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Pediatric Brain Tumor Treatment: Growth Consequences and their Management

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Abstract

Tumors of the central nervous system, the most common solid tumors of childhood, are a major source of cancer-related morbidity and mortality in children. Survival rates have improved significantly following treatment for childhood brain tumors, with this growing cohort of survivors at high risk of adverse medical and late effects. Endocrine morbidities are the most prominent disorder among the spectrum of long-term conditions, with growth hormone deficiency the most common endocrinopathy noted, either from tumor location or after cranial irradiation and treatment effects on the hypothalamic/pituitary unit. Deficiency of other anterior pituitary hormones can contribute to negative effects on growth, body image and composition, sexual function, skeletal health, and quality of life. Pediatric and adult endocrinologists often provide medical care to this increasing population. Therefore, a thorough understanding of the epidemiology and pathophysiology of growth failure as a consequence of childhood brain tumor, both during and after treatment, is necessary and the main focus of this review.

Keywords

Pediatric Brain Tumors; Brain Tumor Treatment; Growth after Tumor Treatment; Irradiation; Chemotherapy; Growth Hormone; Pituitary; Late Sequelae

Introduction

Tumors of the central nervous system (CNS) are the most common solid tumors of childhood and the primary source of cancer-related morbidity and mortality in children (1).

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Over the last two decades, survival rates have improved significantly, predominantly due to improvements in neuroimaging, neurosurgical techniques, radiation therapy (RT), chemotherapy and supportive care. Currently, the relative 5-year survival probability for children with all brain malignancies combined is greater than 65% (2–4). Although newer treatment strategies have substantially decreased mortality rates, improvement in survival has been achieved at a serious cost of late effects. These survivors are at high risk of adverse medical, neurocognitive and psychosocial late effects with endocrine morbidities the most prominent among the spectrum of long-term conditions that are directly attributable to previous cancer treatment (5–8). Growth hormone (GH) deficiency is the most common endocrinopathy found in survivors of brain tumors, either directly from tumor location or more commonly, after irradiation and treatment effects on the hypothalamic-pituitary (HP) unit (9,10). In addition, other anterior pituitary hormone deficiencies can exert negative effects on growth, body image and composition, sexual function, skeletal health, and quality of life. As pediatric and adult endocrinologists often provide care for this growing number of survivors, an understanding of the epidemiology and pathophysiology of growth failure as a consequence of childhood brain tumor is essential. This review focuses on growth disorders seen in children during and after treatment for childhood brain malignancy.

Brain Tumor Prevalence, Treatment, and Survival in Pediatrics

CNS tumors represent approximately 20% of all childhood cancers, with 2.5–4 cases diagnosed per 100,000 children per year. There is a slight male predominance (male:female = 1.29) at all ages less than 20 years. With the exception of infants under 1 year of age, the majority of brain tumors in children occur Infratentorially in the brain stem and cerebellum (1,11,12). While the etiology of most childhood brain tumors is unknown, specific genetic syndromes, such as neurofibromatosis (NF1 and NF2), tuberous sclerosis, Li-Fraumeni and Turcot syndromes are associated with a higher incidence of tumors; however, this group represents fewer than 10% of pediatric brain tumors (3).

The distinction between benign and malignant is often less useful for brain tumors since histologically “benign” tumors may behave in a clinically “malignant” fashion due to an unfavorable location in the brain. The extent of surgical resection may be limited by unacceptably high mortality or morbidity associated with surgery in certain areas of the brain. The most common pediatric malignant brain tumor is medulloblastoma, accounting for 10–20% of CNS neoplasms and about 40% of all tumors within the posterior fossa (13,14). While traditionally malignant tumors are thought of as aggressive and likely to disseminate, certain types, such as completely resected, localized medulloblastoma in children over 3 years of age, have cure rates approaching 90% (15). In contrast, benign (low grade) astrocytomas may continue to grow and become life-threatening despite treatment.

While the reported incidence of pediatric primary malignant brain tumors in the U.S. increased dramatically during the last few decades (4), careful analysis suggests that this change is primarily due to increased detection by magnetic resonance imaging (MRI) and improved techniques for surgical biopsy of previously unapproachable lesions, rather than a true increase in disease frequency (16).

The management of brain tumors depends on histology, tumor location and extent, and patient age, but typically involves surgery, chemotherapy and radiation therapy (Table 1) (17). Surgery in most cases by an experienced pediatric neurosurgeon is required to determine histology and to attempt maximal tumor debulking. Treatment is tailored to specific tumor type and patient age. In general, regardless of tumor type, radiation therapy is avoided in infants and very young children as they are especially vulnerable to irradiation associated toxicities and neurocognitive deficits. Alternative therapies for this population include intensified chemotherapy followed by autologous stem cell transplantation. However, for some brain tumors, such as low-grade gliomas, complete surgical resection may be the only therapy indicated.

Medulloblastoma is the most frequent malignant brain tumor of childhood with extensive studies demonstrating poor growth after therapy. Current treatment regimens for children with metastatic medulloblastoma consist of primary operative debulking followed by craniospinal irradiation, with the dose ranging from 23 to 39 Gy, dependent upon local or national protocols as well as additional radiation doses to the posterior fossa for up to 53 Gy. Adjuvant chemotherapy with various agents including vincristine, cisplatinum and lomustine is necessary to improve treatment outcome. However, in the last few decades, recent protocols have attempted to achieve acceptable cure rates with reduced radiation exposure in the hopes of decreasing late effects in children with local disease (no metastasis). Such individualized therapies targeted to specific patient populations, tumor types, and risk groups are being studied with the goal of minimizing treatment-related toxicities while improving long-term survival.

Issues during Acute Treatment

Pediatric patients diagnosed with brain tumors typically exhibit early growth failure with loss of up to 1 SD of height prior to initiating GH therapy (19). Reasons for inadequate growth during therapy are multi-factorial with chemotherapy-induced nausea, cachexia and poor nutritional intake as significant contributing factors. In a small study by Meacham *et al*, five children with diagnosis of brain tumor were followed quarterly for 2 years with close surveillance of auxological parameters, nutritional indices, and endocrine measurements including GH stimulation testing every 6 months, to identify the onset of GH deficiency. Patients showed a nadir for height velocity 6 months after tumor diagnosis with poor gains in height significantly correlating with decreased caloric intake, poor weight gain, decreased BMI and lowered leptin levels, despite normal secretion of GH during this period. Based on their study results, these investigators proposed a triphasic pattern of growth failure in children diagnosed and treated for brain tumors: initial growth failure occurring from cachexia, followed by a transient phase of normal growth and a subsequent decline in growth velocity from treatment-related GH deficiency (19). No studies have demonstrated catch up growth in childhood survivors of brain tumor after therapy despite adequate hormonal replacement (20–24). Stunted growth of the spine from craniospinal radiation therapy is also a contributing factor to lack of catch-up growth in these patients. Although aggressive nutritional rehabilitation of patients during therapy may mitigate early growth failure during treatment, additional studies with larger cohorts of patients are necessary to further elucidate this issue.

Sequelae of Craniospinal Irradiation

Radiation-induced neurotoxicity depends on total radiation dose, fraction size, and the time allowed between fractions for tissue repair (25–27). Actively dividing tissues such as tumors are highly radiosensitive since the radiosensitivity of any cell is directly proportional to its mitotic activity (28). On the other hand, quiescent cells such as neurons are relatively radioresistant yet more susceptible to the cumulative effects of radiation dose, ultimately leading to progressive damage of the cell's ability to repair itself and late effect sequelae. Therefore, administering radiation in fractionated doses enhances the therapeutic ratio between tumor control and reduced damage to other cells (29,30). In general, radiation schedules do not deliver more than 2 Gy per fraction with no more than 5 fractions per week, as increasing the fraction size above 2 Gy per fraction for the same total dose can induce more injury to neuronal cells than the tumor tissues (25,27,29,30). Mathematical models such as the linear quadratic model are used to calculate the biological effective dose of irradiation (BED) in a systematic way in order to quantify the biological effects of different radiation schedules, and thus, provide a similar method of comparing radiation impact on hypothalamic and/or pituitary function (26,31,32).

Radiation-induced HP dysfunction also depends on the duration of follow-up after treatment (33). Both incidence and severity of hormonal deficits increase with longer time following cranial irradiation. This progressive nature may be due to delayed effects of the radiation directly and/or to loss of hypothalamic releasing hormones or other trophic factors that lead to a secondary atrophy of the pituitary. Thus, long-term surveillance of pediatric brain tumor survivors with serial testing is required to properly diagnose deficiencies as they evolve. Importantly, childhood cranial RT can affect the HP-adrenal axis particularly after exposure to higher radiation doses (>50 Gy), resulting in secondary adrenal insufficiency (25,27). Therefore, life-long surveillance of the HP-adrenal axis is also recommended in survivors of childhood brain tumor, as failure to mount a biologically sufficient cortisol response may lead to deleterious and life-threatening consequences (80). This topic will not be further reviewed as it does not have a major impact on growth.

Growth Hormone Deficiency

Radiation is a potent cause of dysfunction in the HP unit (Figure 1). Remarkable differences observed in the incidence of anterior pituitary hormone deficiencies suggest different radiosensitivities of the various HP cell lines. In addition, younger age at radiation is usually more frequently associated with multiple pituitary hormone deficiencies suggesting a higher vulnerability of the HP axis to radiation damage in children (25,27,34–36).

The most radiosensitive of the HP systems is GH, with GH deficiency (GHD) the first and most frequent manifestation of HP injury following cranial irradiation (34,37). The severity and time to onset of radiation-induced GHD are dose-dependent, and the incidence increases with time elapsed after cranial irradiation. Current evidence suggests that almost 100% of children treated with radiation doses above 30 Gy will have blunted GH responses to insulin tolerance test within two to five years after radiation therapy (38). Importantly, children show greater vulnerability to developing GHD than adults, as isolated GHD can be seen

more frequently in children treated with cranial irradiation doses as low as 18–24 Gy (39–42) or after total body irradiation (TBI) with doses as low as 10 Gy (35,36,42–48).

Growth hormone neurosecretory dysfunction (GHNSD) is a specific form of GHD well described following radiation damage to the HP unit (49–53). GHNSD is typically characterized by diminished endogenous GH secretion yet preserved peak GH responses to provocative testing (54), suggesting intact somatotroph synthetic function and a primary defect in the up-stream signals regulating GH secretion. Importantly, the impaired physiological GH secretion in patients with GHNSD becomes more apparent during puberty with the failed expected increase in GH secretion, accompanied by attenuated pubertal growth velocity (25,27,55,56). Radiation-induced GHNSD usually is dose dependent and often encountered in children with leukemia who require prophylactic cranial irradiation with their treatment (51) and/or TBI after bone marrow transplantation (46,48).

Radiation-induced GHD is a quantitative phenomenon. Recent studies in adult survivors of brain tumor revealed preservation of the diurnal variation and pulsatile character of GH secretion, with marked dampening of the pulse amplitude and relative preservation of tonic (nonpulsatile) GH secretion (57). This preserved basal GH secretion is due to reduction in IGF-1 dependent negative feedback as well as radiation-induced attenuation in somatostatin release, resulting in enhanced tonic GH release from the residual functioning somatotrophs (58). At the same time, reduced hypothalamic GHRH release in conjunction with diminished somatotroph mass is responsible for the decreased amplitude of the GH secretory pulses (58,59). Howeyer, the poorly understood mechanisms controlling GH pulse generation and sleep-entrained diurnal variation remain unaffected by irradiation, even when cranial irradiation is delivered during childhood (57). Therefore, even though the integrity of HP unit and GH neuroregulation appears fundamentally preserved in radiation-induced GH-deficient patients, the overall secretory process is distorted and can manifest as inadequate growth during childhood (25,27,57).

Effects on Puberty and Gonadotropin Secretion

Clinically significant gonadotropin deficiency is usually a late complication after HP irradiation, making it the second most common anterior pituitary hormone deficit recognized in 20–50% of children treated with radiation doses above 40 Gy (60–62). However, this deficiency presents in a wide spectrum of clinical severity from subtle abnormalities of the axis only detected by gonadotropin releasing hormone (GnRH)-stimutated testing to severe impairment with reduced circulating sex hormone levels (25,27,62). Typically, these patients have normal basal levels of LH and FSH with accompanied reduced to low-normal sex hormone concentrations. Concomitantly, GnRH testing reveals a delayed peak gonadotropin response with a subsequent delay in gonadotropin decline, indicating pituitary damage (25,27).

In contrast, lower doses of cranial irradiation in childhood paradoxically can result in early or precocious puberty (63–68) through disinhibition of cortical influences on the hypothalamus and reduction in the inhibitory GABAnergic tone (68,69). There is a sexual dichotomy; precocious puberty predominantly occurs in females after exposure to lower

radiation doses (18–24 Gy), such as those previously used for prophylactic cranial irradiation in patients with acute lymphoblastic leukemia (ALL), while the frequency of precocious puberty is no different between male ALL survivors and that seen in the normal population (66,67). This disparity has been attributed to fundamental gender differences in the interaction between higher centers in the CNS and hypothalamic function, with the restraint on puberty more easily disrupted in females by any insult, including cranial irradiation (65,70).

Higher cranial irradiation doses (25–50 Gy), on the other hand, can cause precocious puberty equally in both sexes with a linear association between the age at irradiation and age at onset of puberty (65). In a study of 46 GH-deficient children after cranial irradiation (25–47.5 Gy) for treatment of brain tumor, an early onset of pubertal development was noted in both sexes, with mean chronological age of puberty occurring at 8.5 years in girls and 9.2 years in boys (65). The occurrence of precocious puberty in the context of GHD is common in children after cranial irradiation, while children with non-radiation associated GHD often exhibit pubertal delay due to concomitant gonadotropin deficiency.

Hypothyroidism

The HP-thyroid axis is the least vulnerable axis to radiation damage with damage occurring only after exposure to radiation doses in excess of 50 Gy (62,71–73). Secondary hypothyroidism has not been noted following low dose prophylactic cranial irradiation or TBI (36,74), with frequency of TSH deficiency as low as 3–6% in survivors of brain tumor not involving the pituitary gland (75,76). Subtle abnormalities in the dynamics of TSH secretion, such as elevated basal and stimulated TSH levels in the presence of normal free T4 levels, are common after cranial irradiation (72,77,78). However, patients treated with craniospinal irradiation are also at risk for radiation-induced primary hypothyroidism with the possibility of developing mixed (primary and secondary) hypothyroidism evident with declining free T4 levels over time. In addition, GH therapy can reduce free T4 levels, unmasking central hypothyroidism in patients with hypopituitarism who exhibit normal free T4 levels at baseline (70,79). Given the importance of thyroid hormone for growth, annual monitoring of thyroid function tests before as well as after starting GH therapy, is essential in these patients.

Spine Growth

Disproportionate growth after craniospinal radiation therapy (CSRT) is well recognized with notable high risk for short adult height. The probability of attaining adult height below the third percentile is increased 6-fold after CSRT (81) with sitting height z-scores of −3 to −3.4 SD (21,82–85). Spinal irradiation most likely causes damage to the growth plates, as patients treated with spinal RT are consistently shorter than patients treated with cranial RT despite treatment with GH (22,76,86–89). Although GH therapy improves linear growth, adult height remains significantly less than expected when compared with mid-parental height and especially when CSRT is combined with chemotherapy (22,90,91). Additional studies addressing this issue have consistently shown a decreased upper to lower segment ratio in patients after spinal RT compared to cranial RT and better improvement in both final

and sitting heights in children treated with GH after cranial RT alone (20,76,81,83,91–94). The impact of spinal irradiation on vertebral growth depends on both radiation dosage and patient age, with greater impairment noted in children irradiated at a young age (24,89). Even at a young age (less than 6 years of age), Xu *et al* reported significantly greater adult and sitting heights in children with medulloblastoma treated with lower doses of CSRT (18 Gy) combined with chemotherapy compared with a similar group of patients treated with higher doses of CSRT (23–25 Gy) and chemotherapy (24).

Spinal RT has a larger negative effect for boys compared to girls (85). This may reflect gender differences in spinal growth potential, as growth curves of sitting height show greater remaining percentage in boys than girls at every age until final height (85,95,96). Although studies reporting these findings have considerable heterogeneity including different methods of radiation treatment, they highlight the notable sex-dependent growth differences in sitting height despite GH treatment after spinal RT (85,97). Analyses with larger cohorts of similar patients are necessary to verify some of these reported findings.

Chemotherapy Effects on Growth

Data on the effects of intensive chemotherapy on growth are controversial, as the majority of studies assessing growth outcome in pediatric patients after cancer therapy include intensive chemotherapy in addition to irradiation. Olshan *et al* reported overall significantly worse growth in prepubertal children with medulloblastoma treated with adjuvant chemotherapy and CSRT compared to CSRT alone, with little or no improvement in growth velocity during the 4 years of post-treatment observation, particularly in patients who were treated with adjuvant chemotherapy (98). Several other studies have shown that despite GH therapy, adult height in children treated with CSRT combined with chemotherapy is significantly less than expected, especially when compared with mid-parental height (20–24). In 2004 Gleeson *et al* reported deleterious effects of adjuvant chemotherapy on growth in addition to negative effects of cranial RT or CSRT with loss of up to 7 cm in adult height in these patients (99), suggesting that cytotoxic drugs potentiate the irradiation damage to the HP unit (50) or directly affect the production of IGF-1 with additional impairment of IGF-1 actions on the growth plate (100). Rose *et al* reported GHD in 15 of 31 identified children in a retrospective chart review of cancer survivors who had received chemotherapy but no cranial or total body RT and no CNS tumor. These findings were not reported as a study of prevalence but rather an evaluation of cancer survivors referred to an endocrinology clinic for abnormal growth following cancer therapy (101). Of note, these authors also reported central hypothyroidism (TSH deficiency) in 16 of 31 (52%) of their small patient cohort, felt due to hypothalamic dysfunction (101), which is much higher than most reported study results on central thyroid dysfunction after cancer treatment (102,103). On the other hand, patients with severe aplastic anemia requiring bone marrow transplantation who are conditioned with only chemotherapy (cyclophosphamide alone or with busulfan) have been reported to grow normally (46,104,105). Thus, while adjuvant chemotherapy may exacerbate poor growth following CSRT, the etiology is multi-factorial and additional well-designed multicenter studies in large cohort of children are necessary to further elucidate if chemotherapy alone can cause GHD.

Clinical Management of Growth Hormone Deficiency in Survivors of Pediatric Brain Tumors

Diagnostic Challenges

The hallmark features of pediatric GHD are abnormally slow growth velocity with progressive decline in height z-score, often associated with delayed skeletal maturation, low levels of circulating IGF-I and/or IGFBP-3, and inadequate GH secretory response to pharmacologic secretagogues (106). The same holds true for GHD in survivors of pediatric brain tumors, though certain situations can lead to diagnostic challenges. For example, children who clearly have GHD from resection of craniopharyngioma may develop hypothalamic obesity and maintain normal or even accelerated statural growth. This phenomenon, called growth without GH, has been attributed to obesity-related increases in leptin, insulin, and sex hormone production (107).

Discordant responses on testing of IGF-I levels, stimulated GH peaks, and sampled endogenous GH secretion can be confusing and have raised questions regarding which test(s) are best for patients following cranial RT (33,108). Numerous limitations have been identified with GH stimulation tests to diagnose GHD in general (109), and are further compounded in pediatric brain tumor survivors by potential HP disruptions that can lead to a result on pharmacologic secretagogue testing that does not reflect the functional status of the endogenous GH system (33). Although abnormally low IGF-I concentrations (<−2 SD) generally indicate GHD in patients following cranial RT (after exclusion of other factors like undernutrition that can independently lower IGF-I levels), IGF-I concentrations above −2 SD are not sensitive enough to exclude abnormal peak GH responses to stimulation testing (33,110,111). Methodological issues may be playing a contributory role to this finding. For example, in a study of 28 children and adolescents following cranial or CSRT, only 7 of the 15 patients with GHD (identified as peak GH level <7.5 ng/ml after a stimulation test) had circulating IGF-I concentrations below −2 SD for age and gender (110). The IGF-I concentrations in this study were measured by radioimmunoassay following acid-ethanol extraction, a method that can be influenced by IGFBP competition with the radiolabelled IGF-I trace (112). Circulating IGFBP-2 levels are elevated in some patients with brain tumors (113,114), and the increased circulating IGFBP-2 may falsely elevate the IGF-I values measured by this technique. In another study of 48 children following bone marrow transplantation or treatment of solid brain tumor, only one of the 22 children with GHD (identified as peak GH level <8 on Arginine/L-DOPA testing) had an IGF-I concentration < −2 SD. However, IGF-I and IGFBP-3 levels correlated with individual height changes while GH peak did not (111). Thus, the diagnosis of GHD in patients following cranial irradiation remains challenging, and requires the integration of multiple clinical clues rather than absolute reliance on a single test.

Adult Height in Treated GH Deficient Survivors

Suboptimal growth in brain tumor patients is multi-factorial and related to poor nutrition, tumor recurrence, impaired spinal growth from spinal irradiation, chemotherapy, radiation-induced GHD, and precocious puberty (Table 2). As noted previously, the majority of

children treated with radiation doses in excess of 27 Gy to the HP unit will become GH deficient (34). In addition, cranial RT doses in excess of 18 Gy can induce early or precious puberty, particularly in females with the age of onset of puberty related to the age at irradiation (64,65). In 1995, Ogilvy-Stuart *et al* demonstrated detrimental effects of spinal irradiation and the additive adverse effect of chemotherapy in a group of 29 children treated with GH for radiation-induced GHD (21). Subsequently, Adan *et al* reported improvements in adult height (AH) in brain tumor survivors treated with GH compared with a previous study 10 years earlier from the same group of investigators, and attributed the improvement to changes in GH regimen as well as the use of GnRH analog (GnRHa) therapy (82). Other factors identified with improvements in AH over time include earlier testing for GHD and a reduction in lag time from completion of RT to start of GH replacement, with GnRHa significantly improving AH outcome in patients treated with cranial RT (86). Although no definitive comparison studies are available to assess the true benefit of GnRHa therapy in AH outcome in children with radiation-induced GHD and precocious puberty, the use of combined GnRHa and GH may contribute to better auxological outcome in these patients.

Unfortunately, the youngest children have the worst prognosis, as they are more sensitive to the damaging effects of cranial RT to the HP unit and becoming severely GH deficient at a younger age. In addition, younger age at irradiation results in a longer period of potential growth affected by spinal RT resulting in greater sitting height deficits compared to AH (89,115). As spinal growth exceeds lower leg growth during puberty, an exaggerated disproportion at AH is noted in children treated with CSRT (116).

Comparison of AH in a group of children treated for GHD after treatment of medulloblastoma to the subset of GH-treated individuals with idiopathic GHD (iGHD) from the Pfizer International Growth Study (KIGS) demonstrated significantly lower height velocity, gain in height as well as responsiveness to GH among medulloblastoma patients than patients with iGHD (117). Following treatment with GH, children with iGHD were significantly taller, gained more height, weighed relatively less in relation to their height and had a greater sitting height even though parental height, birth weight, height and weight at initiation of GH treatment were higher in medulloblastoma patients (117). Similarly, AH correlated positively with both age at the time of tumor diagnosis and height at the start of GH therapy (117), although the “index of responsiveness” was much lower in children with medulloblastoma (118). These studies demonstrate that despite GH therapy, final height gain in GH deficient children after treatment for brain tumor, although improved, is still less than predictive height. Promising changes in future treatment modalities may possibly mitigate the degree of growth impairment in these children.

Risk of Cancer Recurrence and Second Neoplasms with GH Therapy

GHD is the most common endocrinopathy noted in childhood cancer survivors (38), with GH replacement an accepted and beneficial form of therapy for growth failure secondary to GHD induced by cranial RT or direct destruction of the HP region by tumor (119). Because GH has mitogenic properties and induces IGF-I, safety concerns have been raised that treating cancer survivors with GH may possibly result in an increased risk of disease recurrence or the development of secondary neoplasms (SN). These concerns were rooted in

earlier yet still controversial clinical studies demonstrating an increased risk of colon cancer in subjects with acromegaly (120), as well as early reports of increased incidence of leukemias occurring in pediatric patients treated with GH (121,122). However, the reports of increased leukemia were subsequently disproven by other studies, particularly as the original report published in the Lancet included children with other cancer risk factors, thus confounding their interpretation. More recently, epidemiological studies in adults have reported associations between higher risk for common adulthood malignancies and circulating IGF-1 levels in the highest quartile of the normal population, and less consistently, with lower concentrations of circulating IGFBP-3 (123–127).

The effects of IGFs on normal and cancer cells are mediated via the type 1 IGF receptor (128,129). In a study of pediatric leukemia risk, circulating IGF-1 concentration was not found to be a risk factor, but low levels of IGFBP-3 were (130). As GH induces both IGF-1 and IGFBP-3, its role in driving the association between IGF-1 and cancer risk seems less likely, particularly since the co-elevation in IGFBP-3 may counteract the mitogenic effects of IGF-1 (129,131,132). A number of reported studies have failed to demonstrate an increased incidence of cancer among adult GH recipients who were treated for GHD (133,134), nor among pediatric subjects who received GH treatment for various indications (127,131,135). Specifically, careful follow-up of large cohorts of pediatric cancer survivors treated with GH have not indicated an increased risk of solid tumor recurrence, CNS tumor relapse or development of leukemia (134,136–143). Three large series reporting on survivors of pediatric brain tumors treated with GH found a reduced risk of primary disease recurrence (140,142,143), though this reduced relative risk (RR) may represent an inherent selection bias favoring GH treatment in survivors with better prognosis (143). These large series highlight the importance of not withholding GH therapy in survivors with treatment-associated GHD based on fear of primary tumor recurrence. Nonetheless, convention has developed to defer GH therapy until the patient is at least one year tumor-free due to early fears of increased recurrence, which usually is the highest in the first year following cancer treatment even without GH therapy.

Survivors of childhood cancer are known to be at increased risk of developing SN as a consequence of exposure to specific therapies such as irradiation, alkylating agents, and topoisomerase II inhibitors (144–149). Genetic factors play an important role in a small subset of patients with underlying genetic predisposition to cancer; however, only a few studies have assessed the risk of secondary cancer and/or leukemia in cancer survivors treated with GH. Sklar *et al* first reported a possible increased RR (3.21) of developing SN in a cohort of GH-treated cancer survivors from the Childhood Cancer Survivor Study (CCSS) (143). Although the increased risk of secondary leukemia was not increased with GH replacement therapy, these investigators found an increase in the number of secondary solid tumors, specifically osteogenic sarcoma and meningioma (143). The absolute number of excess solid tumors resulting from GH therapy was small (3–4/1000 person year at 15 years from diagnosis), inferring that the small risk of SN in cancer survivors would need to be weighed against the substantial established benefits of GH therapy (143).

In an updated analysis of the CCSS cohort after an additional 32 months of follow-up, even though an elevated risk of developing SN in cancer survivors treated with GH was noted

once again, the RR decreased from 3.21 to 2.15 just with the longer duration of follow-up (150). Meningiomas were the most common type of SN diagnosed, and all of the GH-treated survivors who developed a meningioma had received cranial RT as part of their primary cancer treatment (150). Importantly, a shorter latency period between irradiation and the diagnosis of meningioma in the GH-treated group was evident in comparison with survivors not treated with GH after cranial RT (150), raising the possibility of a true biological effect of GH on the development and progression of these meningiomas (123), Meningiomas are known to develop after irradiation to the head for benign and malignant conditions (144,151,152), and tend to remain asymptomatic for prolonged periods of time (153,154). Thus, the possibility of detection bias due to more consistent and frequent medical surveillance with MRI of the head in GH-treated survivors compared with the group not receiving GH treatment cannot be excluded as a plausible explanation for these findings (135,150). Once again, even though these analyses raise concern for an increased risk of developing SN with GH therapy in survivors of childhood cancer, additional studies are necessary to confirm whether these elevated risks decrease with increasing lengths of follow-up, particularly as the overall risks remain small and must be weighed against the potential benefits of GH therapy in survivors (135).

Future Directions: Proton Therapy

Children cured of their CNS tumors live to experience the long-term sequelae of radiation treatment including developmental, neurocognitive, neuroendocrine, and hearing late effects. Newer RT techniques such as proton therapy are being developed to decrease the inadvertent radiation dose to normal tissues and thereby reduce long-term sequelae. As proton radiation eliminates exit dose and exposes only normal tissue proximal to the tumor, it eliminates over 50% of unnecessary irradiation to normal tissues (155). Thus, proton therapy is the most promising form of external beam RT to date with hopes of reduced treatment-related late effects, particularly among the pediatric population with malignancies requiring RT. As the number of proton facilities in the U.S. and worldwide increases in the near future, more children will receive proton therapy in anticipation of this treatment modality evolving into standard of care for treating curable pediatric CNS tumors requiring RT. As a result, the long term benefits of proton therapy, particularly a substantial reduction of treatment-related deleterious effects on the neuroendocrine axis, will soon become available clinically and reported in the literature.

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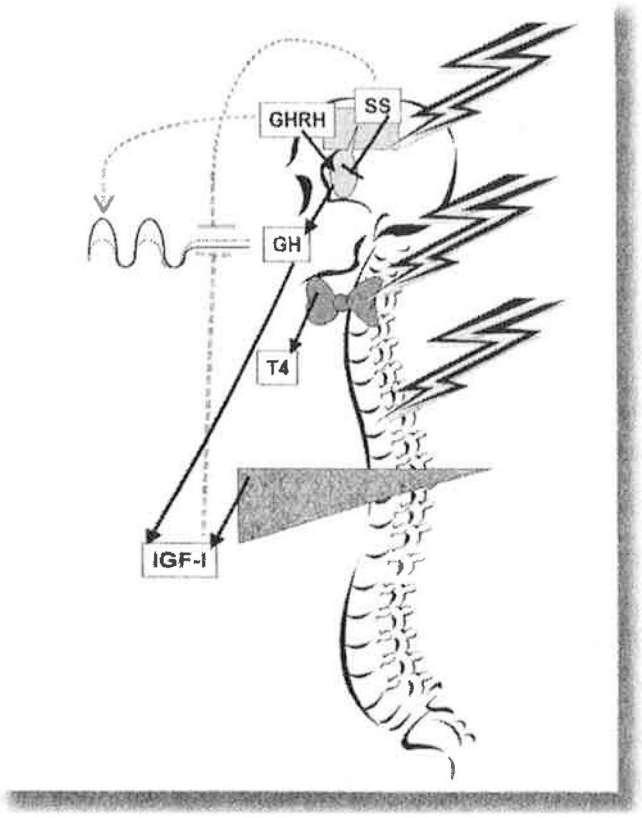

Figure 1. GH system effects of craniospinal irradiation that decrease growth

Levels of all hormones are reduced. Normal growth hormone (GH) secretion is shown by the solid line; following irradiation by the dashed line. Decreased growth hormone releasing hormone (GHRH) secretion diminishes the growth hormone (GH) pulse amplitude and with time, leads to atrophy of the pituitary somatotrophs. Decreased somatostatin (ss) and insulin-like growth factor-1 (IGF-I) inhibition lead to enhanced tonic GH secretion by the remaining functional somatotrophs. Direct radiation injury to the thyroid and reduced thyroid stimulating hormone (TSH) secretion decrease thyroid hormone (T4) production, which further reduces GH secretion centrally and reduces growth plate responsiveness. Likewise, direct radiation injury to the spine decreases its growth response to GH.

Table 1

Common Pediatric Brain Tumors

Tumor Type	Relative Incidence	Treatment
Low Grade Glioma	35–50%	Maximal surgical removal observation
Medulloblastoma/PNET	16–20%	Complete surgical resection cranial/spinal radiation (RT)* and chemotherapy
Brain Stem Glioma	10–20%	Surgical debulking (if possible) and observation, or RT* ± chemotherapy
Ependymomas	8–10%	Complete surgical resection + RT* (chemotherapy in children)
Malignant Glioma	10%	Diagnosis by MRI RT* ± chemotherapy
Germ Cell Tumors	4–7%	Mature teratoma: complete surgical resection Pure germinoma: surgical resection + RT* Non-germinomatous: surgical resection + chemotherapy +RT*
Craniopharyngioma	3%	Complete surgical resection, Reoperation for recurrence/residual, or RT*
Aggressive Infantile Embryonal Tumors (ie. Atypical Teratoid Rhabdoid Tumor)	3%	Complete surgical resection RT* and chemotherapy

RT – Radiation Therapy

* Delay radiation therapy in children younger than 5 years of age

Adapted from: Sievert A, Minturn J. Brian Tumors. In: Florin T, Ludwig S. eds. Netter's Pediatrics. Philadelphia, PA: Elsevier, June 2011 (in press)

Table 2

Factors that improve growth outcome following brain tumor treatment

Older age at treatment
Optimized nutrition during treatment
Radiation exposure: • Lower total dose • Fractionated dosing • Avoid radiating the spine, if possible
Timely diagnosis and replacement of hormone deficiencies • GH • Thyroid
GnRH agonist treatment of precocious puberty, if applicable