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

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*Endorsing Association: The Pituitary Society.

Objective: To formulate clinical practice guidelines for the endocrine treatment of hypothalamic–pituitary and growth disorders in survivors of childhood cancer.

Participants: An Endocrine Society–appointed guideline writing committee of six medical experts and a methodologist.

Conclusions: Due to remarkable improvements in childhood cancer treatment and supportive care during the past several decades, 5-year survival rates for childhood cancer currently are >80%. However, by virtue of their disease and its treatments, childhood cancer survivors are at increased risk for a wide range of serious health conditions, including disorders of the endocrine system. Recent data indicate that 40% to 50% of survivors will develop an endocrine disorder during their lifetime. Risk factors for endocrine complications include both host (*e.g.*, age, sex) and treatment factors (*e.g.*, radiation). Radiation exposure to key endocrine organs (*e.g.*, hypothalamus, pituitary, thyroid, and gonads) places cancer survivors at the highest risk of developing an endocrine abnormality over time; these endocrinopathies can develop decades following cancer treatment, underscoring the importance of lifelong surveillance. The following guideline addresses the diagnosis and treatment of hypothalamic–pituitary and growth disorders commonly encountered in childhood cancer survivors. **(*J Clin Endocrinol Metab* 103: 2761–2784, 2018)**

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Abbreviations: ACTH, adrenocorticotropic hormone; ACTHD, adrenocorticotropic hormone deficiency; AH, adult height; CNS, central nervous system; CPP, central precocious puberty; CRT, cranial radiation therapy; CSI, craniospinal irradiation; fT4, free T4; GHD, GH deficiency; GHT, GH treatment; GnRHa, gonadotropin-releasing hormone agonist; HP, hypothalamic–pituitary; ITT, insulin tolerance test; LH/FSHD, LH/FSH deficiency; RT, radiation treatment; SCFE, slipped capital femoral epiphysis; TBI, total body irradiation; T2DM, type 2 diabetes mellitus; TKI, tyrosine kinase inhibitor; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency.

List of Recommendations

Short stature/impaired linear growth in childhood cancer survivors

Diagnosis and monitoring of short stature/impaired linear growth in childhood cancer survivors

1.1 We recommend prospective follow-up of linear growth for childhood cancer survivors at high risk for short adult height, namely those exposed to cranial radiation therapy, craniospinal irradiation, or total body irradiation at a young age and those with a history of inadequate weight gain or prolonged steroid requirement. (1|⊕⊕⊕O)

1.2 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|⊕⊕OO)

Technical remark: Sitting height is measured directly using a sitting height stadiometer, and the lower segment can be determined by subtracting sitting height from standing height. Alternatively, the lower segment can be determined by measuring from the pubic symphysis to the floor, and the upper segment can be determined by subtracting leg length from height. The upper to lower segment ratio can then be calculated but differs depending on the method used and ethnicity. In situations where clinicians are unable to measure sitting height, measuring arm span and comparing it to standing height will provide an estimate of spinal foreshortening due to prior spinal radiation.

Treatment of short stature/impaired linear growth in childhood cancer survivors

1.3 We suggest against using growth hormone in cancer survivors who do not have growth hormone deficiency to treat for short stature and/or poor linear growth following spinal irradiation. (2|⊕OOO)

1.4 We suggest against treatment with growth hormone in children with short stature and/or impaired linear growth who are being treated with tyrosine kinase inhibitors. (2|⊕OOO)

Growth hormone deficiency in childhood cancer survivors

Diagnosis of growth hormone deficiency in childhood cancer survivors

2.1 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)

Technical remark: The consensus of the writing committee is to assess height in children every 6 to 12 months.

2.2 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)

2.3 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)

2.4 We recommend against the use of growth hormone–releasing hormone alone or in combination with arginine in childhood cancer survivors to diagnose growth hormone deficiency after hypothalamic–pituitary axis radiation. (1|⊕⊕OO)

2.5 We suggest against using spontaneous growth hormone secretion (*e.g.*, 12-hour overnight sampling) as a diagnostic test in determining GH deficiency in childhood cancer survivors. (2|⊕OOO)

2.6 We recommend that formal testing to establish a diagnosis of growth hormone deficiency is not required in childhood cancer survivors with three other confirmed anterior pituitary hormone deficits. (1|⊕⊕OO)

2.7 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)

Treatment of growth hormone deficiency in childhood cancer survivors

2.8 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)

2.9 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)

2.10 In childhood cancer survivors who have chronic stable disease and thus may not ever be "disease-free" (particularly survivors treated for optic pathway tumors), we advise discussing the appropriateness of growth hormone treatment and its timing with their oncologist. (Ungraded Good Practice Statement)

2.11 We advise treating growth hormone-deficient childhood cancer survivors with similar growth hormone treatment regimens as are appropriate for individuals with growth hormone deficiency from the noncancer population. (Ungraded Good Practice Statement)

Central precocious puberty in childhood cancer survivors

Diagnosis of central precocious puberty in childhood cancer survivors

3.1 We recommend periodically assessing childhood cancer survivors for evidence of central precocious puberty if they have a history of hydrocephalus, tumors developing in or near the hypothalamic region, and/or have been exposed to hypothalamic–pituitary radiation. (1|⊕⊕⊕O)

3.2 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)

3.3 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)

Technical remark: 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 to primary gonadal injury rather than to the onset of central puberty.

Treatment of central precocious puberty in childhood cancer survivors

3.4 We advise that the indications and the type of treatment regimens for central precocious puberty in childhood cancer survivors should be similar to those used for central precocious puberty in the noncancer population. (Ungraded Good Practice Statement)

Hypogonadotropic hypogonadism in childhood cancer survivors

Diagnosis of luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors

4.1 We recommend screening for luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors exposed to hypothalamic–pituitary axis radiation at doses ≥30 Gy and in those with a history of tumors or surgery affecting the hypothalamic–pituitary axis region. (1|⊕⊕⊕O)

4.2 We advise using the same strategies to diagnose luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors as are used in the noncancer population. (Ungraded Good Practice Statement)

Treatment of luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors

4.3 We advise following the same treatment approach to luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors as is appropriate in the noncancer population. (Ungraded Good Practice Statement)

Central hypothyroidism–thyroid-stimulating hormone deficiency in childhood cancer survivors

Diagnosis of central hypothyroidism in childhood cancer survivors

5.1 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)

5.2 We advise using the same biochemical tests to screen for thyroid-stimulating hormone deficiency in childhood cancer survivors as are used in the noncancer population. (Ungraded Good Practice Statement)

5.3 We recommend against using serum triiodothyronine, thyroid-stimulating hormone surge analysis, or thyrotropin-releasing hormone stimulation to diagnose thyroid-stimulating hormone deficiency. (1|⊕⊕OO)

Treatment of thyroid-stimulating hormone deficiency in childhood cancer survivors

5.4 We advise using the same approach to treat thyroid-stimulating hormone deficiency in childhood cancer survivors as is used in the noncancer population. (Ungraded Good Practice Statement)

Adrenocorticotropic hormone deficiency in childhood cancer survivors

Diagnosing adrenocorticotropic hormone deficiency in childhood cancer survivors

6.1 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)

6.2 We suggest screening for adrenocorticotropic hormone deficiency in childhood cancer survivors exposed to between ≥24 Gy and 30 Gy hypothalamic–pituitary radiation who are >10 years postradiation or develop clinical symptoms suggestive of adrenocorticotropic hormone deficiency. (2|⊕OOO)

6.3 We advise using the same screening and dynamic testing procedures to diagnose adrenocorticotropic hormone deficiency in childhood cancer survivors as are used in the noncancer population. (Ungraded Good Practice Statement)
Technical remark: Clinicians should consider the influence of oral estrogen on total cortisol levels, as it can increase cortisol-binding globulin raising total, but not free, cortisol levels.

Treating adrenocorticotropic hormone deficiency in childhood cancer survivors

6.4 We advise that clinicians use the same glucocorticoid regimens as replacement therapy in childhood cancer survivors with adrenocorticotropic hormone deficiency as are used in the noncancer population with adrenocorticotropic hormone deficiency. (Ungraded Good Practice Statement)

6.5 We recommend that clinicians instruct all patients with adrenocorticotropic hormone deficiency regarding stress dose and emergency glucocorticoid administration and instruct them to obtain an emergency card/bracelet/necklace regarding adrenal insufficiency and an emergency kit containing injectable high-dose glucocorticoid. (1|⊕⊕⊕O)

Commissioned Systematic Review

The Guideline Writing Committee commissioned two systematic reviews to support this guideline. The first systematic review aimed to evaluate the effect of GH treatment (GHT) in childhood cancer survivors on adult height (AH), risk of type 2 diabetes mellitus (T2DM), abnormal lipids, metabolic syndrome, quality of life, secondary tumors, and disease recurrence. Studies showed that GHT vs no GHT in this patient group was associated with a significant gain in AH and no significant association with the occurrence of secondary tumors or tumor recurrence. Studies that compared childhood cancer survivors receiving GHT to normal age- or sex-matched controls or controls with idiopathic GH deficiency (GHD) or short stature showed that GHT was associated with either improved or unchanged risk of T2DM, lipid profile, or metabolic syndrome. GHT was also associated with improvement in quality of life.

The second systematic review aimed to determine the best screening and diagnostic tests for GHD in childhood cancer survivors exposed to hypothalamic–pituitary radiation. The major challenge in this review was the lack of a "gold" standard to diagnose GHD. There was high variability in the confirmatory testing each study used. The insulin tolerance test (ITT) seems to be the most accepted reference test in the reviewed studies, either alone or in combination with arginine; although standardization of the testing dose and strategy among different practice groups is lacking. Studies included in this report spanned 4 decades; therefore, changes in clinical practice and assay methods can account for some of this variability. IGF-I and IGF-binding protein 3 had a suboptimal diagnostic accuracy, and their results were correlated. The patterns of diagnostic accuracy of all the tests evaluated suggested a similar pattern to what we see in patients who are not childhood cancer survivors.

Introduction

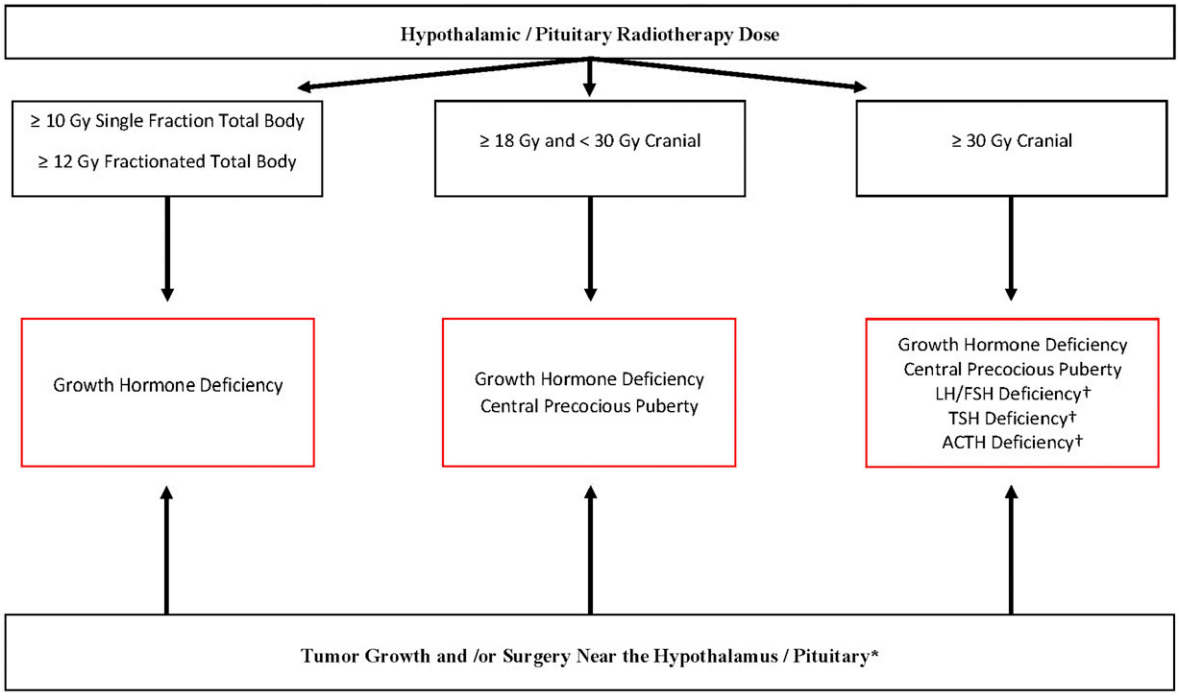
Cancers are relatively rare in the pediatric age group and account for only ~1% of the cancer burden in the entire population (1). Due to improvements in treatment and supportive care, current 5-year survival rates are >80% overall (2). The number of childhood cancers survivors is ever increasing and by the year 2020, it is estimated that there will be half a million survivors of childhood cancer residing in the United States. As the number of survivors has increased, there has been a growing awareness that survivors are at far greater risk of developing serious medical complications compared with noncancer controls (3). In particular, endocrine disorders are highly

prevalent among cancer survivors; recent data indicate that 40% to 50% of survivors will develop at least one endocrinopathy over the course of their lifetime (4, 5). Risk of developing endocrine disorders is dependent on a wide range of variables, including host (*e.g.*, age, sex, genetic background), disease (*e.g.*, diagnosis, tumor location), and treatment (*e.g.*, surgery, chemotherapy, radiation) factors. Radiation exposure to key endocrine organs (*e.g.*, hypothalamus, pituitary, thyroid and gonads) is the single most important risk factor and puts survivors at extremely high risk of developing an endocrine abnormality over time. Importantly, radiation-induced abnormalities are, in general, both dose- and time-dependent such that the higher the dose and the longer the interval following treatment, the greater the risk. Thus, endocrine disorders may not develop for decades after completion of cancer treatment, underscoring the critical importance of lifelong surveillance for those at risk (4, 5).

The current guideline focuses on the diagnosis and treatment of abnormalities of the hypothalamic–pituitary (HP) (Fig. 1) and management of growth disorders commonly encountered in childhood cancer survivors. Impaired linear growth and short AH can be due to both endocrine [*e.g.*, central precocious puberty (CPP), GHD] and nonendocrine (*e.g.*, medications, poor nutrition, radiation to the spine) factors. Not surprisingly, those diagnosed and treated for cancer at the youngest ages are the most affected. Currently, the only proven therapies for short stature are confined to the treatment of CPP and GHD, which follow the same general principles used in children without a cancer history.

Abnormalities of the HP are observed in survivors with tumors in the region of the HP, following surgery in the region of the HP, or, most commonly, following radiation to the HP (Fig. 1). Although HP dysfunction is generally observed acutely in individuals with tumors and/or surgery in the region of the HP, HP dysfunction is usually not observed for months to years following HP radiation. Whereas CPP and GHD occur following relatively low doses of HP radiation [*e.g.*, ≥18 Gy following standard fractionation, ≥12 Gy following hyperfractionation in the setting of total body irradiation (TBI)], deficits of the other anterior pituitary hormones [LH/FSH, thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH)] develop almost exclusively in survivors previously exposed to HP doses ≥30 Gy. For the most part, the diagnosis and treatment of anterior pituitary deficits in cancer survivors follow the same general principles as are used in the noncancer population.

Although there have been a large number of excellent studies assessing disordered growth and HP abnormalities in this population that have informed this guideline, limitations exist. The focus of most studies has been on understanding prevalence and risk factors for the various outcomes, with fewer studies addressing diagnosis and management. Most of the data are descriptive and often limited to relatively small case series. Furthermore, much of the data relate to survivors treated in prior decades



†Deficiencies in LH/FSH, TSH and / or ACTH may appear after treatment with lower doses of radiotherapy with longer follow-up.
*Tumor and surgery –induced damage may acutely cause multiple hypothalamic-pituitary deficits in addition to central diabetes insipidus.

Figure 1. Common hypothalamic pituitary late effects in survivors of childhood cancer.

with therapies that may have been abandoned [*e.g.*, prophylactic cranial radiation therapy (CRT) for acute lymphoblastic leukemia] or modified in the current era [*e.g.*, reduced dose craniospinal irradiation (CSI) for medulloblastoma]. Data on the late effects of newer treatments such as targeted biologicals, immune modulators, and conformal radiation with protons are extremely limited. Additional areas requiring further research include: management of impaired growth following spinal radiation and in those receiving long-term therapy with tyrosine kinases such as imatinib; optimal frequency and duration of screening studies following HP radiation; and risks and benefits of GHT in adult survivors of childhood cancer.

1. Short Stature/Impaired Linear Growth in Childhood Cancer Survivors

Epidemiology, morbidity, and mortality

Impaired growth is defined by a loss in height SD over time and may be transient or progressive. Short stature is characterized by a standing AH of >2 SD below the mean for age and sex. Growth impairment and short stature in childhood cancer survivors may result from: alterations in HP hormone secretion due to tumors in the suprasellar/optic pathway region, surgery or CRT involving the HP axis, primary hypothyroidism (resulting from thyroidal radiation or high-dose alkylating agent chemotherapy) (6, 7), and radiation-induced impairment of spinal growth. The effects of both cranial and spinal radiation are dose- and time-dependent. Additional causes of growth impairment may include a malnourished state, growth suppressive effects of medications (*e.g.*, glucocorticoids, tyrosine kinase inhibitors [TKIs]), and medications associated with accelerated epiphyseal/physeal closure, such as retinoids.

The prevalence of adult short stature ranges from ~9% in studies of childhood acute leukemia survivors (8–10) to as high as 40% among survivors of childhood brain tumors (11).

Etiology and clinical manifestations

The major risk factors for impaired growth and short stature in cancer survivors are CRT, CSI, TBI, and younger age at the time of treatment (Table 1). Exposure to 18 to 30 Gy CRT may result in GHD and precocious puberty, whereas doses >30 Gy may result in multiple pituitary hormone deficiencies (12, 13). Exposure to CRT can also result in an earlier onset or altered tempo of puberty, including onset of breast development between ages 8 and 9 years, peak height velocity at age ≤10 years, and early menarche (14–18). Importantly, children who have both GHD and concomitant early or precocious puberty may not demonstrate a significant growth deceleration due to the stimulatory effects of sex hormones on linear growth, and the treating endocrinologist might miss a diagnosis of GHD unless he/she is knowledgeable in this regard.

Table 1. Established Risk Factors of Short Stature and HP Dysfunction in Childhood Cancer Survivors

Complication	Host Factors	High Risk Treatment Exposures
Short AH or impaired linear growth	• Younger age at cancer/tumor treatment • Precocious puberty • Genetic syndromes (such as neurofibromatosis type 1) • Fanconi anemia	• Radiation fields involving the HP region[a] • Spinal irradiation[b] • TBI • Glucocorticoids • TKIs • Retinoic acid
GHD	• Younger age at cancer/tumor treatment • Greater elapsed time since cancer/tumor treatment	• Tumor or surgery involving the HP region • HP radiation ≥18 Gy • TBI ≥10 Gy in single fraction • TBI ≥12 Gy fractionated
CPP	• Younger age at cancer/tumor treatment • Female sex • Increased body mass index • Neurofibromatosis type 1	• Tumor or surgery involving HP region or optic pathways • Hydrocephalus • HP radiotherapy ≥18 Gy
LH/FSHD	• Greater elapsed time since cancer/tumor treatment • Presence of other HP deficits	• Tumor or surgery involving the HP region • HP radiation ≥30 Gy
TSHD	• Greater elapsed time since cancer/tumor treatment • Presence of other HP deficits	• Tumor or surgery involving the HP region • HP radiation ≥30 Gy
ACTHD	• Greater elapsed time since cancer/tumor treatment • Presence of other HP deficits	• Tumor or surgery involving the HP region • HP radiation ≥30 Gy

[a]Cranial, infratemporal (ear), nasopharyngeal, orbital (eye), and Waldeyer's ring.

[b]Also includes fields involving the abdomen, chest, mediastinum, and pelvis.

Boney structures previously exposed to radiation may be at risk for poor growth; this effect is potentially greater with higher radiation doses and younger age at exposure. Exposure to spinal radiation can result in disproportionate short stature due to impaired spinal growth, which helps differentiate spinal radiation–related growth impairment from the symmetrical impairment caused by other etiologies, such as GHD.

Systemic therapy with retinoic acid and its derivatives is associated with premature epiphyseal closure in both animal models and human studies of noncancer populations (19). Studies of survivors of high-risk neuroblastoma reveal a significantly greater incidence of advanced bone ages in those treated with *cis*-retinoic acid (20, 21). This premature advancement and earlier closure of growth plates may explain, at least in part, the short AH seen in survivors treated with multimodality therapy that includes systemic *cis*-retinoic acid.

TKIs are targeted cancer therapies designed to disrupt specific signaling pathways involved in cellular growth and proliferation. Despite their intended specificity, nonselective, off-target effects on various protein kinases involved in chondrocyte accrual, as well as the GH/IGF-I signaling pathway, may result in growth deceleration and the potential for subsequent short AH (22).

Diagnosis and monitoring of short stature/impaired linear growth in childhood cancer survivors

1.1 We recommend prospective follow-up of linear growth for childhood cancer survivors at high risk for short AH, namely those exposed to CRT, CSI, or TBI at a young age and those with a history of inadequate weight gain or prolonged steroid requirement. (1|⊕⊕⊕O)

1.2 We recommend measuring standing height and sitting height in childhood cancer survivors treated with radiation that included the spine (*i.e.*, TBI, CSI, as well as radiation to the chest, abdomen, or pelvis). (1|⊕⊕OO)

Technical remark: Sitting height is measured directly using a sitting height stadiometer, and the lower segment can be determined by subtracting sitting height from standing height. Alternatively, the lower segment can be determined by measuring from the pubic symphysis to the floor, and the upper segment can be determined by subtracting leg length from height. The upper to lower segment ratio can then be calculated but differs depending on the method used and ethnicity. In situations where clinicians are unable to measure sitting height, measuring arm span and comparing it to standing height will provide an estimate of spinal foreshortening due to prior spinal radiation.

Evidence

The risk of growth impairment and adult short stature (height SD < -2 SD) in survivors of childhood leukemia is significantly higher among survivors treated before puberty, at younger ages, and at CRT doses >20 Gy (10, 23, 24). Among studies of survivors of leukemia, lymphoma, and a broad group of pediatric cancers (*e.g.*, osteosarcoma, Wilms' tumor, neuroblastoma, and soft tissue tumors of the head and neck), younger age at diagnosis and higher doses of CRT remained significant risk factors for adult short stature (9, 18). In a large study of 921 brain tumor survivors exposed to high-dose CRT, Gurney *et al.* (11) found that a significant number of adults diagnosed at younger ages had an AH <10th percentile, including 53% of those diagnosed before age 5 years, 46% of those diagnosed between 5 and 9 years, and 26% of those diagnosed between 10 and 20 years. Independent of age, those exposed to higher doses of CRT were more likely to have adult short stature than those not treated with CRT, with a threefold increased risk among those treated with >20 Gy and a fivefold increased risk among those treated with >60 Gy. These findings may be due to the development of multiple hormone aberrations, as detailed in subsequent sections of these guidelines.

Spinal radiation is an independent risk factor for short AH (10) and is associated with progressive growth impairment (25, 26). Survivors treated with higher doses of spinal radiation (>20 Gy) at younger ages, and to a larger volume of the spine, are at increased risk of short AH (11, 27). Compared with the proportionate short stature seen in GHD children resulting from CRT only, short AH associated with spinal irradiation results in disproportionate short stature, which is evident in the greater loss of spinal height SD relative to lower leg length SD (28–30). This disproportionate growth may be evident as early as 1 year following spinal radiation and becomes progressively more evident during puberty (26). Survivors treated with high-dose CSI (*e.g.*, >30 Gy for medulloblastoma) demonstrate the most significant losses in seated and standing AH (17, 25, 31).

Treatment of short stature/impaired linear growth in childhood cancer survivors

1.3 We suggest against using GH in cancer survivors who do not have GHD to treat for short stature and/or poor linear growth following spinal irradiation. (2|⊕OOO)

1.4 We suggest against treatment with GH in children with short stature and/or impaired linear growth who are being treated with TKIs. (2|⊕OOO)

Evidence

Studies on using GH to treat cancer survivors who do not have GHD are limited to a few small case series. In a study of 13 survivors of acute leukemia treated with cyclophosphamide and TBI, three of whom were not GH deficient, there was a progressive decline in height SD and impaired spine and leg growth despite GHT during a 3-year period (32). In a report of 51 high-risk neuroblastoma survivors treated with multimodal therapy (including TBI), Cohen *et al.* (33) described GHT in seven of these survivors. One had GHD, and six were initially thought to have GH neurosecretory dysfunction. Although short-term response to GH was good, the long-term response was not; of the two that achieved AH, even the patient with GHD remained >2 SD below midparental height.

Studies of GHD childhood cancer survivors treated with GH who were exposed to spinal irradiation also suggest a reduced benefit of GHT after spinal irradiation. Ciaccio *et al.* (34) found that among GH-deficient medulloblastoma survivors treated with 26 to 38 Gy CSI, the mean adult standing height decreased from −1.38 SD to −1.9 SD at AH in those treated with GH, whereas the standing height of those not treated with GH decreased from −1.55 SD to −3.4 SD. However, spinal heights in both groups were similar at AH, that is, −4.56 SD and −4.85 SD, respectively. In another study of 100 survivors with GHD treated with GH, those exposed to CSI had significantly lower growth responses to GHT (4.2 cm/y vs 6.7 cm/y) and significantly greater height loss from time of radiation to AH (−3.6 SD vs −1.6 SD) than those not exposed to spinal radiation (35). Any benefit to AH of GHT may be at the expense of further disproportionate growth (17, 31). Thus, full disclosure of this risk should be made and individual preferences considered when counseling survivors and their families about GHT in patients who have received spinal radiation treatment (RT).

Childhood cancer survivors exposed to TBI are also at risk for reduced spinal height, with the greatest risk among those treated at a younger age and with unfractionated TBI (29, 36, 37). Members of this patient subgroup who receive GHT for GHD may improve AH by preventing further height loss (38, 39); however, they may experience a worsening disproportion due to lack of spinal height gain (37, 40).

TKIs (such as imatinib and dasatinib) are mainstay treatments for chronic myelogenous leukemia and other malignancies that possess the BCR-ABL1 fusion protein; patients generally are treated with them for the long term to maintain molecular remission (41). Most studies report decreased growth in children who are using TKIs, with greater effects observed in prepubertal children and conflicting evidence of catch-up growth in pubertal children (42–44). Although the precise mechanisms underlying the growth deceleration associated with TKI therapy are unknown, reports of low serum IGF-I levels in children on TKI therapy suggest a possible disruption of the tyrosine kinases involved in the GH signaling cascade (44). Additional proposed mechanisms for growth failure include disrupted platelet-derived growth factor receptor-β, leading to altered recruitment and activity of chondrocytes.

We consider patients on continuous TKI therapy as having an active malignancy, as many will develop molecular evidence of persistent disease when TKI therapy is discontinued. Data on the safety and efficacy of GH use in these patients are quite limited (41); therefore, we cannot generally recommend GHT in this setting.

2. GHD in Childhood Cancer Survivors

GHD is characterized by inadequate GH secretion from the pituitary and is defined using different diagnostic tests. GHD can result from damage to the HP area due to tumors, surgery, and/or HP axis RT (8, 45–47). Additionally, researchers have described a few cases of GHD associated with the TKI imatinib (48, 49), and the immune modulator ipilimumab can cause hypophysitis (50).

GHD is the most common endocrine late effect in childhood cancer survivors treated with CRT (46, 51, 52). The prevalence of GHD varies depending on the type of tumor and treatment and is most frequent in survivors of suprasellar tumors and after high-dose HP axis RT (45–47). Adults with hypopituitarism on conventional hormone therapy that does not include GHT have an increased cardiovascular mortality in comparison with the general population (53, 54).

Clinical manifestations

GHD that develops in childhood usually affects linear growth (8, 55, 56). GHD in the cancer population has similar symptoms as we see in the noncancer population and may be associated (particularly in adults) with reduced lean body mass and increased fat mass, an adverse lipid profile, increased cardiovascular morbidity, impaired bone mineral density, impaired quality of life, and psychosocial problems (57–61). In a large cohort of 695 survivors of childhood cancer enrolled in the St. Jude Lifetime Cohort study, survivors with untreated GHD were more likely to have an increased weight-to-height ratio, decreased lean muscle mass, low energy expenditure, muscle weakness, and poor exercise tolerance compared with individuals without GHD (47).

Diagnosis of GHD in childhood cancer survivors

2.1 We recommend lifelong periodic clinical assessment for GHD in survivors treated for tumors in the region of the HP axis and in those exposed to HP axis RT ≥18 Gy (*e.g.*, various brain tumors, nasopharyngeal carcinoma, acute lymphoblastic leukemia, lymphoma). (1|⊕⊕⊕O)
Technical remark: The consensus of the writing committee is to assess height in children every 6 to 12 months.

2.2 We recommend against relying solely on serum IGF-I levels in childhood cancer survivors exposed to HP axis radiotherapy to make the diagnosis of GHD. (1|⊕⊕OO)

2.3 We advise using the same provocative testing to diagnose GHD in childhood cancer survivors as are used for diagnosing GHD in the noncancer population (Table 2). (Ungraded Good Practice Statement)

2.4 We recommend against the use of GHRH alone or in combination with arginine in childhood cancer survivors to diagnose GHD after HP axis radiation. (1|⊕⊕OO)

2.5 We suggest against using spontaneous GH secretion (*e.g.*, 12-hour overnight sampling) as a diagnostic test in determining GHD in childhood cancer survivors. (2|⊕OOO)

2.6 We recommend against formal testing to establish a diagnosis of GHD in childhood cancer survivors with three other confirmed anterior pituitary hormone deficits (Table 2). (1|⊕⊕OO)

2.7 We recommend retesting adult cancer survivors exposed to HP axis RT and with a diagnosis of isolated GHD in childhood (Table 2). (1|⊕⊕OO)

Evidence

HP axis radiation is a potent cause of GHD and the risk is directly related to the total dose delivered, the dose

Table 2. Related Guidelines Content

Recommendation Number	Guideline Title	Organization	Publication Year
Guidelines relevant to the diagnosis content of this guideline			
2.3, 2.6, 2.7	Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency	Pediatric Endocrine Society	2017
4.2, 5.2, 6.3	Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2016
Guidelines relevant to the treatment content of this guideline			
2.11	Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2011
	Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2016
	Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency	Pediatric Endocrine Society	2017
4.3	Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2018
	Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2015
	Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2016
5.4	Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2016
6.4	Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2016
	Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline	Endocrine Society	2016

per fraction, and the time interval postirradiation (62–64). HP axis RT in children frequently causes abnormal HP function later in life (65). HP axis RT initially affects the hypothalamus, which is more sensitive to irradiation than is the anterior pituitary, based on responses to anterior pituitary–releasing hormone stimulation in patients with anterior pituitary hormone deficiencies (65, 66). GHD is usually the first established endocrine sequela of HP axis RT (51, 63). The prevalence varies depending on the population studied, follow-up time, type of stimulation test used, and peak GH cut-off levels (67).

GHD is a frequent consequence in childhood cancer survivors treated for tumors in the region of the HP (45, 68) and in brain tumor and nasopharyngeal carcinoma survivors exposed to HP axis radiotherapy ≥30 Gy (47, 62, 69). Furthermore, GHD is also reported in some acute lymphoblastic leukemia and lymphoma survivors exposed to 18 to 24 Gy to the HP axis (23, 70–72). In the even lower doses used for hematopoietic stem cell transplantation, GHD may occur after a single TBI dose of 10 Gy or fractionated doses of 12 Gy (73); however, with repeated assessments over time, there can be recovery (40).

In children, auxologic data collected every 6 to 12 months should be considered as the initial screen for GHD. Clinicians should further investigate for GHD when there is either linear growth deceleration or no linear growth acceleration during puberty and when they have ruled out other potential etiologies of growth failure (*e.g.*, undernutrition, spinal compromise, hypothyroidism, hypogonadism). Age-adjusted IGF-I levels measured in an accredited laboratory may be useful in screening for severe GHD but have limited utility when using a cut-off of −2 SD (52, 59, 74, 75). For example, Weinzimer *et al.* (74) found a sensitivity of 73% for IGF-I for the prediction of GHD in children with brain tumors. Additionally, clinicians need to interpret IGF-I levels in the context of sex steroid exposure (precocious puberty and hypogonadism). In adults, symptoms of GHD are nonspecific. GH testing should be considered in at-risk individuals with fatigue, increased abdominal fat mass, weight gain, low energy level, or hyperlipidemia. As for children, IGF-I levels may be useful in screening for severe GHD.

Clinicians who suspect GHD in childhood cancer survivors should perform provocative testing unless there are three other pituitary hormone deficiencies (76). In the general population, GHD is established via stimulation testing using the ITT, glucagon, arginine, levodopa, clonidine, or GHRH-arginine (if available) (77–79). Clinicians should not administer GHRH alone when the damage is primarily hypothalamic, as after radiation therapy, because it may give false-negative results (*i.e.*, normal GH responses despite true GHD). Likewise, the GHRH-arginine test can give a falsely normal GH response (71, 78, 80). Both ITT and glucagon testing allow evaluation of the complete hypothalamic–somatotroph axis (81). Based on a recent meta-analysis, the ability to diagnose GHD by different provocative tests after CRT is similar to the general population, with the ITT being most reliable; however, data are limited (82).

The same GH cut-off levels to stimuli are used in childhood cancer survivors as in the general population. Comparing studies to assess prevalence or incidence of GHD is problematic due to the use of different GH antibodies, GH standards, and GH assays (83), as well as the poor reproducibility of these tests (84). Data in noncancer pediatric populations suggest that clinicians often misdiagnose children as having GHD, especially when using peak GH values of 5 to 10 μg/L (83).

Older studies suggested that some children have GH neurosecretory dysfunction after cranial radiation, especially after low doses, where there is subnormal spontaneous GH secretion despite normal GH responses to stimulation testing (85). However, Darzy *et al.* (86) demonstrated normal physiologic GH secretion in adults who received cranial radiation in childhood, suggesting that this particular entity (radiation-induced GH neurosecretory dysfunction) either does not exist or is very rare. Additionally, due to the poor reproducibility of 12-hour overnight GH sampling and the overlap of responses in normal children and nonchildhood cancer survivors with GHD (76), as well as the impracticality of this test in clinical practice, we suggest against using spontaneous GH sampling, for example, 12-hour overnight sampling, as a diagnostic test in determining GHD in the childhood cancer survivors. In adults, the peak GH cut-off levels to diagnose GHD range from 3 to 5 μg/L for ITT and 3 μg/L for glucagon (52, 87, 88). Obesity, sex-steroid deficiency, and hypothyroidism can blunt GH secretion and yield a false-positive result (*e.g.*, falsely low GH levels) (83); for example, in an obese individual, the cut-off of 1 μg/L is used for glucagon (89, 90).

Treatment of GHD in childhood cancer survivors

2.8 We recommend offering GHT in childhood cancer survivors with confirmed GHD based on the safety and efficacy demonstrated in that population. (1|⊕⊕OO)

2.9 In childhood cancer survivors, we suggest waiting until the patient has been 1 year disease-free following completion of therapy for malignant disease, before initiating GHT. (2|⊕OOO)

2.10 In childhood cancer survivors who have chronic stable disease and thus may not ever be "disease-free" (particularly survivors treated for optic

pathway tumors), we advise discussing the appropriateness of GHT and its timing with their oncologist. (Ungraded Good Practice Statement)

2.11 We advise treating GH-deficient childhood cancer survivors with similar GHT regimens as are appropriate for individuals with GHD from the noncancer population (Table 2). (Ungraded Good Practice Statement)

Evidence

GHT is approved for both children and adults with confirmed GHD. GH dosing guidelines in the transition period after growth cessation are not well established. However, as GH secretion and IGF-I levels peak in puberty and decline overtime thereafter (91, 92), the effective GH dose needs to be higher in the transition period after growth cessation than in adulthood.

Childhood cancer survivors with GHD who receive GHT have a significant gain in height as compared with those who are not treated [see accompanying meta-analysis (82)]. However, those childhood cancer survivors with GHD who were also treated with CSI or TBI may have impaired spinal growth and not achieve target height. Higher spine radiation doses and radiation at a younger age are associated with impaired spinal growth (see section 1. "Short Stature/Impaired Linear Growth in Childhood Cancer Survivors"). GHT results in either an improvement or no difference in the risk of T2DM, dyslipidemia, and metabolic syndrome [see accompanying meta-analysis (82)]. The discrepant results between studies may be due to metabolic improvements being offset by the effect of GH on increasing insulin resistance. Likewise, quality of life after GHT is either improved or unchanged (58, 60, 93).

Concerns have been raised regarding the long-term safety of GHT in childhood cancer survivors, as GH and the target hormone, IGF-I, have *in vitro* proliferative effects, and IGF-I also has proangiogenic and antiapoptotic properties (94). Available data on the safety of GH in childhood cancer survivors are based on observational studies with selection bias and a lack of randomized placebo-controlled studies. Childhood cancer survivors have an increased risk of developing meningioma and glioma due to radiation exposure (95, 96); they also are at risk for GHD and will be potential candidates for GHT (67). Previous data on GH-treated childhood cancer survivors indicated that GHT might potentially induce a small increase in the relative risk of developing second neoplasms compared with survivors not receiving GHT (97, 98), with research indicating that meningiomas are the most common second neoplasm (97). However, the elevated risk decreased over time (99). Although the reason for this decrease is unknown, it has been speculated that GH-treated individuals may have been subjected to earlier and increased surveillance (100). Recent studies have shown no significant association between GHT and the development of a second neoplasm of the central nervous system (CNS) in childhood cancer survivors (100–102). In the systematic review and meta-analysis conducted for this guideline, there was no statistically significant difference in the occurrence of secondary tumors in survivors treated with GH compared with those not treated (OR, 1.34; 95% CI, 0.92 to 1.96). Similarly, studies show no significant change in the risk of tumor recurrence in survivors treated with GH, compared with those not treated (overall OR, 0.57; 95% CI, 0.31 to 1.02) [see accompanying meta-analysis (82)]. At a recent workshop, the Growth Hormone Research Society concluded that there are no indications of an increased risk of recurrence of primary cancers after GHT in children, and the association between GHT and risk of second tumors is insufficient to make recommendations against GHT (103).

However, few data are available to provide recommendations when to initiate GHT after cancer treatment (103). Traditionally, clinicians start GHT for survivors of malignant tumors at least 1 year after a childhood cancer survivor is disease-free; thus, the safety of GHT prior to that time is not clear. An exception is craniopharyngiomas (which are considered benign tumors); in these cases, GHT has been safely initiated earlier (as early as 0.7 year from diagnosis) (104). Additionally, there are patients who may have stable disease, rather than being disease-free. This is often the case in subjects with optic pathway gliomas (low-grade tumors frequently found in association with neurofibromatosis type 1). In these cases, disease can remain stable for prolonged periods, despite radiation and/or chemotherapy treatments (105). For these patients, clinicians should discuss whether to initiate GHT and its timing with the patient's oncologist.

It is important to note that GHT in children with GHD who had been treated with CSI and TBI may result in improvement in leg length but not spinal height (see section 1. "Short Stature/Impaired Linear Growth in Childhood Cancer Survivors"). Additionally, GHT may exacerbate an existing scoliosis, a condition not uncommon following either spinal surgery and/or spinal RT. GHT in the noncancer population is associated with an increased incidence of slipped capital femoral epiphysis (SCFE) (76). GHT in the noncancer population also commonly results in a decrease in insulin sensitivity and a compensatory increase in insulin secretion (76). As childhood cancer survivors are at increased risk for both SCFE (106) and metabolic

syndrome (107, 108) (particularly after TBI), the potential risk for SCFE and T2DM should be a factor when clinicians consider GHT in survivors. Therefore, when considering GHT, clinicians need to carefully weigh the potential risks against the potential benefits. Similar to the Pediatric Endocrine Society's recommendations for the noncancer population (76), we recommend that clinicians monitor serum IGF-I concentrations in patients on GHT and ensure they are kept within the normal range for sex, age, and pubertal status.

3. Central Precocious Puberty in Childhood Cancer Survivors

Epidemiology, morbidity, and mortality

The prevalence of CPP in childhood cancer survivors is estimated at 11.9% to 15.2% (109, 110). CPP in the context of a CNS insult may be associated with the accelerated fusion of the growth plates and potentially significant losses in AH (109, 111). Early sexual development may also result in challenges regarding the psychosocial adjustment of patients (112).

Etiology and clinical manifestations

CPP is defined by the onset of pubertal development before the age of 8 years in girls and 9 years in boys as a result of the premature activation of the HP gonadal axis (109, 113). Table 1 summarizes the risk factors of CPP in childhood cancer survivors.

Diagnosis of central precocious puberty in childhood cancer survivors

3.1 We recommend periodically assessing childhood cancer survivors for evidence of CPP if they have a history of hydrocephalus, tumors developing in or near the hypothalamic region, and/or have been exposed to HP radiation. (1|⊕⊕⊕O)

3.2 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)

3.3 We recommend measuring serum testosterone, preferably using liquid chromatography–tandem mass spectroscopy, and LH 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 CPP and were exposed to gonadotoxic treatments. (1|⊕⊕OO)

Technical remark: 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 to primary gonadal injury rather than to the onset of central puberty.

Evidence

CPP is among the most common endocrine complications in children with tumors arising near the hypothalamus or optic pathways (such as low-grade gliomas), and it is often associated with neurofibromatosis type 1 (109, 111, 113–115). The prevalence of CPP in patients with these tumors is between 26% and 39% (109, 111, 115). Exposure to HP axis radiation at a wide range of doses (20 to 50 Gy) has also been associated with CPP, albeit with a lower frequency (6.6%) (109). Additional risk factors for CPP include hydrocephalus (113), young age at HP axis RT, and (in patients exposed to HP axis RT) female sex and increased body mass index (110, 116).

The clinical diagnosis of pubertal onset in female childhood cancer survivors primarily relies on the observation of breast development (as in the noncancer population). The diagnosis of pubertal onset in male childhood cancer survivors previously exposed to gonadotoxic treatments (*e.g.*, alkylating agents, testicular radiation) requires a different approach than in males in the noncancer population, in whom increasing testicular volume is an early clinical indicator of the onset of puberty. Testicular volume is known to be affected by gonadotoxic cancer treatments because of germ cell and Sertoli cell injury (117–119). Research has indicated that testicular size plots below the 10th percentile for chronologic age in up to 50% of male survivors of acute lymphoblastic leukemia treated with CRT and extended abdominal radiotherapy (117), and it averages −2.0 SD in pediatric hematopoietic stem cell transplant recipients exposed to TBI (119). Studies have shown that the testes of adult childhood cancer survivors are significantly smaller than controls (118) and correlate with impaired germ cell function (120).

Given the limited reliability of testicular volume as a means of pubertal staging in male childhood cancer survivors treated with gonadotoxic modalities, laboratory markers such as AM serum testosterone and LH plasma levels may allow an earlier and more accurate assessment in this subset of patients whose Leydig cell function is less frequently affected than their germ cell function (117, 119). Liquid chromatography–tandem mass spectroscopy should preferably be used to measure serum testosterone levels (79). Medical providers should be aware that serum LH elevations could be due to primary gonadal injury rather than to the central onset of

puberty in patients exposed to gonadotoxic treatments, and clinicians should interpret laboratory data in the context of the patient's cancer history and clinical presentation (121). Measuring serum testosterone is especially helpful in boys exposed to gonadotoxic therapies and who are at risk for CPP given the challenges in the interpretation of clinical parameters (*e.g.*, testicular volume) and LH values. In girls with elevated gonadotropins, the assessment of pubertal progression based on Tanner staging (breast development), the measurement of estradiol levels, and the assessment of uterine length and shape via ultrasound can help distinguish between CPP and primary gonadal insufficiency (122).

As discussed in section 1 ("Short Stature/Impaired Linear Growth in Childhood Cancer Survivors"), the interpretation of growth velocity in childhood cancer survivors should be based not only on chronological age, but also on pubertal stage because of the frequent association between CPP and GHD (109, 111). Patients with genetic syndromes (such as neurofibromatosis type 1) and those exposed to craniospinal radiotherapy may also experience CPP (26, 123). GHD may compromise a patient's ability to experience linear growth acceleration during puberty in general and CPP in particular. Otherwise, the diagnostic work-up of childhood cancer survivors suspected of CPP follows the general steps followed in the general pediatric population (Table 2) (121, 124–126).

Treatment of central precocious puberty in childhood cancer survivors

3.4 We advise that the indications and the type of treatment regimens for CPP in childhood cancer survivors should be similar to those used for CPP in the noncancer population (Table 2). (Ungraded Good Practice Statement)

Evidence

Historical data on patients with tumor-related CPP who were not treated with pubertal suppression are scarce but suggest poor AH outcomes; although these patients may not have received treatment for other complications, including GHD (127). Studies have shown that pubertal suppression with gonadotropin-releasing hormone agonist (GnRHa) improves the AH of patients with CPP (not necessarily childhood cancer survivors) in comparison with their predicted AH at baseline (128–131). One study compared a cohort of 26 patients with CPP (31% related to a CNS insult) diagnosed at a young age (median 5 years) and treated with GnRHa to historical controls matched for demographic factors and etiology (131). The report showed a significant improvement in final or near AH in the treated group (-0.9 ± 0.3 SD in females, -1.7 ± 1.6 in males) in comparison with nontreated historical controls (-1.9 ± 0.2 in females, -3.2 ± 6.4 SD in males; $P = 0.01$ for both) (131). These data allow speculation that childhood cancer survivors with CPP most likely benefit from pubertal suppression with GnRHa (109, 113). Available AH data have nevertheless indicated that patients may not experience a complete recovery of their growth, and patients and families should be informed of the multifactorial nature of growth impairment in childhood cancer survivors (109, 129). Children with a history of hydrocephalus, HP tumors, and/or radiotherapy may experience nonprecocious but early onset puberty (8 to 9 years in girls or 9 to 10 years in boys) or rapid tempo of puberty (132, 133). Data are limited regarding the benefits of treatment with GnRHa on these forms of puberty in childhood cancer survivors, except in patients who also have GHD and in whom pubertal suppression, in association with GH therapy, seems to result in improved height outcomes (17, 132). There are no data supporting the use of GnRHa to augment the AH prospects of childhood cancer survivors experiencing normal pubertal development. The overall course of treatment of CPP in childhood cancer survivors can follow the advice in place for noncancer populations (121, 134).

4. Hypogonadotropic Hypogonadism in Childhood Cancer Survivors

Epidemiology, morbidity, and mortality

The estimated prevalence of LH/FSH deficiency (LH/FSHD) in childhood cancer survivors is 10.8% (47). Depending on the age of onset, LH/FSHD may manifest as delayed puberty (absence of signs of puberty after the ages of 13 years in girls and 14 years in boys) (135) or interrupted puberty, or LH/FSHD may manifest during adulthood as amenorrhea (females) or symptoms related to low testosterone (males). Untreated LH/FSHD in older childhood cancer survivors may be associated with adverse cardiovascular and bone health outcomes (47). Confounders related to the interpretation of low testosterone levels in obese men have complicated the understanding of the true impact of this problem (47, 136).

Etiology

LH/FSHD may occur within the context of panhypopituitarism following the direct anatomical injury of the HP area due to tumor growth or surgery. LH/FSHD may also occur as a late effect of HP axis radiation, especially at doses ≥30 Gy (47, 65, 137).

Diagnosis of LH/FSHD in childhood cancer survivors

4.1 We recommend screening for LH/FSHD in childhood cancer survivors exposed to HP axis radiation at doses ≥30 Gy and in those with a history of tumors or surgery affecting the HP axis region. (1|⊕⊕⊕O)

4.2 We advise using the same strategies to diagnose LH/FSHD in childhood cancer survivors as are used in the noncancer population (Table 2). (Ungraded Good Practice Statement)

Evidence

Childhood cancer survivors who are at risk for developing LH/FSHD because of their tumor or treatment history require periodic evaluation of their HP gonadal function (47, 65, 137–139). These assessments are important given the potential occurrence of LH/FSHD as a late effect and the rather nonspecific symptoms associated with this deficiency, especially in males (47, 79, 136).

The diagnosis of LH/FSHD in the general pediatric and adolescent population is complicated by the high prevalence of constitutional delay of growth in boys and by the presence of several congenital causes for LH/FSHD such as Kallmann syndrome, pituitary stalk interruption, and midline defects (140). Although such considerations may pertain to childhood cancer survivors experiencing pubertal delay, exposure to HP axis radiation and the presence of other pituitary deficiencies are generally robust indicators of LH/FSHD (135). Undetectable, low, or declining serum testosterone levels (males) or undetectable or low estradiol levels (females) in the setting of low or inappropriately normal levels of gonadotropins past 13 years of age in girls and 14 years of age in boys are suggestive of LH/FSHD during adolescence (135, 140). The diagnosis of LH/FSHD in adult childhood cancer survivors follows the same steps as those outlined by the Endocrine Society for the general population (79). Medical providers should cautiously interpret gonadotropin and sex hormone levels in obese or underweight individuals. It is important to note that childhood cancer survivors exposed to high-dose HP axis radiation, especially in the range ≥50 Gy, are at risk for developing hyperprolactinemia (65), which may also occur as a side effect of various drugs, especially antipsychotics. Hyperprolactinemia should be ruled out in patients with suspected LH/FSHD, as is the case in the general population (79).

Treatment of LH/FSHD in childhood cancer survivors

4.3 We advise following the same treatment approach to LH/FSHD in childhood cancer survivors as is appropriate in the noncancer population (Table 2). (Ungraded Good Practice Statement)

Evidence

Pubertal induction in adolescent female childhood cancer survivors with LH/FSHD can follow guidelines available for the general pediatric population (135, 140). The use of testosterone to induce puberty in boys during adolescence does not seem to adversely impact future fertility prospects in patients with LH/FSHD (141); however, data specific to childhood cancer survivors are limited (142).

Clinicians can use the same guidelines for the diagnosis and management of LH/FSHD in adult childhood cancer survivors as they do for adults with LH/FSHD (Table 2). Other measures potentially improving bone health, such as adequate dietary calcium intake and vitamin D supplementation, should be offered, along with sex hormone replacement (79). The benefits of estrogen replacement have been deemed to outweigh the risk of breast cancer in women 40 to 49 years in the general population (79). There are no data to support the need for a different approach in female childhood cancer survivors requiring estrogen/progesterone replacement for LH/FSHD. Preliminary studies do not support an increased risk of secondary breast cancer following spinal radiotherapy (143). In a recent study of hormone replacement therapy in women with premature ovarian insufficiency and a history of exposure to chest RT, the risk of breast cancer remained significantly lower than in childhood cancer survivors who retained normal ovarian function (144). Those with premature ovarian insufficiency who received hormone replacement therapy had a modestly increased risk of breast cancer, but not to the same degree as those with endogenous hormone production.

Medical providers should be aware of known drug interactions between antiepileptic medications and estrogen replacement, with potential repercussions on the efficacy of either treatment when the other is added or doses are changed (79). Antiepileptic drugs with enzyme-inducing properties (such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and topiramate) may decrease the efficacy of sex hormones by interfering with their metabolism or by increasing the secretion of sex hormone–binding globulin. Other, nonenzyme-inducing, antiepileptic drugs such as lamotrigine, valproate, and levetiracetam have been shown to cause changes in plasma sex hormone concentrations but the mechanisms are unknown. Conversely, estrogen replacement may increase seizure risk in patients treated for epilepsy because of increased neuron excitability and/or interference with drug metabolism (as with lamotrigine) (145).

Estrogen replacement therapy increases the production of thyroid-binding globulin and may decrease the production of IGF-I; these interactions may require increasing the doses of levothyroxine and human recombinant GH in patients on treatment of hypothyroidism and GHD, respectively (79). The effect of estrogen replacement on circulating IGF-I may be avoided if transdermal formulations are used in lieu of oral forms (79). Clinicians should discuss the risks and benefits of estrogen replacement with patients and base treatment decisions on relevant guidelines and patient preferences.

5. Central Hypothyroidism–TSH Deficiency in Childhood Cancer Survivors

Epidemiology, Morbidity, and Mortality

The diagnosis of central hypothyroidism or TSH deficiency (TSHD) is complicated, and there is no uniform definition by which to make the diagnosis. Most endocrinologists diagnose TSHD in a patient recognized to be at risk for hypothalamic damage based on a low-normal or below-normal free T4 (fT4) level with a TSH level in the normal, below normal, or mildly elevated range (146). The diagnosis is more likely when based on progressively declining fT4 levels over time (147, 148). In the context of this broad definition, studies have reported that the prevalence of TSHD in childhood cancer survivors who have CNS tumors or were treated with HP axis RT is 2.6% to 14.9% (47, 111, 149–157). Symptoms are subtle, often delaying diagnosis.

Etiology

TSHD and ACTH deficiency (ACTHD) are among the least common anterior pituitary hormone deficits. TSHD is most often present after high-dose HP RT (47, 151); however, neither TSHD nor ACTHD is commonly present with doses <24 Gy or after TBI. A study of adult survivors of childhood cancer reported TSHD in 7.5% of participants with HP RT dose ≥30 Gy as an independent risk factor (47). Clinicians should evaluate patients with tumors in the HP region for TSHD if they have had suprasellar surgery or other hypothalamic deficiencies.

Factors associated with TSHD include hypothalamic involvement, radiation site and dose, and time elapsed since radiation exposure (111, 150, 152, 156). In general, chemotherapeutic agents have not been associated with TSHD (150, 155).

Diagnosis of central hypothyroidism in childhood cancer survivors

5.1 We recommend lifelong annual screening for TSHD in childhood cancer survivors treated for tumors in the region of the HP axis and those exposed to ≥30 Gy HP radiation. (1|⊕⊕⊕O)

5.2 We advise using the same biochemical tests to screen for TSHD in childhood cancer survivors as are used in the noncancer population (Table 2). (Ungraded Good Practice Statement)

5.3 We recommend against using serum triiodothyronine, TSH surge analysis, or thyrotropin-releasing hormone stimulation to diagnose TSHD. (1|⊕⊕OO)

Evidence

Clinicians should obtain fT4 and TSH levels at least annually (47, 147, 149, 151, 152). An fT4 level at the lower limits of normal or below the reference range in conjunction with a low, normal, or mildly elevated TSH level that does not appear appropriate for the fT4 level in the setting of disruption to the hypothalamus or pituitary is evidence of TSHD. The case for TSHD is made stronger with progressively decreasing fT4 levels (148). TSHD can develop many years after radiation exposure, and for this reason we recommend lifelong surveillance (158).

Previous data indicated that hidden central hypothyroidism was an early, subtle hypothalamic abnormality that clinicians could detect via the TSH surge pattern or TSH response to stimulation testing (159). Subsequent research indicated that the abnormalities of TSH dynamics uncovered by TSH surge analysis and thyrotropin-releasing hormone stimulation testing represent subtle variations that are not indicative or predictive of TSHD (160).

Treatment of TSHD in childhood cancer survivors

5.4 We advise using the same approach to treat TSHD in childhood cancer survivors as is used in the noncancer population (Table 2). (Ungraded Good Practice Statement)

Evidence

The treatment of central hypothyroidism in childhood cancer survivors is no different than in other children/adolescents with TSHD. The thyroid axis is one of the more resilient axes, and there is an increased risk of damage to other HP endocrine axes, which should be addressed. Clinicians should therefore perform regular, careful surveillance for GHD, full and partial ACTHD, and abnormalities of LH/FSH secretion in childhood cancer survivors who had RT, tumors, or surgery in the area around the hypothalamus and pituitary and who are diagnosed with TSHD (13, 147, 149). Clinicians should confirm the existence of an intact adrenal axis before beginning thyroid hormone replacement, recheck fT4 levels 4 to 6 weeks after dose adjustment or starting GH replacement, and maintain fT4 levels in the middle to upper half of the normal range. TSH levels are not useful

in monitoring the adequacy of thyroid hormone replacement in subjects with TSHD (79, 161). Many survivors at risk for TSHD are also at risk for seizures, and treatment with antiepileptic medications such as phenytoin, carbamazepine, oxcarbazepine, and topiramate can accelerate the metabolism of thyroid hormones. Consequently, clinicians should monitor thyroid hormone levels after starting or changing the dose of antiepileptics (145, 162). Commonly used fT4 assays, which use competitive binding methods, may give artifactually low fT4 levels in patients who are treated with antiepileptics (*e.g.*, phenytoin, carbamazepine, oxcarbazepine) due to displacement of thyroid hormone from binding proteins (163). Confirmation of the low fT4 level by a direct method, such as equilibrium dialysis or ultrafiltration, may be indicated in these patients.

6. ACTHD in Childhood Cancer Survivors

Epidemiology, morbidity, and mortality

ACTHD is characterized by inadequate cortisol secretion due to impaired production/secretion of ACTH. It can result from damage to the hypothalamus and/or pituitary gland due to tumors and/or surgery in the HP region (*e.g.*, craniopharyngiomas, suprasellar germinomas, optic pathway gliomas) (45, 164, 165) or to HP injury following high-dose (>30 Gy) HP radiation (47).

The prevalence of ACTHD (excluding exogenous steroid use) varies by tumor type and treatment (164–166). ACTHD has been associated with increased morbidity and mortality in pediatric survivors (167, 168).

Etiology and clinical manifestations

We list the major risk factors for ACTHD in Table 1. Although transient ACTHD secondary to exogenous glucocorticoids is very common in this population, particularly during active cancer treatment, this guideline focuses on permanent forms of ACTHD. The clinical symptoms most commonly associated with ACTHD in cancer survivors are similar to those described in the noncancer population (79). Given the nonspecific nature of these symptoms, it may be very difficult to distinguish between symptoms related to the underlying cancer, comorbidities from the disease and its treatment, or the presence of ACTHD. Partial ACTHD may be asymptomatic; thus, clinicians might not diagnose it unless they have a high degree of suspicion.

Diagnosing ACTHD in childhood cancer survivors

6.1 We recommend lifelong annual screening for ACTHD in childhood cancer survivors treated for tumors in the HP region and in those exposed to ≥30 Gy HP radiation. (1|⊕⊕⊕O)

6.2 We suggest screening for ACTHD in childhood cancer survivors exposed to between ≥24 Gy and 30 Gy HP radiation who are >10 years post-radiation or develop clinical symptoms suggestive of ACTHD. (2|⊕OOO)

6.3 We advise using the same screening and dynamic testing procedures to diagnose ACTHD in childhood cancer survivors as are used in the noncancer population (Table 2). (Ungraded Good Practice Statement)

Technical remark: Clinicians should consider the influence of oral estrogen on total cortisol levels, as it can increase cortisol-binding globulin raising total, but not free, cortisol levels.

Evidence

Radiation-induced ACTHD is known to be both time- and dose-dependent (169). Following HP radiation, ACTHD appears to occur less commonly than GH and LH/FSH deficiencies and is present primarily in childhood cancer survivors treated with doses of HP radiation >30 Gy (47, 151, 166, 170, 171), although the precise prevalence varies depending on the population studied, length of follow-up, and the type of biochemical testing used (4% to 43%). The two largest studies to assess ACTHD risk following HP radiation reported most cases of ACTHD in survivors exposed to >30 to 40 Gy HP radiation (47, 166). Although ACTHD is uncommon in subjects treated with HP doses ≤24 Gy (47, 166, 170, 172), a recent study of adult survivors of acute leukemia followed for >10 years reported biochemical evidence of ACTHD in more than a third of survivors exposed to a mean HP dose of 24 Gy (173). Data indicate that new cases of ACTHD emerge as late as 25 or more years after HP radiation (47).

A variety of tests are available for diagnosing ACTHD, including the ITT, standard- and low-dose ACTH stimulation test, glucagon stimulation test, and the overnight oral metyrapone test. Controversy exists as to which modality is the most reliable in establishing a diagnosis of ACTHD, irrespective of the underlying cause (90, 166, 169, 174, 175). Additionally, several factors can affect the determination of cortisol levels in plasma, including changes in cortisol-binding globulin. Of note, females taking oral contraceptives have elevated cortisol-binding globulin levels, which can make the interpretation of cortisol levels difficult (174). Although many view the ITT as the "gold standard" to diagnose ACTHD, most clinicians use the ACTH stimulation test due to its convenience and safety profile (174). The Endocrine Society's guideline on hormonal replacement in hypopituitarism in adults (79) includes

recommendations for testing for ACTHD. Two recently published systematic reviews and meta-analyses on ACTH stimulation tests for diagnosing adrenal insufficiency—one performed by the Endocrine Society in both adults and children (176) and one confined only to ACTHD in children (177)—concluded that the standard- and low-dose ACTH stimulation tests had similar accuracy for diagnosing ACTHD. Moreover, the study by Ospina *et al.* (176) concluded that both standard- and low-dose ACTH stimulation tests are adequate to rule in, but not rule out, ACTHD. Depending on the dilution method used when performing the low-dose ACTH stimulation test, there may be considerable variation in the actual dose delivered, raising the risk of inaccurate dosing and invalid results (178). Appreciation of the pretest probability of ACTHD and the limitations of the assays for cortisol (as well as the limitations of the various dynamic tests) are critical in establishing a diagnosis of ACTHD.

Treating ACTHD in childhood cancer survivors

6.4 We advise that clinicians use the same glucocorticoid regimens as replacement therapy in childhood cancer survivors with ACTHD as are used in the noncancer population with ACTHD (Table 2). (Ungraded Good Practice Statement)

6.5 We recommend that clinicians instruct all patients with ACTHD regarding stress dose and emergency glucocorticoid administration and instruct them to obtain an emergency card/bracelet/necklace regarding adrenal insufficiency and an emergency kit containing injectable high-dose glucocorticoid. (1|⊕⊕⊕O)

Evidence

The Endocrine Society's guidelines on primary adrenal insufficiency (179) and treating ACTHD in adults (79) include recommendations for physiologic daily replacement and for treating suspected adrenal crisis. Separate studies exist for treating ACTHD during childhood and adolescence (174). However, there are no specific studies addressing the treatment of ACTHD in childhood cancer survivors. Glucocorticoid deficiency has been shown to impair free water clearance, which can mask the symptoms of polyuria in subjects with central diabetes insipidus (180). Thus, when initiating glucocorticoid replacement therapy, clinicians should monitor for the development of diabetes insipidus in at-risk patients and the exacerbation of symptoms in those with pre-existing partial diabetes insipidus. Some antiepileptics enhance hepatic CYP450 isoenzyme activity (*e.g.*, phenytoin, carbamazepine, oxcarbazepine, and topiramate), which can affect the metabolism of glucocorticoids, especially dexamethasone. A recent guideline reviews the management of glucocorticoids in subjects taking enzyme-inducing antiepileptics (79).

Method of Development of Evidence-Based Clinical Practice Guidelines

GRADE approach

The guideline writing committee followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group, an international group with expertise in the development and implementation of evidence-based guidelines (181). A detailed description of the grading scheme has been published elsewhere (182). The writing committee used the best available research evidence to develop the recommendations. The writing committee also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of a recommendation, strong recommendations use the phrase "we recommend" and the number 1, and conditional recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕OOO denotes very low–quality evidence; ⊕⊕OO, low quality; ⊕⊕⊕O, moderate quality; and ⊕⊕⊕⊕, high quality. The writing committee has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Conditional recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that the writing committee considered in making the recommendation. In some instances, there are remarks in which the writing committee offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the writing committee and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the writing committee made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of treatment of hypothalamic–pituitary and growth disorders in childhood cancer survivors. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not

systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

Conflict of interest

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All writing committee members must declare any potential conflicts of interest by completing a conflict-of-interest form. The Clinical Guidelines Subcommittee reviews all conflicts of interest before the Society's Council approves the members to participate on the writing committee and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The Clinical Guidelines Subcommittee and the writing committee have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

Appendix. Conflict of Interest of Endocrine Disorders in Survivors of Childhood Cancer Guideline Writing Committee

Writing Committee Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Information
Charles A. Sklar, MD (Chair)	Director, Long-Term Follow-Up Program, Memorial Sloan-Kettering Cancer Center	Pediatric Endocrine Society	None Declared	• Sandoz (conference honorarium) • St. Jude Children's Research Hospital (research consultant, compensated)	None declared	None declared
Zoltan Antal, MD	Chief of Pediatric Endocrinology, Weill Cornell Medicine and New York Presbyterian Hospital; Assistant Attending, Memorial Sloan-Kettering Cancer Center	None declared	None declared	• Novo Nordisk (speaker's bureau, compensated 12/2016)	None declared	None declared
Wassim Chemaitilly, MD	Assistant Member and Director, Division of Endocrinology, St. Jude Children's Research Hospital	None declared	None declared	• Novo Nordisk (compensated consultant 2/2014 and 9/2015) • Pfizer (compensated consultant 12/2016)	None declared	None declared
Laurie E. Cohen, MD	Clinical Chief of Division of Endocrinology, Director of Neuroendocrinology Program, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School	Pediatric Endocrine Society, Program Committee, Growth Hormone Guideline Task Force, Society for Pediatric Research, Children's Oncology Group, American Academy of Pediatrics, Women in Endocrinology, Growth Hormone Research Society	None declared	• Scherer Clinical Communications, speaker (Grant from Novo Nordisk)	• Versartis Pharmaceuticals (site PI) • Ascendis Pharmaceuticals (site PI)	None declared
Cecilia Follin, PhD	Skåne University Hospital, Lund, Sweden	European Society of Endocrinology	None declared	None declared	None declared	None declared
Lillian R. Meacham, MD	Professor of Pediatrics, Medical Director Cancer Survivor Program, Emory University School of Medicine	• Pediatric Endocrine Society • Children's Oncology Group	National Children's Cancer Society (Medical Advisory Board)	None declared	None declared	None declared
M. Hassan Murad, MD	Professor of Medicine, The Mayo Clinic	None declared	None declared	None declared	None declared	None declared

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Disclosure Summary: See the Appendix.

Disclaimer: The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgement of healthcare providers and each patient's individual circumstances.

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