

## **Long Term Follow Up of Childhood Cancer Survivors**

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Cure of childhood cancer is now approaching a 5-year old survival rate of 80%. The childhood cancer survival study (CCSS) estimated that in 2009 there were an estimated 363,00 survivors of childhood cancer in the US. This contributes to the growing number of long-term survivors into adulthood as well as adult onset cancer. Unlike adults, children can withstand larger amounts of chemotherapy, radiation, and surgery. However, this can lead to late complications, which may not be seen until years after therapy. CCSS cohort reported that 2 out of 3 cancer survivors would suffer chronic health conditions. The CCSS cohort consists of 14,357 five-year survivors of childhood cancer, diagnosed between 1970-1986. Those who participated filled out questionnaires regarding wide range of health related outcomes. The data gathered from this study has helped developed guidelines and promote further research on survivorship. The Children's Oncology Group (COG) have developed guidelines to help aid in follow up care of children who completed treatment. Ideally, all childhood cancer survivors should follow up at long term follow up clinic at least once a year, however, sometimes it will be the primary care provider that will taking care of their overall needs. Below are some common late effects and suggestions for follow up.

### **Endocrine:**

#### **Growth:**

Decreased linear growth is a common problem in children who have cancer. Depending on what type of treatment and cancer children can suffer severe growth retardation, which is defined as a standard height below the fifth percentile. Children who have had brain tumors suffer from this the most, as many as 30-35%. Children diagnosed and treated less than 5 years are the ones who suffer most from growth retardation. Radiation is contributing factor, especially in doses of 3,000 cGY to they hypothalamus or pituitary gland in treatment of certain brain tumors. Radiation involved in treatment for acute lymphoblastic leukemia, however, uses doses of 1,800 or 2,400 cGY, which does not usually cause an issue. This is not to say that these patients do not have a growth delay, which occurs when diagnosed and undergoing treatment. Therefore, it is important to monitor growth problems in long-term survivors using standardized growth plots. For children, who have a abnormal growth, further work up maybe needed. This may include appropriate consultations, bone age, growth hormone tests, and thyroid function tests.

#### **Gonadal Function:**

Problems in germ cell depletion and gonadal endocrine function have been seen in male survivors. These changes occur secondary to chemotherapy, radiation

or surgery. The effect of sperm production and amount of radiation received to the testicular area has been shown to be dose related. Some amounts of radiation are tolerated to this area and sperm counts recover within 6 months to 2 years. However, cumulative doses of 140-300 cGy to both testes is shown to cause irreversible azoospermia. Along with radiation, chemotherapy has also been known to effect sperm counts. Alkylating agents are the most well known group of chemotherapeutic agents that cause decreased sperm counts. Effects of surgery on the gonads may cause impotence or retrograde ejaculation. Male patients should all be counseled on the effect that radiation, chemotherapy, or surgery may have on their future ability to reproduce. Patients should be screened routinely for problems of gonadal function. This screen should include questions, which inquire in regards to problems with libido, impotence, fertility. Labs should also be drawn, which include FSH, LH, and testosterone.

In female patients, ovarian failure is a main concern as a late effect of therapy. Radiation doses of 400 to 700 cGy can almost always cause primary or secondary ovarian failure. Failure can also be seen with chemotherapy. Alkylating agents such as cyclophosphamide and busulfan are the two main therapies that have shown to cause issues. Just as with radiation, the effect that the chemotherapy has will be based on age and dose. These patients should have diagnostic evaluation of ovarian dysfunction. This requires a careful history and physical,, any menstrual irregularity, any difficulties getting pregnant. It is important to note tanner staging, obtain serum estradiol.

### **Obesity:**

The presence of obesity after therapy of leukemia is 16-56% and can be caused by radiation, steroid therapy, physical inactivity, or increased food intake. Therefore, it is important to monitor weight gain. It is also important to counsel patients on healthy eating and exercise. If needed lipid panels and diabetes monitoring should also be done yearly.

### **Cardiac:**

The intensive irradiation and chemotherapy that is used in order to obtain such high cure rates can also be associated with problems with the heart. Cardiomyopathy associated with doxorubicin has been recognized since the early 1970s. Children who are long-term survivors are 15-fold more likely to suffer from congestive heart failure (CHF) compared to other age matched controls. The strongest association with acute and chronic issues with the heart is with anthracycline exposure. There is even more of a risk with younger age, history of radiation, and female gender. Incidence of CHF approaches around 20% with doses between 300-600 mg/m<sup>2</sup>, and is greater than 40% in doses greater than 600 mg/m<sup>2</sup>. Mediastinal radiation, at doses greater than 30 cGy also pose a risk for late onset cardiac disease. Radiation to the mediastinum can cause vascular damage and fibrosis. Besides the anthracyclines, other agents have also been reported to cause cardiotoxic events. 5-Fluorouracil has been known to cause angina. Patients are also at risk of coronary artery disease. Risk factors include treatment at age less

than 21 years, large daily doses of radiation, doses greater than 4,000 cGy and lack of cardiac shielding.

Detection and management of symptoms is vital for long term follow up care. The COG has devised a recommended screening guideline based on age of diagnosis, amount of anthracyclines received, and if they had radiation. This should only be used as a guideline. Recent studies and chemotherapy protocols have attempted to prevent these late effects by using different dose schedules and also using cardioprotectants along with chemotherapy after a certain amount of anthracycline.

### **Pulmonary:**

The airways and interstitium are sites of late toxicity of chemotherapy or radiation. The most common late effects that occur are pulmonary fibrosis and pneumonitis. These types of problems are most common in patients with thoracic malignancies. Patients who have received radiation to more than 50% of the lung fields are more likely to suffer symptoms. Chemotherapeutic agents such as bleomycin, vinblastine, methotrexate, and other alkylating agents, are also known to cause pulmonary late effects. Other factors that may contribute to chronic pulmonary toxicity include superimposed infection, respiratory toxicity. Symptoms of pulmonary infection include cough with fever, dyspnea. It is important to obtain a good history. Patients often are followed up with chest radiographs, and pulmonary function tests on a year to five-year basis depending on therapy.

### **Neurocognitive Late Effects:**

Neurocognitive testing has been most studied in patients with CNS tumors or in patients with acute lymphoblastic leukemia. One report looked at 36 children who had various intracranial tumors and had survived 5 years off treatment. Of these 36 patients, 45% had intelligence quotients of less than 90, and 17% had IQs less than 70. These patients need to have a yearly history and physical done and ideally be followed yearly with neuropsychological testing if clinically indicated. It is also important to take a good history on how the patient is doing at school. Many survivors have problems with math and science and may need extra help.

### **Eyes, Ears, Teeth and Gums:**

Cataracts may be observed in patients that have received radiation, steroids, and busulfan. Patients should have yearly eye exams and routine follow up with an ophthalmologist. Hearing loss is also a common side effect of certain chemotherapies and therefore, patients should have yearly hearing tests. Poor dentition is a common late effect of chemotherapy and radiation. Therefore, routine dental examinations are also encouraged.

### **Secondary Malignancies:**

Skin cancer, breast cancer, thyroid cancer, secondary leukemias, and sarcomas are all secondary malignancies that cancer survivors are at risk for depending on the type of chemotherapies and radiation they received. Patients therefore, are encouraged to wear sunscreen at all times. Patients that have received chest radiation are encouraged to perform monthly breast examinations and yearly

mammograms beginning five years after diagnosis. If patients have received radiation in neck area, the thyroid should be checked yearly with thyroid levels.

**Conclusion:**

The number of long-term adult survivors of childhood cancer therapy will continue to increase, and almost 75% will have a chronic health problem secondary to therapy. There are patient handouts available on the COG website- [www.curesearch.org](http://www.curesearch.org). This is a helpful website that provides excellent information for not only providers but for patients as well. If there are more questions please do not hesitate to contact me at [Shivani.Upadhyay@cshs.org](mailto:Shivani.Upadhyay@cshs.org).

**References:**

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