Endocrine Complications of the Successful Treatment of Neoplastic Diseases in Childhood

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This article will appear in a future issue of Growth Genetics & Hormones
Introduction

Cancers are relatively rare in children and adolescents; approximately 12,500 individuals less than age 20 years are diagnosed with a new malignancy yearly. The most prevalent cancers observed before 20 years of age include leukemias (25%; acute lymphoblastic leukemia being most common), tumors of the central nervous system (CNS) (17%), lymphomas, including Hodgkin’s disease (15%), and tumors of bone and soft tissue (13.4%).

In contrast to incidence rates, which have either increased slightly or remained steady for the past 25 years, mortality rates have decreased dramatically during the same time period. The current overall 5-year survival rate for childhood cancers is in excess of 70%; survival rates are currently 80% for children with acute lymphoblastic leukemia and greater than 90% for children and adolescents diagnosed with Hodgkin’s disease.

These remarkable improvements in survival are due to both advances in supportive care (eg, prevention and treatment of infections, blood and blood product support) and, most importantly, to the changes in therapy that have occurred over the past 25-30 years. This includes the use of combined modality therapies (eg, the use of surgery combined with chemotherapy and radiation therapy) and the use of aggressive multi-agent chemotherapeutic regimens.

What are the long-term consequences of such exposures when they occur during childhood and adolescence? From our experience at Memorial Sloan-Kettering Cancer Center, as well as the experience of others, it appears that approximately two-thirds of pediatric cancer survivors will develop some type of medical complication or disability.
that can be directly attributed to their previous cancer treatment. The most prevalent late effects of cancer therapy are endocrine disturbances, which have been documented in 20-50% of survivors. In the following sections we will present an overview of the late endocrine complications that can develop following the successful treatment of childhood cancers. We have emphasized observations that have appeared in the literature during the past several years.

**Growth**

Impaired linear growth and adult short stature occur frequently in survivors of childhood cancer, particularly in individuals treated at a young age. A variety of factors, both endocrine and non-endocrine, can contribute to the poor growth that is observed following cancer therapy (Table 1).

**Non-endocrine factors**

The chief non-hormonal factors affecting growth are intensive chemotherapy and irradiation of skeletal structures. Recent data support that the administration of chemotherapy is often associated with reduced growth. While the impairment in growth is usually mild to moderate and, in many instances, only temporary, there are data indicating that the adverse effects on growth can persist more long-term. The deleterious effects on growth are dependent on the intensity of the regimen (ie, the number and dosages of the drugs) and the duration of treatment. Specific drugs that have been implicated in the inhibition of normal growth include glucocorticoids, 6-mercaptopurine, and methotrexate. While the mechanism(s) of chemotherapy-induced growth failure remain uncertain, studies suggest that chemotherapy may act both directly on bone
growth, by suppressing osteoblast and osteoclast activity, as well as indirectly, through alterations of the growth hormone (GH)-insulin-like growth factor (IGF-1) system⁴,⁵.

Children who receive direct external beam radiation to the spine and, to a lesser degree, long bones, can experience profound losses in growth potential. The ultimate impact on final height depends on the dose of radiotherapy, the volume irradiated and the age of the subject at the time of treatment. Fortunately, the height reduction that occurs following contemporary radiation regimens for the treatment of diseases such as Hodgkin's disease⁶ and Wilms' tumor⁷ are generally quite modest and usually not clinically important.

**Endocrine factors**

The predominate endocrine disorders that can disrupt the normal pattern of growth in survivors of childhood cancer are GH deficiency and premature sexual development. Both of these neuroendocrine disturbances are the consequence, primarily, of hypothalamic-pituitary irradiation. Primary hypothyroidism may also contribute to poor linear growth in these children, but it will be discussed in the section on thyroid abnormalities.

GH deficiency can be seen in individuals who suffer from tumors arising in or near the region of the hypothalamus and pituitary (e.g., germinomas, optic nerve gliomas), either as a direct result of the tumor or as a consequence of the surgery required to remove the tumor. More frequently, however, GH deficiency is diagnosed after exposure of the hypothalamus (less commonly after exposure of the pituitary) to high-dose, external beam radiotherapy. Radiation-induced GH deficiency most often is seen following whole brain irradiation for acute leukemia or a variety of CNS tumors; after
localized radiotherapy for sarcomas and carcinomas of the orbit, face, and nasopharynx; following total body irradiation, which is used as preparative therapy for bone marrow/stem cell transplantation\textsuperscript{3,8,9}.

GH deficiency following radiotherapy is both dose- and time-dependent. At higher doses (eg, >30 Gy) of external beam radiation GH deficiency typically develops within 5 years of treatment, whereas after lower doses (eg, 18-24 Gy) GH deficiency may not become evident for 10 or more years\textsuperscript{10}. Once established, however, radiation-induced GH deficiency is usually permanent and irreversible. Establishing a diagnosis of GH deficiency can be problematic in this population. First, neither plasma concentrations of IGF-1 or IGFBP3 appear to be reliable indicators of the GH status following cranial irradiation and thus, cannot be recommended as screening tests for the presence of GH deficiency in irradiated subjects\textsuperscript{11}. Second, standard provocative tests of GH can produce false negative results (ie, normal GH levels despite low endogenous secretion of GH), requiring the use of 12-24 hr frequent sampling studies, particularly in subjects treated with lower doses (<30 Gy) of irradiation. False negative results, however, appear to be less common if one utilizes the insulin tolerance test\textsuperscript{12}.

Over the past several years it has become evident that cranial irradiation, both low dose (ie, 18-24 Gy) and higher dose (ie, 35-50 Gy), is associated with the development of precocious and early puberty\textsuperscript{13,14}. Girls appear to be affected more often than are boys (Figure 3). Age at onset of puberty is directly correlated with age at treatment but indirectly correlated with body mass index. While earlier studies suggested that the tempo of puberty is also accelerated in these patients, recent data have been unable to confirm this. The vast majority of subjects with early onset of puberty will also suffer
from GH insufficiency. Clinical signs of GH deficiency may be obscured by the seemingly "normal" rate of growth these children manifest, owing to the inappropriate production of sex steroids. However, when viewed within the context of their pubertal status and bone age, these children usually are found to be growing at a suboptimal rate.

Final height is most affected in individuals who are diagnosed at a young age and are treated with high doses (ie, >30 Gy) of radiation to the whole brain or whole brain and spine\textsuperscript{15}(Table 1). Additionally, there is some evidence to suggest that females do worse than males, presumably because girls are more likely to enter puberty at an early age.

GH therapy appears to improve the growth rate of children who develop GH deficiency following cancer therapy, at least in the short-term. Previous data suggested, however, that most patients achieved a final height that was significantly below their target height. The poor response to GH therapy has been attributed to both patient factors (eg, spinal irradiation, early puberty) and treatment variables (eg, suboptimal dosing schedules, older age at start of GH). Recent data do suggest that improvements in growth and final height can be achieved when more contemporary dosing regimens of GH are utilized\textsuperscript{16}. Moreover, the addition of a GnRH agonist, to suppress puberty, in individuals with early onset of puberty may also augment final height, but this is based on data derived solely from retrospective, uncontrolled studies\textsuperscript{15}. Growth hormone-releasing hormone therapy may also improve growth in subjects with radiation-induced GH deficiency, but the data are quite limited.

Concerns over the safety of GH therapy stem from the fact that GH is a potent growth promoting agent with mitogenic and proliferating properties. To date, there have
been several large-scale studies assessing the risk of tumor recurrence in brain tumor survivors treated with GH, all of which have consistently demonstrated no increased risk associated with GH replacement therapy\textsuperscript{17, 18}. Due to the paucity of data, there remains uncertainty about the risk of disease recurrence when GH therapy is administered to survivors of pediatric cancers other than brain tumors. Similarly, there is little information available about the effect of GH replacement therapy on the risk of second neoplasms in pediatric cancer survivors. The possibility that cancer survivors, particularly survivors of leukemia, treated with GH are at greater risk of developing slipped epiphyses compared to children treated with GH for idiopathic GH deficiency has also been raised.

Young adult survivors with either childhood- or adult-onset GH deficiency (eg, following low dose cranial irradiation at a young age) may also benefit from GH therapy, especially if they manifest any of the metabolic derangements (eg, increased body fat, raised plasma lipids, decreased bone density) and/or quality of life issues that have come to be recognized as the Adult GH Deficiency syndrome. To date, however, there are no studies that have addressed the risks and benefits associated with long-term GH therapy in adult survivors of childhood cancer.

**Hypothalamic-Pituitary Dysfunction**

External radiation to the whole brain, orbit, face or nasopharynx that includes the hypothalamic-pituitary axis can cause a variety of neuroendocrine abnormalities. As noted previously, the larger the dose of radiation and the longer the time interval since completion of therapy, the greater the likelihood of developing a given problem. In the majority of instances, the site of damage appears to be at the level of the hypothalamus rather then the pituitary gland itself. GH deficiency and early puberty are the most
common neuroendocrine disturbances observed in survivors of childhood cancer. The threshold dose necessary to induce these problems appears to be about 18 Gy, when given in conventional daily fractions. Both entities were discussed in the previous section.

Clinically evident deficits of LH/FSH, TSH, and ACTH occur less often and generally only following doses of radiation > 30-40 Gy\textsuperscript{19}. Moreover, these disorders generally do not develop for several years following exposure to irradiation. Interpretation of the available literature is complicated by the fact that different investigators have employed different hormonal tests and varying criteria for what constitutes "abnormal". For example, Rose et al\textsuperscript{20} report a very high incidence of "hidden" central hypothyroidism following cranial irradiation. According to the authors, establishing this diagnosis often requires performing both a TRH stimulation test and an assessment of the nocturnal TSH surge, which involves obtaining multiple blood samples during the day and at night. It is unclear at the present time whether this subtle form of TSH dysfunction correlates with any clinical findings and, thus, whether one can justify, on clinical grounds, the time and expense involved in this diagnostic protocol. Hyperprolactinemia can also be observed following high-dose irradiation (>50 Gy) of the hypothalamus. Rarely, this can cause clinical symptoms such as secondary amenorrhea and galactorrhea.

Obesity is a well-established sequela of cancer therapy and is often observed in survivors of acute leukemia and various brain tumors. Several recent reports suggest that in survivors of acute lymphoblastic leukemia, a high incidence of obesity or overweight is seen but confined to those survivors who received cranial irradiation\textsuperscript{21}. Additional risk
factors for obesity other than cranial irradiation include female sex and exposure to
dexamethasone. The mechanism(s) underlying the propensity for survivors to become
obese remains unresolved. It is unlikely, however, that there is an endocrine basis for the
weight gain observed in the majority of individuals. One possible explanation is that
radiation damages centers within the brain that normally control eating behaviors and/or
regulate body composition. There are, in fact, preliminary data to suggest that cranial
irradiation may induce a state of relative leptin-resistance.

Thyroid Disorders

Primary Hypothyroidism

Primary hypothyroidism is the most common thyroid disturbance that occurs in
this population. It generally results from direct damage to the thyroid gland following
external beam radiation. Thus, it can be detected in survivors who have been treated with
neck/mantle irradiation for Hodgkin’s disease, craniospinal radiation for brain tumors,
and total body irradiation as cyto-reduction for bone marrow/stem cell transplantation.\textsuperscript{8,22,23}
Primary hypothyroidism has also been described in individuals who have been treated
with a radiolabeled monoclonal antibody (eg, I\textsuperscript{131}-MIBG for neuroblastoma).

The incidence of primary thyroid dysfunction is determined primarily by the total
dose to the thyroid and by the duration of follow-up. In a recent study of 1,791 young
adult survivors of Hodgkin’s disease, we observed a cumulative incidence of
hypothyroidism of 28\%\textsuperscript{23}. Moreover, the actuarial risk of developing an underactive
thyroid 20 years after treatment was 50\% for survivors who had received 45 Gy or more
irradiation to the thyroid (Figure 5). Additional risk factors for developing
hypothyroidism were female sex and age >15 years at diagnosis. Of great clinical importance, new cases were observed more than 25 years following diagnosis and treatment of Hodgkin’s disease.

**Hyperthyroidism**

Hyperthyroidism, while far less prevalent than hypothyroidism, does develop at an increased rate in certain subsets of childhood cancer survivors. The more common setting is following external radiation of the neck region for Hodgkin’s disease; the chances of becoming hyperthyroid are eight times greater than that observed in the general population. Doses of radiation to the thyroid >35 Gy is the major risk factor for the development of an overactive thyroid. A second, but less common cause of hyperthyroidism, has been the appearance of autoimmune thyroid disease post-allogeneic bone marrow/stem cell transplant. The published data are most consistent with the hypothesis that the patients’ thyroid disorder is due to adoptive transfer of abnormal clones of T or B cells from donor to recipient.

**Thyroid Neoplasms**

Radiation to the thyroid gland is a known risk factor for the subsequent development of thyroid neoplasms, both benign and malignant. Subjects at greatest risk include those less than 5 years of age at the time of treatment and those who are treated with lower doses of radiation (<20 Gy). Nonetheless, the risk of developing thyroid neoplasms remains elevated following even relatively high-dose radiotherapy. Thyroid nodules are particularly common in females and after a long-latency period (>10 years).
Recently, we reported that the risk of thyroid cancer was increased 18-fold in a large cohort of young adult survivors of Hodgkin’s disease\textsuperscript{23}. Of note, the median dose of radiation to the thyroid was 35 Gy (range 25-35 Gy). Fortunately, the vast majority of cancers noted after radiotherapy are well differentiated and have an excellent prognosis.

**Gonadal Dysfunction**

*Testicular Function*

*Treatment-Induced Leydig Cell Failure*

Leydig cell failure or dysfunction results from damage or loss of the machinery required for testosterone synthesis and release. While damage to germ cells and infertility are common following cancer therapy, Leydig cell failure and androgen insufficiency are relatively uncommon.

Chemotherapy-induced Leydig cell failure resulting in androgen insufficiency and requiring testosterone replacement therapy is quite rare\textsuperscript{24}. Nonetheless, prior studies suggest that subtle forms of Leydig cell dysfunction may be observed following chemotherapeutic protocols that include high-doses of one of several alkylating agents. As the majority of males undergo a normal puberty and most produce normal adult levels of testosterone, it would appear that Leydig cell dysfunction is generally subclinical.

Leydig cells are, however, susceptible to damage from external irradiation, although the doses required are much higher than the doses needed to cause germ cell failure. The data obtained from individuals treated with radiotherapy for a variety of malignancies indicate that the likelihood of sustaining radiation-associated Leydig cell failure is directly related to the dose delivered but inversely related to age at treatment.
The majority of males who receive ≤ 20 Gy fractionated irradiation to the testes appear to retain their ability to produce normal amounts of testosterone\(^24\). Since raised plasma concentrations of LH, both at baseline and following GnRH stimulation, are found in many of these young men, one must assume that subclinical injury to the Leydig cell does occur even at these low levels of radiation exposure. The clinical importance of this phenomenon is unclear but there are data to suggest that subtle forms of Leydig cell insufficiency may predispose to decreased bone density and changes in body composition over time\(^25\).

Young males who receive >24 Gy fractionated testicular irradiation as therapy for testicular relapse of ALL are at very high risk for Leydig cell dysfunction. Essentially all boys who are prepubertal at the time that they receive 24 Gy testicular irradiation develop frank Leydig cell failure and require androgen replacement therapy. Most, but not all, boys who are older and/or in early puberty at the time they are treated with 24 Gy will also ultimately need therapy with testosterone.

**Treatment-Induced Germ Cell Loss**

Unlike Leydig cells, which are resistant to damage from most chemotherapeutic agents and lower doses of irradiation, male germ cell are quite sensitive to many classes of drugs and to low dose irradiation.

The chemotherapeutic agents most commonly associated with impaired male fertility include alkylating agents (Table 2). Although earlier studies suggested that the germ cells of younger males were less vulnerable to the toxic effects of chemotherapy compared to older boys and young adults, recent studies have failed to support this contention\(^26\). Overall, approximately 40-60\% of young adult male survivors of childhood
cancer have impaired fertility. A high probability of oligo-azoospermia and infertility is likely if an individual has been exposed to $>20 \text{ g/m}^2$ of cyclophosphamide, a commonly employed alkylating agent. By contrast, many individuals treated with a cumulative dose of cyclophosphamide of $<7.5-10 \text{ g/m}^2$ will retain normal sperm production$^{26,27}$.

Radiation below the diaphragm is associated with reduced fertility. Impaired sperm production has been recorded following doses to the testicle as low as 0.15 Gy but recovery is generally common if the dose remains under 1-2 Gy. At testicular doses $>2$-3 Gy, recovery of sperm production is rare$^{28}$.

Infertility resulting from cancer therapy, both radiation and chemotherapy, is associated with the following clinical and hormonal findings: reduced testicular volume, raised plasma concentrations of FSH, and reduced plasma concentrations of inhibin B. While there are good correlations overall between these markers and sperm counts in large groups of survivors, there is considerable overlap between normal and abnormal individuals. Many male survivors with documented azoospermia fail to manifest either a reduced testicular volume or an elevated level of FSH. Thus, at the present time there is no substitute for a sperm analysis to determine an individuals current fertility status$^{29}$.

**Ovarian Function**

Due to the structural and functional interdependence within the follicle between the sex hormone producing cells and the oocyte, insults that cause disruption and damage to the germ cells lead to loss of both endocrine function as well germ cell failure and infertility. Likewise, toxic injury to granulosa cells results in estrogen insufficiency as
well as oocyte death\textsuperscript{24}. This is in contrast to the testis, where, despite the loss of germ cells following cytotoxic therapy, the ability to produce sex hormones is often preserved.

The ovaries of prepubertal females with their greater complement of follicles, are relatively resistant to chemotherapy-induced damage compared to the ovary of the adult. Nonetheless, certain chemotherapeutic agents particularly, alkylating agents, when given at high doses are toxic even to the young ovary (Table 2). The majority of prepubertal girls and adolescent females who receive standard combination chemotherapy will retain or recover ovarian function during the immediate posttreatment period\textsuperscript{24}.

Increased plasma concentrations of FSH have been noted in young women treated with alkylating agents for acute leukemia, brain tumors, and Hodgkin’s disease. Fortunately, many of these young women demonstrate normalization of FSH levels over time and only a minority appear to experience irreversible ovarian failure requiring long-term hormone replacement therapy. Of note, recovery may not occur for many years following completion of therapy\textsuperscript{30}. However, some of these young women may experience a premature menopause when they reach their 20’s and 30’s\textsuperscript{31}.

Females who receive high-dose, myeloablative therapy with alkylating agents in the context of allogeneic or autologous bone marrow transplantation, are at high risk of developing ovarian failure. The agents most commonly utilized in this setting include busulfan, melphalan, and thiotepa.

Patients who receive abdominal, pelvic, or spinal irradiation are at increased risk of developing ovarian failure, especially if both ovaries are within the treatment field. The data suggest that the ovary of younger individuals is more resistant to damage from irradiation than is the ovary of older individuals. Thus, while radiation doses of 6 Gy may
be sufficient to produce irreversible ovarian damage in women >40 years of age, doses in the range of 20 Gy are needed to induce permanent ovarian failure in the majority of females treated during childhood\textsuperscript{24,32}. 
Reference List


Table 1. Factors predictive of adult short stature in survivors of childhood cancers

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<th>Clinical variables</th>
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<td>Young age at treatment</td>
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<th>Treatment variables</th>
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<td>High-dose radiotherapy (eg, cranial, craniospinal)</td>
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<td>Intensive chemotherapy</td>
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<th>Endocrine abnormalities</th>
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<td>Growth hormone deficiency</td>
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<td>Early puberty</td>
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<td>Hypothyroidism</td>
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Table 2. Chemotherapeutic agents associated with germ cell damage

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