Narrative review of endocrine and metabolic consequences of childhood cancer survivors

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Abstract: Survivor rate of childhood cancer has increased to more than 80%. As survivor rate increases, number of childhood cancer survivors (CCS) are also increasing. CCS can develop various chronic health problems after treatment. Endocrine and metabolic complications are among the most common complications. Our study aimed to summarize the endocrine and metabolic late complications of childhood cancer, and to describe briefly the guidelines for management and treatment of these complications. CCS suffer from various endocrine and metabolic complications including thyroid disorders, reproductive and pituitary dysfunction, and metabolic syndrome. Radiation can cause various endocrine and metabolic dysfunctions. Incidence rate and types of complications are dependent on field and dose of radiation. Radiation involving central nervous system (CNS) can develop various types of endocrine complications by disrupting hypothalamic-pituitary axis. Chemotherapeutic agents also increase the risk of endocrine and metabolic complications. For example, alkylating agent can cause gonadal dysfunction, tyrosine kinase inhibitors can cause thyroid dysfunctions, and glucocorticoids can cause hyperglycemia, obesity, hyperlipidemia, and low bone mineral density. Hematopoietic stem cell transplantations also increase the risk of endocrinopathy due to preconditioning with chemotherapy and or total body irradiation. This review will provide knowledge of these possible consequences for primary care physicians and endocrinologists, and help to develop guidelines for evaluation and treatment of these complications.

Keywords: Childhood cancer survivor; endocrine complications; metabolic complications

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Introduction

Five-year survival rate of childhood cancer has steadily increased and now exceeds 80% in USA (1). Many factors including earlier detection, improvement in treatment modalities contribute to increasing survival. Though survival rate is increasing, childhood cancer survivors (CCS) can develop many late complications due to delayed effects of treatment for childhood cancer. Both physiologic and psychological consequences lead to long-term mortality and morbidity. In addition, late complications can also impair health-related quality of life (HRQOL) which is defined by individual’s or a group’s perceived physical and mental health over time. There have been efforts to reduce late complications such as development of proton therapy to reduce radiation hazard. Nevertheless, significant proportions of CCS suffer from late complications.

Complications can develop many years after completion of cancer treatment and endocrine complications are the most common among these complications. According to the report of Childhood Cancer Survivor Study, endocrine sequelae increased cumulatively with time. Thirty-five years after cancer treatment, 67.3% of survivors developed one or more endocrinopathies. The risk of endocrinopathy was greater in specific cancers such as Hodgkin lymphoma and central nervous system (CNS) tumor (2).

Risk of late complications are related with cumulative
doses of radiation or chemotherapy. Genetic susceptibility is also thought to be related with late-complications (3). But there is no definite model to predict occurrence of late complications, so early screening and timely intervention is essential to reduce adverse outcomes.

Though significant complications, about half of survivors are lost to follow-up 10 years after completion of therapy (4). Well-established guidelines will be also helpful to survivors to conduct structured follow-up, which will provide continuous care and improve care for this rapidly growing patient population. So physicians monitoring CCS should know increased risk and evaluation guidelines of endocrine dysfunctions. Brief review of endocrine complications focused on risk-based evaluation will be especially helpful for primary care physicians who are not familiar with care of CCS.

So, in this article, we aimed to summarize the endocrine and metabolic complications of CCS based on guidelines, focused on evaluation.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/pm-20-96).

**Therapy modalities leading to endocrine complications**

**Radiation therapy**

Endocrine late effects are common in survivors who received radiation that includes the hypothalamus-pituitary, thyroid, or gonads. Radiation therapy cause direct DNA damage of target tissues, creates free radical that impairs DNA, damages cells involved in neuronal support and vascular supply, and may trigger chronic inflammation (5). As a result, skeletal growth, bone health, body composition, and metabolic homeostasis may be impaired.

Radiation injury is lesser when delivered in smaller dose and more fractions over a longer duration of time, except for testicular radiation (5). Age, gender, and pubertal status of patient also affect the extent of damage. Proton beam therapy delivers more localized radiation, which can minimize damage of surrounding tissues.

Craniospinal radiation can cause short stature, hypopituitarism, low bone mineral density, thyroid, or ovarian dysfunction. Total body irradiation (TBI) can cause growth hormone deficiency, direct thyroid toxicity, gonadal and sexual dysfunction, metabolic syndrome, low bone mineral density. Mantle or neck radiation can affect thyroid and parathyroid gland. Abdominal and pelvic radiation can develop metabolic syndrome and reproductive dysfunction. Testicular radiation can cause infertility and hypogonadism (6,7). Iodine-131 meta-iodobenzylguanidine (I-131 MIBG), which is used for high-risk neuroblastoma, can result in primary thyroid dysfunction, thyroid cancer, and premature ovarian insufficiency (8,9).

**Chemotherapy**

Chemotherapeutic agents can directly damage cancer cells. Alkylating agents attach alkyl groups to DNA, which result in DNA breakage and cell death. They damage proliferating cells preferentially. They can cause gonadal failure, hypothyroidism, and thyroid cancer.

Cyclophosphamide equivalent dose is used to quantify extent of exposure to alkylating agents. Heavy metals (platinum-based compounds) also preferentially affect gonadal tissue resulting in gonadal failure.

Asparaginase is used for treatment of childhood acute lymphoblastic leukemia. Asparaginase can cause hyperglycemia, hypertriglyceridemia, pancreatitis, and even permanent diabetes mellitus (10).

Methotrexate is a DNA nucleotide analog which inhibits cell mitosis. Methotrexate particularly affects osteoblasts causing low bone mineral density (11).

Tyrosine kinase inhibitors (TKIs) inhibit pathways related with cell proliferation and cell death. Selective TKIs usually cause fewer side effects than nonspecific TKIs. Hypothyroidism is the most common endocrine complication associated with TKIs. TKIs can also cause growth impairment, infertility, subclinical adrenal insufficiency, and hypo or hyperglycemia (12,13).

Immune checkpoint inhibitors inhibit T cell activation pathways, mostly the cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1 pathways. Due to activation of immune system, they can cause autoimmune primary hypo- or hyperthyroidism, hypophysitis, primary adrenal insufficiency, and autoimmune diabetes mellitus (14). Despite the general consensus that checkpoint inhibitors are more easily tolerated than chemotherapy, their unique side effect profile is important to recognize given the possibility of life-threatening adverse events (15).

Glucocorticoids can develop hyperglycemia, obesity, hyperlipidemia, and low bone mineral density. Iatrogenic adrenal insufficiency also can occur.
Hematopoietic stem cell transplantation

Hematopoietic stem cells derived from peripheral blood or bone marrow are used for transplantation. The patient’s own cells (autologous) or stem cells derived from donor (allogeneic) can be used for transplantation. Preconditioning with chemotherapy and/or TBI is required, which increases risk of endocrinopathies. Tacrolimus and glucocorticoid are used for prophylaxis and treatment of graft versus host disease (GvHD), which can also cause endocrine dysfunction (16). Alemtuzumab, anti-CD52 monoclonal antibody which is used in preconditioning, can cause thyroid dysfunction (17).

Endocrine complications in each endocrine organ

Hypothalamic-pituitary dysfunction

Surgery for CNS tumors may immediately impair hypothalamic-pituitary function. Surgery can also lead to diabetes insipidus. Damages on pituitary function by radiation are both dose and age dependent, and the risk for dysfunction increases with time. Both hypothalamus and pituitary gland damage can be caused by radiation GH. Secretion of GH is the most vulnerable to radiation, and the risk of GHD increases when radiation dose exceeds 18 Gy in cranial radiation or 10 Gy in TBI. The risk for GHD is higher when exposed at younger age (5). There has been concerns that GH treatment in cancer survivors can increase the risk of recurrence or secondary neoplasm. But some suggest that risk of secondary malignancy is increased due to the radiation exposure and not due to GH treatment (18). Endocrine Society guidelines recommend that GH therapy can be considered in CCS who are proved as GHD and in remission from there cancer for more than 1 year (19).

Effect of radiation on LH and FSH secretion is affected by radiation dose, gender, and age. At relatively lower doses of radiation of 18–24 Gy, risk of precocious puberty is increased because of alteration of inhibitory pathways which suppress pubertal onset. But at higher doses exceeding 25 Gy, hypogonadotropic hypogonadism usually occurs because LH and FSH secretion is decreased. Hypothalamic-pituitary-gonadal function can be assessed with morning gonadotropin and sex hormone level. Testis volume is not a reliable indicator of puberty, because Sertoli cell (which comprises most of testis volume) is more vulnerable to alkylating agent and radiation therapy than Leydig cell, so testis volume can be reduced but hormone synthesis by Leydig cell can be maintained (19). Precocious puberty is treated by gonadotropin-releasing hormone (GnRH) agonist therapy to minimize impairment of growth potential. Hypogonadism is treated with sex hormone replacement. Estrogen is replaced by oral agent or patch, and testosterone is replaced by intramuscular injection.

Central adrenal insufficiency is rare but can be life-threatening. Survivors who were exposed to more than 30 Gy of cranial radiation should receive annual screening for adrenal insufficiency with morning cortisol level (7). Adrenal insufficiency should be suspected in those who were exposed to more than 24 Gy, or who have symptoms and signs suggestive of adrenal insufficiency such as fatigue, weight loss, low blood pressure or hypoglycemia. For confirmation insulin tolerance test or cosyntropin stimulation test is used. Central adrenal insufficiency is treated with glucocorticoid. Patients should be educated for the use of stress dose of steroid (19).

Hyperprolactinemia can occur after high dose of radiation exceeding 40 Gy. Hyperprolactinemia is usually asymptomatic. But Hyperprolactinemia can induce hypogonadism by interfering with the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, so hyperprolactinemia should be ruled out as a possible cause of hypogonadism (20).

Anti-diuretic hormone secretion is the most resistant to radiation, so diabetes insipidus rarely occur with radiation therapy (5).

Thyroid disorders

Thyroid gland is involved in the radiation filed of head and neck radiation, TBI, and mantle radiation. These increase the risk of developing primary hypo- or hyperthyroidism, thyroid nodules, and thyroid cancer (2). Cranial radiation can increase the risk for central hypothyroidism, though thyrotrophs are more resistant to radiation damage compared with other pituitary hormone secreting cells (5). I-131-MIBG therapy for high-risk neuroblastoma can cause primary hypothyroidism, thyroid nodules, and thyroid cancer (9). Alkylating agents are also associated with thyroid dysfunction. Thyroid function test and physical examination should be performed in survivors with previous head and neck radiation (7). Hypothyroidism is treated with supplementation of levothyroxine.

Incidence of thyroid nodule and thyroid cancer is
4 and 2.5 times higher in CCS than in their siblings, respectively (2). Thus, when thyroid nodule is present, more careful monitoring and consideration for fine needle aspiration is required. The risk of developing thyroid cancer increased until radiation dose up to 30 Gy, but declines in higher doses, possibly due to absolute destruction of the thyroid gland (2). Thyroid cancer in CCS is not more aggressive than in the general population. Thus, only routine surveillance with physical examination is recommended (21).

**Primary hypogonadism and infertility**

In CCS, sex hormone production and fertility are impaired. Risk of hypogonadism include chemotherapy with alkylating agent, abdominal/pelvic radiation, testis radiation, and the combination of therapies increases the risk (22). In females, hormone production and fertility are affected equally. But for males, fertility is impaired at lower levels of exposure than levels at which testosterone production is affected (22,23).

In females, younger patients are more resistant to ovarian damage than older patients because of higher follicular reserve. According to childhood cancer survivor study, among 3,390 adult female cancer survivors, acute ovarian failure occurred in 215 (6.3%) patients and 126 (4.5%) experienced early menopause (24,25). Older age, procarbazine exposure, cyclophosphamide exposure at age 13–20 are risk factors for acute ovarian failure (26). Alkylating agent exposure increased the risk of infertility, but did not affect the outcome of pregnancy (rate of stillbirth, abortion) (27).

The risk of ovarian damage increase with increased dose of radiation to ovary, and when received more than 20 Gy of radiation 70% of survivors developed acute ovarian failure (26). Alkylating agent also increase the risk of ovarian failure. When both radiation and alkylating agent are used, cumulative incidence of ovarian failure was about 30% (25). When received TBI before 10 years of age, most survivors experienced normal onset of puberty and menarche. But most of those who received TBI after age of 10 developed acute ovarian failure (28). But it is not possible to predict whether ovarian insufficiency will be transient or permanent. So, it is recommended to wait for at least 1 year before starting hormone replacement to see if ovarian function is recovered.

In males, as the age of radiation exposure is older, the likelihood of infertility is lower. Testis radiation more than 6 Gy is associated with irreversible azoospermia (23). Cyclophosphamide exposure more than 7.5 g/m\(^2\) can lead to oligospermia, and azoospermia can develop when exposure exceeds 19 g/m\(^2\). Testosterone production by Leydig cell can be affected with radiation doses of >12 Gy, and more likely to be impaired when radiation dose exceeds 20 Gy. Leydig cell function is more easily impaired in survivors exposed to radiation prior to puberty than those exposed during puberty (23,29).

For survivors who are at risk of gonadal failure, growth and pubertal progression should be monitored annually. Sexual dysfunction should be assessed by asking about decreased libido, erectile dysfunction, or vaginal dryness. Further evaluation should be considered if puberty does not occur by age 13 years in girls and age 14 years in boys.

As for effects on offsprings, children of cancer survivors do not have significantly increased risk for congenital anomalies due to their parent’s exposure to mutagenic cancer treatments (30).

There is increasing efforts to preserve fertility before cancer therapy. For pubertal female survivors, oocyte or embryo cryopreservation can be used. Oophoropexy can be considered when radiation field includes ovary. For prepubertal girls, ovarian tissue cryopreservation can be an option. For pubertal males, sperm cryopreservation is used (7).

**Short stature**

Height potential is impaired in CCS due to GH deficiency, direct radiation effects, chemotherapy, malnutrition, and other health conditions. CNS radiation can result in premature epiphyseal closure due to precocious puberty. CNS radiation can also cause hypogonadism which result in decreased pubertal growth spurt. Radiation can also cause direct injury of the vertebral body growth plates and develop a skeletal dysplasia (31). Glucocorticoids, TKIs, and retinoic acid also can cause growth impairment.

Growth hormone can increase final height of CCS. So, it can be used in CCS who have GHD. Though CCS without GHD also have impairment in final height, the 2018 Endocrine Society guideline does not recommend to use GH in the absence of GH deficiency (19).

**Central precocious puberty**

The risk of central precocious puberty is increased with young age of treatment. Precocious puberty can be caused
by both low dose and high dose of radiation. Premature menarche, which means menarche before 10 years of age, occurs in 14.5% of CNS cancer survivors who received CNS radiation. The risk of premature menarche is increased when diagnosed with cancer before 4 years of age (32). Precocious puberty can be diagnosed by presence of pubertal sign, increased bone age compared with chronologic age, and peak LH level <5 IU/L in GnRH stimulation test. Central precocious puberty is treated with GnRH agonist. One-month or three-month GnRH agonist have been used, and 6-month GnRH agonists started to be used recently.

**Obesity and metabolic syndrome**

Cranial radiation can lead to obesity, often exacerbated by concurrent GH deficiency and hypothyroidism (33). Females, age <4 years at the time of treatment, hypothalamic radiation doses >18 Gy are risk factors for obesity (34). Incidence of diabetes mellitus was 1.8 times higher in CCS than siblings, though rate of obesity was similar (2). Risk of diabetes increases with TBI or abdominal radiation.

The Children’s Oncology Group Long Term Follow Up Guideline suggest annual assessment of blood pressure and body mass index. Fasting blood glucose, serum insulin, and lipid profile should be screened every 2 years in overweight or obese survivors, and every 5 years in normal weight patients.

**Low bone mineral density**

Reduced bone mineral density (BMD) is defined as a z-score below −2 in survivors <20 years old or a T-score below −1.0 in survivors ≥20 years old (7). Risk factors of decreased BMD in CCS are glucocorticoid, methotrexate, craniospinal radiation or TBI, hypogonadism, and GH deficiency. It is recommended that baseline BMD should be evaluated in patients with risk factors of reduced BMD. Adequate intake of calcium and vitamin D, and physical activities should be recommended to maintain bone health of CCS (7). Regular weight-bearing exercise and adequate sunlight exposure are also recommended to improve BMD (35).

**Conclusions**

Here we provided summary on the late endocrine and metabolic complications in CCS. Guidelines provided in this study were mostly derived from Children’s Oncology Group guideline. Guidelines should be developed for developing countries, considering different medical resources in each country. In summary, endocrine and metabolic complications are common and can significantly affect well-being of survivors. Careful monitoring and adequate intervention for these complications are required.

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**Footnote**

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