Endocrinological Complications of Radiotherapy

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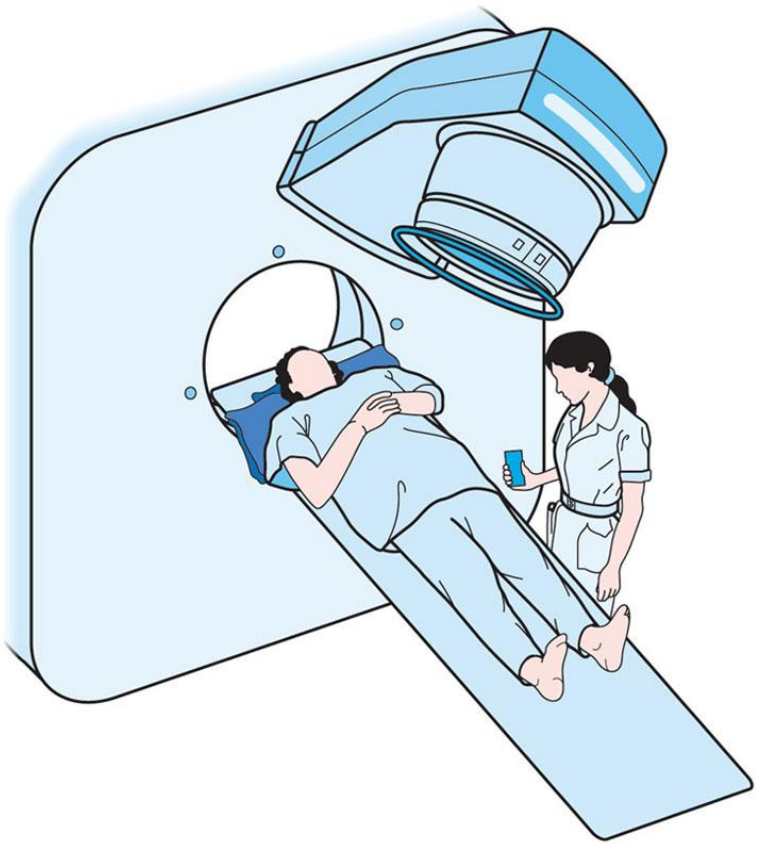


Objectives

- Discuss the main endocrine complications of radiotherapy including:
  - Disorders of the hypothalamic–pituitary axis
  - Disorders of pubertal development
  - Thyroid dysfunction
  - Gonadal dysfunction
  - Decreased bone mineral density,
  - Obesity

Radiotherapy Dose

- The amount of radiation used in photon radiation therapy is measured in gray (Gy), and varies depending on the type and stage of cancer being treated
- For curative cases, the typical dose for a solid epithelial tumor ranges from 60 to 80 Gy, while lymphomas are treated with 20 to 40 Gy

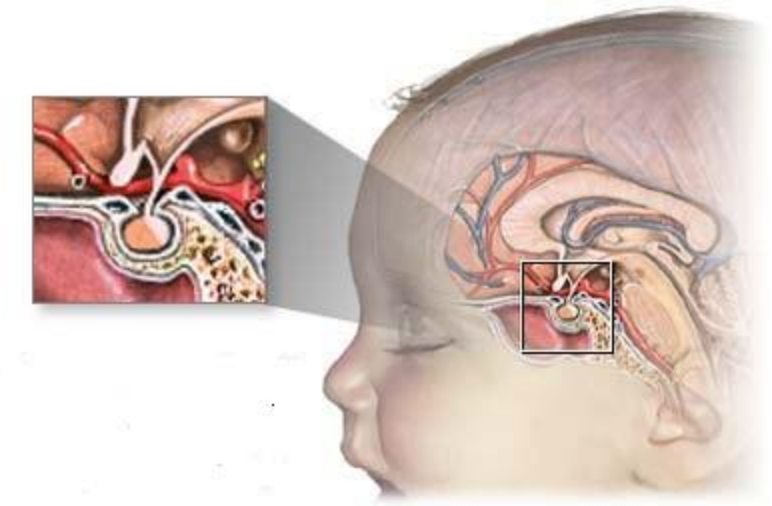
Introduction

- Major advances in the care of children diagnosed with cancer have resulted in a significant increase in survival rates over the past 30 years
- The improvement in survival rates is attributed to the use of cancer treatments combining surgery, multiagent chemotherapy, and radiotherapy, in addition to remarkable advances in supportive care

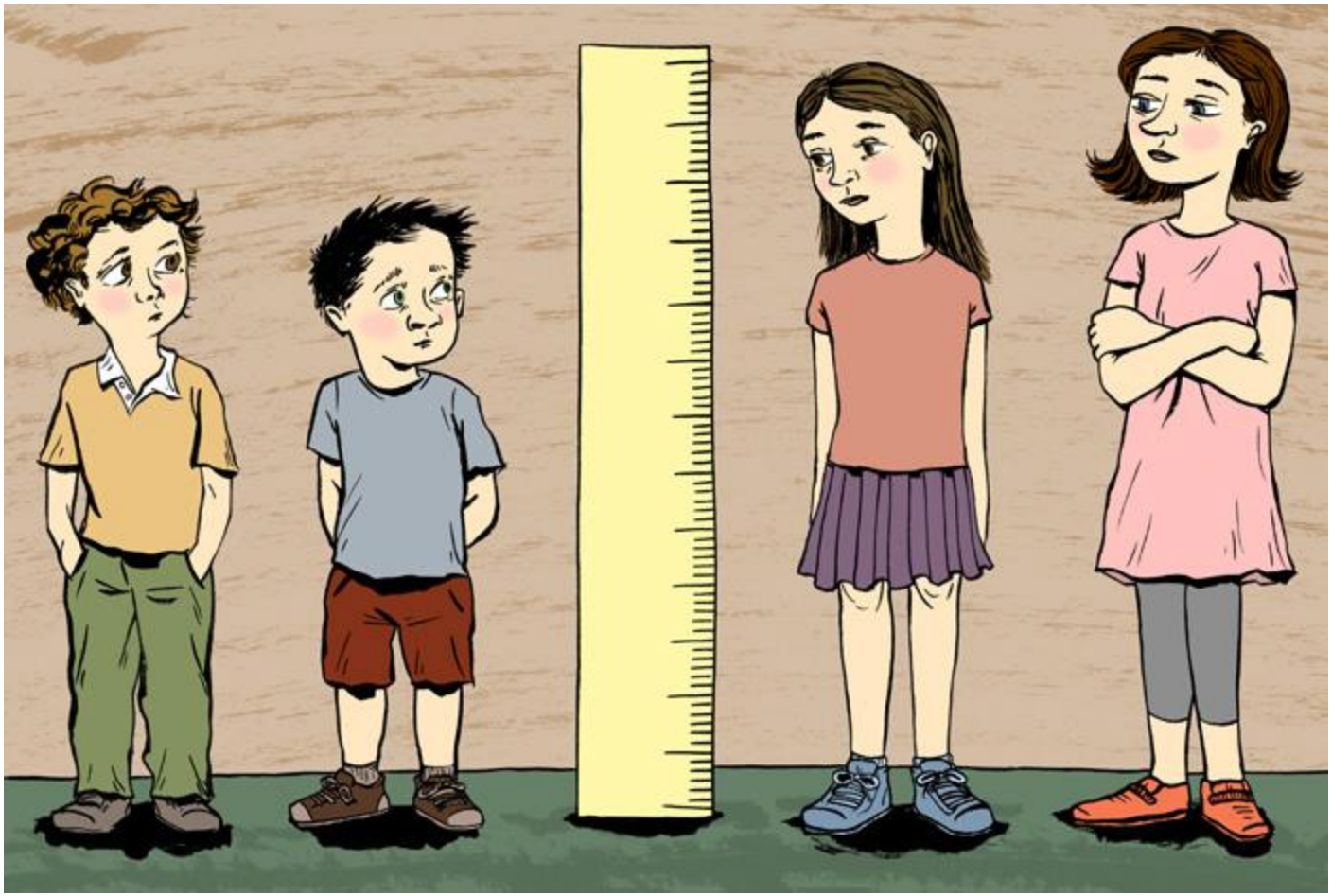
- Most endocrine complications are the result of prior cancer treatments, especially radiotherapy
- Approximately 70% of pediatric cancer survivors will develop at least one medical complication or disability by 30 years from diagnosis, most of which can be attributed to their previous cancer treatments

(Oeffinger *et al*. 2006)

Disorders of the hypothalamic–pituitary axis



GH deficiency



Growth failure

- Impaired linear growth resulting in adult short stature occurs frequently in childhood cancer survivors, particularly in individuals treated at a young age
- Both endocrine and non-endocrine factors can contribute to growth retardation
- Endocrine factors include GH deficiency, central precocious puberty and primary hypothyroidism
- The impact of non-endocrine factors mainly represented by the direct damage to the growth plate, mainly of the vertebrae, by high-dose radiotherapy, as following total body irradiation (TBI)
  - result is a skeletal dysplasia where the sitting height is more affected than the standing height

Shalet *et al*. 1987, Clayton & Shalet 1991*a*,*b*, Brauner *et al*. 1993, Thomas *et al*. 1993), (Gleeson *et al*. 2003, Gurney *et al*. 2003*b*).

GH deficiency

- Is the most common and frequently deficit to develop after cranial irradiation

  (Sklar & Constine 1995, Laughton *et al*. 2008)
- Hypothalamus, is more sensitive to irradiation than the pituitary, and can be affected by low doses of irradiation (i.e. 18 Gy of conventional fractionated radiotherapy

  Costin 1988, Oglivy-Stuart *et al*. 1994)
- The pituitary gland itself appears to be damaged only at higher doses of irradiation

- GHD should be suspected in patients with a decreased growth velocity observed over a 6-month time interval (Reiter & Rosenfeld 2003)
- Measurement of the sitting height in patients who received irradiation to the spine is helpful for the diagnosis and monitoring of radiation-induced skeletal dysplasia

  (Clayton & Shalet 1991*a*,*b*)
- Pubertal staging is important as concurrent precocious puberty can mask the clinical signs of GHD with seemingly normal growth rates owing to the inappropriate secretion of sex steroids
- Body weight and body mass index (BMI) are important markers of nutritional status that can influence linear growth

SAFETY OF GH THERAPY IN CANCER SURVIVORS

Given the anti-apoptotic, mitogenic, and proliferating properties of GH and IGF1, the safety of the use of GH in childhood cancer survivors has been the subject of large-scale studies

- GH replacement has been shown to improve final height prospects in childhood cancer survivors with GHD (Adan *et al*. 2000, Gleeson *et al*. 2003).
- Younger bone age at the beginning of GH replacement and higher doses of GH positively correlated with a better final height
- Children previously treated with radiation doses > 20 Gy to the spine respond less well to GH
- For the subset of patients with both GHD and precocious puberty, the combination of GH and GnRH agonist that temporarily suppresses puberty appears to improve final height outcome (Gleeson *et al*. 2003)

- The studies assessing the risk of tumor recurrence, largely confined to brain tumor survivors treated with GH, have consistently reported no increased risk associated with GH replacement therapy (Swerdlow *et al*. 2000, Packer *et al*. 2001, Sklar *et al*. 2002)
- There was no evidence for an increased risk of disease recurrence or death following GH replacement therapy in a report on 361 GH-treated individuals, including 122 survivors of acute leukemia and 43 survivors of soft tissue sarcomas (Sklar *et al*. 2002)
- However, the data suggested that treatment with GH may slightly increase the risk of a secondary solid tumor, especially in survivors of acute leukemia. (Sklar *et al*. 2002)
- Cancer survivors treated with GH may be at a higher risk of developing slipped epiphyses compared with children treated with GH for idiopathic GHD (Blethen & Rundle 1996)

Pubertal sequel of Radiation

- Cranial Radiation could affect HPG in either way either:
  - Precocious puberty
  - Delayed puberty

- Radiotherapy could rarely lead to gonadal failure

Pubertal sequel of Radiation

- Cranial irradiation at both lower doses (18–35 Gy) and higher doses (>35 Gy) is associated with the development of Precocious puberty, by presumably disrupting inhibitory cortical influences

  (Brauner *et al*. 1984, Constine *et al*. 1993, Oberfield *et al*. 1996, Chow *et al*. 2008, Armstrong *et al*. 2009).
- Risk factors associated with CPP following hypothalamic irradiation include female sex, young age at treatment, and increased BMI
  - (Ogilvy-Stuart & Shalet 1995, Oberfield *et al*. 1996)

Early Puberty

- In a study on CNS tumor survivors, early menarche (defined by the onset of menstrual cycles before 10 years of age) occurred in 14.5% of girls with a history of radiation to the hypothalamus–pituitary area, which was significantly more common than what was observed in siblings
- Risk factors for early menarche included radiation before the age of 5 years or with doses >50 Gy

(Armstrong *et al*. 2009).

Pubertal sequel of Radiation

- In contrast, radiation doses > 50 Gy are also associated with Hypogonadotropic hypogonadism within the context of combined hormonal pituitary deficiencies

(Lam *et al*. 1991, Constine *et al*. 1993, Armstrong *et al*. 2009).

Hypogonadotropic hypogonadism

- Insufficient LH and FSH secretion has been reported in childhood cancer survivors
- Deficits of LH and FSH secretion following irradiation of the hypothalamic–pituitary region occur less often than GHD, and generally only occur following doses to the sellar region, >30 to 40 Gy (Sklar & Constine 1995, Relander *et al*. 2000, Byrne *et al*. 2004, Armstrong *et al*. 2009, Green *et al*. 2009).

Gonadal Failure

Gonadal dysfunction

- In addition to the derangements related to gonadotropin secretion, childhood cancer survivors are at risk of gonadal dysfunction related to a direct insult to the testes or ovaries
- It is not common
- Most of the time due to chemotherapy, rather than radiotherapy

Testicular Failure

- In the testis, Germ cells and Sertoli cells form the seminiferous tubules where spermatogenesis takes place, and Leydig cells which are responsible for the production of testosterone
- Leydig cells lie in proximity to the basal compartment of the seminiferous tubules, where they can deliver high concentrations of testosterone, which are necessary for normal spermatogenesis
- Despite their interconnection, these two functional compartments are affected in different ways by cancer treatments

Defective spermatogenesis

- Impaired sperm production can occur at doses of radiation as low as 0.15 Gy
- If the dose is under 1–2 Gy, recovery is common
- At doses > 2 to 3 Gy, recovery of sperm production is rare (Meistrich *et al*. 1997)
- Germ cell dysfunction is present in essentially all males treated with TBI (Sanders *et al*. 1996)
- Azoospermia is the rule for patients studied in the first few years after treatment with TBI
- Recovery of germ cell function has occurred rarely and primarily following single-dose irradiation (Sklar *et al*. 1984, Sanders *et al*. 1996)

Ovarian failure

- Females receiving abdominal, pelvic, or spinal irradiation are at increased risk of ovarian failure, especially if both ovaries were within the treatment field

  (Horning *et al*. 1981, Damewood & Grochow 1986, Hamre *et al*. 1987, Clayton *et al*. 1989, Wallace *et al*. 1989*a*, Thibaud *et al*. 1992, Sklar *et al*. 2006, Chow *et al*. 2008).

- However, when ovarian transposition is performed prior to radiotherapy, ovarian function is retained in the majority of young girls and adolescent females (Thibaud *et al*. 1992, Sklar 1999)
- Radiation doses of 6 Gy may be sufficient to produce irreversible ovarian damage in women >40 years of age, doses in the range of 10–20 Gy are needed to induce permanent ovarian failure in the majority of females treated during childhood (Wallace *et al*. 1989*a*, Thibaud *et al*. 1992)

- In a report , radiation doses to the ovary >20 Gy were associated with the highest rate of AOF (70%), with higher rates in older individuals (13–20 years) when compared with those who were younger (0–12 years) at the time of treatment (Chemaitilly *et al*. 2006)
- Ovarian failure is seen in essentially all patients who are aged >10 years at the time they are treated with TBI (Sanders *et al*. 1988, Matsumoto *et al*. 1999)
- Recovery of ovarian function has, nevertheless, been documented in a small number of women who have received TBI (Sanders *et al*. 1996).
- If radiation is being given in association with alkylating agent chemotherapy, ovarian dysfunction may occur despite the use of lower doses

ACTH deficiency

ACTH deficiency

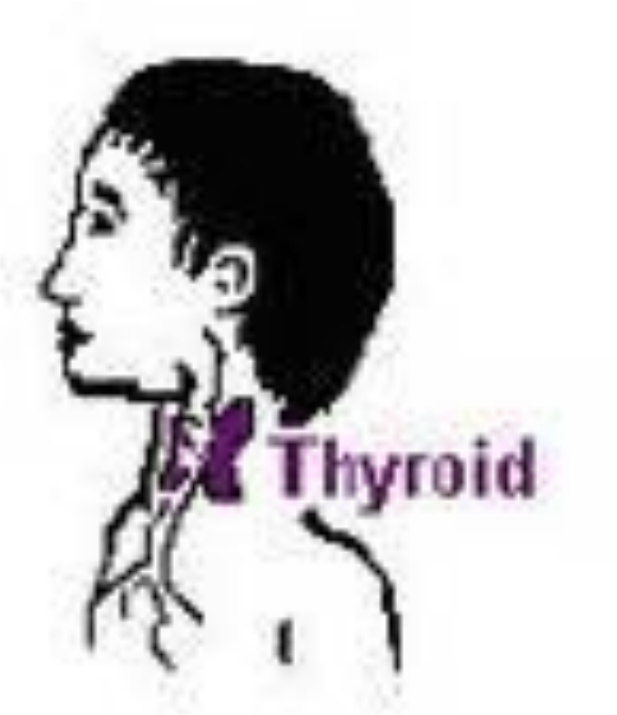
- ACTH deficiency in childhood cancer survivors is relatively uncommon
- It can be observed either as a result of direct tumor impingement on the hypothalamic–pituitary axis and surgery in that region, or following high-dose (>30 Gy) radiation

  (Rose *et al*. 2005, Patterson *et al*. 2009).
- In a study on children receiving high doses of radiation to the hypothalamic–pituitary area (median dose 44 Gy), the 4-year cumulative incidence of ACTH deficiency was 38%

  (Laughton *et al*. 2008

Disorders of the thyroid

PRIMARY / CENTRAL HYPOTHYROIDISM



Disorders of the thyroid

- Abnormalities of the thyroid gland are among the most frequent endocrine complications that are observed in childhood cancer survivors
- Early recognition and treatment of thyroid dysfunction are crucial in this population, given the importance of thyroid hormones for normal growth and development during childhood

Radiotherapy-induced primary hypothyroidism

- Primary hypothyroidism is the most frequently observed thyroid disorder following exposure of the gland to radiation
- This exposure with the following types of radiation: neck/mantle irradiation for Hodgkin's lymphoma
- In a large study on young adult survivors of Hodgkin's lymphoma, a cumulative incidence of hypothyroidism of 28% was observed; for those treated with doses >45 Gy, there was a 50% incidence of hypothyroidism 20 years after diagnosis (Sklar *et al*. 2000*a*,*b*)
- Survivors who received >20 Gy cranial radiation plus any spinal radiotherapy had the highest risk for developing hypothyroidism *et al*. 2009

TSH deficiency

- TSH deficiency, resulting in central hypothyroidism, occurs less often than GHD and CPP following the irradiation of the hypothalamic–pituitary area
- It has been reported following doses >30 to 40 Gy (Sklar & Constine 1995, Rose *et al*. 1999, Schmiegelow *et al*. 2003, Laughton *et al*. 2008)
- In a study on children receiving treatment for CNS tumors resulting in high doses of radiation to hypothalamus–pituitary area, the cumulative incidence of TSH deficiency was 23% at 4 years with a significant risk for patients with doses to the hypothalamic–pituitary area above 42 Gy (Laughton *et al*. 2008)

Hyperprolactinaemia

- High-dose hypothalamic irradiation, in the range of 50 Gy or greater, can be associated with hyperprolactinemia
- Up to 75% of adult patients and 30% of pediatric patients had elevated baseline prolactin levels in a report on 32 patients who received high-dose cranial radiotherapy (39.6–70.2 Gy, with a mean 53.6 Gy) as treatment for brain tumors (Constine *et al*. 1993).

Bone density and risk of osteoporosis

- Childhood cancer survivors as a group have reduced BMD, and are at an increased risk for osteopenia, osteoporosis, and fractures (Aisenberg *et al*. 1998, Sala & Barr 2007, Wasilewski-Masker *et al*. 2008).
- This is the result of mainly three factors:
  - primary disease itself
  - exposure to glucocorticoids and other chemotherapeutic agents such as methotrexat;
  - other hormonal deficiencies associated with cancer and its treatments , GHD and sex hormone deficiencies

    Aisenberg *et al*. 1998, Nysom *et al*. 2000, Sala & Barr 2007, Wasilewski-Masker *et al*. 2008)

- Fractures were shown to occur in up to 39% of children during treatment for ALL (Halton *et al.* 1996)
- Although BMD improves after the completion of treatment, childhood cancer survivors remain at in increased risk of osteopenia long term
- Subjects at high risk for the development of osteoporosis should undergo periodic bone density studies
- Dual energy X-ray absorptiometry (DEXA) remains the most widely used tool for measuring BMD

Prevention/Therapy for osteoporosis

- Preventive measures (supplementation with calcium and vitamin D, good nutrition, and weight-bearing exercise) should be encouraged in all individuals with low or borderline BMD
- Bisphosphonate therapy, sex hormone replacement therapy and GH replacement are useful in improving BMD in subjects with established osteoposis

Overweight, obesity, and disorders of glucose homeostasis

- Obesity and being overweight are often observed in survivors of acute leukemia and various brain tumors (Sklar *et al*. 2000*a*,*b*)
- Risk factors for obesity include cranial irradiation, female gender, and exposure to dexamethasone
- A report from multicentre study, found that cranial radiotherapy >20 Gy, especially in females treated at a young age (<4 years), was significantly associated with obesity (i.e. BMI>30; Oeffinger *et al*. 2003).
- In a more recent study that examined change in BMI over time in the same cohort of ALL survivors, female gender, treatment at a young age, and cranial radiotherapy were associated with a more rapid rate of BMI increase (Garmey *et al*. 2008)

- GHD in adulthood has been associated with obesity, and may contribute to the observed changes in body composition in ALL survivors who received high-dose cranial radiotherapy (Talvensaari *et al*. 1996).
- Childhood ALL survivors have also been shown to have reduced physical activity (Reilly *et al*. 1998).
- Brain tumors developing near the sellar region and their treatments (e.g. surgery and radiation) can also disrupt hypothalamic and pituitary functions and induce states of morbid obesity (Lustig *et al*. 2003*a*,*b*).
- hypothalamic insult has been hypothesized to alter satiety centers and cause hyperphagia, another mechanism involving an increased parasympathetic tone leading to hyperinsulinemia (the latter promoting fat storage) has been suggested as a contributing factor to obesity in these patients

Summary

- Childhood cancer survivors have an increased risk of endocrine disease affecting many areas: hypothalamic–pituitary function, gonadal and reproductive function, thyroid function, body composition, and glucose homeostasis
- The major risk factors include radiation therapy to key endocrine organs
- These endocrine abnormalities may evolve over many years
- Early recognition and treatment can reduce morbidity and mortality in this vulnerable population
- The importance of long-term surveillance of those at risk cannot be overemphasized.


THANKS