Endocrine Health in Childhood Cancer Survivors

Hanneke M. van Santen, MD, PhD[a,b,*], Wassim Chemaitilly, MD, PhD[c], Lillian R. Meacham, MD, PhD[d], Emily S. Tonorezos, MD, MPH[e], Sogol Mostoufi-Moab, MD, PhD, MSCE[f,g]

KEYWORDS

• Growth hormone deficiency • Metabolic syndrome • Hypothyroidism • Bone health
• Late effects • Childhood cancer survivor • Radiation effects
• Secondary thyroid cancer

KEY POINTS

- Endocrine late effects, including reproductive disorders, have been reported in up to 50% of childhood cancer survivors (CCS).
- Radiation-induced hypothalamic-pituitary dysfunction may present several months or many years after treatment, with multiple disorders appearing over time, growth hormone deficiency being the most common deficiency.
- CCS who have been exposed to external radiation or meta-iodobenzylguanidine are at risk for primary hypothyroidism, radiation thyroiditis, hyperthyroidism as well as benign nodules and differentiated thyroid cancer.
- CCS with a history of total body irradiation, abdominal radiotherapy, cranial radiotherapy, surgery to the hypothalamus, or corticosteroids are at increased risk for the development of metabolic syndrome or its components.
- Skeletal abnormalities owing to bone toxicity is common in CCS. The spectrum ranges from mild bone pain to debilitating osteonecrosis.

[a] Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, UMCU, PO Box 85090, Utrecht 3505 AB, the Netherlands; [b] Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands; [c] Division of Endocrinology, St. Jude Children's Research Hospital, Memphis, TN, USA; [d] Division of Hematology/Oncology/BMT, Department of Pediatrics, Emory University, Atlanta, GA, USA; [e] Department of Medicine, Memorial Sloan Kettering and Weill Cornell Medical College, Memorial Sloan Kettering Cancer Center, 485 Lexington Avenue, 2nd Floor, New York, NY 10017, USA; [f] Division of Endocrinology, Department of Pediatrics, The Children's Hospital of Philadelphia, Roberts Pediatric Clinical Research Building, 2716 South Street, Philadelphia, PA 19146, USA; [g] Division of Oncology, Department of Pediatrics, The Children's Hospital of Philadelphia, Roberts Pediatric Clinical Research Building, 2716 South Street, Philadelphia, PA 19146, USA
* Corresponding author. Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, UMCU, PO Box 85090, Utrecht 3505 AB, the Netherlands.
E-mail address: h.m.vansanten@umcutrecht.nl

Pediatr Clin N Am 67 (2020) 1171–1186
https://doi.org/10.1016/j.pcl.2020.08.002 **pediatric.theclinics.com**

INTRODUCTION

Endocrine late effects have been reported in up to 50% of childhood cancer survivors (CCS) >5 years after treatment.[1–4] Most endocrine disorders are amenable to treatment; awareness of symptoms is therefore of great importance. Timely treatment of endocrine disorders improves quality of life in CCS and may prevent possible consequences, such as short stature, bone and cardiovascular disorders, and depression. However, recognition of these symptoms may be delayed because many are nonspecific. At-risk CCS must therefore be regularly monitored and systematically screened. This article provides a summary of the most commonly reported endocrine late effects in CCS, with the exception of late effects affecting the reproductive system, which are described in a separate article.

HYPOTHALAMIC-PITUITARY DYSFUNCTION

CCS with tumors arising near the hypothalamic-pituitary (HP) region and those treated with surgery or radiotherapy involving this region are at risk for HP dysfunction (**Table 1**). HP dysfunction includes growth hormone (GH) deficiency, luteinizing hormone (LH)/follicle stimulating hormone (FSH) deficiency, thyroid stimulating hormone (TSH) deficiency, adrenocorticotrophic hormone (ACTH) deficiency, central precocious puberty (CPP), hyperprolactinemia, and central diabetes insipidus (CDI).

Tumor and surgery involving the HP region are major risk factors for HP dysfunction.[5] In this setting, multiple HP disorders, including CDI, may occur in the immediate postoperative setting. By contrast, radiation-induced HP dysfunction frequently presents several months or years after treatment, with multiple disorders appearing over time.

The reported prevalence of HP dysfunction depends on follow-up time, age, and kind of CCS included in the studied cohort. In a large cohort of 3141 CCS with a median follow-up time of 24.1 years, prevalence of GH deficiency, TSH deficiency, LH/FSH deficiency, ACTH deficiency, and CPP was 22.2%, 5.5%, 5.1%, 4.1%, and 1.1%, respectively, in all and 40.2%, 11.1%, 10.6%, 3.2%, and 0.9%, respectively, among those treated with HP radiotherapy.[2] As the cumulative incidence of radiation-induced HP disorders increases with length of time in follow-up, at-risk CCS require lifelong monitoring.[3] CDI, which is reported in 2.6% of pediatric central nervous system (CNS) tumors patients at time of diagnosis or after neurosurgery, does not occur as a late effect.[6]

Growth Hormone Deficiency

GH is the most common HP deficiency following cranial radiation (CRT)[7–9] (**Fig. 1**). The likelihood of developing GH deficiency and a shortened time to onset is directly related to radiation dose whereas inversely related to the number of fractions used to deliver the radiation.[10,11] GH deficiency has been reported after a single fraction of 10 Gy, has been reported after fractioned doses of 12 Gy given as total body irradiation (TBI), and is common after conformal radiotherapy used to treat CNS tumors.[12] Likewise, GH deficiency is seen after doses of 18 to 24 Gy used to treat acute leukemia.[13] Treatment before puberty, and especially at a younger age, may increase the risk for compromised final adult height.[13–16] Data on rates of GH deficiency after proton beam irradiation are limited at this time.

GH deficiency after traditional chemotherapy is unlikely; however, newer agents, such as immune checkpoint inhibitors and tyrosine kinase inhibitors (TKI), appear to interfere with normal growth.[17–19] The checkpoint inhibitors have been associated with autoimmune hypophysitis.[17,20] TKI may interfere with GH/insulin-like growth factor 1 (IGF-1)

Table 1
Radiotherapy-associated endocrine late effects

Radiotherapy Field	Treated Conditions	Possible Late Effects
Cranial, includes • Whole brain • Infratemporal • Nasopharyngeal • Orbital • Waldeyer ring	CNS tumors ALL with CNS disease Nonbrain solid tumors: • Rhabdomyosarcoma • Nasopharyngeal carcinoma • Retinoblastoma	Anterior pituitary disorders[a] Obesity Metabolic syndrome
Craniospinal	Medulloblastoma PNET	Anterior pituitary disorders[a] Obesity Short stature Primary hypothyroidism Hyperthyroidism Thyroid nodules Differentiated thyroid cancer Premature ovarian insufficiency
Total body irradiation	Conditioning for HSCT	Growth hormone deficiency Obesity Short stature Primary hypothyroidism Hyperthyroidism Thyroid nodules Differentiated thyroid cancer Premature ovarian insufficiency Male germ cell failure Decreased bone mineral density Abnormal glucose metabolism Metabolic syndrome
Neck, thorax, mediastinum • Neck • Chest • Lung • Mantle • Nasopharyngeal • Oropharyngeal • Supraclavicular	Hodgkin lymphoma Solid tumor located within field: • Rhabdomyosarcoma • Neuroblastoma • Ewing sarcoma • Nasopharyngeal carcinoma	Primary hypothyroidism Hyperthyroidism Thyroid nodules Differentiated thyroid cancer
Abdominal, pelvic, genitourinary, includes • Flank or hemiabdomen • Whole abdomen • Inverted Y • Bladder • Vaginal • Prostate, testes • Iliac • Inguinal, femoral	Hodgkin lymphoma Solid tumor located within field: • Rhabdomyosarcoma • Neuroblastoma ALL	Premature ovarian insufficiency Male germ cell failure Leydig cell failure Abnormal glucose metabolism
^{131}I-MIBG	Neuroblastoma	Primary hypothyroidism Thyroid nodules Differentiated thyroid cancer Premature ovarian insufficiency

Abbreviation: PNET, primitive neuroectodermal tumors.

[a] Includes GH, LH/FSH, TSH, and ACTH deficiency, CPP, and hyperprolactinemia.

Adapted from Chemaitilly W, Sklar CA. Childhood Cancer Treatments and Associated Endocrine Late Effects: A Concise Guide for the Pediatric Endocrinologist. *Horm Res Paediatr.* 2019;91(2):74-82. https://doi.org/10.1159/000493943; with permission.

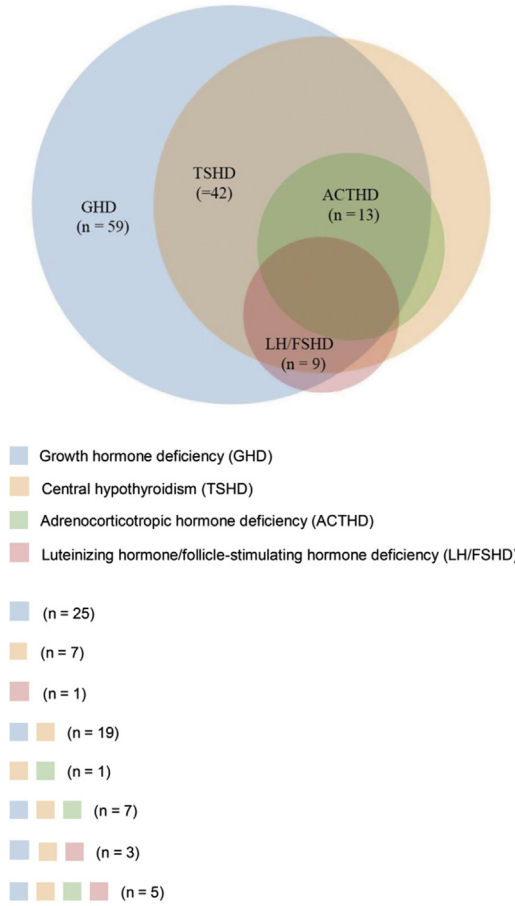

Fig. 1. Relative proportions and overlap among anterior pituitary deficiencies following cranial radiotherapy for childhood cancer. ACTHD, adrenocorticotropic hormone deficiency; GHD, growth hormone deficiency; TSHD, thyroid-stimulating hormone deficiency.[3] (*From* Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol*. 2015;33(5):492-500. https://doi.org/10.1200/JCO.2014.56.7933, p. 496.; with permission.)

signaling pathways or affect the growth plates.[18,19,21] There is conflicting evidence regarding catch-up growth in patients following treatment with TKIs.[18,22,23]

There are many causes of poor growth in CCS that are not associated with GH deficiency. Poor nutrition, suboptimal body mass index (BMI), and long-term treatment with glucocorticoids can cause transient decreases in growth velocity.[24] Treatment with cis-Retinoic acid is associated with short stature secondary to premature closure of the growth plates and therefore is not amenable to GH treatment.[25] Spinal radiation, especially at young age, may result in disproportionate growth with deficits in the upper segment resulting in arm span being greater than standing height.[14,26] Last, the timing and velocity of puberty can complicate the interpretation of growth. GH deficiency can be masked in children with early-onset puberty and seemingly normal growth rate, often resulting in delayed diagnosis of GH deficiency.

Screening for GH deficiency is done by measuring height, sitting height, weight, BMI percentiles, and height velocity every 6 months and should be interpreted in light of past height percentiles, mid–parental height, and Tanner stage. It is not recommended to rely solely on serum IGF-1 levels in CCS exposed to HP axis radiotherapy to make the diagnosis of GH deficiency.[27] When GH deficiency is suspected, GH stimulation tests must be done to confirm the diagnosis.

The risks and benefits of replacement therapy with human recombinant GH (hGH) should be discussed with the family. It should be mentioned that hGH may exacerbate scoliosis and increase the risk for slipped capital femoral epiphysis. There is currently no definitive evidence that the administration of hGH treatment increases the risk of cancer recurrence or secondary neoplasms.[28] Although the Childhood Cancer Survivor Study reported a 2- to 3-fold increase in risk for subsequent neoplasms, other reports suggest no significant increased risk for second cancers.[28–34]

GH replacement is typically delayed at least until 1 year after completion of cancer therapy,[27] although in children with low-grade neoplasms, such as craniopharyngioma, there may be arguments to commence earlier. GH treatment regimens used in the general population appear to also be appropriate for CCS.[27] In CCS treated with GH, height velocity will improve, but other factors, including end-organ resistance owing to radiation damage, timing, and velocity of puberty and other concurrent endocrinopathies, may limit final height.[35] Increased weight-to-height ratio, decreased lean muscle mass, muscle weakness, poor exercise tolerance, and frailty have been described in adult GH-deficient CCS,[36] but the presence of these conditions is less well documented in pediatric-aged CCS with GH deficiency. While treating with hGH, it is prudent to maintain IGF-1 levels in the normal range for age, sex, and pubertal status.[27] The risks and benefits of long-term GH replacement in adult CCS are not well established and represent areas of active research.[3]

Luteinizing hormone/follicle stimulating hormone deficiency

Depending on the attained stage of puberty at the time of onset of LH/FSH deficiency, survivors may present differently. Prepubertal children may present with pubertal delay; peripubertal children may present with arrested puberty, and postpubertal survivors may present with signs of hypogonadism, such as secondary amenorrhea in women and symptoms of androgen deficit (decreased libido and erectile dysfunction) in men. Untreated, LH/FSH deficiency may have repercussions on bone health, cardiovascular morbidity, and quality of life.[37] Low or declining serum estradiol (women) or morning testosterone (men) without elevation in LH levels is suggestive of the diagnosis. The treatment relies on sex-hormone replacement therapy.[27]

Thyroid stimulating hormone deficiency

Decreased or progressively declining serum free thyroxine (FT4) levels with low or inappropriately normal TSH levels are suggestive of the diagnosis TSH deficiency.[38] Untreated individuals may experience increased cardiovascular risk.[38] Treatment relies on replacement with levothyroxine.[27]

Adrenocorticotrophic hormone deficiency

Patients with ACTH deficiency may present with symptoms of adrenal insufficiency, including fatigue and vulnerability to medical stressors. Untreated, ACTH deficiency exposes survivors to the risk of adrenal crisis, which if not expeditiously managed could lead to shock, hypoglycemia, seizures, and death.[27] The diagnosis relies on the measurement of a low cortisol level after stimulation with low-dose or high-dose ACTH.[39] Treatment requires replacement with hydrocortisone at maintenance doses and stress dosing during illness.[27]

Central precocious puberty

Increased intracranial pressure or neoplasms in the HP region are risk factors for developing CPP. Children with CPP present with pubertal development and growth acceleration before the age of 8 years in girls (breast development) and 9 years in boys (testicular enlargement). Testicular volume enlargement may not be a reliable sign in boys treated with gonadotoxic therapies, such as alkylating agents or testicular radiotherapy,[40] and growth acceleration may be lacking because of the presence of GH deficiency. Untreated, CPP may lead to short stature and psychosocial adjustment issues.[41] The treatment relies on pubertal suppression using gonadotropic-releasing hormone agonists.[27]

Hyperprolactinemia

Radiation-induced hyperprolactinemia is rarely symptomatic, and treatment of hyperprolactinemia for its suppressive effects on gonadotropins is almost never necessary.[42]

Central diabetes insipidus

CDI is not considered a late effect of CCS but is most frequently present from the outset or immediately after neurosurgery in patients with neoplasms near the HP region (craniopharyngioma, germinoma, Langerhans cell histiocytosis). Patients with CDI present with polyuria and polydipsia owing to antidiuretic hormone deficiency.[43] A small subset, with extensive hypothalamic injury, experiences loss of thirst sensation. Management relies on treatment with desmopressin and monitoring fluid intake and output.[43,44]

THYROID DISORDERS

CCS, mainly those who have been exposed to radiation to a field including the thyroid gland, are at increased risk for primary hypothyroidism, subclinical (compensated) hypothyroidism, radiation thyroiditis, Graves hyperthyroidism followed by hypothyroidism as well as benign nodules and differentiated thyroid cancer (DTC).[45–48]

Thyroid Dysfunction

Radiation to a field including the thyroid gland and treatment with ^{131}I-meta-iodobenzylguanidine (MIBG) are the main risk factors for thyroid function disorders in CCS.[49] Survivors of neuroblastoma and Hodgkin lymphoma have the highest rate of hypothyroidism, with a prevalence up to 50% and 32%, respectively.[14,50] The risk for hypothyroidism increases with radiation dose, with 50% of CCS exposed to doses $\geq$45 Gy developing hypothyroidism by 20 years of follow-up.[51] Additional risk factors include younger age at radiotherapy and female gender.

Some evidence suggests that chemotherapy may affect thyroid function[52] (**Table 2**). In a study of the Late Effects Surveillance System in Germany, thyroid disorders were reported in survivors of sarcoma treated with chemotherapy alone.[53] Thyroid disorders have also been reported in up to 30% of survivors of hematopoietic stem cell transplantation (HSCT) conditioned with chemotherapy alone.[54] No difference was found in risk to develop hypothyroidism between a TBI or busulphan-based regimen. The BEAM (carmustine, etoposide, cytarabin and melphalan) combination used for conditioning was associated with a higher prevalence of thyroid disorders when compared with busulfan and fludarabine-based regimens.[55]

Immunotherapy, such as treatment with cytokines and check-point inhibitors, may cause thyroiditis resulting in an increased or decreased thyroid function.[56] Treatment with TKIs may result in thyroid dysfunction probably because of thyroiditis, although

Table 2
Chemotherapeutic agents associated with endocrine late effects

Category	Drug	Possible Late Effects
Alkylating agents	Busulfan Carmustine Chlorambucil Cyclophosphamide Dacarbazine Ifosfamide Lomustine Mechlorethamine Melphalan Procarbazine Temozolomide Thiotepa	Premature ovarian insufficiency Male germ cell failure Leydig cell dysfunction (subclinical mostly) Primary hypothyroidism (busulfan)
Heavy metals	Carboplatin Cisplatin	Premature ovarian insufficiency Male germ cell failure
Glucocorticoids	Dexamethasone Prednisone	Obesity Decreased bone mineral density Metabolic syndrome
Tyrosine kinase inhibitors	Imatinib Sorafenib Sunitinib	Impaired linear growth Primary hypothyroidism
Immunomodulator	Interferon	Autoimmune thyroiditis
Immune checkpoint inhibitor–anti-CTLA4 monoclonal antibody	Ipilimumab	Immune hypophysitis with anterior pituitary disorders[a] Autoimmune thyroiditis
Other	Retinoic acid Hedgehog pathway inhibitor	Skeletal dysplasia–short stature

[a] Includes GH, LH/FSH, TSH, and ACTH deficiency.

Adapted from Chemaitilly W, Sklar CA. Childhood Cancer Treatments and Associated Endocrine Late Effects: A Concise Guide for the Pediatric Endocrinologist. *Horm Res Paediatr*. 2019;91(2):74-82. https://doi.org/10.1159/000493943; with permission.

other mechanisms have been proposed.[57] A transient period of thyrotoxicosis may precede definitive hypothyroidism in individuals with thyroiditis. Effects of immunotherapy and TKIs are mainly seen in the first months after treatment.

Monitoring of thyroid function is recommended with yearly determination of TSH and FT4 in all CCS whose thyroid was potentially exposed to radiotherapy or therapeutic ^{131}I-MIBG.[27] Persistently high concentrations of TSH may increase the risk for thyroid nodules, but evidence is lacking in regards to an association with thyroid cancer.[58] In the case of hypothyroidism, it is recommended to replace thyroid hormone using regimens similar to those used in noncancer populations. It is currently not advised to screen thyroid function in CCS after treatment with chemotherapy alone.[58]

Thyroid Neoplasia

CCS treated with radiation therapy that includes the thyroid gland or with ^{131}I-MIBG are at an increased risk of developing benign thyroid nodules and DTC.[58–60] Neuroblastoma survivors who were treated with external beam irradiation to a field including the thyroid gland have been shown to have an increased risk for DTC when compared

with Hodgkin survivors.[58,61] The risk for DTC is linear up to approximately 10 Gy, plateaus between 10 and 30 Gy, and declines at higher radiation doses (Fig. 2).[62] Because of the fact that DTC has been reported after thyroid radiation doses of less than 1 Gy and in individuals who received doses exceeding 40 Gy, all CCS with thyroid radiation exposure should be considered as having increased risk for DTC. Female CCS seem to be at increased risk when compared with male CCS[63]; however, other studies have reported no association with gender.[58]

Chemotherapy may increase the risk to develop thyroid cancer, although this has not been consistently reported. In a pooled analysis of 4 studies, the relative risk for DTC following treatment with anthracyclines was 4.5 (95% confidence interval [CI], 1.4–17.8) in nonirradiated patients.[63] This finding has been confirmed in an updated pooled analysis of 12 studies, in which exposure to chemotherapy was significantly associated with thyroid cancer (see Fig. 2).[62]

DTC has an excellent prognosis. There is no evidence that DTC in CCS has a different behavior or prognosis than sporadic DTC, although it may be argued that it is favorable to diagnose DTC in CCS at an early stage.[64,65] The workup for a thyroid nodule possibly indicating DTC and treatment of DTC should be the same as in non-CCS. An expert panel of the International Guideline Harmonization Group evaluated evidence for the benefits and harms related to surveillance for DTC in CCS with thyroid ultrasound versus neck palpation. It was recommended that survivors be advised of the disadvantages (false negatives and subsequent unnecessary evaluations) versus the advantages (early detection of DTC) of both surveillance modalities and to decide by shared decision making between the health care provider and the survivor if thyroid ultrasounds would be obtained.[58]

METABOLIC SYNDROME

Adults diagnosed with the metabolic syndrome have at least three of the following criteria: elevated blood pressure, elevated fasting triglycerides, elevated fasting glucose, low high-density lipoprotein cholesterol level, and increased waist circumference and are at increased risk for cardiovascular morbidity. CCS with a history of TBI, abdominal radiotherapy, CRT, surgery to the hypothalamus, or corticosteroids use are

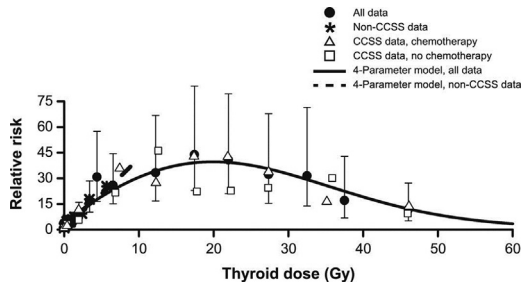

Fig. 2. Relative risk to develop thyroid cancer after radiation and chemotherapy in CCS. Category-specific relative risks for thyroid radiation dose for all data (*solid circle*) with selected 95% CIs, for non-CCSS data (*star*) and CCSS data for those who were (*open triangle*) or were not (*open square*) treated with chemotherapy, and the 4-parameter fitted dose-response model to all data (*solid line*) and to non-CCSS data only (*dash line*). Display includes full range of doses.[62] CCSS, childhood cancer survivor studies. (*From* Veiga LHS, Holmberg E, Anderson H, et al. Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies. Radiat. Res. 2016; 185: 473-484; with permission © 2020 Radiation Research Society.)

at increased risk for the development of metabolic syndrome or its components. In light of the risk for cardiovascular morbidity and early mortality among CCS,[66–68] attention to the metabolic syndrome in this population is essential to high-quality care.

Evidence suggests that the prevalence of the metabolic syndrome is increased among CCS, compared with the general population.[69] In the St. Jude Lifetime Cohort Study, 508 of 1598 (31.8%) CCS (median age 32.7 years) met criteria for metabolic syndrome.[70] The highest risk was among acute lymphoblastic leukemia (ALL) survivors with a history of CRT. Among ALL survivors, individual metabolic late effects, including obesity, insulin resistance, dyslipidemia, hypertension, and cardiovascular events, have been reported.[70,71] In an analysis of the Childhood Cancer Survivor Study, CCS were more likely to take medications for hypertension (odds ratio [OR], 1.9; 95% CI, 1.6–2.2), dyslipidemia (OR, 1.6; 95% CI, 1.3–2.0), or diabetes (OR, 1.7; 95% CI, 1.2–2.3) than their siblings; however, they were not more likely to be obese or to have the cardiovascular risk factor cluster. CCS at highest risk were those who had a history of TBI or radiation to the chest or abdomen and also those who were physically inactive or were older at the time of follow-up.[72]

Causes for the Metabolic Syndrome in Childhood Cancer Survivors

HP deficiencies and obesity caused by (neurosurgical) damage to the HP region increase the risk for metabolic syndrome.[73] Survivors of craniopharyngioma are especially at risk for hypothalamic obesity, because of destruction of the ventromedial hypothalamus,[74] which may induce severe hyperphagia. In addition, insulin resistance may result from excess insulin secretion from the β cell of the pancreas because of overactive vagal neural transmission.

Corticosteroids have been repeatedly implicated in the observed metabolic risk for CCS. Acutely, corticosteroid administration may disturb glucose levels while causing weight gain and height loss.[75] Corticosteroids are also known to increase circulating free fatty acids, resulting in dyslipidemia and inhibition of myocellular glucose transport, increased gluconeogenesis and fatty acid synthesis, with decreased adiponectin levels.[76] Furthermore, corticosteroids can alter appetite regulation and have been reported to result in decreased physical activity, both contributing to metabolic risk. The metabolic impact of corticosteroids does not appear to end with discontinuation. A recent retrospective analysis of 184 children with ALL found that weight gain and height loss that occurred during the corticosteroid-containing reinduction phase persisted throughout intensification, maintenance, and survivorship.[77]

Multiple chemotherapy agents, most notably heavy metals and alkylating agents, have been associated with metabolic syndrome components.[76]

CCS with a history of TBI, radiation to the chest or abdomen, and CRT are at increased risk for the metabolic syndrome.[72] As noted above, GH deficiency following CRT may be implicated in the observed metabolic risk in this setting. However, metabolic syndrome and its components have also been described in survivors with a history of CRT without GH deficiency.[78] Survivors with a history of exposure to abdominal radiation were at 3.4-fold increased risk for diabetes when compared with siblings, after adjusting for BMI.[79]

TBI may cause the metabolic syndrome without obesity.[80] In a large single-institution study of 1885 one-year HSCT survivors (52% with a history of TBI), the prevalence of cardiovascular risk factors was significantly higher among transplant recipients, compared with community controls. Transplant recipients with a history of TBI were at highest risk for cardiovascular risk factors.

Similar to the general population, physical inactivity and poor-quality diet are significant contributors to metabolic and cardiovascular risk among CCS.[81] Subsequent studies

have suggested that higher levels of physical activity and adherence to a Mediterranean diet are associated with better cardiometabolic risk factor profiles in CCS.[82,83]

BONE TOXICITY IN CHILDHOOD CANCER SURVIVORS

Skeletal abnormalities owing to bone toxicity are common in CCS. The spectrum ranges from mild bone pain to debilitating osteonecrosis (ON) and fractures.[84] The growing skeleton is particularly vulnerable to the effects of childhood cancer therapies and complications that interfere with skeletal metabolism and result in muscle deficits or poor muscle function. Musculoskeletal abnormalities can be recognized at the time of cancer diagnosis and during treatment and/or persist as long-term sequelae after treatment. Osteotoxic chemotherapy, prolonged treatment with glucocorticoids, poor nutrition, vitamin D insufficiency, and poor muscle mass are recognized risk factors that contribute to bone pathologic condition during and after cancer therapy, resulting in negative skeletal outcomes.[85]

ALL is associated with significant skeletal morbidity, including vertebral compression fractures, severe bone mineral density (BMD) deficit (BMD Z score ≤ -2), and ON.[86] The prevalence of severe vertebral compression fractures in children with newly diagnosed ALL is as high as 16% and associated with substantial risk for subsequent vertebral as well as nonvertebral fractures during and after completion of ALL treatment.[87] Prolonged therapy with glucocorticoids can also result in ON that further contributes to bone morbidity and altered quality of life. Although skeletal recovery in ALL survivors is noted after completion of therapy, BMD deficits may still persist over years depending on other chronic health conditions and lifestyle factors.[88]

The cause for BMD deficits in HSCT recipients may be due to the direct effect of leukemia on bone structure or as a consequence of treatments including glucocorticoids and transplant-related complications. Additional risk factors are TBI or CRT, young age at treatment, graft-versus-host disease, GH deficiency, and LH/FSH deficiency.[89] CCS treated with retinoids are at marked risk for reduced longitudinal bone growth, abnormal osteoblast differentiation, and premature epiphyseal closure.[25] Changes in bone remodeling and hyperparathyroidism have recently been described in pediatric patients treated with prolonged TKI.[21]

Recommendation for early detection of an abnormal BMD are inconsistent. An international guideline harmonization working group is developing an international guideline on this topic (www.ighg.org). If a diagnostic test is needed for bone health assessment after childhood cancer therapy, dual-energy x-ray absorptiometry is recommended.[90] Treatments for low BMD in CCS include treatment of hormonal deficiencies, repletion of vitamin D deficiency, supplementation of poor calcium intake, and consultation about the benefits of regular physical activity and deleterious effects of smoking and alcohol consumption.[91]

Current treatment options for ON include analgesia, limited weight bearing, physical therapy, and surgical procedures, including core decompression and/or joint replacement.[92] Alternative treatments have not shown clear benefits. Although treatment with bisphosphonates contributes to pain improvement with a reduced requirement in oral analgesia, their use has failed to demonstrate the prevention, destruction, and subsequent collapse in most affected weight-bearing joints, such as the hip joint.[93]

SUMMARY

Endocrine, metabolic, and bone disorders are frequent in CCS. Because recognition of the symptoms of HP deficiency may be masked, the (pediatric) endocrinologist should be part of the late-effects team for early recognition and treatment. CCS should

be counseled on risk factors for bone and metabolic problems, and regular physical activity and healthy diet should be encouraged. Active counseling regarding BMI and timely treatment of HP disorders may improve quality of life of the survivors.

DISCLOSURE

H.M. van Santen has received speakers fees from Pfizer BV and Ferring BV. The remaining authors have nothing to disclose.

REFERENCES

1. Chemaitilly W, Sklar CA. Childhood cancer treatments and associated endocrine late effects: a concise guide for the pediatric endocrinologist. Horm Res Paediatr 2019;91:74–82.
2. van Iersel L, Li Z, Srivastava DK, et al. Hypothalamic-pituitary disorders in childhood cancer survivors: prevalence, risk factors and long-term health outcomes. J Clin Endocrinol Metab 2019;104(12):6101–15.
3. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 2015;33:492–500.
4. Barnes N, Chemaitilly W. Endocrinopathies in survivors of childhood neoplasia. Front Pediatr 2014;2:1–12.
5. Gan HW, Phipps K, Aquilina K, et al. Neuroendocrine morbidity after pediatric optic gliomas: a longitudinal analysis of 166 children over 30 years. J Clin Endocrinol Metab 2015;100:3787–99.
6. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: a nationwide, multicenter study. J Clin Oncol 2016;34:4362–70.
7. Schmiegelow M, Lassen S, Poulsen HS, et al. Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. Clin Endocrinol (Oxf) 2000;53:191–7.
8. Shalet SM, Beardwell CG, Pearson CG, et al. The effect of varying doses of cerebral irradiation on growth hormone production in childhood. Clin Endocrinol (Oxf) 1976;5:287–90.
9. Shalet SM, Beardwell CG, Aarons BM, et al. Growth hormone deficiency in children with brain tumors. Cancer 1976;37:1144–8.
10. Merchant TE, Goloubeva O, Pritchard DL, et al. Radiation dose-volume effects on growth hormone secretion. Int J Radiat Oncol Biol Phys 2002;52:1264–70.
11. Darzy KH, Shalet SM. Hypopituitarism as a consequence of brain tumours and radiotherapy. Pituitary 2005;8:203–11.
12. Brennan BMD, Shalet SM. Endocrine late effects after bone marrow transplant. Br J Haematol 2002;118:58–66.
13. Viana MB, Vilela MIOP. Height deficit during and many years after treatment for acute lymphoblastic leukemia in children: a review. Pediatr Blood Cancer 2008; 50:509–16.
14. Chow EJ, Friedman DL, Yasui Y, et al. Decreased adult height in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Pediatr 2007;150:370–5.
15. Dalton VK, Rue M, Silverman LB, et al. Height and weight in children treated for acute lymphoblastic leukemia: relationship to CNS treatment. J Clin Oncol 2003; 21:2953–60.

16. Gurney JG, Ness KK, Stovall M, et al. Final height and body mass index among adult survivors of childhood brain cancer: Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2003;88:4731–9.
17. Corsello SM, Barnabei A, Marchetti P, et al. Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab 2013;98:1361–75.
18. Narayanan KR, Bansal D, Walia R, et al. Growth failure in children with chronic myeloid leukemia receiving imatinib is due to disruption of GH/IGF-1 axis. Pediatr Blood Cancer 2013;60:1148–53.
19. Tauer JT, Hofbauer LC, Jung R, et al. Impact of long-term exposure to the tyrosine kinase inhibitor imatinib on the skeleton of growing rats. PLoS One 2015;10: e0131192.
20. Joshi MN, Whitelaw BC, Palomar MTP, et al. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. Clin Endocrinol 2016;85: 331–9.
21. Lodish MB, Stratakis CA. Endocrine side effects of broad-acting kinase inhibitors. Endocr Relat Cancer 2010;17:R233–44.
22. Shima H, Tokuyama M, Tanizawa A, et al. Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. J Pediatr 2011;159:676–81.
23. Rastogi MV, Stork L, Druker B, et al. Imatinib mesylate causes growth deceleration in pediatric patients with chronic myelogenous leukemia. Pediatr Blood Cancer 2012;59:840–5.
24. Meacham LR, Mason PW, Sullivan KM. Auxologic and biochemical characterization of the three phases of growth failure in pediatric patients with brain tumors. J Pediatr Endocrinol Metab 2004;17:711–7.
25. Mostoufi-Moab S. Skeletal impact of retinoid therapy in childhood cancer survivors. Pediatr Blood Cancer 2016;63:1884–5.
26. Clayton PE, Shalet SM. The evolution of spinal growth after irradiation. Clin Oncol 1991;3:220–2.
27. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic–pituitary and growth disorders in survivors of childhood cancer: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018;103:2761–84.
28. Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2002;87: 3136–41.
29. Ergun-Longmire B, Mertens AC, Mitby P, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab 2006;91:3494–8.
30. Woodmansee WW, Zimmermann AG, Child CJ, et al. Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS. Eur J Endocrinol 2013;168:565–73.
31. Raman S, Grimberg A, Waguespack SG, et al. Risk of neoplasia in pediatric patients receiving growth hormone therapy - a report from the pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab 2015;100: 2192–203.
32. Mackenzie S, Craven T, Gattamaneni HR, et al. Long-term safety of growth hormone replacement after CNS irradiation. J Clin Endocrinol Metab 2011;96: 2756–61.

33. Brignardello E, Felicetti F, Castiglione A, et al. GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution. J Endocrinol Invest 2015;38:171–6.
34. Allen DB, Backeljauw P, Bidlingmaier M, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol 2016;174:P1–9.
35. 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 2004;89:4422–7.
36. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 2013;31:4496–503.
37. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101:3888–921.
38. van Iersel L, Xu J, Potter BS, et al. Clinical importance of free thyroxine concentration decline after radiotherapy for pediatric and adolescent brain tumors. J Clin Endocrinol Metab 2019;104:4998–5007.
39. Patterson BC, Truxillo L, Wasilewski-Masker K, et al. Adrenal function testing in pediatric cancer survivors. Pediatr Blood Cancer 2009;53:1302–7.
40. Sklar CA, Robison LL, Nesbit ME, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. J Clin Oncol 1990;8:1981–7.
41. Chemaitilly W, Merchant TE, Li Z, et al. Central precocious puberty following the diagnosis and treatment of paediatric cancer and central nervous system tumours: presentation and long-term outcomes. Clin Endocrinol (Oxf) 2016;84:361–71.
42. Constine LS, Woolf PD, Constine CD, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993;328:87–94.
43. Di Iorgi N, Napoli F, Allegri AE, et al. Diabetes insipidus - diagnosis and management. Horm Res Paediatrics 2012;77:69–84.
44. Mishra G, Chandrashekhar SR. Management of diabetes insipidus in children. Indian J Endocrinol Metab 2011;15(Suppl 3):S180–7.
45. Waguespack SG. Thyroid sequelae of pediatric cancer therapy. Horm Res Paediatrics 2019;91:104–17.
46. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. Int J Radiat Oncol Biol Phys 1995;31:1165–70.
47. Hancock SL, Cox RS, Mcdougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991;325:599–605.
48. Inskip PD, Veiga LHS, Brenner AV, et al. Hyperthyroidism after radiation therapy for childhood cancer: a report from the Childhood Cancer Survivor Study. Int J Radiat Oncol Biol Phys 2019;104:415–24.
49. Jereczek-Fossa BA, Alterio D, Jassem J, et al. Radiotherapy-induced thyroid disorders. Cancer Treat Rev 2004;30:369–84.
50. Clement SC, van Rijn RR, van Eck-Smit BL, et al. Long-term efficacy of current thyroid prophylaxis and future perspectives on thyroid protection during 131I-metaiodobenzylguanidine treatment in children with neuroblastoma. Eur J Nucl Med Mol Imaging 2015;42:706–15.

51. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the childhood cancer survivor study. J Clin Endocrinol Metab 2000;85:3227–32.
52. Berger C, Le-Gallo B, Donadieu J, et al. Late thyroid toxicity in 153 long-term survivors of allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. Bone Marrow Transplant 2005;35:991–5.
53. Paulides M, Dörr HG, Stöhr W, et al. Thyroid function in paediatric and young adult patients after sarcoma therapy: a report from the Late Effects Surveillance System. Clin Endocrinol (Oxf) 2007;66:727–31.
54. Sanders JE, Hoffmeister PA, Woolfrey AE, et al. Thyroid function following hematopoietic cell transplantation in children: 30 years' experience. Blood 2009; 113:306–8.
55. Veiga LH, Bhatti P, Ronckers CM, et al. Chemotherapy and thyroid cancer risk: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 2012;21:92–101.
56. Cima LN, Martin SC, Lambrescu IM, et al. Long-term thyroid disorders in pediatric survivors of hematopoietic stem cell transplantation after chemotherapy-only conditioning. J Pediatr Endocrinol Metab 2018;31:869–78.
57. Torino F, Corsello SM, Longo R, et al. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol 2009;6:219–28.
58. Clement SC, Kremer LCM, Verburg FA, et al. Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. Cancer Treat Rev 2018;63:28–39.
59. Bhatti P, Veiga LH, Ronckers CM, et al. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the Childhood Cancer Survivor Study. Radiat Res 2010;174:741–52.
60. van Santen HM, Tytgat GA, van de Wetering MD, et al. Differentiated thyroid carcinoma after 131I-MIBG treatment for neuroblastoma during childhood: description of the first two cases. Thyroid 2012;22:643–6.
61. de Vathaire F, François P, Schlumberger M, et al. Epidemiological evidence for a common mechanism for neuroblastoma and differentiated thyroid tumour. Br J Cancer 1992;65:425–8.
62. Veiga LHS, Holmberg E, Anderson H, et al. Thyroid cancer after childhood exposure to external radiation: an updated pooled analysis of 12 studies. Radiat Res 2016;185:473–84.
63. Veiga LHS, Lubin JH, Anderson H, et al. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. Radiat Res 2012;178:365–76.
64. Acharya S, Sarafoglou K, LaQuaglia M, et al. Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. Cancer 2003;97: 2397–403.
65. Clement SC, Kremer LC, Links TP, et al. Is outcome of differentiated thyroid carcinoma influenced by tumor stage at diagnosis? Cancer Treat Rev 2015;41:9–16.
66. Chen Y, Chow EJ, Oeffinger KC, et al. Traditional cardiovascular risk factors and individual prediction of cardiovascular events in childhood cancer survivors. J Natl Cancer Inst 2019. https://doi.org/10.1093/jnci/djz108.
67. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31: 3673–80.

68. Van Nimwegen FA, Schaapveld M, Janus CPM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015; 175:1007–17.
69. Talvensaari KK, Lanning M, Tapanainen P, et al. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab 1996;81:3051–5.
70. Smith WA, Li C, Nottage KA, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer 2014;120:2742–50.
71. Malhotra J, Tonorezos ES, Rozenberg M, et al. Atherogenic low density lipoprotein phenotype in long-term survivors of childhood acute lymphoblastic leukemia. J Lipid Res 2012;53:2747–54.
72. Meacham LR, Chow EJ, Ness KK, et al. Cardiovascular risk factors in adult survivors of pediatric cancer-a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev 2010;19:170–81.
73. Nandagopal R, Laverdière C, Mulrooney D, et al. Endocrine late effects of childhood cancer therapy: a report from the children's oncology group. Horm Res 2008;69:65–74.
74. Schwartz MW, Woods SC, Porte D, et al. Central nervous system control of food intake. Nature 2000;404:661–71.
75. Arguelles B, Barrios V, Buno M, et al. Anthropometric parameters and their relationship to serum growth hormone-binding protein and leptin levels in children with acute lymphoblastic leukemia: a prospective study. Eur J Endocrinol 2000; 143:243–50.
76. Rosen GP, Nguyen HT, Shaibi GQ. Metabolic syndrome in pediatric cancer survivors: a mechanistic review. Pediatr Blood Cancer 2013;60:1922–8.
77. Touyz LM, Cohen J, Neville KA, et al. Changes in body mass index in long-term survivors of childhood acute lymphoblastic leukemia treated without cranial radiation and with reduced glucocorticoid therapy. Pediatr Blood Cancer 2017;64(4): e26344.
78. Gurney JG, Ness KK, Sibley SD, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer 2006;107:1303–12.
79. Meacham LR, Sklar CA, Li S, et al. Diabetes mellitus in long-term survivors of childhood cancer - increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med 2009;169:1381–8.
80. Adachi M, Oto Y, Muroya K, et al. Partial lipodystrophy in patients who have undergone hematopoietic stem cell transplantation during childhood: an institutional cross-sectional survey. Clin Pediatr Endocrinol 2017;26:99–108.
81. Florin TA, Fryer GE, Miyoshi T, et al. Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev 2007;16:1356–63.
82. Järvelä LS, Kemppainen J, Niinikoski H, et al. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2012;59:155–60.
83. Tonorezos ES, Robien K, Eshelman-Kent D, et al. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. Cancer Causes Control 2013;24:313–21.
84. Mostoufi-Moab S, Ward LM. Skeletal morbidity in children and adolescents during and following cancer therapy. Horm Res Paediatrics 2019;91:137–51.

85. Chemaitilly W, Cohen L, Mostoufi-Moab S, et al. Endocrine late effects in childhood cancer survivors. J Clin Oncol 2018;36:2153–9.
86. Mostoufi-Moab S, Halton J. Bone morbidity in childhood leukemia: epidemiology, mechanisms, diagnosis, and treatment. Curr Osteoporos Rep 2014;12:300–12.
87. Cummings EA, Ma J, Fernandez CV, et al. Incident vertebral fractures in children with leukemia during the four years following diagnosis. J Clin Endocrinol Metab 2015;100:3408–17.
88. Gurney JG, Kaste SC, Liu W, et al. Bone mineral density among long-term survivors of childhood acute lymphoblastic leukemia: results from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer 2014;61:1270–6.
89. Mostoufi-Moab S, Ginsberg JP, Bunin N, et al. Bone density and structure in long-term survivors of pediatric allogeneic hematopoietic stem cell transplantation. J Bone Miner Res 2012;27:760–9.
90. Crabtree NJ, Arabi A, Bachrach LK, et al. Dual-energy x-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD pediatric official positions. J Clin Densitom 2014;17:225–42.
91. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;309:2371–81.
92. Barr RD, Sala A. Osteonecrosis in children and adolescents with cancer. Pediatr Blood Cancer 2008;50:483–5.
93. Padhye B, Dalla-Pozza L, Little DG, et al. Use of zoledronic acid for treatment of chemotherapy related osteonecrosis in children and adolescents: a retrospective analysis. Pediatr Blood Cancer 2013;60:1539–45.