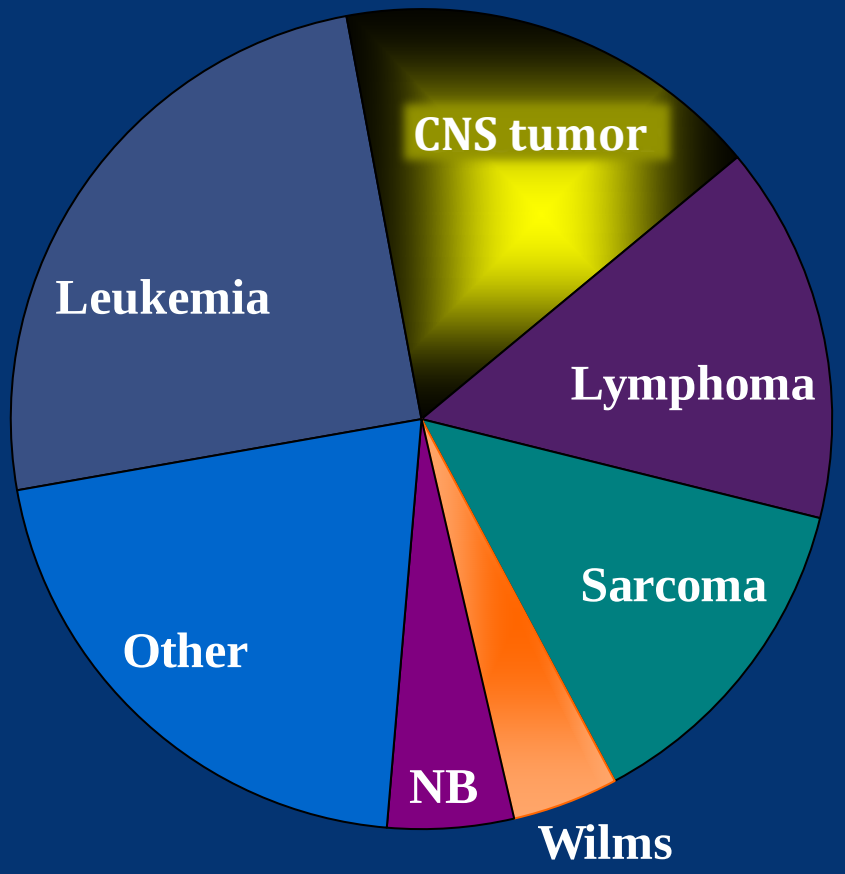
Age-specific Cancer Incidence



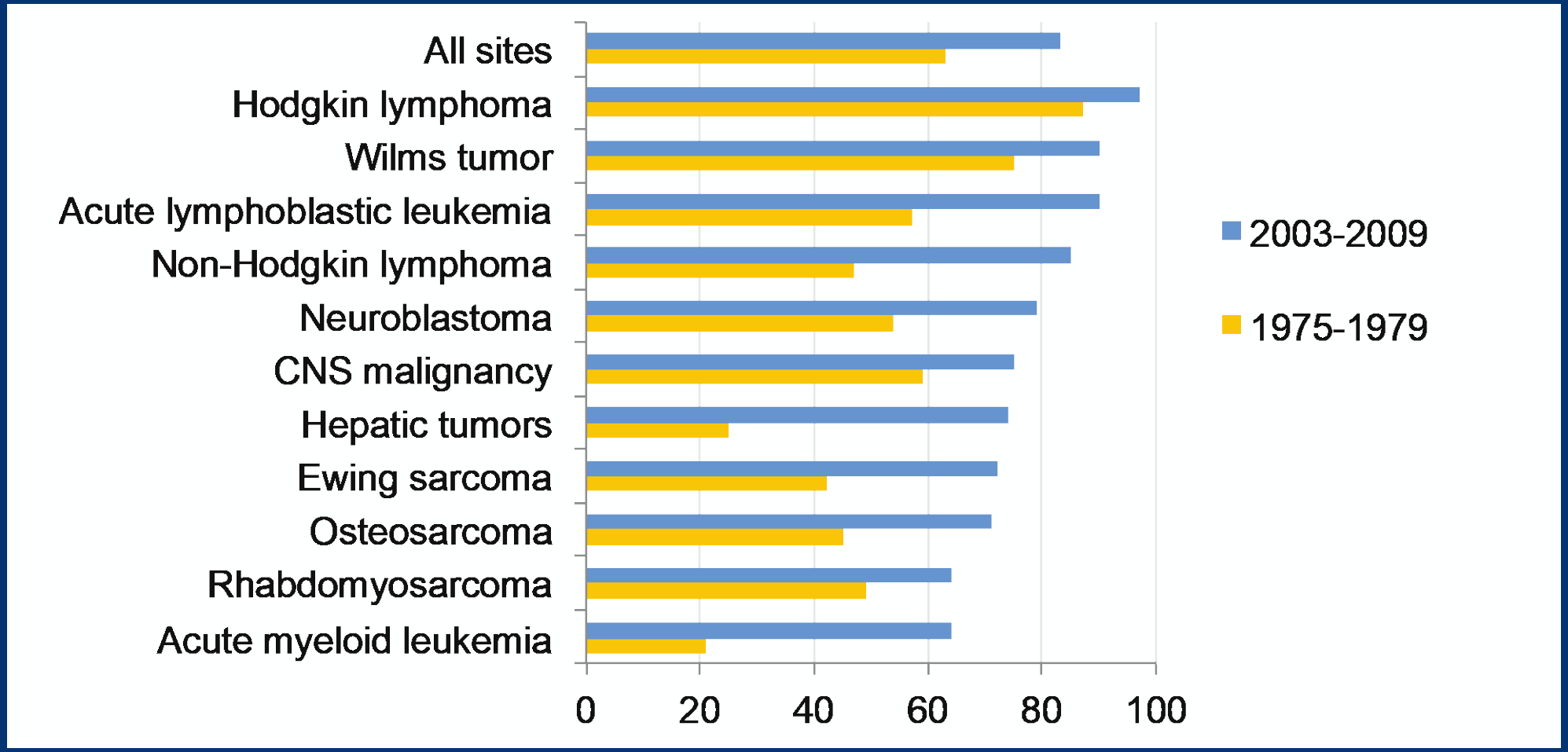
Data Source: SEER 2010

Robison and Hudson, Nature Rev Cancer, 2014;14: 61

Common Childhood Cancers



Change in Cure Rates of Childhood Cancers by Diagnosis

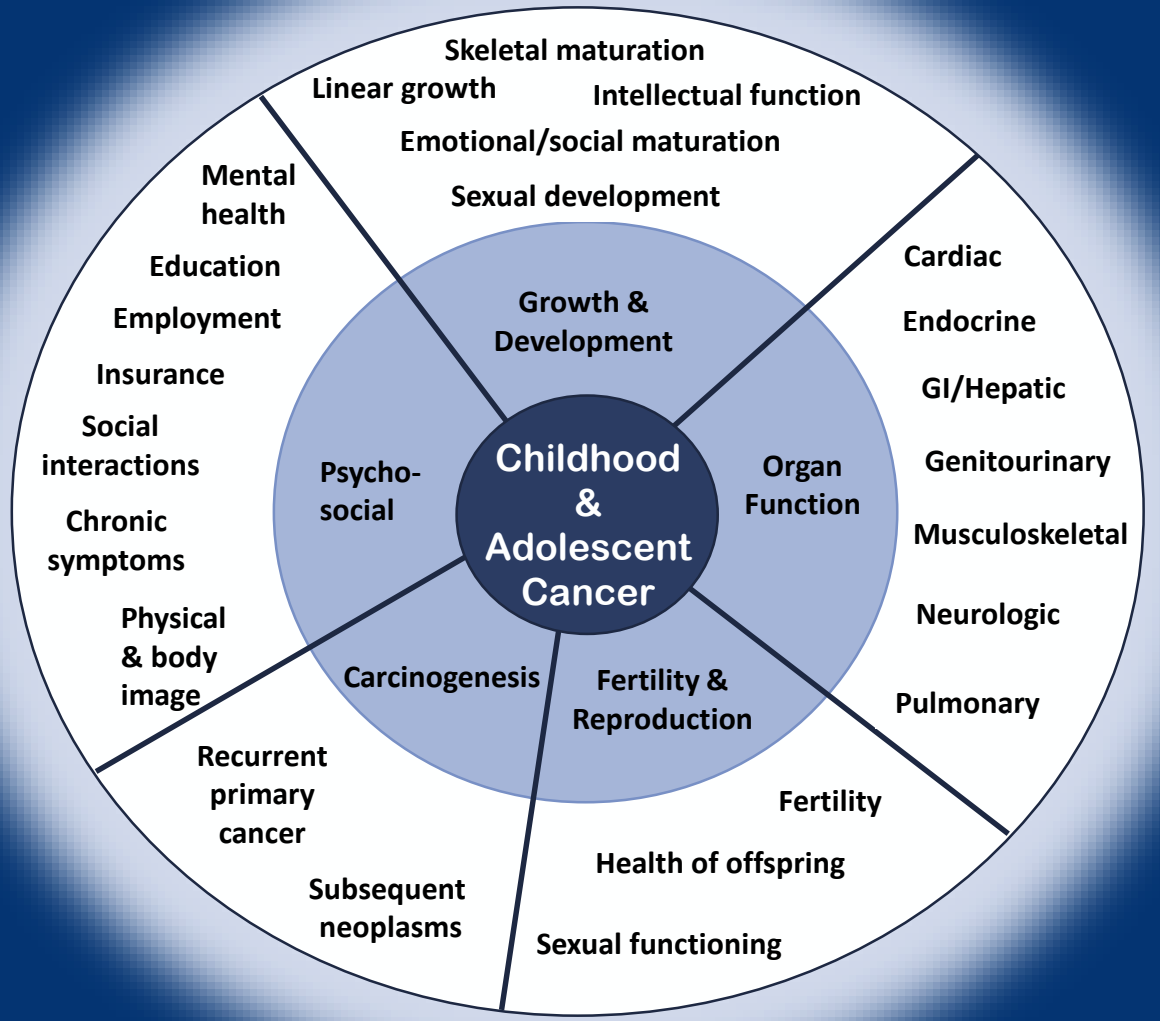


Hudson MM et al, *J Clin. Onc 2014*

Childhood Cancers: Survivorship Statistics

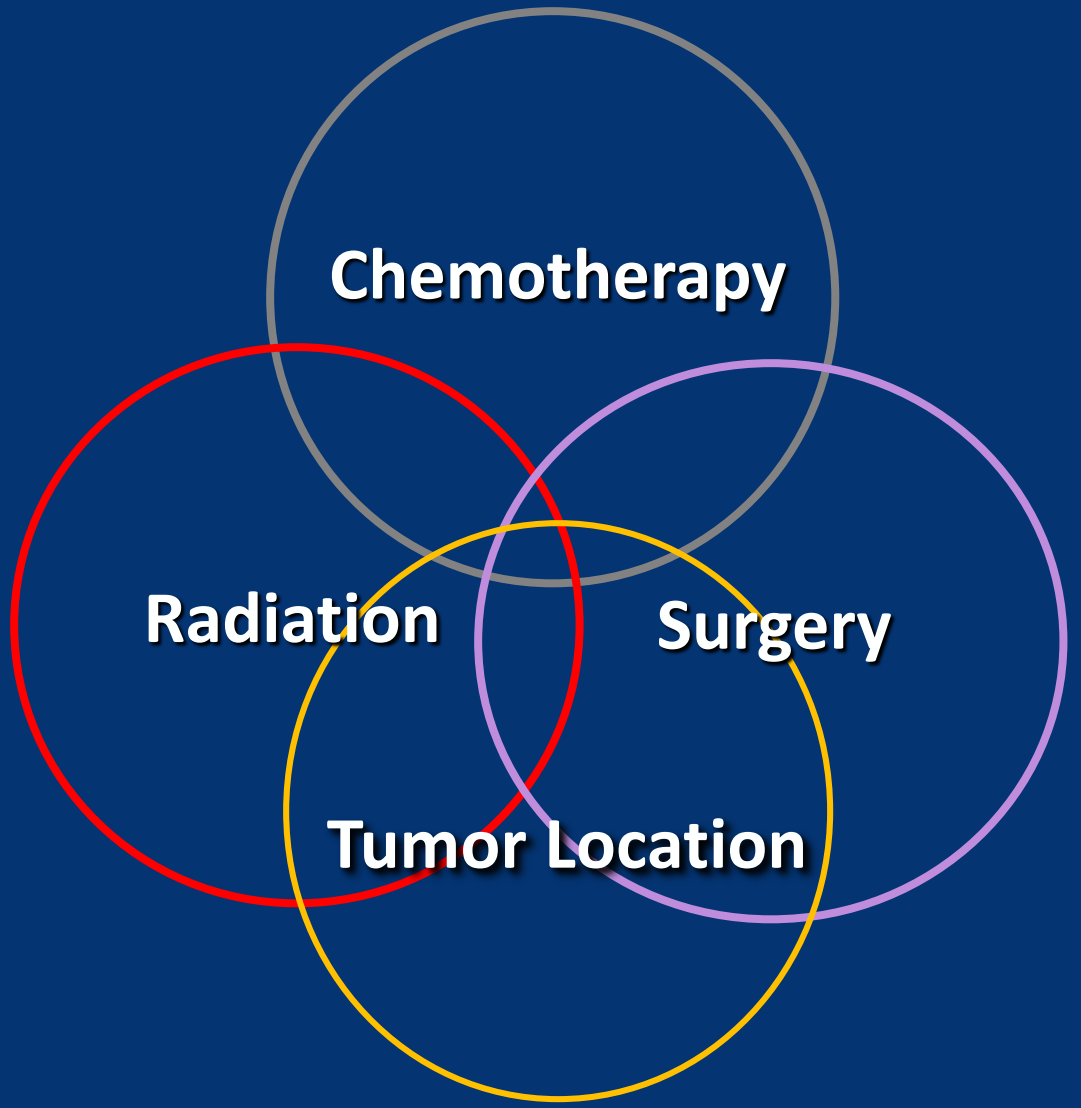
- Estimate 13,500 newly diagnosed cases annually
- 2010, estimated 379,100 survivors living in US
- 1 in 750 in the US is a childhood cancer survivor
- Number of survivors in US will approach 500,000 by 2020

Spectrum of Health-related and Quality of Life Outcomes

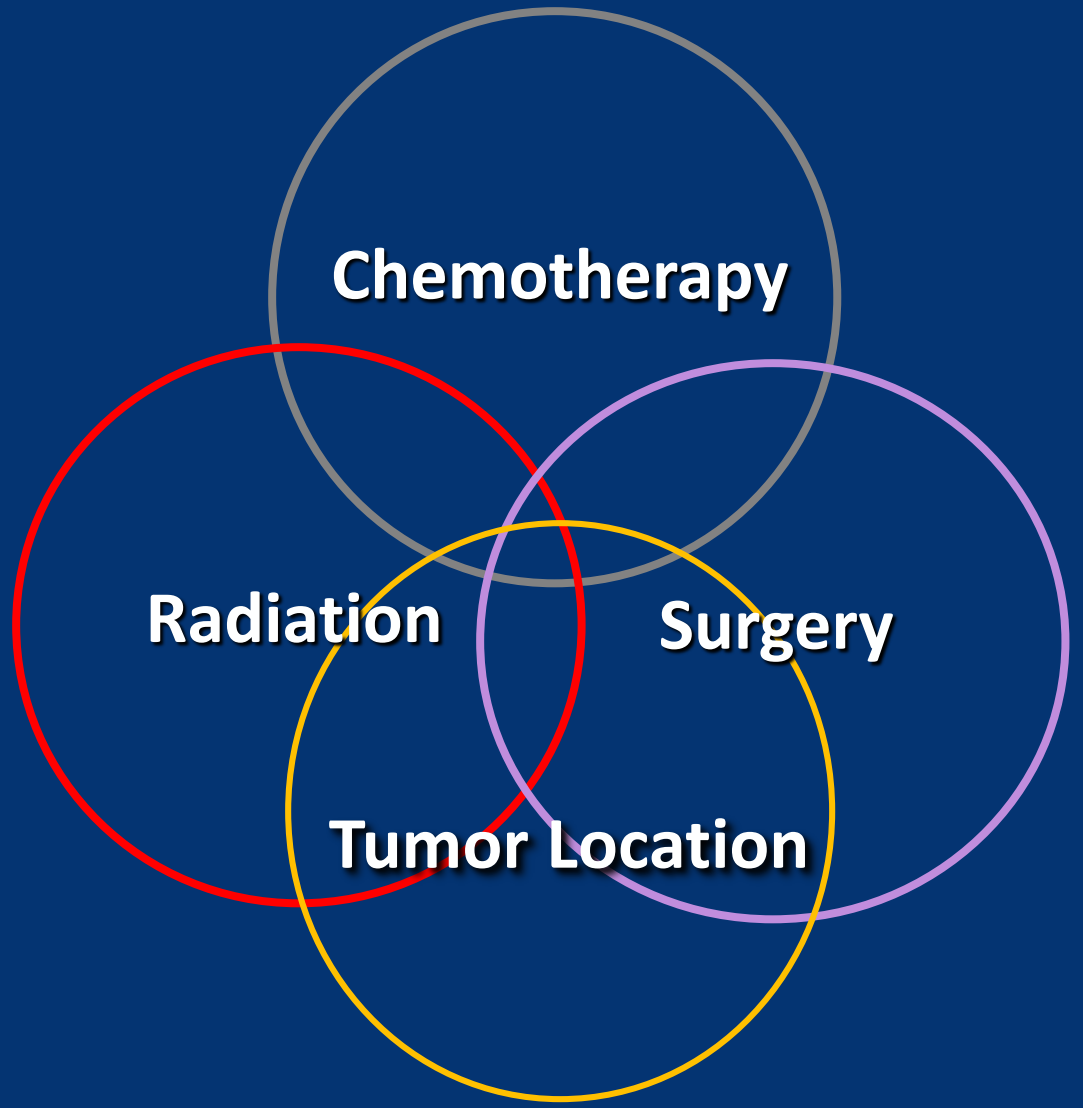


Robison and Hudson, Nature Rev Cancer, 2014;14: 61

Risk Factors for Late Effects



Risk Factors for Late Effects



Modified by:
Age
Gender
Genetics
Lifestyle
Co-morbidities

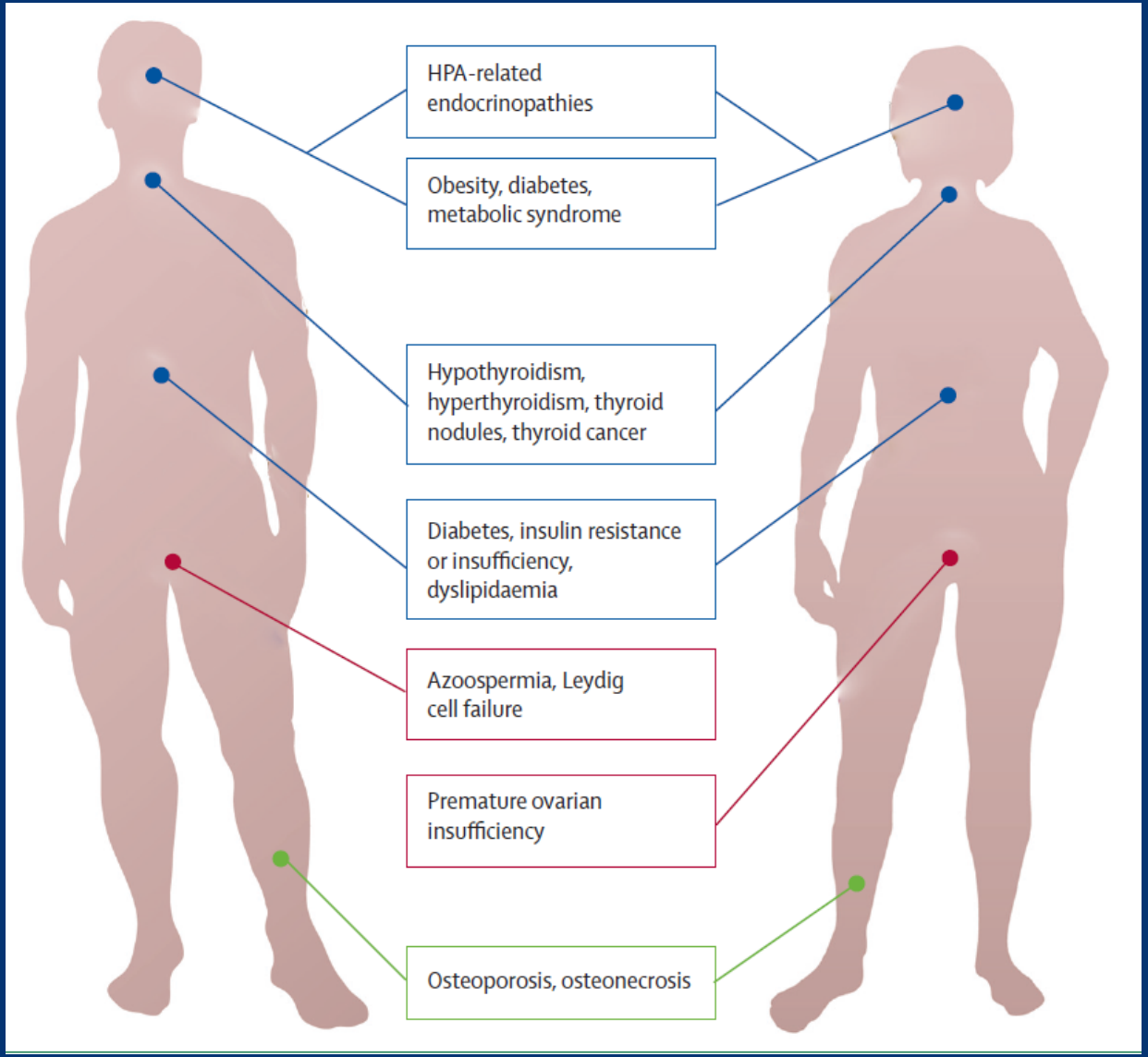
Overview of Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer

HM van Santen, MD

Pediatric Endocrinologist

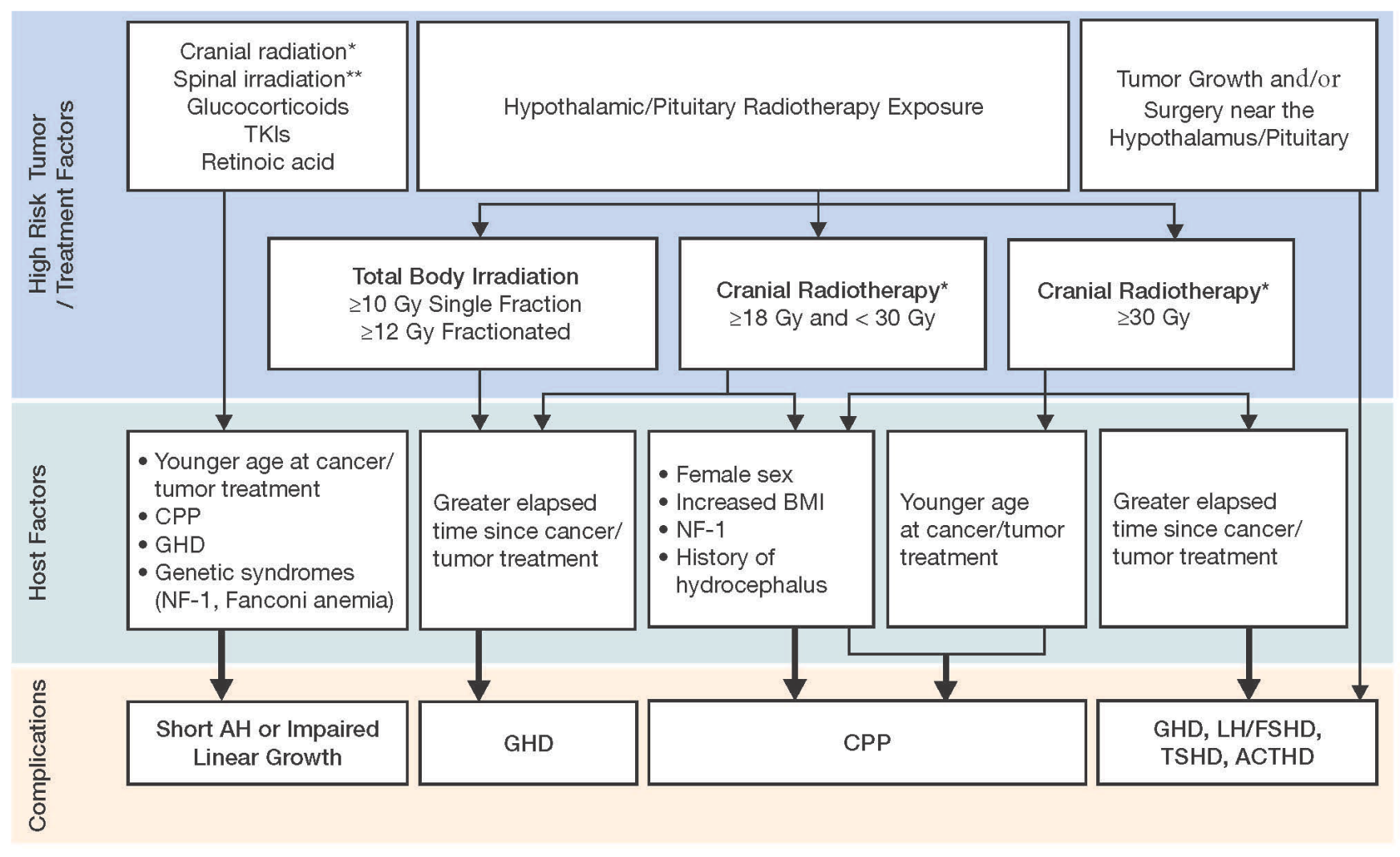
Wilhelmina Children's Hospital, UMCU, Utrecht

Endocrine Outcomes After Treatment for Childhood Cancer



Lancet Diabetes Endocrinol. 2015 **Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer.** Tonorezos ES, Hudson MM, Edgar AB, Kremer LC, Sklar CA, Wallace WH, Oeffinger KC.

Risk Factors of Short Stature and HP Dysfunction in Childhood Cancer Survivors



** Cranial, Infratemporal (ear), nasopharyngeal, orbital (eye), and Waldeyer's ring*

*** Also includes fields involving the abdomen, chest, mediastinum, and pelvis*

Key Points

- Hypothalamic-pituitary dysfunction is frequently observed in CCS
- High risk for tumors involving the hypothalamic-pituitary region or after CNS radiation.
- Dysfunction after RT dose and time dependent
  - <30 Gy primarily growth hormone deficiency and precocious puberty
  - > 30 Gy LH/FSH-D, TSH-D, ACTH-D
- May occur years after completion of cancer therapy.

Key Points *(cont.)*

- Risk factors for impaired linear growth and short stature are radiation at young age, to CNS, TBI and spinal.
- The guideline emphasizes key differences and unique features/findings that are specific to the cancer survivor.

Question

Who should do the screening for endocrine dysfunction in CCS? *(Audience Response)*

A. The pediatric oncologist
B. The general practitioner
C. The (pediatric) endocrinologist
D. A trained nurse
E. A late effects clinician

Comments from the Panel

- Who should do the screening for endocrine dysfunction in CCS?

Case Questions

Case 1

Case 1

Presentation:

- 8-year old girl
- Metastatic posterior fossa medulloblastoma diagnosed at age 5 years. Metastases to the thoracic and lumbar spine.

Treatments:

- surgery with total resection of the posterior fossa mass
- surgical resection of spinal metastatic lesions
- chemotherapy with cisplatin, cyclophosphamide, and vincristine with stem-cell rescue

Treatments (cont.):

- radiotherapy with 36 Gy craniospinal with boosts to the posterior fossa (total 54 Gy) and to the spinal lesions [T6-L2] (total 50 Gy)

Toxicity:

- meningitis, encephalopathy, and seizures during treatment

Complete remission: age 5 years and 9 months

Question 1.1

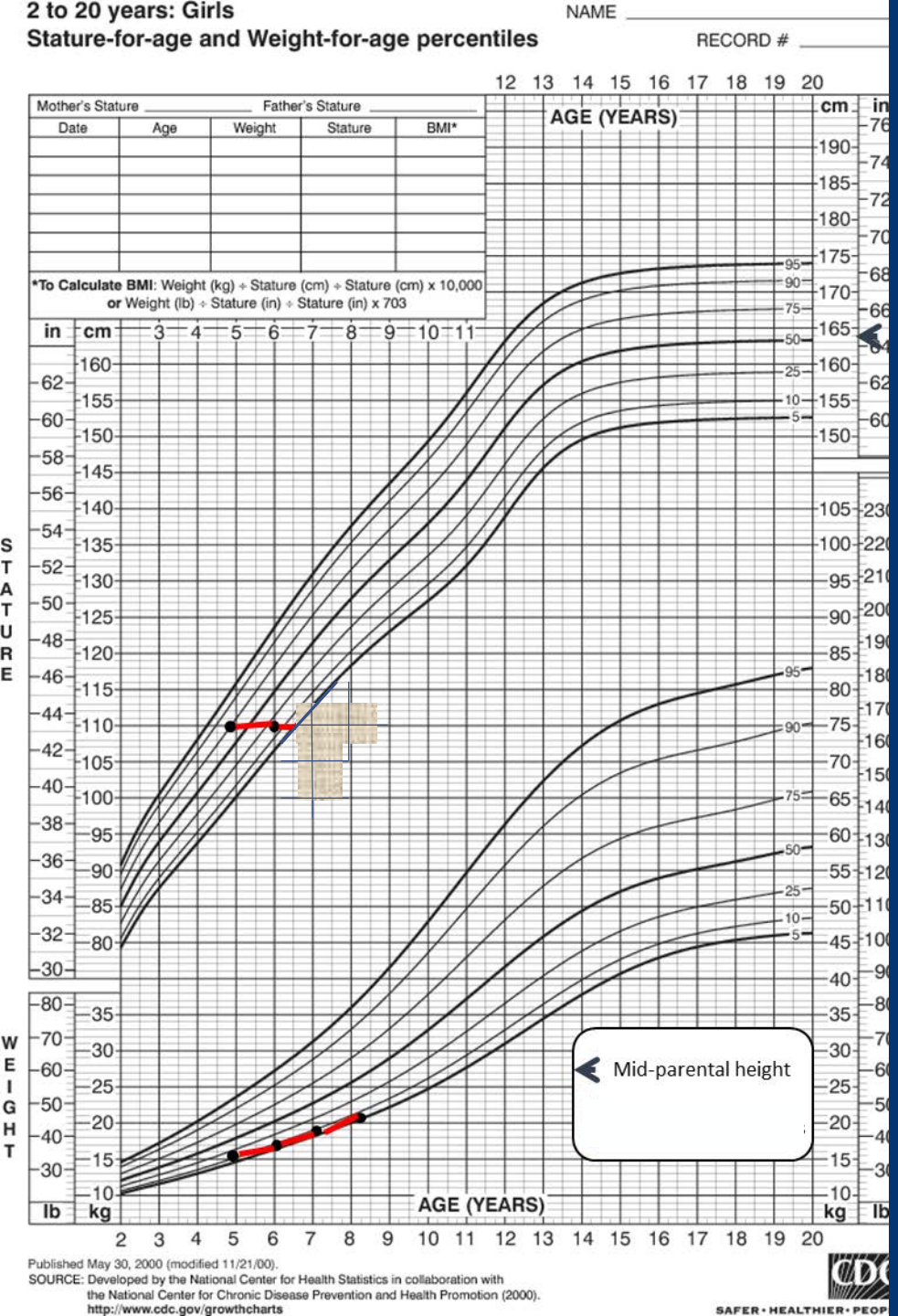
Do you have access to detailed information about the oncologic diagnosis and treatment at referral?*(Audience Response)*

I have access to:

A. **Limited information about the diagnosis and treatment**
B. **Detailed information about the diagnosis and chemotherapy but no access to organ specific radiation doses**
C. **Detailed information on all aspects of care including diagnosis, chemotherapy doses, and radiation fields and dose exposures**
D. **No information**

Comments from the Panel

What specific information is needed by the treating endocrinologist when a childhood cancer survivor is referred to an endocrine clinic?



Reason for referral: Short Stature

Question 1.2: Which of the following are the best next steps to further investigate the reason for this patient's poor growth?

(Audience Response)

A. Thyroid function tests
B. GH stimulation tests
C. IGF-I
D. Bone age
E. Sitting height
F. A and B
G. A, B, D, E

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Comments from the Panel

What are the most appropriate diagnostic tests for short stature after radiotherapy in childhood?

Lab Tests Return

- Mild primary hypothyroidism (TSH 15 mU/L, FT4 low)
- GH deficiency

Because of the radiation dose to the HPA (>30 Gy), the adrenal axis is evaluated before thyroxine treatment is started

- Low dose ACTH test shows ACTH deficiency
- Start hydrocortisone
- Start levothyroxine
- Start GH?

Question 1.3

Is it safe to start GH after treatment for medulloblastoma?

(Audience Response)

A. No, GH treatment should not be given
B. Yes, but GH should be started > 1 year after achieving complete remission
C. Yes, GH can be started as soon as GHD has been diagnosed
D. Yes, but GH has to be administered at a lower dose

Comments of the Panel

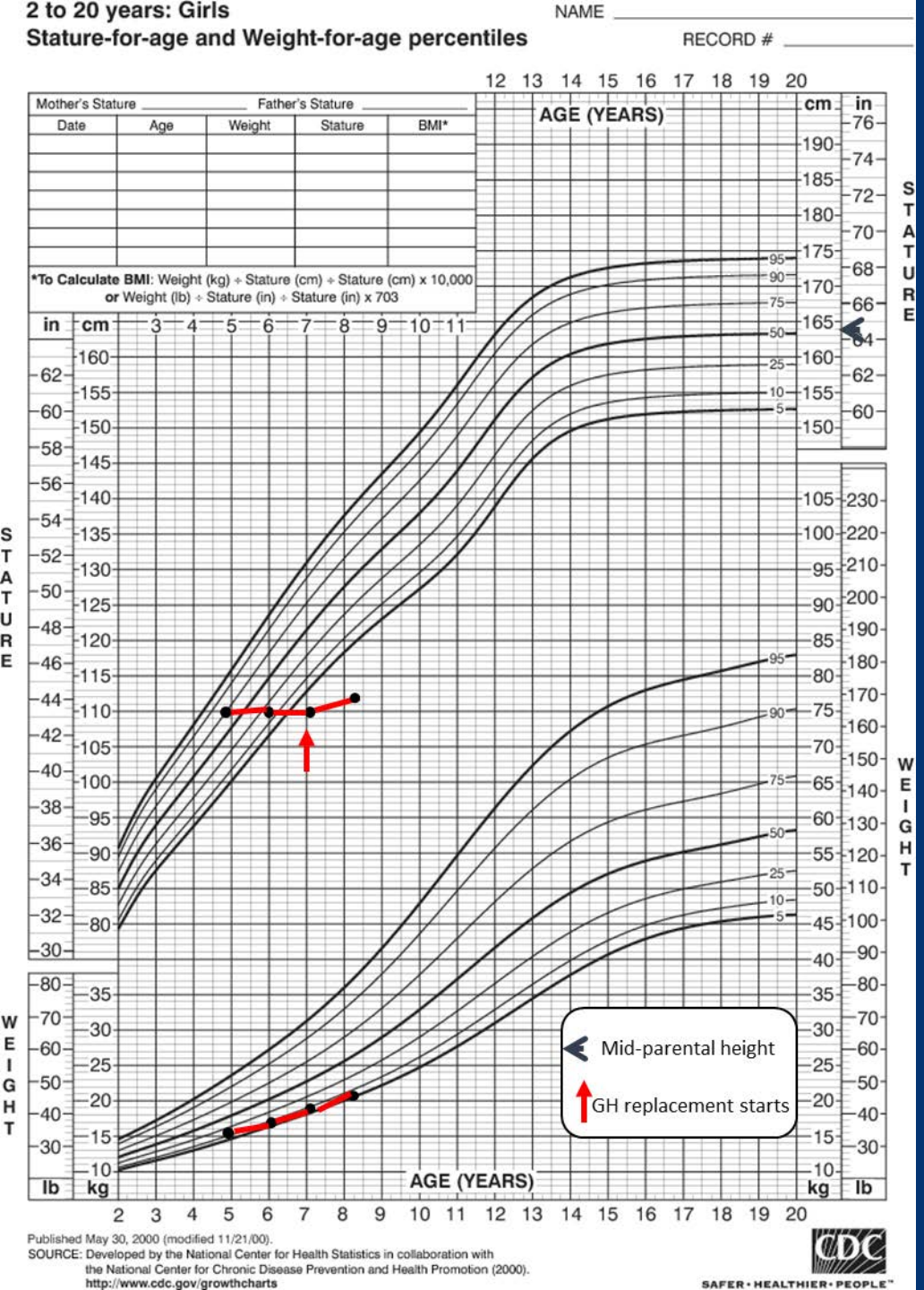
Recommendations for GH treatment in childhood cancer survivors

Follow up: 1 ½ year after GH replacement

- GH treatment 0.2 mg/kg per week (0.6 IU/kg per week)
- Frail appearance with pallor and alopecia
- Wearing hearing aids
- Independent for most daily life tasks
- Second grade

- Examination findings :
  - surgical scars on the back of the head and along the spine
  - decreased spinal mobility

- Tanner stage 1 for breast development and pubic hair.



Growth 1½ years after GH treatment

- Laboratory test results:
  - Free T_4 = 1.5 ng/dL (0.8-1.8 ng/dL)
  - TSH = 0.1 mIU/L (0.5-5.0 mIU/L)
  - IGF-I = 250 ng/mL (64-358 ng/mL)
- Skeletal maturation : consistent with a bone age of 6 years.

Question 1.4

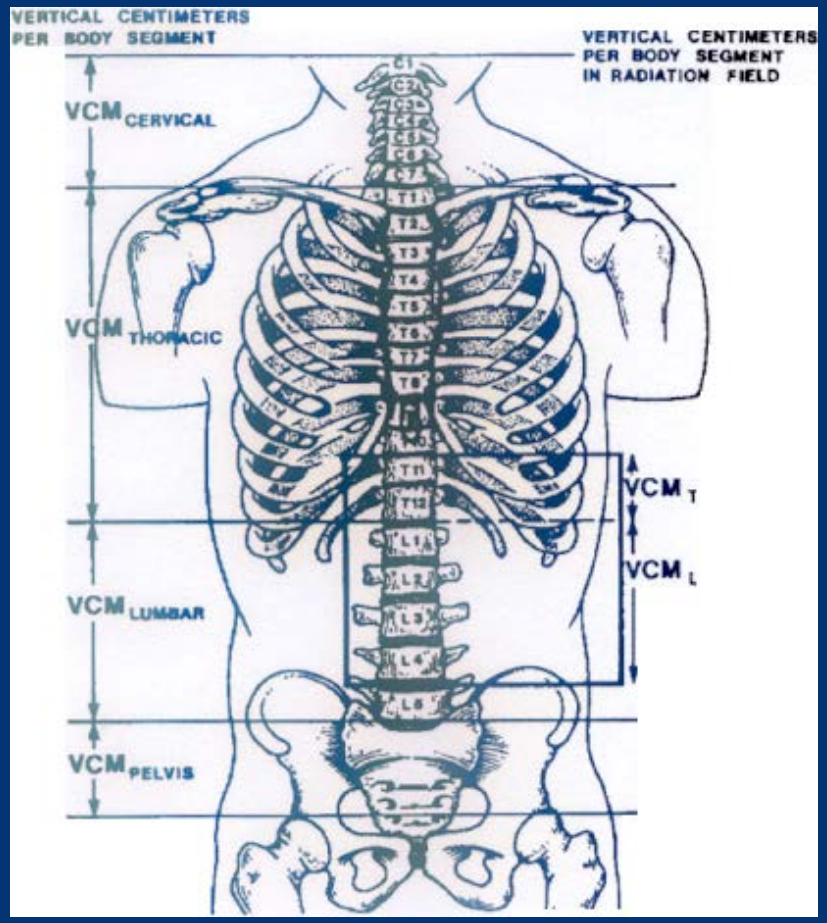
What should be done with regards to the poor growth response? *(Audience Response)*

A. Reduce thyroxine supplementation
B. GH dose needs to be increased
C. Sex steroids should be added
D. Sitting height should be measured
E. Order karyotype analysis
F. Screen for celiac disease

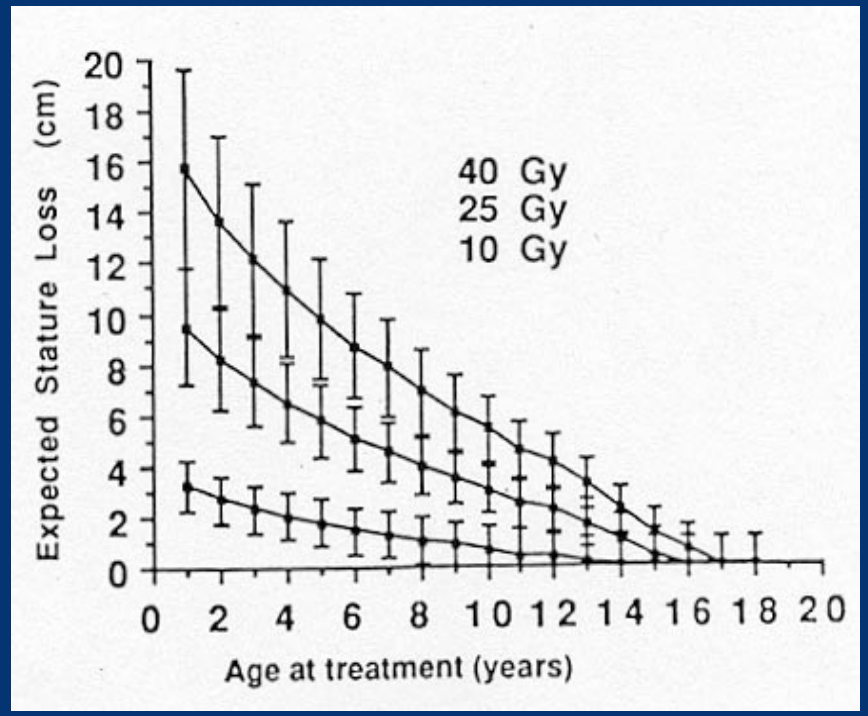
Comments of the Panel

What is the reason for the poor growth response?

Diagnose non–GH-related causes of growth failure such as spinal irradiation



T10-11 to L4-5



Silber et al, JCO 1990

Guideline Recommendations Relevant to Case Question

- We recommend measuring standing height and sitting height in childhood cancer survivors treated with radiation that included the spine (i.e., total body irradiation, craniospinal irradiation, as well as radiation to the chest, abdomen, or pelvis). (1⊕⊕⊕O)
- We recommend against relying solely on serum insulin-like growth factor-1 levels in childhood cancer survivors exposed to hypothalamic-pituitary axis radiotherapy to make the diagnosis of growth hormone deficiency. (1⊕⊕OO)
- We advise using the same provocative testing to diagnose growth hormone deficiency in childhood cancer survivors as are used for diagnosing growth hormone deficiency in the noncancer population. (Ungraded Good Practice Statement)

Guideline Recommendations Relevant to Case Question (cont.)

- We recommend offering growth hormone treatment in childhood cancer survivors with confirmed growth hormone deficiency based on the safety and efficacy demonstrated in that population. (1⊕⊕OO)
- We suggest waiting until the patient has been 1 year disease-free, following completion of therapy for malignant disease, before initiating growth hormone treatment. (2⊕OOO)

Audience Questions

Case 2

Case 2

- Boy, 9 years of age

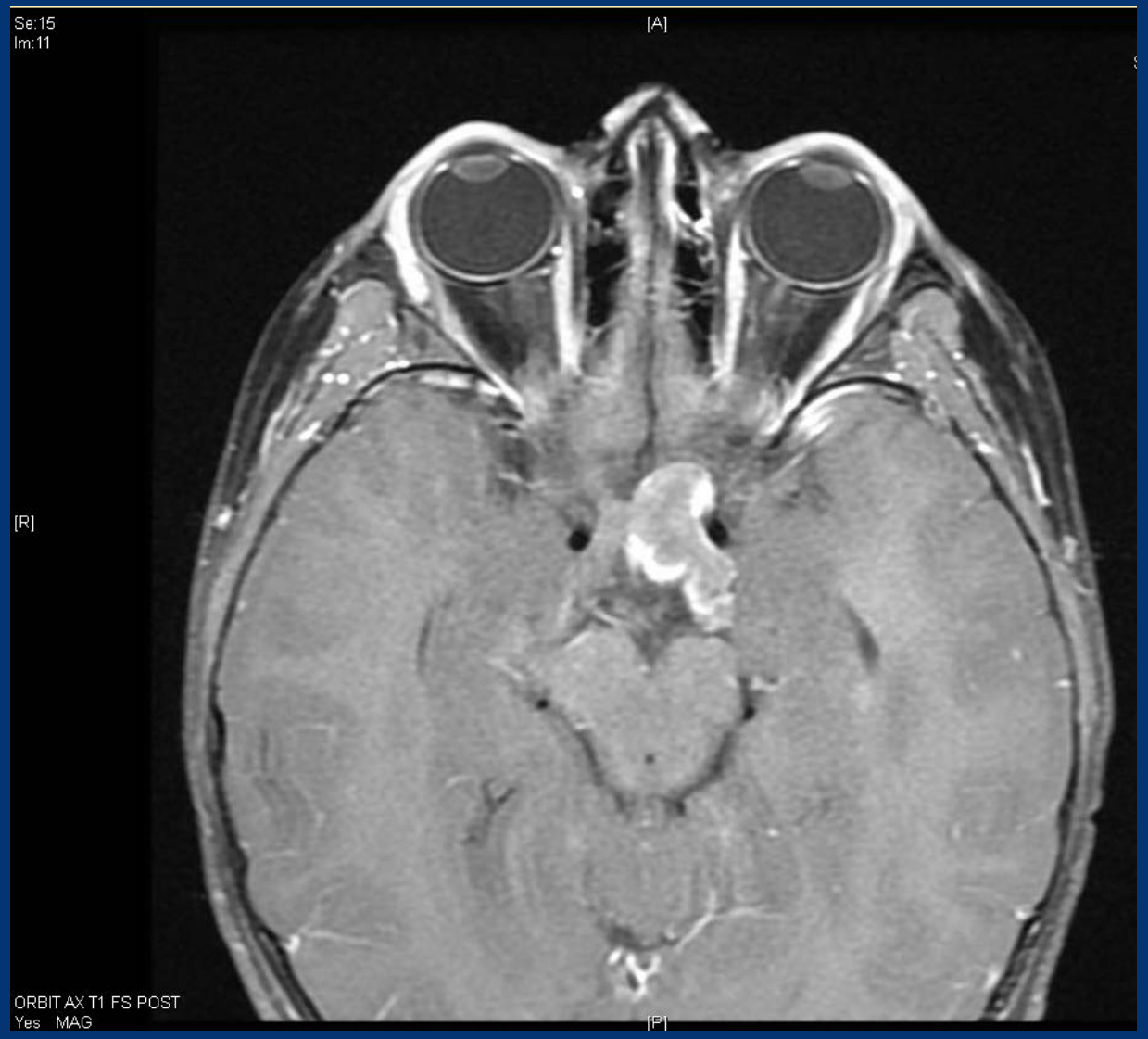
- History of optic pathway glioma at age 5 years

Treatment:
- Vincristine, lomustine (CCNU), thioguanine, procarbazine
- Cyclophosphamide equivalent dose* (CED) 14.8 gm/m2
- No radiation therapy

- Completion of therapy at age 6 years

*Green D, et al. The cyclophosphamide equivalent dose an approach for quantifying alkylating agent exposure. A report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer* 2014, 61:53-67.

MRI Results

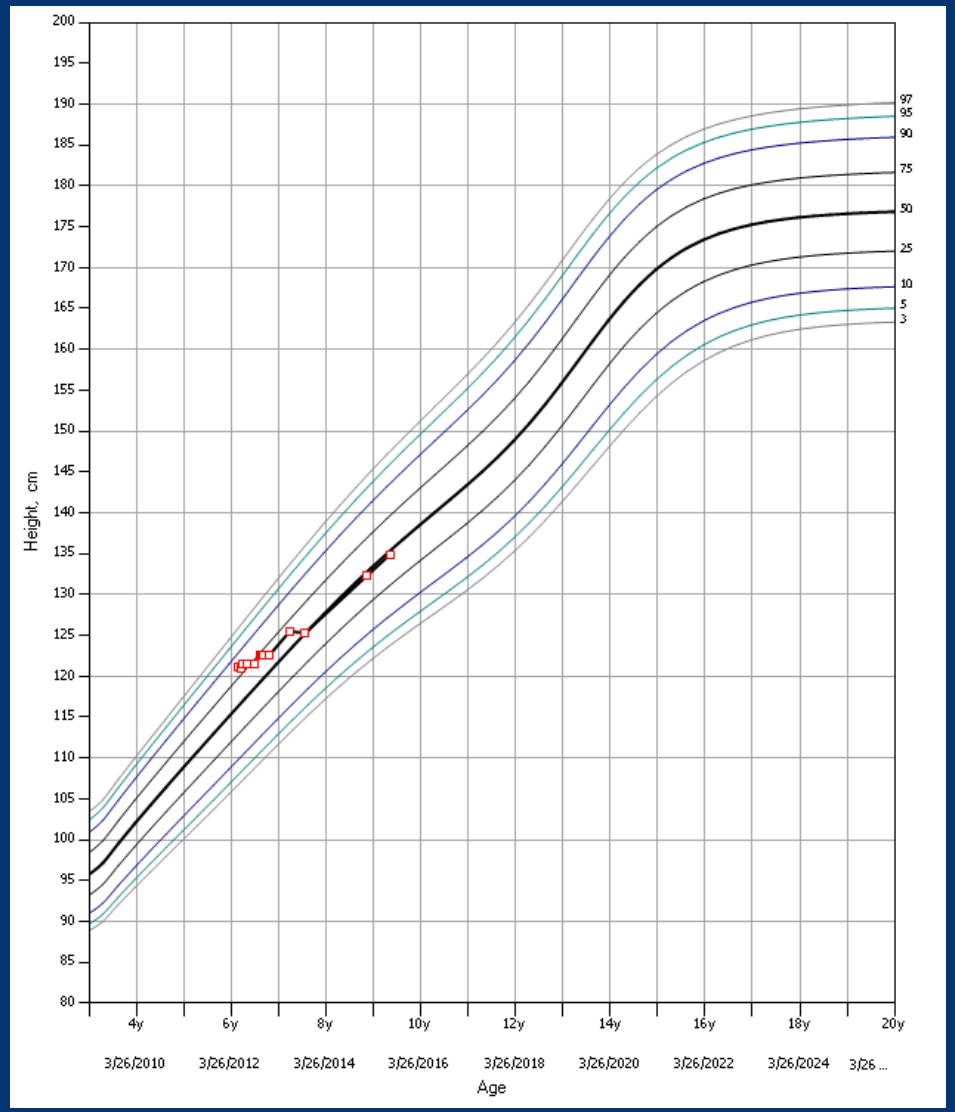


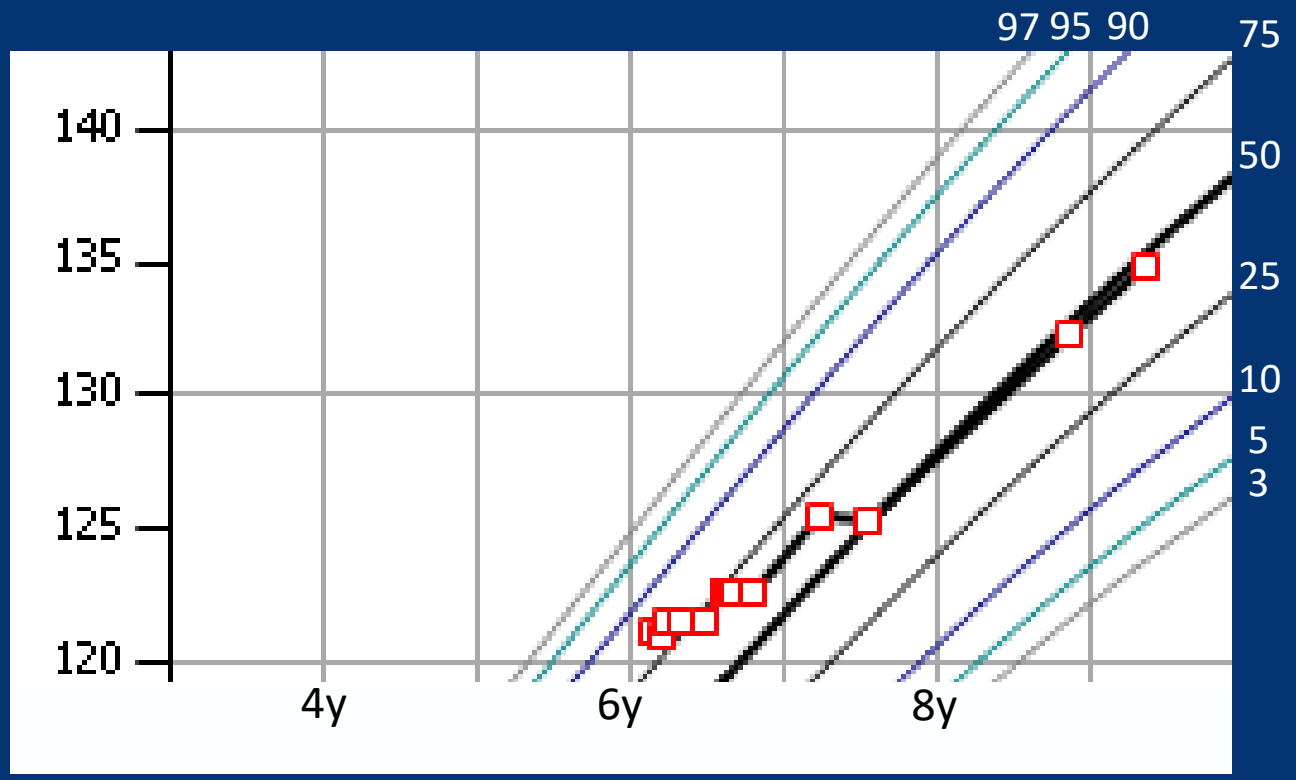
Endocrine Assessment at Age 9

- Endocrine evaluation at diagnosis was negative
- Doing well, active, extra-support in school
- Some new pubic hair over past several months

- PE:
  - Height 47th percentile
  - Weight 78th percentile;
  - BMI 85th percentile
  - Tanner II PH, Tanner II-III genitalia, testicular volume 3/3 cc

Height for Age, 3-20 years (CDC)





Question 2.1

What is the correct next step? *(Audience Response)*

A. Testicular volume is reassuring. Pubic hair is due to premature adrenarche. No additional investigations necessary.

B. Height velocity is reassuring. No additional investigations necessary.

C. Testicular volume and growth rate are unreliable. Additional investigations should be considered.

Comments of the Panel

What is the best next step?

Additional Endocrine Tests

Thyroid axis:

Free T4 0.9 ng/dl (0.9-1.8)

TSH 2.2 mU/L (0.4-4.9)

Bone age :

13 yrs (CA 9 4/12)

Adrenal axis:

Cortisol 13.7 mcg/dl (378 nmol/L)

Gonadal axis:

Testosterone 191 ng/dl (normal prepubertal male <10; adult 240-871)

LH 2.4 mU/ml

FSH 10.4 mU/ml

Question 2.2

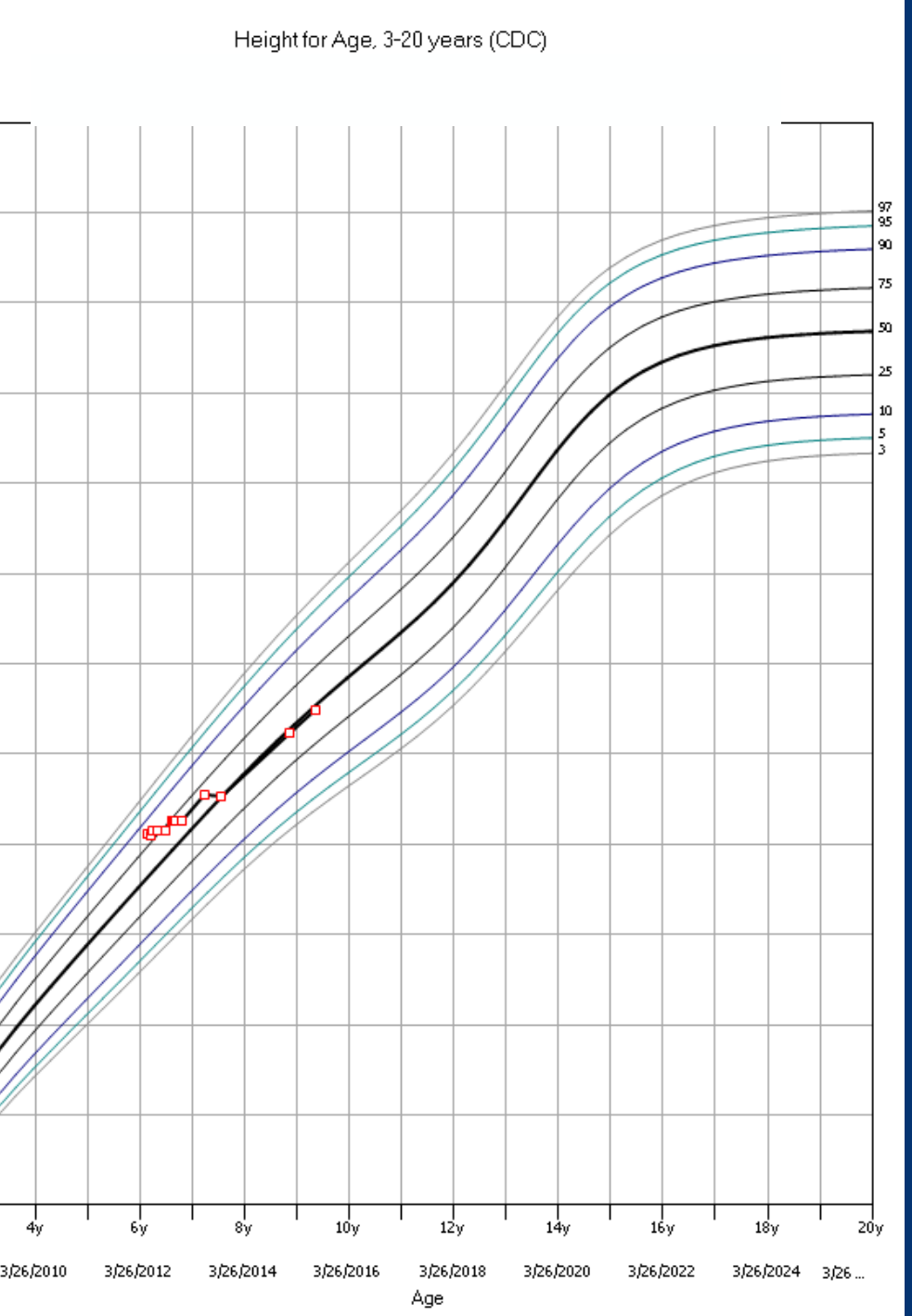
What is your conclusion? *(Audience Response)*

A. High testosterone and accelerated bone age is caused by premature adrenarche (testes volume 3 cc).

B. High testosterone is caused by central precocious puberty (testicular volume is unreliable).

Comments of the Panel

Reliability of testicular volume after treatment with gonadotoxic chemotherapy?



Additional Endocrine Investigations

Suspicion of GHD due to lack of growth acceleration despite ongoing puberty

Question 2.3

What is the recommended diagnostic test for GHD in CCS? *(Audience Response)*

A. Determination of IGF-I and IGF-BP3
B. GH stimulation test
C. Spontaneous GH secretion
D. No laboratory investigation is necessary; this diagnosis is made upon growth rate in combination with Tanner stage, bone age and MRI findings.

Comments of the Panel

What is the best screening modality for growth hormone deficiency in CCS ?

Additional Endocrine Investigations

- IGF-I : -1 SD for age
- Arginine and clonidine testing:
  - Peak GH 5.3 ng/ml (>/= 10)
- C/ GH deficiency and central precocious puberty
- Rx/ GH sc daily with GnRH agonist

Guideline Recommendations Relevant to Case Question

- We recommend against relying solely on serum insulin-like growth factor-1 levels in childhood cancer survivors exposed to hypothalamic-pituitary axis radiotherapy to make the diagnosis of growth hormone deficiency. (1⊕⊕OO)
- We advise using the same provocative testing to diagnose growth hormone deficiency in childhood cancer survivors as are used for diagnosing growth hormone deficiency in the noncancer population. (Ungraded Good Practice Statement)

Guideline Recommendations Relevant to Case Question (cont.)

- We recommend against using testicular volume as the primary or sole indicator of degree of sexual development in male childhood cancer survivors previously treated with gonadotoxic agents, such as alkylating agents or testicular radiotherapy. (1⊕⊕⊕O)

Guideline Recommendations Relevant to Case Question (cont.)

- We recommend measuring serum testosterone, preferably using liquid chromatography-tandem mass spectroscopy, and luteinizing hormone levels prior to 10:00 am to complement the clinical assessment of male childhood cancer survivors who are suspected of or are at risk for developing central precocious puberty and were exposed to gonadotoxic treatments. (1⊕⊕OO)

  <u>Technical Remarks:</u>

  - *Clinicians need to interpret plasma LH levels in patients exposed to gonadotoxic treatments in the context of their medical history and physical examination.*
  - *Elevated LH levels in such patients may be due primary gonadal injury rather than to the onset of central puberty.*

Audience Questions

Case 3

Case 3

Presentation:

- Male, 28 years
- At age 8, medulloblastoma, metastases C3-Th11

Treatment:

- Proton radiotherapy, 36 Gy craniospinal with boost to the posterior fossa (total 54 Gy) and to the spinal lesions.
- Chemotherapy ACNS 0332
  - Vincristine, cyclophosphamide, carboplatin, cisplatin

Complete Remission:

- Age 9

Known from age 9 at the pediatric endocrine department

- Central hypothyroidism; levothyroxine
- Central hypocortisolism; hydrocortisone
- GH deficiency: GH until age 16, FH -1 SDS
- No hypogonadism
  - Treatment with GnRH analogues from age 9-11

Transfer to the adult endocrine department at age 18

- GH treatment stopped upon achieving final adult height
- Now returns at age 28 with complaints of fatigue
- Is taking thyroxine and hydrocortisone daily

Question 3.1

Which endocrine diagnostic tests would you do? *(Audience response)*

A. Thyroid function tests
B. LH/ FSH and morning testosterone
C. IGF-I
D. All of the above

Comments of the Panel

What is the latency time for dysfunction of the different pituitary axes after cranial radiation in childhood?

Can this patient still develop hypogonadism after all these years?

Hypopituitarism in Survivors of Childhood Cancer

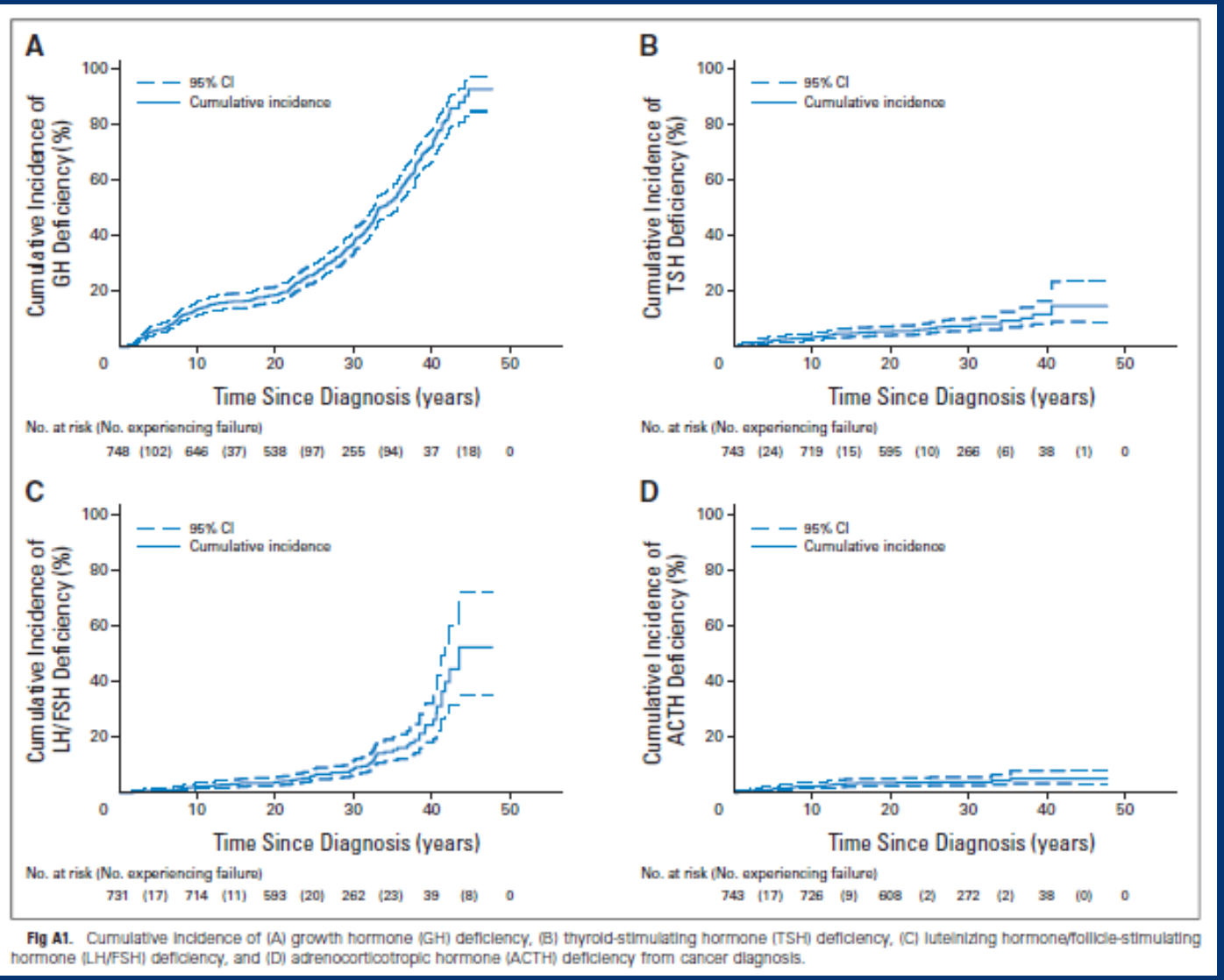


Fig A1. Cumulative incidence of (A) growth hormone (GH) deficiency, (B) thyroid-stimulating hormone (TSH) deficiency, (C) luteinizing hormone/follicle-stimulating hormone (LH/FSH) deficiency, and (D) adrenocorticotropic hormone (ACTH) deficiency from cancer diagnosis.

Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: A report from the St Jude Lifetime Cohort study. Chemaitilly W, Li Z, Huang S, Ness KK, Clark KL, Green DM, Barnes N, Armstrong GT, Krasin MJ, Srivastava DK, Pui CH, Merchant TE, Kun LE, Gajjar A, Hudson MM, Robison LL, Sklar CA. J Clin Oncol. 2015 Feb

Lab Tests

(uses levothyroxine and hydrocortisone)

Free T4	1.6 ng/dl(0.9-1.8)
TSH	0.3 mU/L (0.4-4.9)
Testosterone	180 ng/dl (normal adult 240-871)
LH	1.1 mU/ml
FSH	1.3 mU/ml
IGF-I	60 ng/mL (64-358 ng/mL)

Conclusion: Panhypopituitarism

Comment of the Panel

Is the recommendation for GH treatment in CCS adults different than for non-CCS adults?

Guideline Recommendations Relevant to Case Question

- We recommend lifelong periodic clinical assessment for growth hormone deficiency in survivors treated for tumors in the region of the hypothalamic-pituitary axis and in those exposed to hypothalamic-pituitary axis radiation treatment ≥18 Gy (e.g. various brain tumors, nasopharyngeal carcinoma, acute lymphoblastic leukemia, lymphoma). (1⊕⊕⊕O)
- We recommend retesting adult cancer survivors exposed to hypothalamic-pituitary axis radiation treatment and with a diagnosis of isolated growth hormone deficiency in childhood. (1⊕⊕OO)

Guideline Recommendations Relevant to Case Question (cont.)

- We recommend lifelong annual screening for thyroid-stimulating hormone deficiency in childhood cancer survivors treated for tumors in the region of the hypothalamic-pituitary axis and those exposed to ≥30 Gy hypothalamic-pituitary radiation. (1⊕⊕⊕O)
- We recommend lifelong annual screening for adrenocorticotropic hormone deficiency in childhood cancer survivors treated for tumors in the hypothalamic-pituitary region and in those exposed to ≥30 Gy hypothalamic-pituitary radiation. (1⊕⊕⊕O)

Audience Questions

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