



THE UNIVERSITY OF TEXAS

MD Anderson ~~Cancer Center~~

Children's Cancer Hospital®

Endocrinopathies Related to Cancer Therapy

ANGELA R. YARBROUGH, DNP, APRN, FNP-BC, CPHON
THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

CARLEE LEOPARD, MSN, CPNP
GEORGIA CANCER CENTER AUGUSTA UNIVERSITY

Conflict of Interest Disclosure

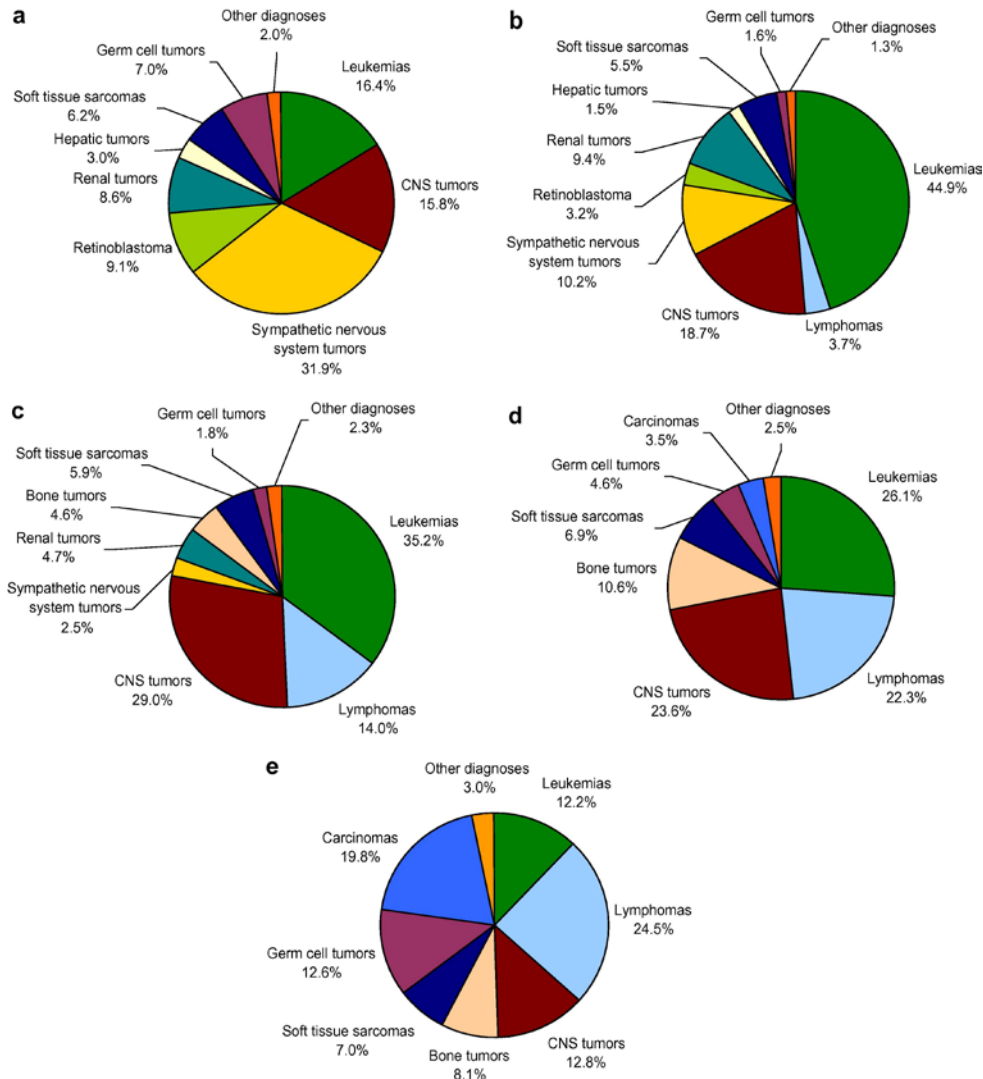
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OBJECTIVES

- Describe the endocrine sequelae of childhood cancer therapies.
- Discuss the common risk factors for developing endocrinopathies after cancer treatment.
- Explain guidelines for monitoring, diagnosis and treatment.

The Scope of Childhood Cancer



➤ 11,500 new cases per year in the U.S. under the age of 15 (2020)

➤ 5,000-6,000 adolescents in the U.S. ages 15-19

(Key Statistics for Childhood Cancers. American Cancer Society. 2020; Key Statistics for Cancers in Adolescents. American Cancer Society. 2019)

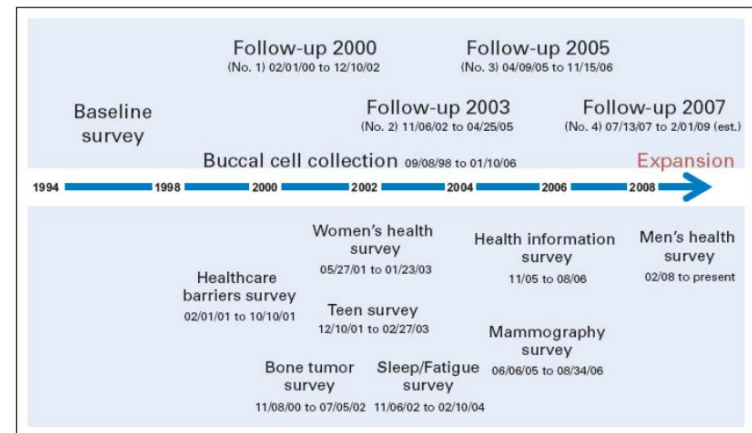
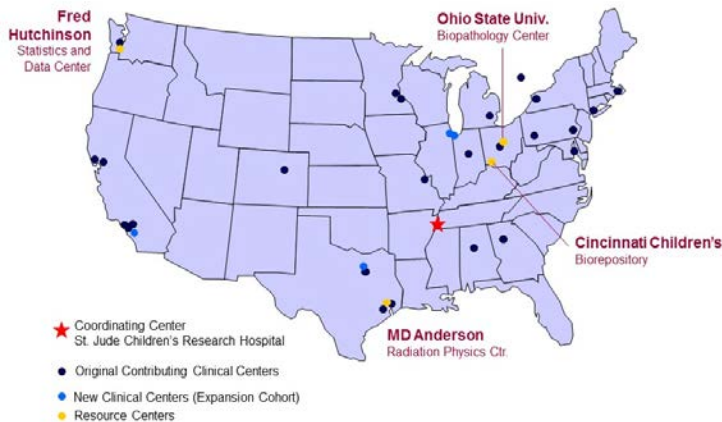
Fig. 1. Relative frequencies for the main ICCC-3 diagnostic groups by age groups: (a) age <1 year; (b) age 1-4 years; (c) age 5-9 years; (d) age 10-14 years; (e) age 15-19 years. Kaatsch. Epidemiology of Childhood Cancer. 2010

Childhood Cancer & Survivorship

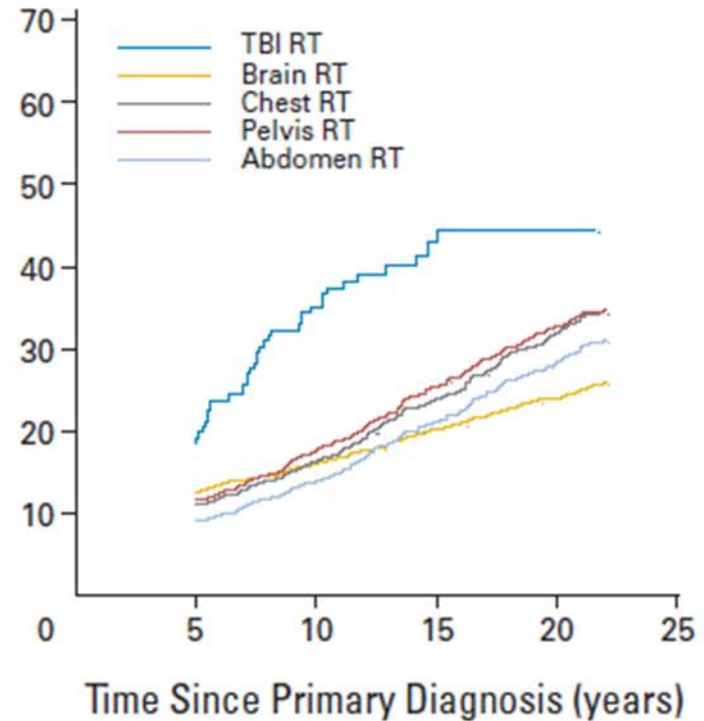
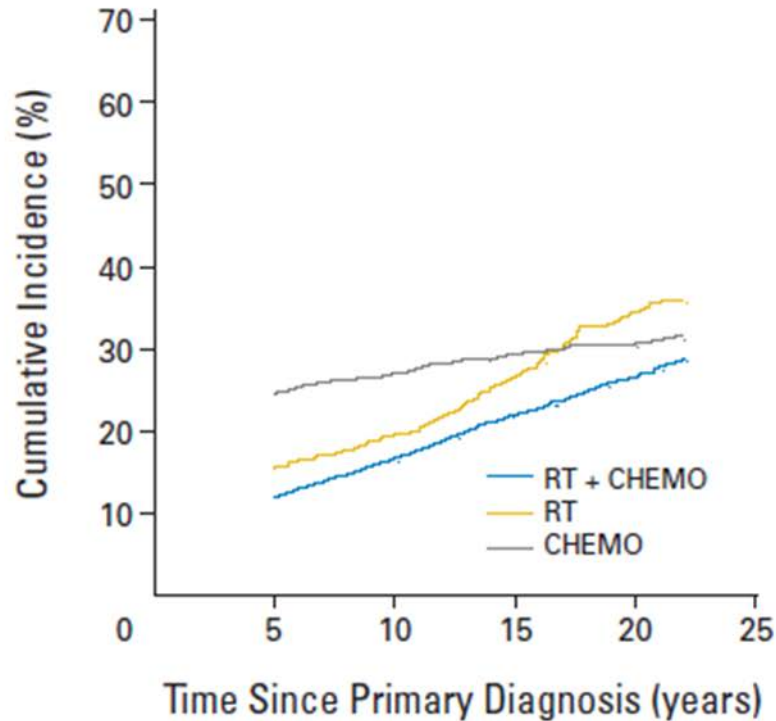
- 5-year survival rate has increased from 58% in the 1970s to 84% currently
- There are ~375,000 adult survivors of childhood cancer in the U.S. which equates to 1 in 530 adults ages 20-39.

Childhood Cancer Survival Study (CCSS)

- <21 at time of diagnosis, diagnosed between 1970-1986, and at least 5 years survival
 - leukemia, CNS cancers, HD, non-Hodgkin's lymphoma, Wilms, neuroblastoma, sarcomas
- 14,000 survivors / 3,500 siblings; Expansion Cohort 11,000+
- Medical Record Abstraction and Questionnaires



Cumulative Toxicities from Childhood Cancer Treatment



- Endocrine Sequelae

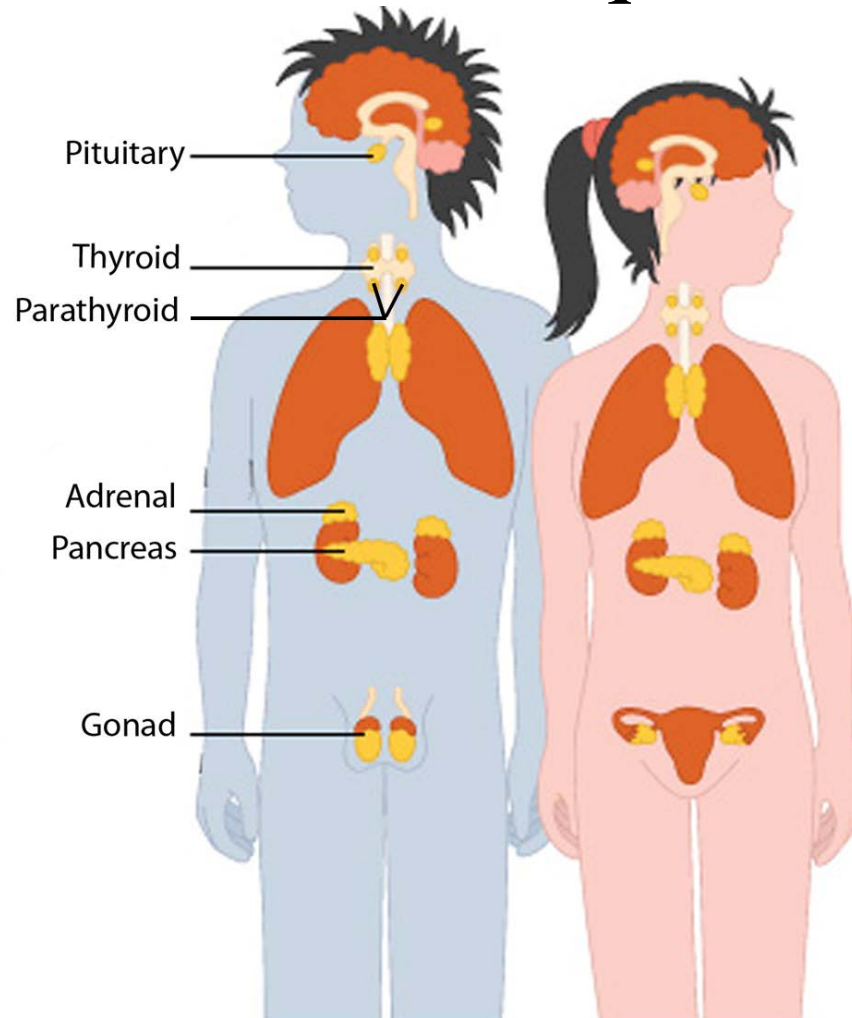
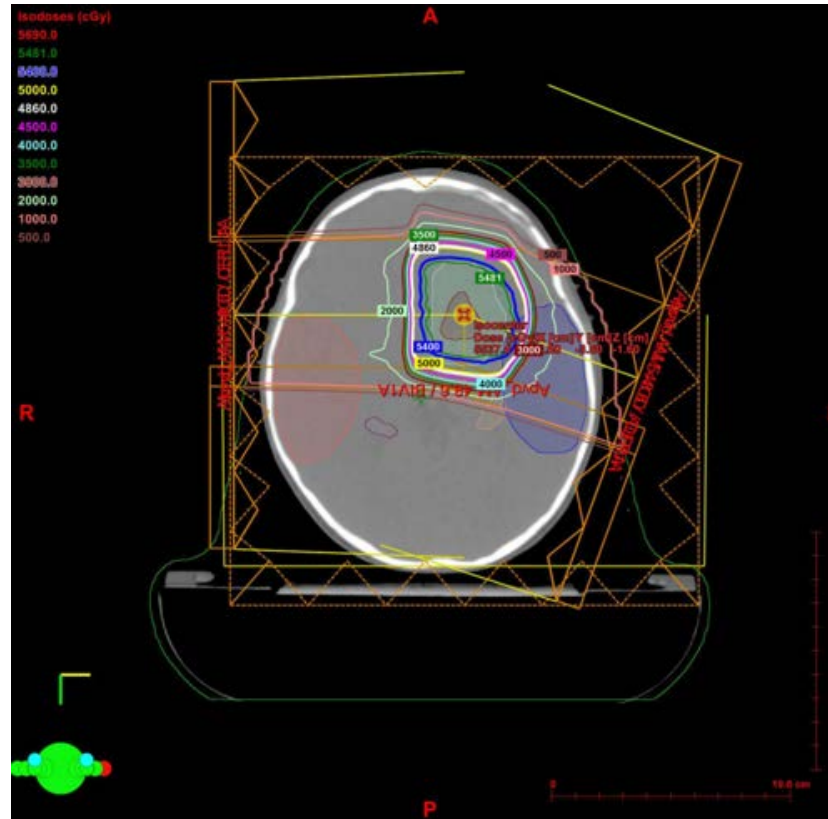


Figure Adapted From: National Taiwan Science Education Center

Treatment Plan



**CHILDREN'S
ONCOLOGY
GROUP**

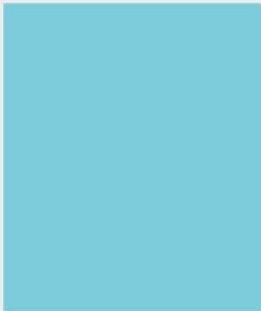
The world's childhood
cancer experts



Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent,
and Young Adult Cancers

Version 5.0 - October 2018



Website: www.survivorshipguidelines.org
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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
52	Head/Brain TBI	Growth hormone deficiency	HISTORY Assessment of nutritional status Every 6 months until growth is completed, then yearly PHYSICAL Tanner staging Every 6 months until sexually mature Height Weight BMI Every 6 months until growth is completed, then yearly	HEALTH LINKS Growth Hormone Deficiency Hypopituitarism RESOURCES www.magicfoundation.org POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION For skeletally immature children, refer to endocrinology if radiation dose ≥ 30 Gy. For those treated with < 30 Gy, obtain x-ray for bone age in poorly growing children. Endocrine consultation for: Poor growth for age or stage of puberty as evidenced by decline in growth velocity and change in percentile rankings on growth chart, weight below 3rd percentile on growth chart. Evaluate thyroid function in any poorly growing child. Consult with endocrinologist regarding risks/benefits of adult growth hormone replacement therapy. Consider bone density testing in patients who are growth hormone deficient.

SYSTEM = Endocrine/Metabolic
SCORE = 1

Additional Information

Growth charts available on-line at www.cdc.gov/growthcharts/.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: Surgery in supra-sellar region, higher radiation dose (especially radiation dose ≥ 18 Gy), pretransplant radiation (especially pretransplant cranial radiation), TBI ≥ 10 Gy in single fraction, ≥ 12 Gy fractionated, TBI given in single fraction

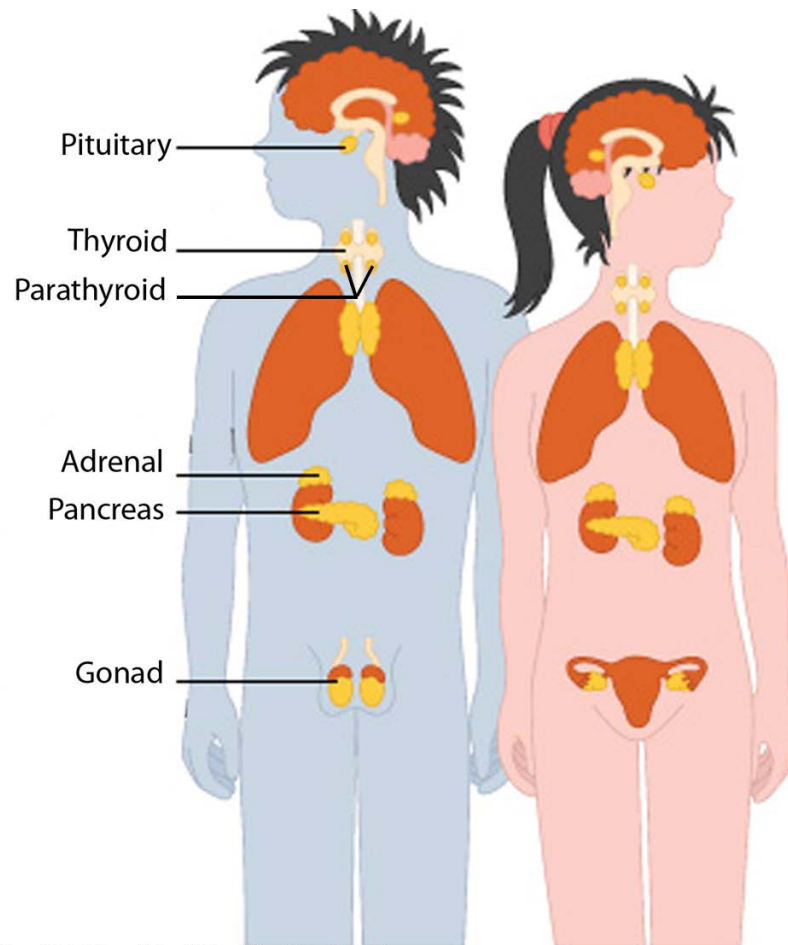
References

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- Brownstein CM, Mertens AC, Mitby PA, et al: Factors that affect final height and change in height standard deviation scores in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 89:4422-7, 2004
- Couto-Silva AC, Trivin C, Esperou H, et al: Final height and gonad function after total body irradiation during childhood. *Bone Marrow Transplant* 38:427-32, 2006
- Frisk P, Arvidson J, Gustafsson J, et al: Pubertal development and final height after autologous bone marrow transplantation for acute lymphoblastic leukemia. *Bone Marrow Transplant* 33:205-10, 2004
- Gurney JG, Ness KK, Sibley SD, et al: Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer* 107:1303-12, 2006

Endocrine Sequelae: Clinical Pearls

- Highest risk patients are those treated with radiation & chemotherapy (In CNS tumors, the prevalence of an endocrinopathy is >70%)
- May be overlooked by the provider and the patient (after all they have gone through...)
- May not present for years to decades after Rx
- May not present as you would anticipate

The Pituitary



Endocrine Sequelae: Clinical Pearls

➤ Possible Endocrinopathies

- GH deficiency
- Central Hypothyroidism
- Central Adrenal Insufficiency
- Hyperprolactinemia
- Precocious Puberty/Hypogonadotropic Hypogonadism
- Overweight/Obesity

➤ Risk Factors

- Cranial Radiation
 - Hypothalamus more sensitive than pituitary
 - Higher radiation doses
 - Potentiating effects of chemotherapy, which may also have direct effects
- Surgery
- Younger age of treatment

➤ Surveillance

- Monitor growth and pubertal development every 6 months
- Routinely monitor hormone levels
- Consider routine BA assessment in at-risk patients

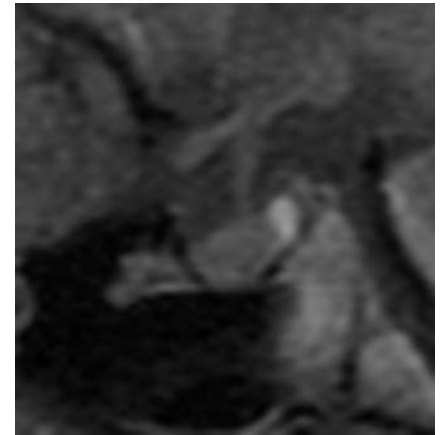
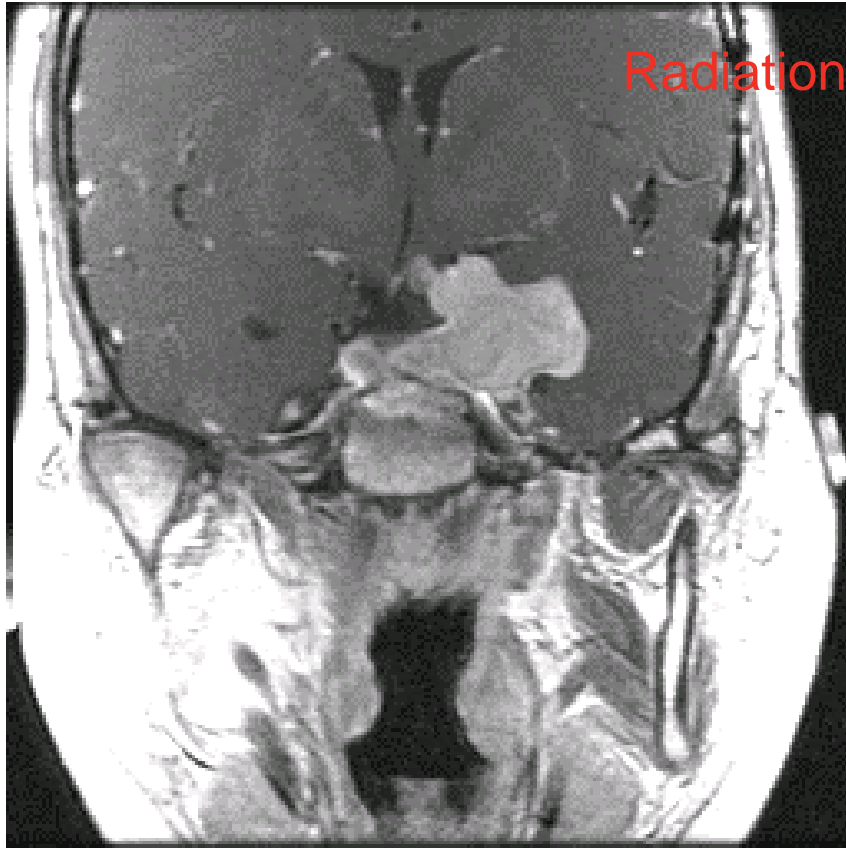


Table 1 Hypothalamic–pituitary axis dysfunction after cranial radiotherapy.

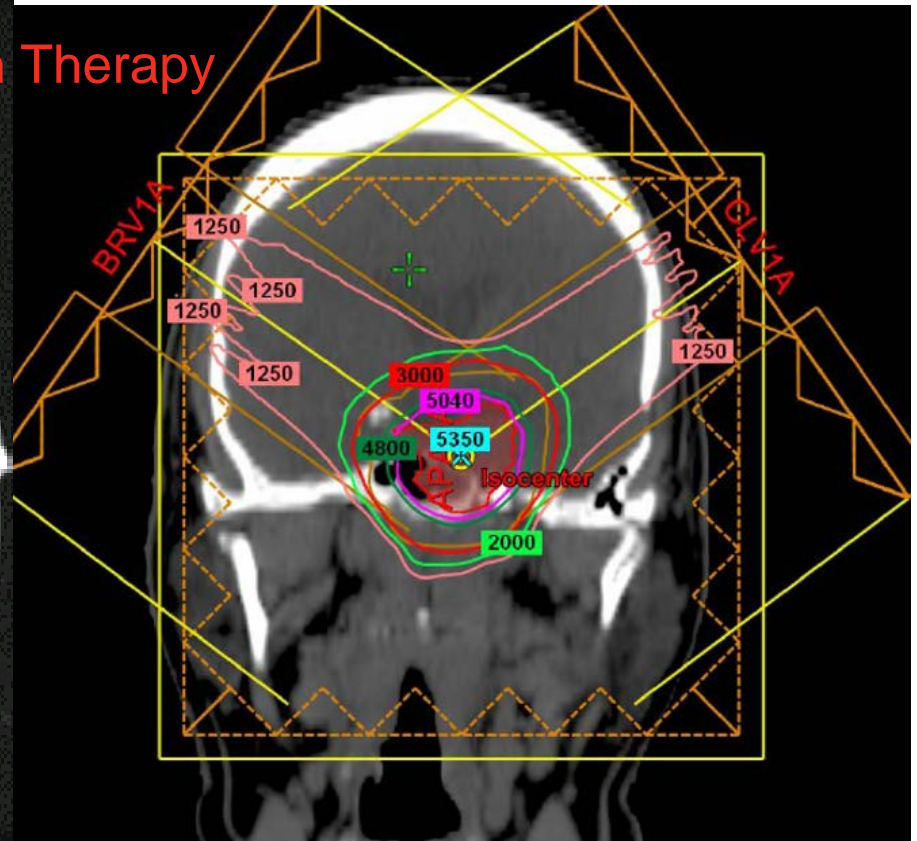
Condition treated	Radiation schedule	Hypothalamic–pituitary axis dysfunction
Leukemia and lymphoma	Fractionated TBI (7–16 Gy)	Isolated GHD, mostly in pubertal children
Leukemia and lymphoma	Fractionated prophylactic cranial irradiation (18–24 Gy)	Isolated GHD (<30% of children only) Pubertal GH insufficiency Compensated GHD in adults ^a Increased spontaneous cortisol secretion ^b Precocious puberty (girls only)
Nonpituitary brain tumors	Conventional fractionated cranial irradiation (30–50 Gy)	GHD (30–100%) Compensated GHD in adults ^a Precocious puberty (both sexes) Gonadotropin deficiency (>20% long-term) TSH deficiency (3–9% long-term) Subtle abnormalities in TSH secretion (30%) ACTH deficiency (3% long-term) Increased spontaneous cortisol secretion ^b Hyperprolactinemia (5–20%, mostly in women) ^c
Nasopharyngeal carcinoma and skull-base tumors	Conventional fractionated cranial irradiation (50–70 Gy)	GHD (almost all patients after 5 years) Gonadotropin deficiency (20–50% long-term) TSH deficiency (≤60% long-term) ACTH deficiency (27–35% long-term) Hyperprolactinemia (20–50%, mostly in women) ^c
Pituitary tumors	Conventional fractionated cranial irradiation (30–50 Gy)	GHD (almost all patients after 5 years) Gonadotropin deficiency (≤60% after 10 years) TSH deficiency (≤30% after 10 years) ACTH deficiency (≤60% after 10 years) Hyperprolactinemia (20–50%, mostly in women) ^c

Conventional XRT

Stereotactic Radiosurgery



Radiation Therapy



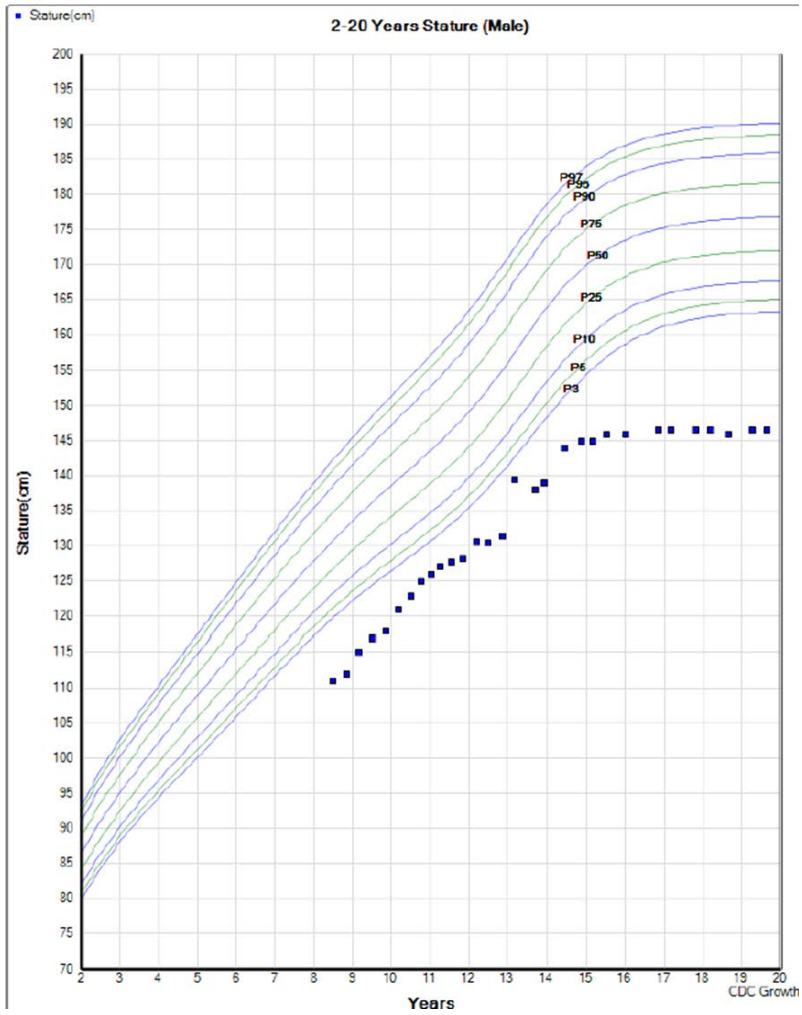
Proton Therapy

Growth and Final Adult Height

- **Growth disturbance common and multifactorial**
 - Poor Nutrition
 - GH deficiency
 - Illness in general
 - Growth velocity is diminished during all phases of therapy for childhood ALL--likely true for any tumor
 - Use of glucocorticoids
 - Other endocrinopathies (hypothyroidism, hypogonadism)
- Risk highest in survivors exposed to cranial or craniospinal RT, particularly those **diagnosed <10 years**
 - Adult short stature
 - 3-fold increase with XRT doses from 20 to 59 Gy
 - 6-fold increase with XRT doses from >59 Gy
- Spinal RT can directly damage the epiphyses and lead to disproportionate growth and short stature (late puberty growth failure)

GH Deficiency-A Common Sequela

- Directly related to dose of XRT and inversely related to age of exposure
- Clinical presentation may be subtle and may be manifested only by a diminished pubertal growth spurt
 - IGF1 levels may be normal
 - Be alert for concomitant precocious puberty, which may cause apparently normal growth
 - Obesity may also normalize growth with a disproportionate BA advance



GH RX and Risk of Primary Tumor Recurrence

Table 2. Multivariate Analysis of Risk of Disease Recurrence in Patients Treated With GH by Initial Diagnosis⁴⁰

Diagnosis	RR	95% CI	P
CNS tumors	0.31	0.13 to 0.77	.01
Medulloblastoma	0.13	0.02 to 0.94	.04
Astroglial	0.98	0.35 to 2.75	.96
Ependymoma	0*	0 to 13	.41
Germ cell	†		
Acute leukemia	0.85	0.12 to 6.14	.87
Rhabdomyosarcoma	0 ¹	0 to 4	.31
Neuroblastoma	0 ¹	0 to 35	.73

Abbreviations: GH, growth hormone; RR, relative risk.

*No recurrences occurred after GH therapy in patients in these diagnostic groups and, thus, the RR estimate is 0. The 95% CIs are calculated using the offset method in the time-dependent Cox model.

†No recurrences occurred in either the GH- or non-GH-treated groups, therefore, the RR cannot be determined.

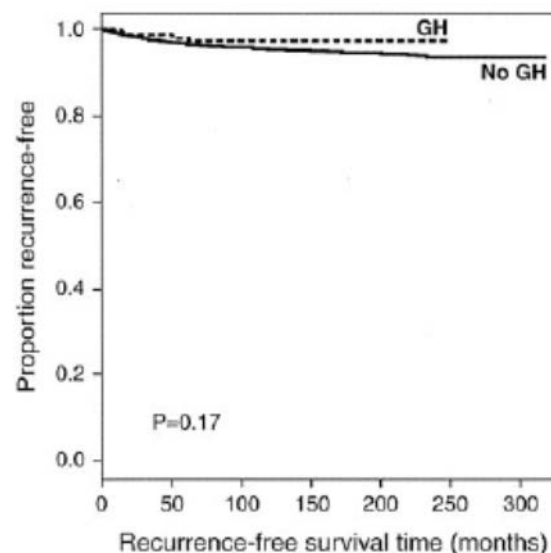


FIG. 1. The proportion of survivors who did not experience a recurrence of their primary cancer. Survivors treated with GH are compared with survivors who never received GH treatment.

Covariate	RR (95% CI)	P
GH		0.65
No	1.00	
Yes	0.83 (0.37–1.86)	

Diller L et al. J Clin Onc 27(14) 2009.

Sklar CA et al. JCEM 87, 2002:3136–3141

Abnormal Puberty

- Girls may be more sensitive
- The spectrum ranges from CPP to gonadotropin deficiency to both
 - Lower XRT doses (PP, girls)
 - Higher doses (girls and boys; CPP, HH, or both)
- Rethink standard definitions of CPP (Is this child too short to be entering puberty?)

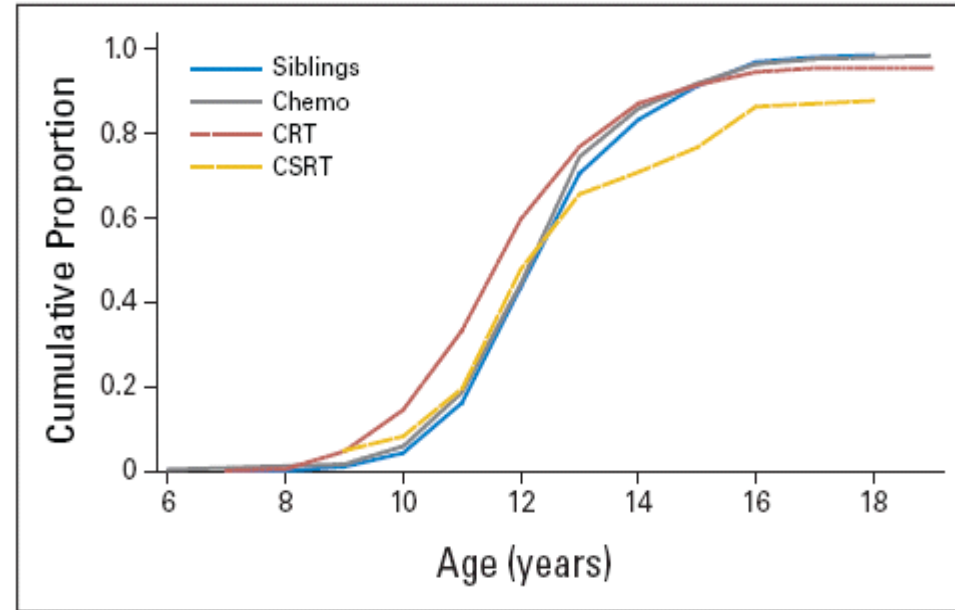


Fig 10. The proportion of women who achieve menarche over time, adjusted for ethnicity, birth year, and abdominal radiotherapy. Compared with siblings, survivors treated with chemotherapy only (chemo) did not report menarche earlier ($P = .76$), in contrast to those treated with cranial radiotherapy (CRT; $P < 0.01$). Craniospinal radiotherapy (CSRT) was associated with delayed menarche compared with siblings ($P < .01$).

Central Hypothyroidism

- Major Risk
 - Radiation dose ≥ 30 Gy
- Diagnosis difficult to make (particularly when mild)
- Can occur as an isolated event
- Low threshold for treatment
 - Rule out concomitant adrenal insufficiency

Secondary Adrenal Insufficiency (SAI)

➤ Occurs less frequently than other endocrinopathies

➤ **Symptoms**

- Anorexia/FTT
- Fatigue
- Unexplained Hypotension, Dizziness
- Nausea/Vomiting, Abdominal Pain
- Hyponatremia, hyperkalemia, hypoglycemia (less frequent)



Secondary Adrenal Insufficiency (SAI)

➤ Risk Factors

- Radiation to the brain, especially in doses of 30Gy (3000 cGy) or higher, including the following fields:
 - Cranial (whole brain or focal to the central area of the brain, near the HPA)
 - Craniospinal (CSI)
 - Nasopharyngeal (nose and throat)
 - Oropharyngeal (mouth and throat)
 - Orbital
 - Eye
 - Ear
 - Infratemporal (midfacial area behind the cheekbones)
- Exogenous steroids (glucocorticoids, megestrol)
- Surgical removal of the pituitary gland
- CNS tumors



SAI - Management

➤ Treatment

- PO medication: Hydrocortisone – BID - TID dosing

➤ Stress dose

- When the body is under stress, a higher HTC dose may be indicated

➤ Early recognition of symptoms



SAI - Screening

- Evaluate yearly for up to 15 years post-radiation, in pts who received >30 Gy (or as clinically indicated)
 - Random 8am cortisol level
- Factors of misdiagnosis or insufficient screening
 - Insufficient length of follow-up and testing methods
 - Relapse
- Improve screening



Hyperprolactinemia

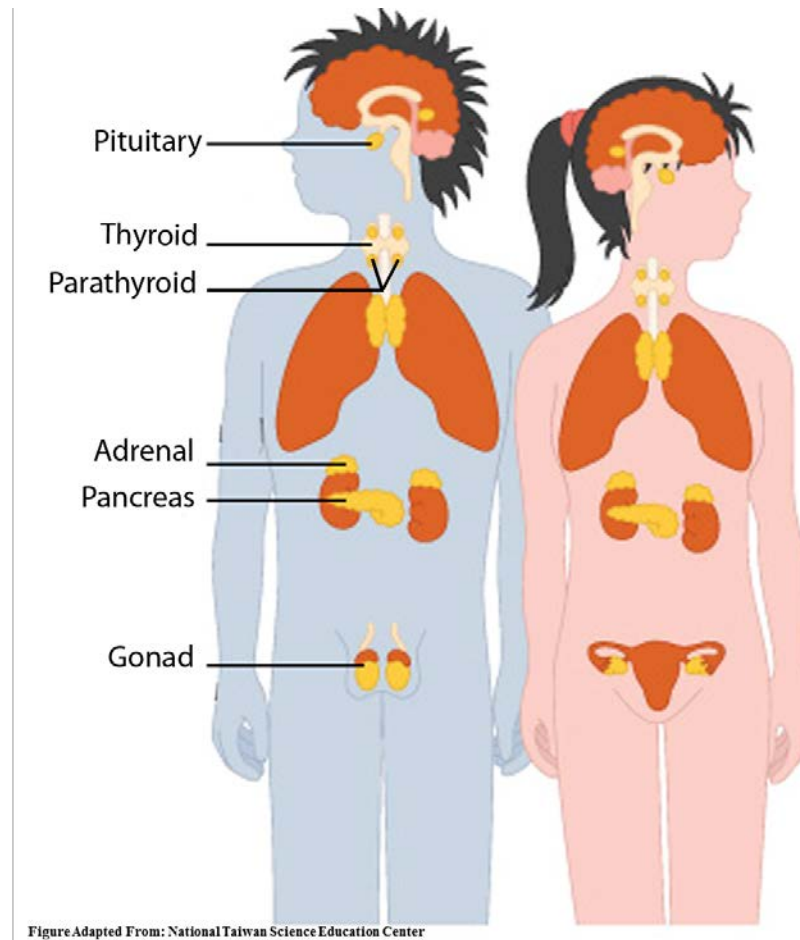
➤ Major Risk

- Radiation dose \geq 40 Gy

➤ Elevated prolactin levels

- Galactorrhea in females
- Hypogonadism in either gender

The Thyroid



Endocrine Sequela: The Thyroid

➤ Possible Endocrinopathies

- Hypothyroidism
- Hyperthyroidism
- Benign Thyroid Nodules
- Thyroid carcinoma (PTC)

➤ Risk Factors

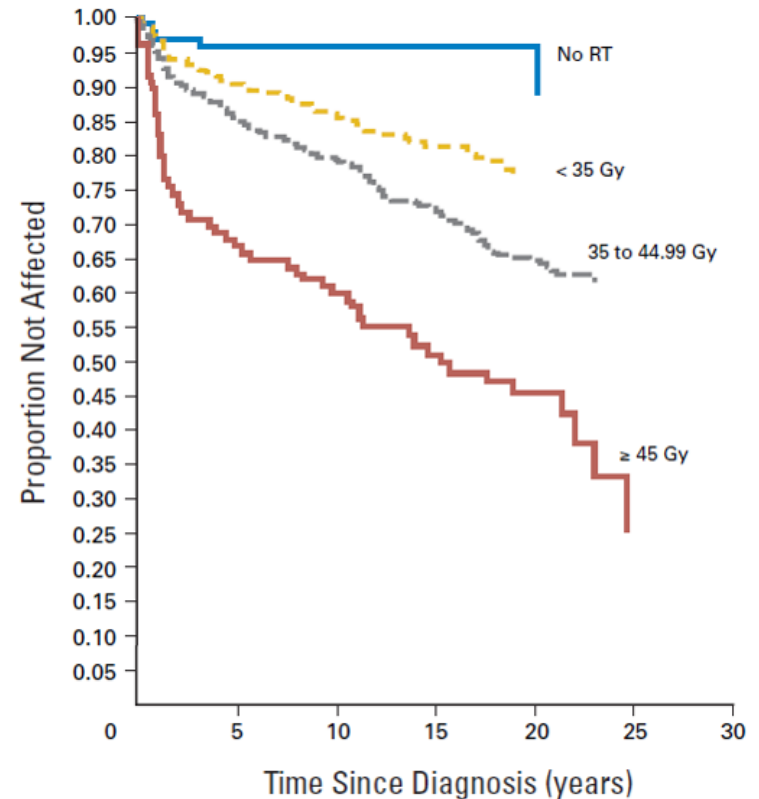
- Radiation to the head and neck
- Surgery
- Younger age of treatment
- Female Gender

➤ Surveillance

- Monitor TFTs
- Perform annual thyroid examination
 - No routine ultrasound.

Hypothyroidism

- Most common thyroid Dx
- Direct damage to thyroid from XRT
- Hodgkin lymphoma, CNS tumor & soft tissue sarcoma survivors
- Chemo alone not a risk



Hypothyroidism

- Major Risk Factors
 - Higher radiation dose
 - Female Gender
 - Surgery (+/- involving the thyroid gland)
- Not clear risk factors
 - Age
 - Chemotherapy

Hyperthyroidism

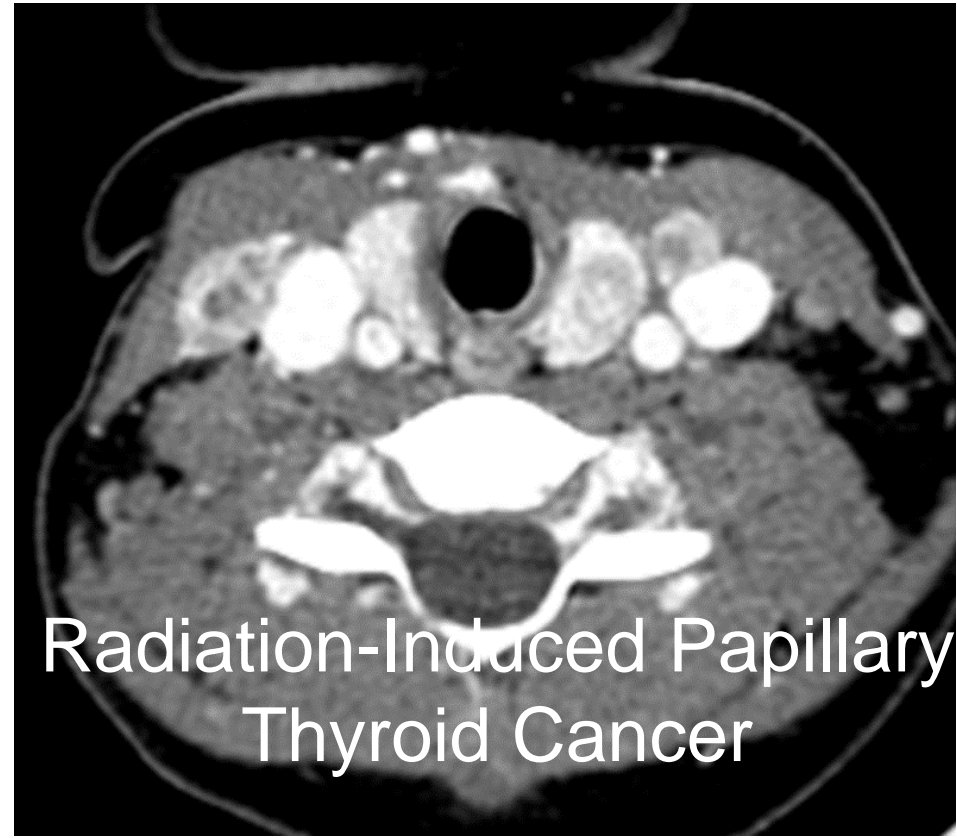
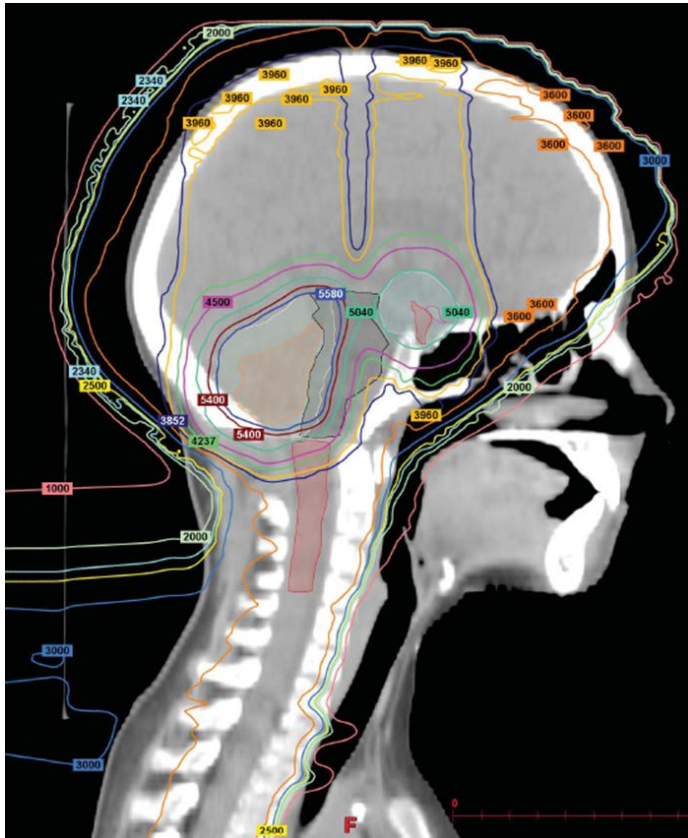
- XRT major risk factor
 - Thyroid dose ≥ 30 Gy
 - ?Radiation affects immune response
- 5% rate in a large HD study
- Mean Dx 8 years after cancer Dx

TABLE 1. Incidence of thyroid abnormalities in HD survivors compared to controls

Abnormality	HD survivors		Controls		RR (95% CI)	P value
	Cases	Rate/1000 py	Cases	Rate/1000 py		
Underactive	156	0.6	20	0.6	17.1 (12.5–24.2)	<0.0001
Overactive	82	1.6	13	0.2	8.0 (4.6–15.1)	<0.0001
Nodules	146	2.9	7	0.1	27.0 (13.6–63.9)	<0.0001

py, Person-years.

Thyroid Neoplasia



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.

Screening for Thyroid Disease

COG LTFU guidelines

Thorough Review of Systems

Thyroid Dysfunction

- Annual TFT's
- More frequently during periods of rapid growth

Thyroid Neoplasia

- Annual PE
- US and FNA if palpable nodule

H/O cervical radiation or systemic exposure to radiation
(e.g. 131 MIBG)

Thyroid Neoplasia Screening via US

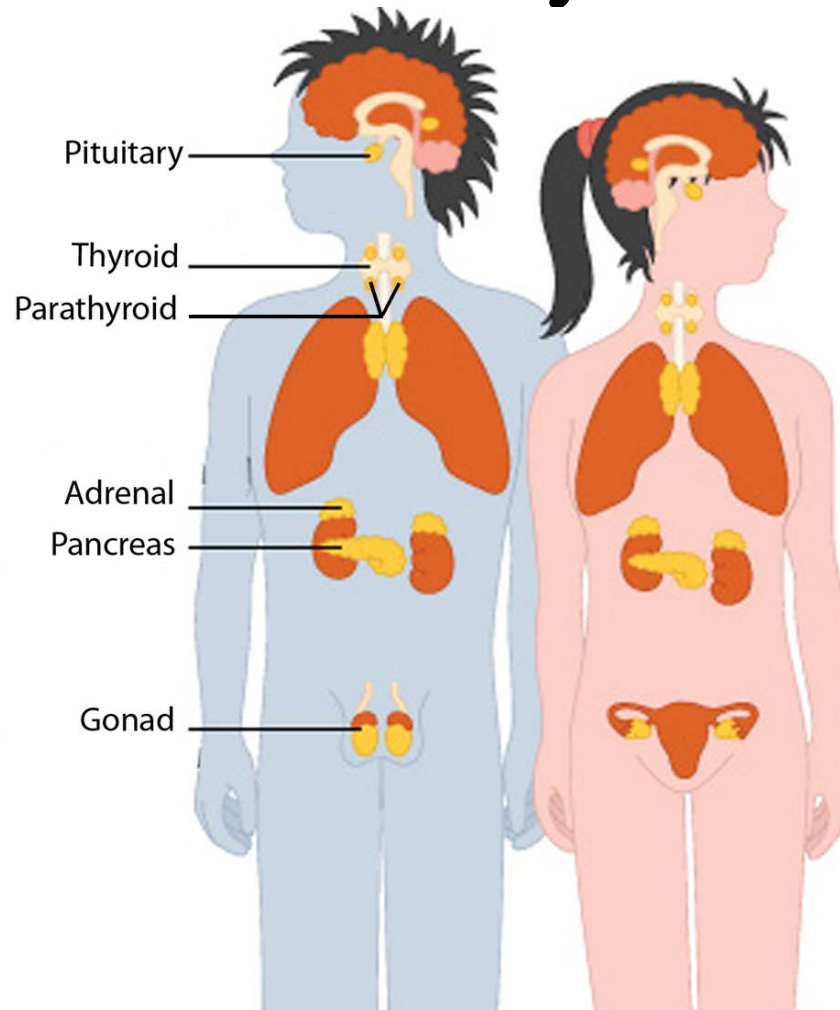
PROs

- Early Dx of Thyroid Cancer
 - Identifies disease when curable
 - ??prevent death from thyroid cancer

CONs

- Incidental thyroid findings common
- Benign thyroid disease >>> cancer
- ↑ ↑ anxiety among patients/families (and health care providers)
- Potential over-testing & over-treatment

The Parathyroids



Endocrine Sequelae: The Parathyroids

➤ Possible Endocrinopathies

- Primary Hyperparathyroidism
- ?Hypoparathyroidism

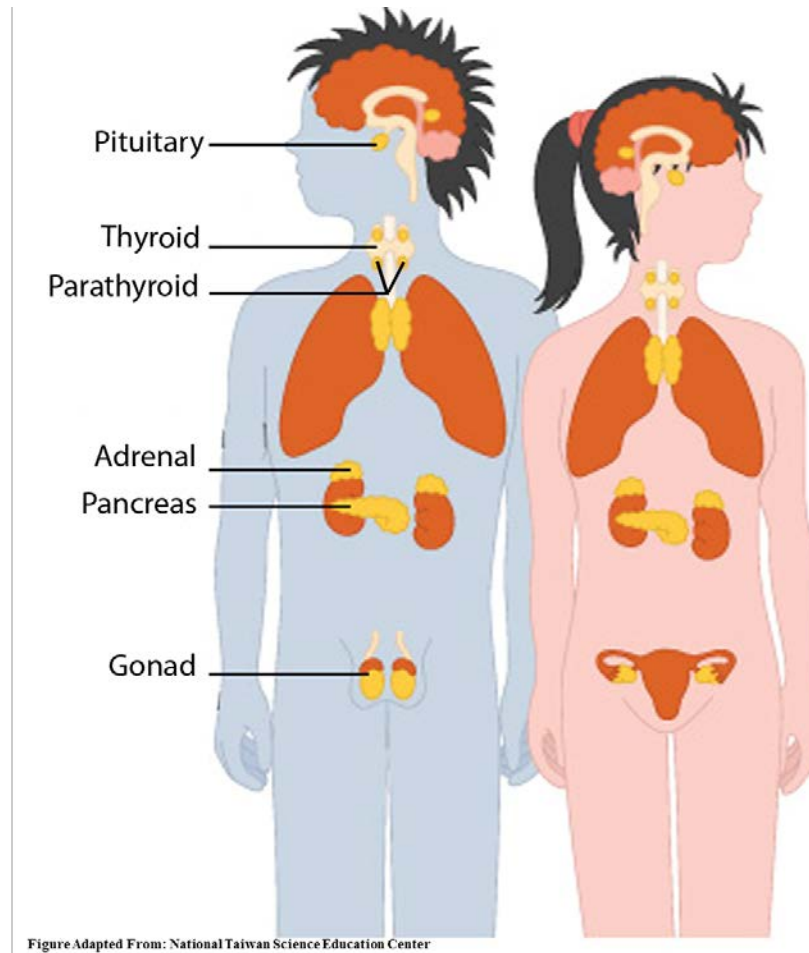
➤ Risk Factors

- Radiation
- Younger age of treatment

➤ Surveillance

- None recommended during childhood as the latency period is quite long (>25 yrs)

The Pancreas



Endocrine Sequelae: Metabolism

➤ Possible Endocrinopathies

➤ Risk Factors

- Previous ALL, CNS tumor, stem cell transplant
- Decreased physical activity/Inability to exercise
- Radiation ($\geq 18\text{Gy}$) and/or surgery impacting neuroendocrine axis; TBI
- Younger age (<4 years) at radiation
- Chronic glucocorticoid use
- Genetic background

➤ Surveillance

- Monitor weight, BMI, and blood pressure annually
- Evaluate for other co-morbid conditions, including dyslipidemia, hypertension and impaired glucose metabolism.

Risk of DM in the CCSS

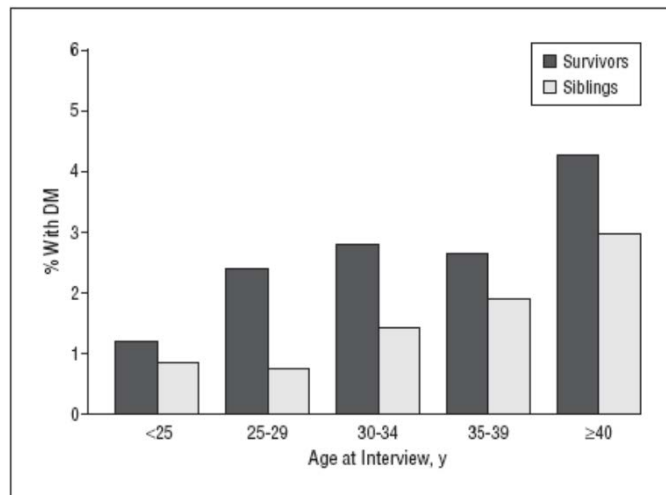
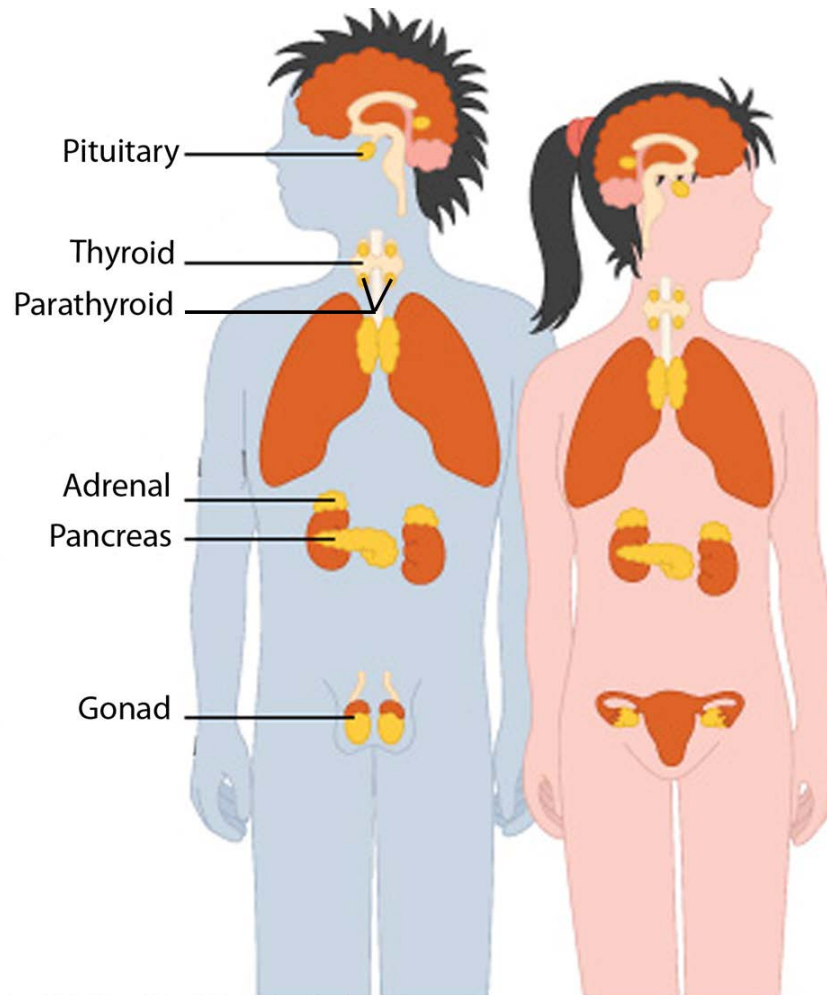


Figure 1. Percentage of childhood cancer survivors and siblings with diabetes mellitus (DM) by age at interview.

Childhood cancer survivors treated with TBI or abdominal irradiation have an increased risk of diabetes that appears unrelated to body mass index or physical inactivity.

The Gonads



Endocrine Sequelae: The Gonads

➤ Possible Endocrinopathies

- Primary Ovarian Failure - Low sex steroids and germ cell failure
- Primary Testicular Failure - Germ cell failure \pm low sex steroid production

➤ Risk Factors

- Radiation

Girls: Older age of radiation

- Prepubertal female: Radiation dose ≥ 10 Gy
- Pubertal female: Radiation dose ≥ 5 Gy

Boys: Age not as critical

- > 12 Gy testicular exposure may cause hormonal dysfunction
- Up to 6 Gy azoospermia may be transient; > 6 Gy azoospermia is likely permanent

Both: Potentiating effects of cyclophosphamide conditioning for BMT

- Surgery
- Chemotherapy: Alkylating agents

➤ Surveillance

- Monitor pubertal development q 6-12 months depending on age of patient
- LH/FSH & either estradiol or testosterone levels as clinically indicated in patients with delayed/arrested puberty (age 13 girls, age 14 boys)

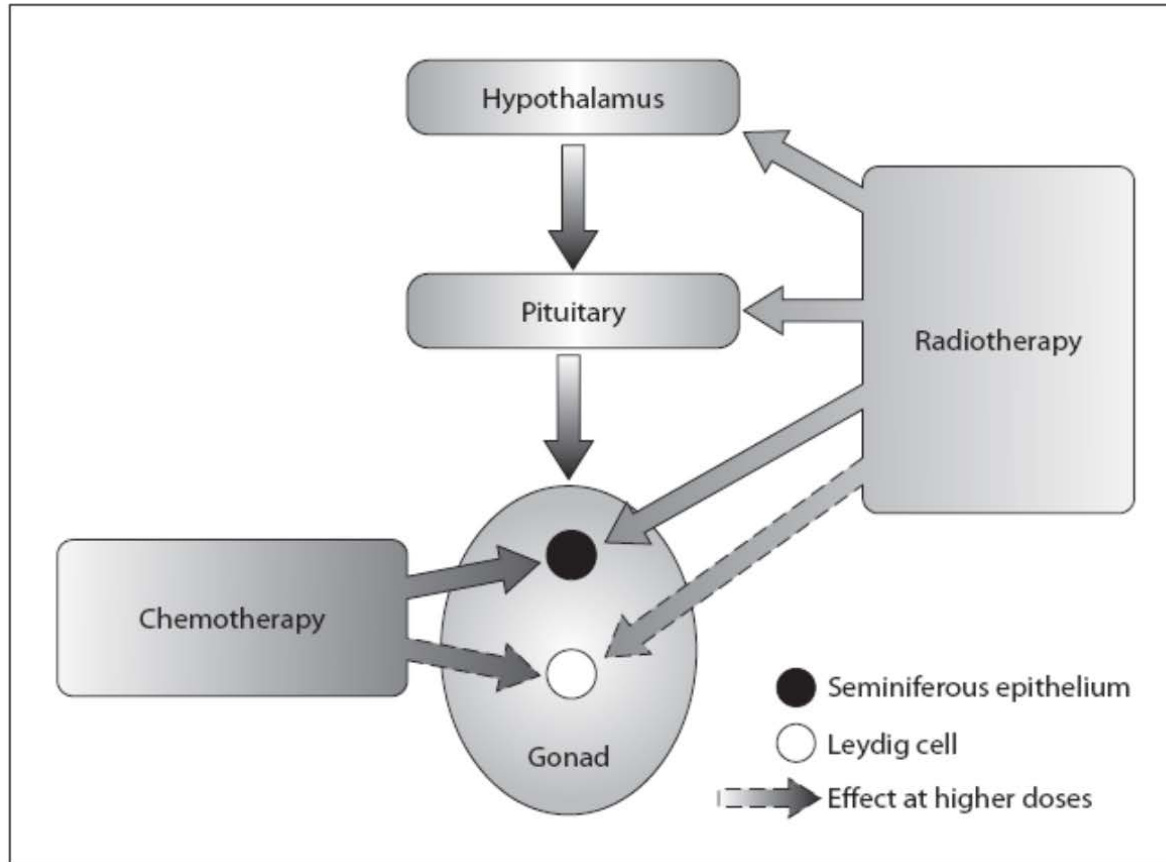
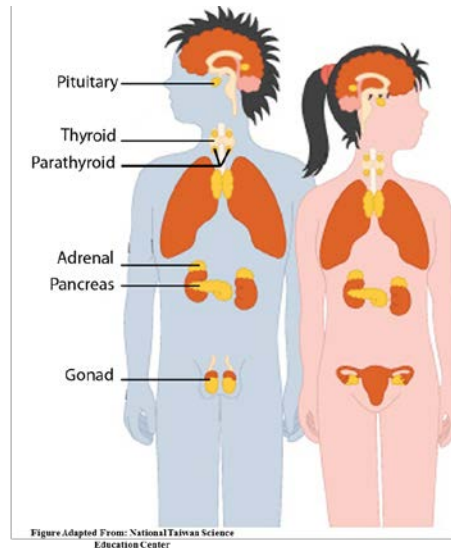


Fig. 8. Potential targets for impairment of fertility following chemotherapy and/or radiotherapy.

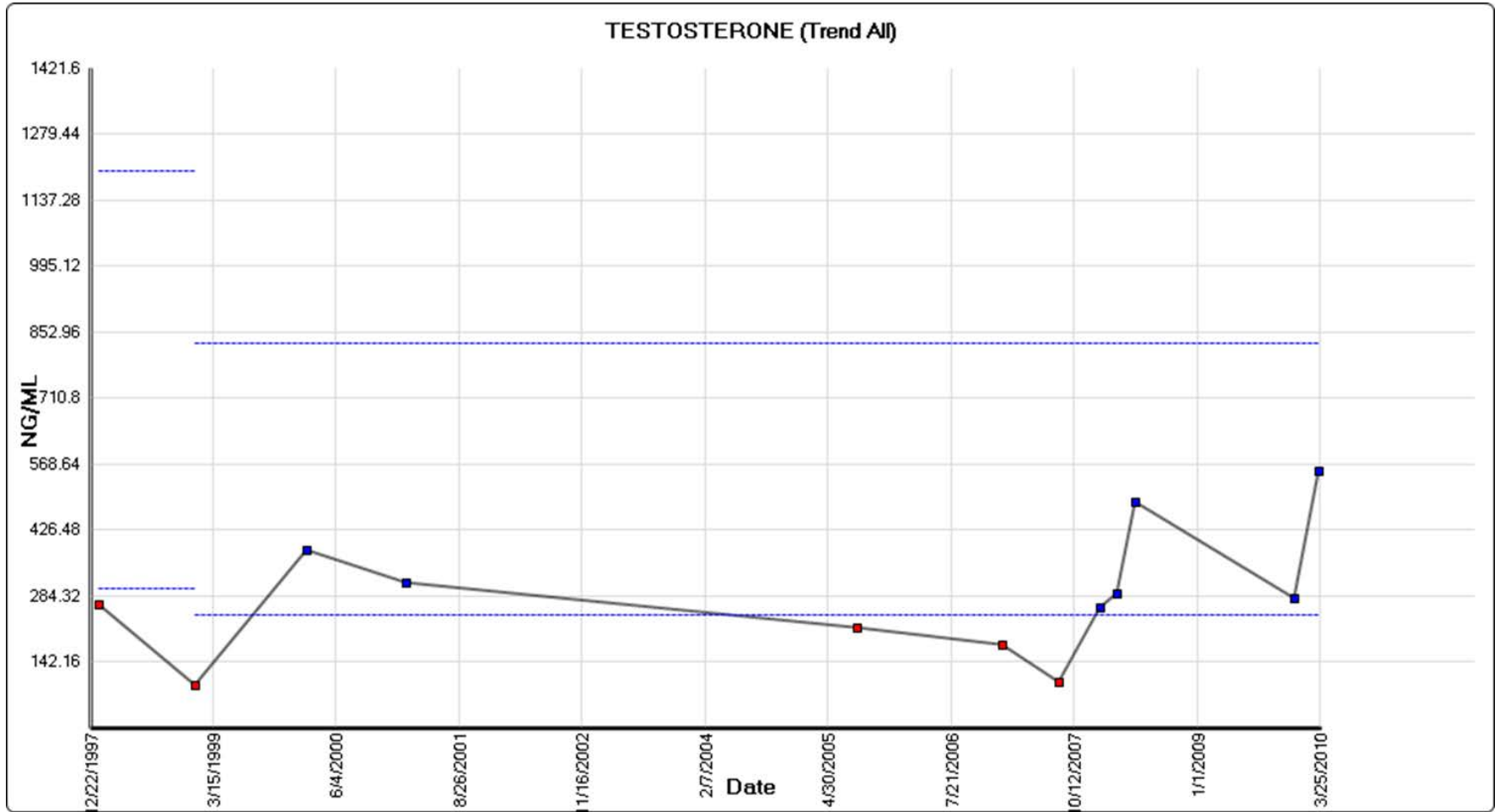
Case #1, August 2005, Age 19

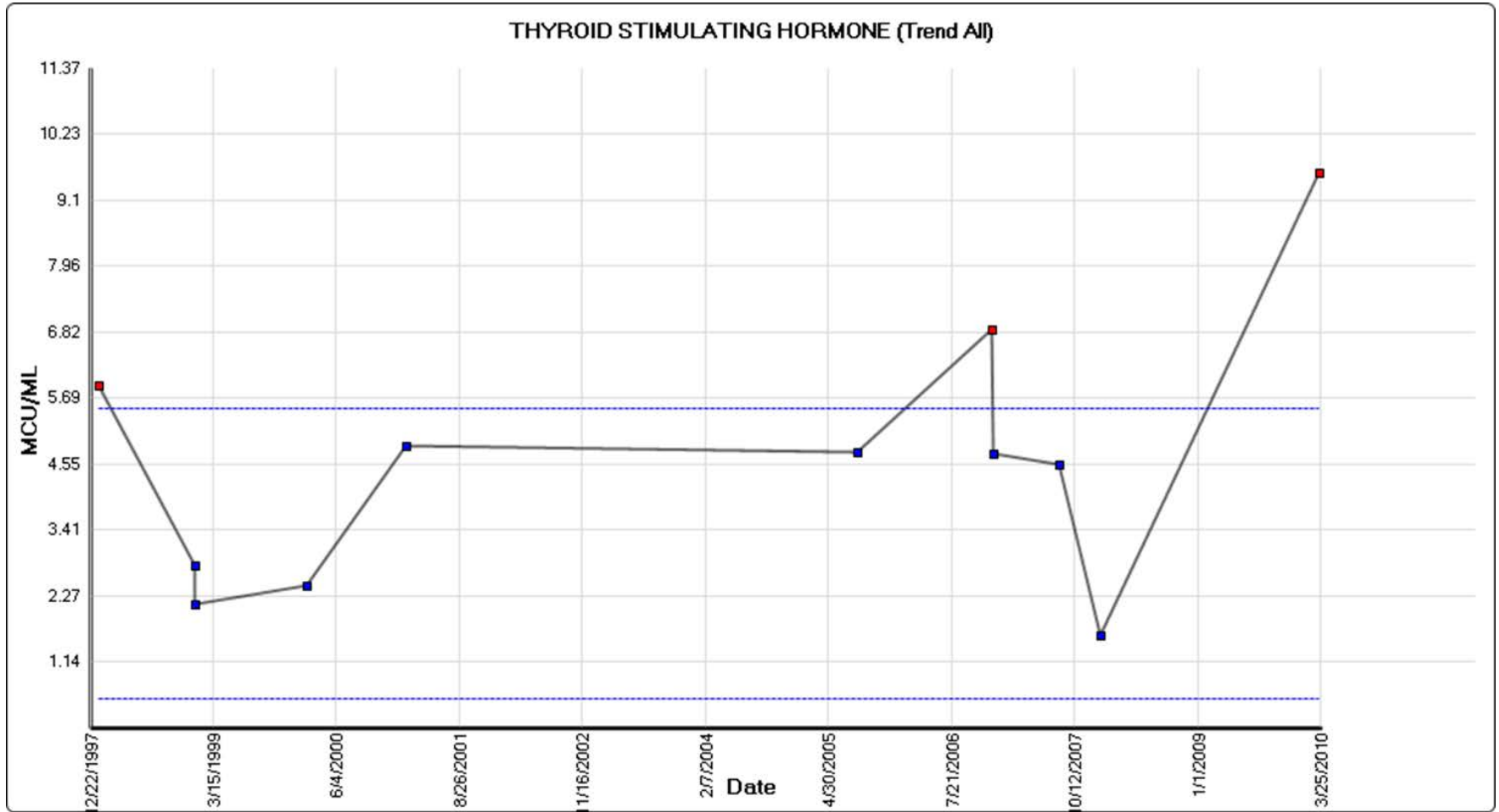
What endocrinopathies is this patient at risk for?



Case #1 August 2005 Age 19

T4 (THYROXINE),FREE	0.8	NG/DL	(0.9-1.8)
TSH	9.56	MCU/ML	(0.50- 5.50)
IGF-1	287	ng/mL	(182-780)
CALCIUM	9.8	MG/DL	(8.4- 10.2)
PHOSPHORUS	3.8	MG/DL	(2.8- 4.6)
GLUCOSE	99	MG/DL	(70- 110)
LH	19.3 H	MIU/ML	(1.7- 11.2)
FSH	20.7	MIU/ML	(1.0- 42.5)
TESTOSTERONE	180L	NG/DL	(241- 827)





What endocrinopathies can be identified?

What do you do now?

Case #2

12 yo Caucasian female with history of Wilms tumor

Age at diagnosis: 22 months

Treatment included:

- Chemotherapy - Vincristine, actinomycin-D, and Adriamycin.
- Radiation - Abdominal (unknown dose)
- Surgery - Nephrectomy, liver biopsy and exploratory laparotomy

Chief complaint: short stature

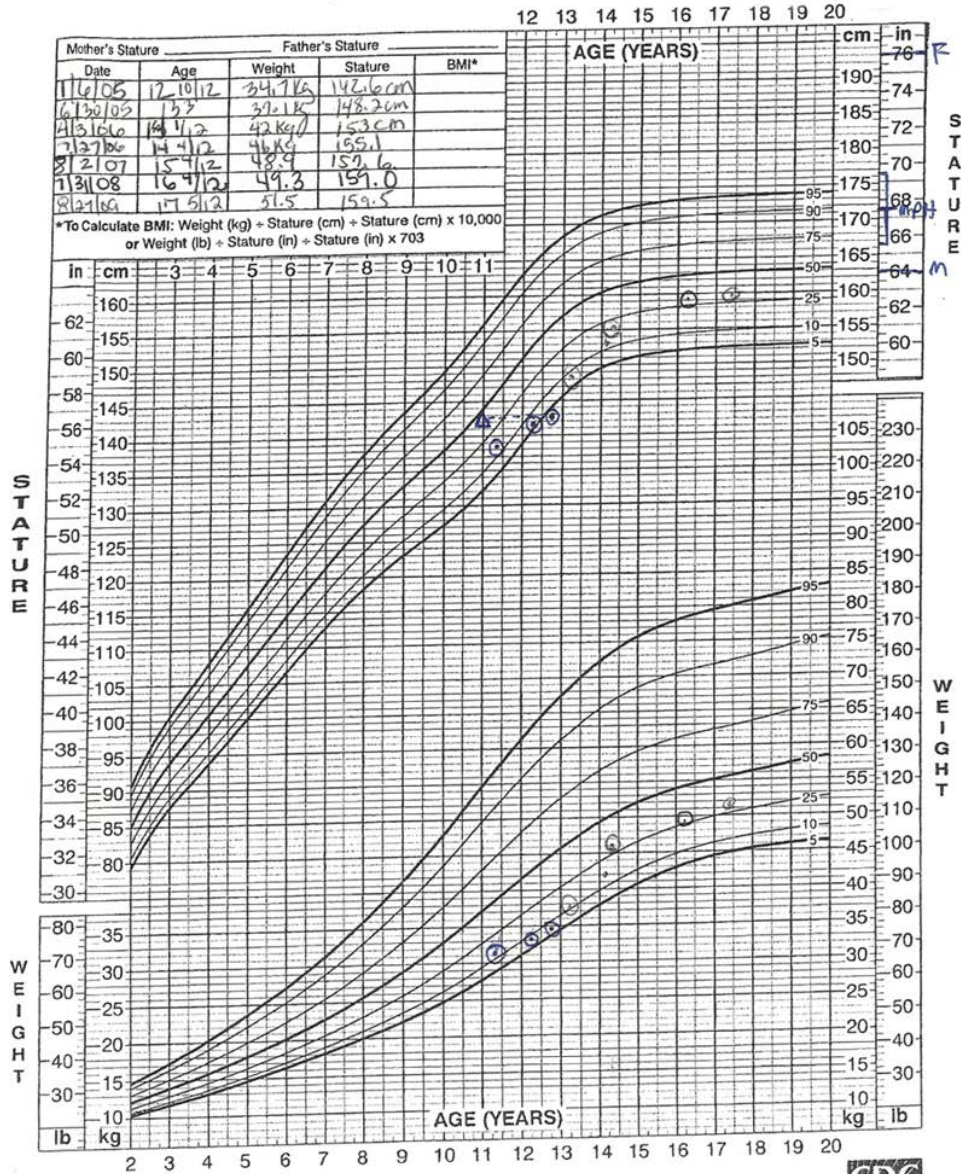
Physical examination:

- Height 143 cm (~3%ile) (MPH at 90%ile)
- Tanner I breast; Tanner II PH
- BA < CA by almost two years

What endocrinopathies is this patient at risk for?

Stature-for-age and Weight-for-age percentiles

Case #2



FSH 158.6 MIU/ML
Postmenopausal 25.0 -160.0

IGF-1 270 NG/ML
(261- 1096)

TSH 2.27 MCU/ML
(0.50- 5.50)

LH 34.5 MIU/ML
Postmenopausal 14.4 -62.2

Free T4 1.0 NG/DL
(0.9- 1.8)

IGFBP 3 1.8 L mg/L
2.2-4.2

Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>

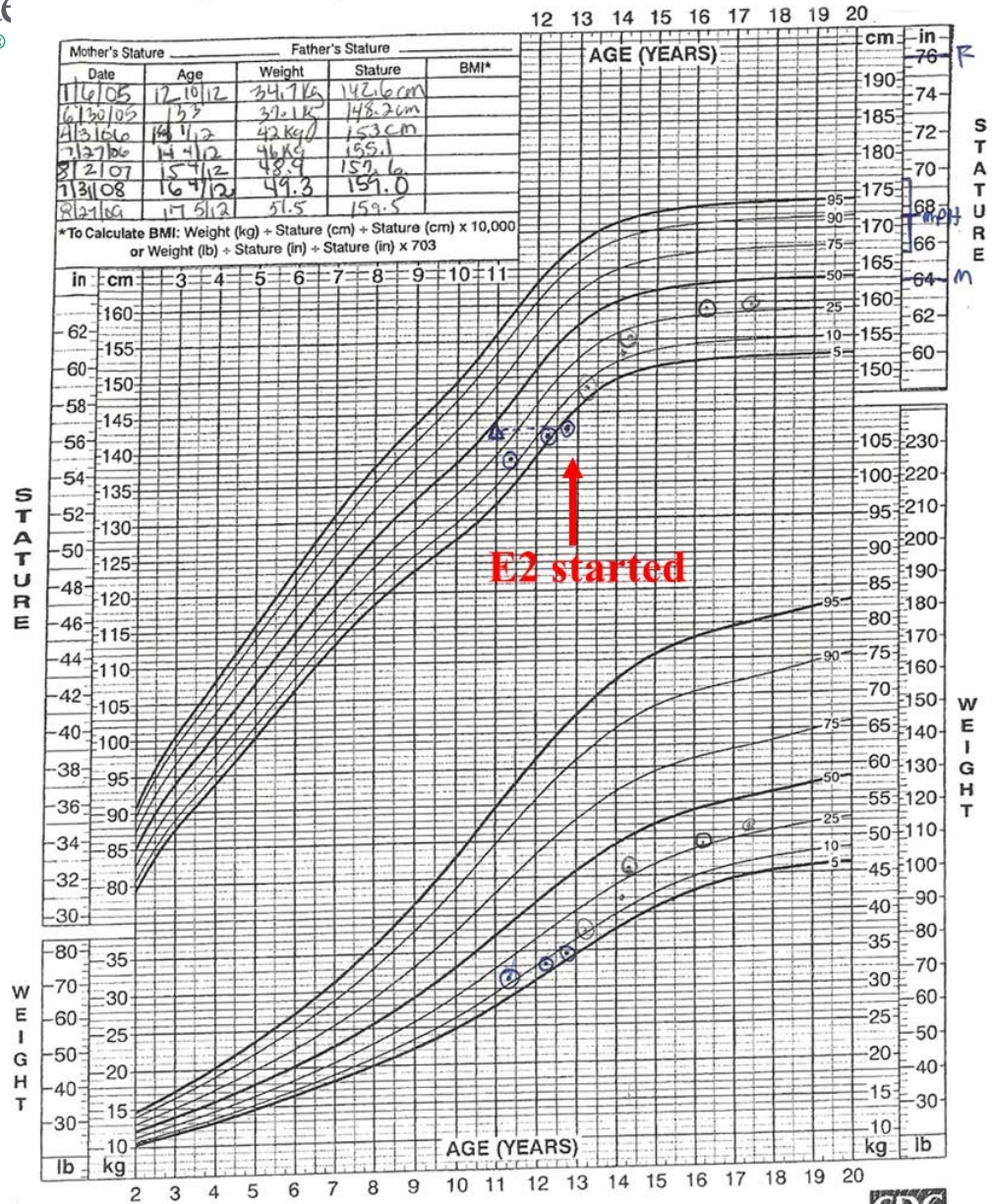


Case #2

What is the diagnosis?

How would you treat?

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles



Published May 30, 2000 (modified 11/21/00).
 SOURCE: Developed by the National Center for Health Statistics in collaboration with
 the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>

Case # 3

13yo Asian-American female with history of multiply relapsed medulloblastoma

Age at diagnosis: 6 years

Treatment included:

Initial Diagnosis

- Chemotherapy – Vincristine, Cisplatin, Cyclophosphamide, Lomustine
- Radiation – CSI 18 Gy w/ PF boost to 55.8 Gy

1st Relapse

- Chemotherapy – Etoposide, Sorafenib
- Re-irradiation – CSI 24 Gy

2nd Relapse

- Chemotherapy – Carboplatin
- Re-irradiation – Focal to PF tumor in brain 30 Gy, followed

3rd Relapse

- Chemotherapy – Temodar combined with oral immunotherapy
- Re-irradiation – Focal to spinal cord tumors to 30 Gy

4th Relapse

- Chemotherapy – Cyclophosphamide and Etoposide, combined with oral immunotherapy

Presentation: extreme fatigue, lactic acidosis, hypotension, hyponatremia

H&P:

- Height 121.8 cm (~25thile)
- Weight 21.6 kg (<5th %ile)
- Hx of anorexia/FTT
- Intermittent dyspnea
- Somnolence

What endocrinopathies is this patient at risk for?

Case # 3

What is the diagnosis?

How would you treat?

Conclusions

- Endocrine late effects occur in 50-60% of childhood cancer survivors
- It may take years-decades to recognize a late effect
- Advanced Practice Registered Nurses are uniquely positioned to follow the growing population of cancer survivors.

QUESTIONS?