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Late Effects of Childhood Cancer and Treatment

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Introduction

Survival rates for almost all types of childhood cancer have improved dramatically over the last 30 years. Estimates suggest that 1 of every 450 adolescents and young adults is a long-term survivor of childhood cancer. This is based on estimates that cancer occurs in 1 per 600 children and in 1 per 300 adolescents. With current therapy, 75% are cured. The increased number of survivors has focused attention on the many long-term or late sequelae of treatment. Late effects can be defined as any adverse effect that does not resolve after completion of therapy or any new problem that becomes evident after completion of therapy. Most of these effects are not detectable at the end of therapy but become evident with maturation (puberty), growth, and the normal aging process.^[1,2,3]

These effects are discussed by organ system, keeping in mind that many survivors have at least one organ system affected. Psychosocial issues and development of second malignancies are also addressed. Late relapses of the primary cancer, although uncommon, do occur and are the major contributor to late mortality. Late effects following bone marrow transplantation are discussed in Bone Marrow Transplantation, Long-Term Effects.

For excellent patient education resources, visit eMedicine's Endocrine System Center. Also, see eMedicine's patient education article Thyroid Problems.

Cardiopulmonary Effects

General cardiac toxicity

- Heart damage can occur secondary to radiation therapy (RT) that includes all or part of the heart within the radiation field (eg, mantle irradiation for Hodgkin disease, spinal irradiation for some brain tumors). Patients who present with cardiac toxicity due to RT alone generally present with pericardial effusions or constrictive pericarditis. Radiation can also lead to premature coronary artery disease. Heart damage can also be caused by chemotherapy, especially the anthracycline drugs, such as doxorubicin and daunomycin, and occasionally cyclophosphamide when administered at high doses.
- Patients with anthracycline-induced cardiomyopathy usually present with symptoms of congestive heart failure (CHF), which may develop spontaneously or be initiated by stressors such as extreme exertion, as in weight lifting or difficult labor. Pericarditis may also be present, further compromising cardiac function. Additionally, ventricular arrhythmias may occur.
- Subclinical or mild toxic effects can be found in a significant number of treated children depending on the methods used to assess damage. One study of children who received anthracyclines for acute lymphoblastic leukemia (ALL) showed that 57% had abnormalities of afterload or contractility on echocardiography (ECHO). Abnormalities are more frequent and more severe in patients who receive both RT and chemotherapy. However, the incidence of early and late CHF from anthracycline chemotherapy is still only 1-2%. Problems in predicting which patients are going to develop clinically significant heart disease are still recognized.

Risk factors for cardiac toxicity

- Age at diagnosis: Infants and toddlers with ALL or neuroblastoma who receive anthracyclines have more frequent abnormalities on ECHO than older children who receive the same treatment. This suggests the heart is not capable of increasing its workload sufficiently to keep up with a growing child.
- Sex: In several studies, girls had about a 2-fold higher risk of cardiac toxicity than boys.
- Cumulative dose of anthracyclines: In adults, the incidence of CHF was 3% at a cumulative dose of 400 mg/m² of doxorubicin, 7% at a cumulative dose of 550 mg/m², and 18% at cumulative doses over 700 mg/m². In a review of 6493 children on Pediatric Oncology Group studies, the risk of developing CHF was 5 times higher with cumulative doses over 550 mg/m² than with lower doses. This phenomenon has been best studied with the anthracycline doxorubicin. Other anthracyclines have different threshold doses for cardiac toxicity.
- Method of anthracycline delivery: Fewer toxic effects were observed with intravenous infusion over 24 hours than with intravenous bolus or infusion over 15-30 minutes.
- Anthracycline schedule: Fewer toxic effects were observed with weekly infusions than with infusions every 3 weeks.
- Mediastinal or spinal irradiation: Radiation-induced fibrosis occurs most often in the pericardium, causing acute and late pericarditis. Myocardial infarction and death can occur from fibrosis of the myocardium or the coronary vessels. Studies in children receiving mantle irradiation for Hodgkin disease show a greater susceptibility to premature coronary artery disease in adolescents exposed to mediastinal radiation doses greater than 4000 cGy. In one study of 16 children treated with spinal irradiation for malignancies, 75% had a maximal cardiac index below the fifth percentile and the group as a whole had significantly higher estimated posterior wall stress. Thirty one percent had pathologic Q waves in the inferior leads.
- Length of time since diagnosis: Studies in both adults and children have shown increasing incidence of abnormal findings on ECHO in patients monitored for more than 10 years than in those monitored for less than 10 years.

Pathophysiology of anthracycline cardiotoxicity

- Free radical damage
- Focal fibrosis
- Dropout of muscle fibers
- Increased wall stress and afterload
- Dilated cardiomyopathy

Cardiac toxicity from radiation therapy

- Pericarditis can be acute, occurring during RT or years later, or chronic, with pericardial effusion or constrictive pericarditis. Children who receive mantle irradiation for Hodgkin disease have a 0-2.5% long-term incidence of pericarditis. As many as 43% of patients in one study were found to have pericardial thickening by ECHO; the rate was even higher in patients monitored for at least 6 years.
- Late coronary artery disease with development of myocardial infarction is observed in patients who receive mantle irradiation for Hodgkin disease.
- Mitral insufficiency and myocardial fibrosis are other cardiotoxic effects.

Cardiac monitoring tests

- Serial ECG: Low QRS voltage and ST-T wave abnormalities occur late and are not useful for detecting early cardiac damage. Prolongation of the QTc interval may be predictive of late cardiac decompensation. Significant dysrhythmias can be asymptomatic and may be missed by routine ECG, so 24-hour Holter monitor ECG has been recommended as part of routine long-term follow-up.
- Serial ECHO (two-dimensional and M-mode): Noninvasive and easy to perform in children, ECHO provides measurements of left ventricular shortening fraction, diastolic filling times, and end-systolic wall stress (a measure of afterload). Studies conducted with stress or exercise tend to show more abnormalities than those conducted at rest.
- Radionuclide angiocardigraphy (RNA) or multiple gated acquisition (MUGA) scan: Well studied in adults, these tests measure left ventricular ejection fraction and are used to evaluate regional wall motion. Again, exercise studies show more abnormalities than resting ones.
- Endomyocardial biopsy: This procedure is invasive, requiring cardiac catheterization, but it allows quantitation of cardiac toxicity that is predictive of later decompensation. It can also be used to differentiate between malignant infiltration, infection, and anthracycline toxicity.
- Serum markers: Plasma natriuretic peptides (NP) have been studied in children treated with anthracyclines as measures of subclinical ventricular dysfunction. B-type NP may be more sensitive than atrial NP for detection of left ventricular damage. Serum cardiac troponin T levels are also being studied as markers of mild myocardial damage.

General pulmonary toxicity

- Toxicity can be acute and lethal or, more commonly, insidious in onset over a period of months to years, resulting in pneumonitis and pulmonary fibrosis. Symptoms include a dry hacking cough, dyspnea on exertion, and exercise intolerance.
- Physical examination may reveal crackles in the lung bases and, rarely, a pleural friction rub. The chest radiograph may show infiltrates, although more often the findings are normal. Pulmonary function tests (PFTs) usually reveal evidence of restrictive lung disease with a decreased forced vital capacity or total lung capacity as well as decreased diffusing capacity (DLCO).
- Corticosteroids have been used with some success in radiation-induced pneumonitis. However, results in pneumonitis secondary to bleomycin have widely varied. Radiation pneumonitis is associated with significant morbidity and mortality.

Pathophysiology of lung injury

The pulmonary pathologic processes for most chemotherapeutic agents and RT are thought to be similar. Because most alveolus formation and enlargement occurs in infancy and childhood, the effects of chemotherapy and radiation may be more severe in children than in adults.

- Initial response is oxidative injury to the pulmonary capillary endothelium and pneumocytes.
- An influx of granulocytes releases chemotactic actors, elastase, collagenase, and myeloperoxidase.
- Lymphocytes and plasma cells then infiltrate, secreting growth factors that stimulate fibroblasts to deposit collagen.
- Pulmonary fibrosis ensues.

Pulmonary toxicity from chemotherapeutic agents

- Drugs such as bleomycin, busulfan, the nitrosoureas, and methotrexate can cause long-term toxic effects on the lungs. Effects are additive or synergistic with RT.
- Bleomycin is used most commonly in children with germ cell tumors and lymphomas. Pulmonary toxicity is related mainly to dose and increases exponentially with cumulative doses over 200 units (12-17% incidence in adults). Although DLCO is a rather insensitive predictor, most oncologists advocate monitoring it and stopping bleomycin if DLCO drops below 50% of predicted.
- Nitrosoureas, especially carmustine (BCNU), have been shown to cause pneumonitis in children with brain tumors. One study reported a mortality rate of 35% in children treated with BCNU and RT to the spine. One group has found a significantly increased risk of BCNU pneumonitis when high-dose BCNU is administered within 120 days of mantle irradiation.
- Methotrexate administered weekly by mouth for ALL in adults and in patients with rheumatoid arthritis has been shown to cause restrictive lung disease. The incidence is probably less than 1%.

Pulmonary toxicity from radiation therapy

- The most common causes of pulmonary toxic effects include mantle or mediastinal irradiation for Hodgkin disease, lung irradiation in children with lung metastases from sarcomas or Wilms tumor, and spinal irradiation in children with brain tumors.
- In mantle irradiation for Hodgkin disease, toxicity is dose related; 40-55% of children studied had abnormal findings on PFTs or abnormal DLCO, although most received chemotherapy as well as RT. Few were symptomatic. One study from St. Jude Children's Hospital prospectively evaluated 37 children with Hodgkin disease who received chemotherapy that included bleomycin and low-dose (ie, 1800-2000 cGy) involved-field RT. Decreases in vital capacity and DLCO were noted over the first 6 months, but these were followed by improvement. Only one patient was symptomatic, but DLCO per unit of alveolar volume still was decreased significantly in most patients at the 2-

year follow-up visit.

- Studies in children who received 1200-cGy to 2000-cGy lung irradiation for metastases from Wilms tumor have also shown significant drops in total lung capacity and vital capacity, with worsening of function, 18-48 months after therapy. On the other hand, 1600 cGy of whole lung irradiation to children (mostly adolescents) with osteosarcoma did not produce any long-term abnormalities in PFT findings.
- In patients who were treated as young children, the appearance of restrictive lung disease may relate to the inadequate growth of the chest wall and lung cavity following radiation therapy, a problem not observed in the older pediatric patient.

Endocrine Effects

As many as 40% of all long-term survivors of childhood cancer have evidence of endocrine toxicity. Radiation to the hypothalamic-pituitary axis, thyroid gland, or gonads can affect growth and reproductive capabilities. Alkylating agents can affect ovarian and testicular function as well.

The hypothalamus tends to be more sensitive to effects of radiation than the pituitary gland. Growth hormone is the first hormone to be affected, followed by gonadotropins and then adrenocorticotrophic hormone secretion. This is related to total dose and fraction size of radiation received. Age at the time of treatment is also a factor; younger patients are more sensitive than older children to the growth hormone-lowering effects of radiation.

Effects on growth

Short stature can result from growth hormone deficiency (GHD), hypothyroidism, and poor skeletal growth after radiation therapy (RT).

GHD is the most common toxic endocrine effect of RT caused by cranial radiation. (Hypothyroidism is more common but results from RT directly to the gland.) Infants and toddlers are more likely to develop GHD than older children who, in turn, are more sensitive to the effects of radiation than adults. The incidence of GHD is 100% in children who receive more than 4500 cGy for optic chiasm gliomas and as much as 75% in children who receive 2900-4500 cGy for medulloblastoma. As many as 50% of children who receive 2400 cGy prophylactic cranial irradiation (CRT) for ALL develop GHD during the year or two after treatment, while those who receive 1800 cGy are less prone to GHD (0-14% incidence). Although most children recover adequate hormone levels, they do not experience catch-up growth. Treatment with growth hormone also does not result in catch-up growth, especially in children who also received spinal irradiation because of a direct growth-inhibiting effect on bone and soft tissue.

Precocious puberty has been reported in some children after CRT. Younger age at the time of radiation increases the risk, and both sexes may be affected. Studies in girls with acute lymphoblastic leukemia (ALL) report onset of puberty about 1 year earlier than in the general population.

Spinal irradiation (and thoracic/abdominal radiation including the spine) impairs growth by limiting growth of vertebral bodies. Estimates suggest that a 10-year-old child who undergoes spinal radiation loses 5.5 cm of final adult height with proportionately more growth retardation in younger children.

Thyroid dysfunction

Damage to the thyroid gland is common after neck or mantle irradiation, as used in children with Hodgkin disease, or spinal irradiation, as in children with brain tumors.^[4]

Hypothyroidism is the most common thyroid abnormality after cancer therapy. Compensated hypothyroidism (ie, elevated thyroid-stimulating hormone [TSH], normal thyroxine levels) occurs in 14-75% of children irradiated for Hodgkin disease with doses of 4000 cGy or more and about 9% of children who receive prophylactic CRT with doses greater than or equal to 2400 cGy for ALL. Overt hypothyroidism occurs in 16-21% of Hodgkin disease patients and 2% of ALL patients after radiation with 2400 cGy. In one large study from Stanford of children irradiated for Hodgkin disease, the incidence of compensated or overt hypothyroidism after 26 years of follow-up was 47%. Compensated or overt hypothyroidism is observed in 47-68% of children who receive spinal irradiation for medulloblastoma.

In the Stanford study of children irradiated for Hodgkin disease and monitored for 26 years, the incidence of benign thyroid nodules was 3.3%; Graves disease, 3.1%; thyroid cancer, 1.7%; and Hashimoto thyroiditis, 0.7%. The contribution of chemotherapy to the development of hypothyroidism has been controversial. Although most studies did not show an increased risk, others question whether hypothyroidism occurs earlier in patients treated with both radiation and chemotherapy than in those treated with radiation alone.

Despite prophylaxis with oral iodide, children who receive therapeutic doses of iodine I 131 metaiodobenzylguanidine for relapsed neuroblastoma have developed primary hypothyroidism.

Thyroid replacement is recommended even in those with compensated hypothyroidism because chronic stimulation of the thyroid gland by elevated TSH has been suggested, but not proven, to increase the risk of secondary thyroid cancer in humans.

Gonadal dysfunction

Degree of gonadal damage depends on the type and total doses of chemotherapy used as well as the site and dosage of RT received. Of chemotherapeutic agents, alkylating agents such as nitrogen mustard, procarbazine, and cyclophosphamide are the most damaging to the gonads. Cyclophosphamide-induced gonadal dysfunction has been studied in children with nephrotic syndrome, Hodgkin disease, and leukemia. In one study, almost 30% of prepubertal boys had evidence for gonadal dysfunction with total doses greater than 400 mg/kg (12 g/m²) compared to no effect on prepubertal girls. Midpubertal and sexually mature boys frequently had gonadal dysfunction even with total doses as low as 100 mg/kg (3 g/m²). When girls receive chemotherapy during or after puberty, they are affected more severely but nevertheless are less sensitive than boys.

Girls who receive abdominal irradiation for Hodgkin disease or Wilms tumor (ie, ovaries in the radiation field) have a 50% incidence of ovarian failure if both ovaries are in the field and the dose is greater than 1500 cGy; the rate is higher if alkylating agents are also used.

Early menopause is a major concern. In one large study (the Five Center Study), the average age at menopause was 31 years in women treated with abdominal irradiation and alkylating agents combined. Early menopause increases the risk of osteoporosis and heart disease at a younger age and also has implications for patient education and family planning.

Fertility

Radiation to the gonads can also affect fertility.^[5] As little as 200-300 cGy to the testes causes 100% aspermia with no recovery after as many as 40 months of follow-up. This is important for boys receiving testicular radiation for testicular germ cell tumors or testicular disease from ALL, abdominal irradiation for advanced Hodgkin disease, or total body irradiation with bone marrow transplant.

Data on the offspring of childhood cancer survivors were collected in 12 series. The overall rate of congenital malformations was 3-4% (no different from the general population and sibling controls). No increased rate of cancer was found in offspring of cancer survivors. Interpret these data regarding the offspring cautiously because mean follow-up was only 11 years and the survivors received less intensive therapy by today's standards. The incidence of stillbirth and premature delivery is higher than normal in women who received abdominal irradiation that included the uterus.

Obesity

Several studies of children with ALL who received prophylactic CRT (especially doses over 2000 cGy) have found increased body mass index (BMI), especially in girls.^[6] Depending on the study endpoint (4 y after therapy or time adult height was reached), 12-57% of the girls and 21-45% of the boys were obese. Recent small studies have suggested a link between glucocorticoids, elevated leptin levels, leptin insensitivity, and obesity even in children with ALL who did not receive CRT. Current protocols use CRT only in very high-risk children (ie, those with CNS disease or high WBC counts at diagnosis). Most of these children have not reached final adult height yet; thus, their risk of obesity remains to be determined. Interventions for treating obesity in children have been reviewed.^[7]

Neurocognitive Effects

Most of the data regarding neurocognitive effects of therapy center around 2 groups of patients: children with acute lymphoblastic leukemia (ALL) and children with brain tumors. Interpretation of early data in children was hindered by methodological problems, small sample sizes, and relatively short follow-up intervals. However, recent studies using more comprehensive tests of neurocognitive function and academic achievement confirm the deleterious effects of radiation on the young brain. Effects are much more severe in survivors of medulloblastoma than in survivors of ALL, principally because of higher radiation doses used in the former.

Factors affecting severity of brain injury include age at diagnosis, dose of radiation, type of cancer (eg, brain tumors), and type of surgery and concurrent treatment such as chemotherapy. Frequent and extended school absences may also contribute to neurocognitive deficits.

Neuropsychological effects in children treated for acute lymphoblastic leukemia

Abnormalities found on CT and MRI scans of children with ALL treated with cranial radiation therapy (CRT) include leukoencephalopathy and mineralizing microangiopathy.^[8] Leukoencephalopathy, an abnormality of white matter, usually develops 4-5 months after combined CRT and intravenous methotrexate; presenting symptoms and signs include seizures, lethargy, ataxia, slurred speech, and memory loss. Similar events can occur in children who receive high-dose intravenous and intrathecal methotrexate without CRT. Generally, the severity of leukoencephalopathy has no correlation with results of neuropsychological testing or academic performance, although deficits are frequently found. Pathologic mechanisms proposed include demyelination and vascular insufficiency. The former may explain the increased incidence of toxic effects in younger people.

Neuropsychological deficits are common in children who receive 1800-2400 cGy of CRT. Results of full-scale intelligence quotients (FSIQ) and verbal IQ tests are lower than in age-matched controls and in patients with solid tumors who did not receive CRT. Children irradiated with 2400-cGy CRT when younger than 7 years lose an average of 13-14 points on FSIQ. Specific deficits have been shown on tests of fine motor functioning, visual-spatial functioning, nonverbal memory, and attention and concentration. Expressive language skills and verbal learning are largely unaffected. Academically, children most often have difficulties with mathematics; difficulties with reading and spelling are less frequent.

Results of one study from St. Jude Children's Hospital revealed similar deficits in children with ALL who received intrathecal and intravenous intermediate-dose methotrexate with and without CRT. Significant decreases in FSIQ (about 20% of patients), verbal IQ, and mathematics scores (about 24-27% of patients) were observed in both groups of patients. Children younger than 4 years had greater decreases in FSIQ than older children. Behavioral problems were no more common than in the general population.

Neurocognitive deficits in children with brain tumors

Few large studies have been conducted on survivors of childhood brain tumors, although these patients show patterns of neurocognitive defects similar to those of children with ALL.^[9] Age at the time of CRT and total dose of radiation are the major factors in determining the extent of deficits, and these children generally receive much higher doses of CRT than patients with ALL. Deficits in short-term (or working) memory and focused attention result in decreased ability to learn new things. With longer follow-up, survivors fall further behind their peers.

Irradiated survivors of medulloblastoma have significant deficits. In one study of 32 children who survived more than 5 years from diagnosis, all had FSIQ less than 90 and 4 had less than 70 (ie, mentally retarded range). Children treated when younger than 3 years had lower mean FSIQ (65) than children treated when older than 3 years (80). Similar patterns were observed in verbal and performance IQ and achievement tests in reading, spelling, and mathematics. Thirty-eight percent were classified as learning disabled. In another study, 60% of children treated when younger than 3 years had FSIQ less than 70, whereas only 10% of those treated when older than 3 years had FSIQ less than 70.

Several small studies have compared neurocognitive functioning in children with medulloblastoma who were irradiated and children with cerebellar astrocytoma who were never irradiated. Deficits in verbal IQ, tests of attention, spatial memory, perceptual-motor coordination, and motor domains were noted in the irradiated medulloblastoma group. The survivors of cerebellar astrocytoma scored generally in the low-normal range for most tests. Both groups showed continued worsening over time, but the rate of progression was steeper in the medulloblastoma group.

Tumor location and surgery may also contribute to later neurocognitive deficits, although the significance of these factors has been more difficult to elucidate because of the small numbers of survivors in studies to date. For example, in one study, more than 50% of children who underwent surgery for craniopharyngioma had some form of memory impairment. Children with temporal lobe tumors had both verbal and nonverbal memory deficits.

Effect of total body irradiation

Total body irradiation is commonly used as part of the conditioning regimen for bone marrow transplantation. Typical doses range from 1200-1400 cGy. Significant concern exists about the use of total body irradiation in younger patients, especially those younger than 2-3 years. One study showed minimal late neurocognitive defects in patients who were older than 6 years at the time of their bone marrow transplant and total body irradiation treatment. The patients aged 3-6 years had more pronounced abnormalities on neuropsychological testing, and the group younger than 3 years at the time of transplant was the most heavily affected.

Psychosocial Issues

Survivors of childhood cancer are at risk of psychological problems stemming from the diagnosis of cancer, its treatment, and the multitude of physical late effects that may accompany survival. In addition, educational, occupational, and insurance issues complicate overall quality of life. Despite numerous methodological problems, most studies have concluded that cancer survivors are generally well adjusted and, as stated by one report, "specific difficulties exist within an overall context of normal emotional adjustment."

Because of physical and neurocognitive deficits, many survivors of brain tumors have more difficulties than usual functioning in society. They are less likely to go to college (about 10%), get married (only one third have married, while one quarter have been divorced), and be employed (only one half are employed, with salaries significantly lower than those of other survivors or controls).

Psychosocial adaptation

Most studies have not found an increased incidence of psychiatric disorders in survivors.

With the exception of children who survive brain tumors, childhood cancer survivors are no different from the general population in terms of educational attainment, marital status, and whether they live with their parents.

A study from the Candlelighters Childhood Cancer Foundation surveyed 300 survivors and compared them with a control group of young adults. Most survivors reported feeling different from peers, although two thirds felt the differences were more positive than negative. Self-reported health status was more often negative in survivors than in peers, and survivors had more worries about late effects such as second cancers and fertility issues. On the other hand, the survivors had fewer general health worries than their peers.

Adjustment difficulties have been observed in some areas, most notably initiation and maintenance of interpersonal relationships. Symptoms of posttraumatic stress disorder were noted in 12% of survivors surveyed in one study. Adolescent survivors have been found to be less anxious than their peers, with a tendency to employ avoidance strategies more often to deal with problems of adolescence.

Several studies have found that one of the strongest predictors of survivors' adjustment was maternal coping.

Educational attainment and school problems

Children irradiated for acute lymphoblastic leukemia (ALL) or brain tumors can have neurocognitive deficits that have an impact on learning new material and performance in mathematics, reading, and spelling. In addition, school absence continues to be a problem even after children finish therapy.

Excluding children with brain tumors, childhood cancer survivors' rates of high school graduation and college attendance are similar to those of controls.

Occupational attainment and problems

Rates of employment and salaries are similar between survivors and controls. One exception is that cancer survivors have a higher likelihood of being denied entry into the military services. Survivors have experienced problems in the workplace with respect to job discrimination in the past, although recent studies suggest this is occurring less often.

Insurance issues

Barriers to obtaining health insurance include refusal of new applications, policy cancellations or reductions, higher premiums, waived or excluded preexisting conditions, and extended waiting periods. One study from North Carolina found that childhood cancer survivors were more likely to be denied health insurance than their siblings. These problems seem to lessen as the survivors become older.

Childhood cancer survivors are more likely to be rejected for life insurance or be required to pay higher premiums.

Other Systems

Genitourinary tract

Tubular damage and hypertension from renal artery stenosis can be observed with doses of radiation greater than 2000 cGy. Cisplatin and high-dose carboplatin frequently cause transient glomerular and tubular damage. Tubular damage may persist for months to years. Ifosfamide administered in high doses (total >90 g/m²) can cause a renal Fanconi syndrome, with electrolyte and protein wasting that can be severe, and eventual renal failure.

Bladder damage from acrolein, a metabolite of cyclophosphamide and ifosfamide, is usually observed during, not after, therapy. The regular use of mesna during the administration of high doses of cyclophosphamide and ifosfamide usually prevents long-term bladder damage. The risk of secondary bladder cancer in children treated with these agents may be increased if frequent damage occurs as demonstrated by hematuria. Radiation to the bladder can result in fibrosis and diminished capacity.

GI tract and liver

Transfusions increase the risk of viral hepatitis. Hepatitis C has been found in 4-8% of survivors tested, and more than half of those show evidence of chronic active hepatitis. Results of treatment with interferon have been generally disappointing so far.

Radiation to the abdomen can cause bowel adhesions and fibrosis, malabsorption, and lactose intolerance. The bowel is also in the field of spinal irradiation.

Ophthalmic structures

Radiation therapy (RT) is used in some patients with retinoblastoma and almost all with orbital rhabdomyosarcoma. Radiation retinopathy is a frequent complication of doses greater than 4000 cGy for retinoblastoma. CRT for some brain tumors and total body irradiation for bone marrow transplantation can also affect the eye and orbit.

Cataracts can develop with even fairly low doses of radiation. A single large dose is more cataractogenic than a similar but fractionated total dose. Younger children may be more susceptible to developing cataracts than older children. In a study of 102 survivors of orbital rhabdomyosarcoma, 82% of those irradiated developed cataracts and 70% had decreased visual acuity.

Orbital hypoplasia, decreased tear production, keratoconjunctivitis, and ptosis or enophthalmos have also been observed following RT.

Aural structures

Hearing loss can result in difficulties with communication, speech and language acquisition, and development of learning skills.

Platinum-based chemotherapy (cisplatin and high-dose carboplatin), aminoglycoside antibiotics, loop diuretics, and CRT all can damage the cochlea, resulting in significant sensorineural hearing loss. Hearing loss due to platinum-based chemotherapy is caused by cumulative dose-related damage to inner hair cells of the cochlea. Loss of high-frequency hearing (ie, 6000- to 8000-Hz range) occurs most commonly, but it can extend into the speech range (ie, 1000-2000 Hz) at higher cumulative doses. Children are more sensitive to this damage than adults. Receiving cisplatin after CRT causes synergistic hearing loss.

In one study from the Dana Farber Cancer Institute, 39 children with brain tumors received cisplatin 100 mg/m² every 3 weeks for 3 doses, followed by CRT and weekly vincristine. After the 3 courses of cisplatin, 20% had hearing loss in the 6000- to 8000-Hz range, 16% in the 3000- to 4000-Hz range, and 11% in the speech range.

Musculoskeletal structures

Hypoplasia or impaired growth of bone and muscle can occur after RT. Short stature, scoliosis, and asymmetric bone and soft tissue growth are potential problems after spinal or abdominal irradiation.

Osteonecrosis or avascular necrosis (AVN) has been reported after RT and, more recently, as a result of high-dose steroids in children with ALL. A study from the Children's Cancer Group reported AVN in 111 of 1409 children (9.3%) treated for high-risk ALL. Girls aged 10-15 years had an AVN incidence of 19.2% and boys aged 15-20 years had an AVN incidence of 20.7%, while the incidence in children younger than 10 years was only 0.9%. Almost all patients were affected in weight-bearing joints, and 74% had multifocal disease. More than 99% presented within 3 years of their cancer diagnosis. Risk factors included age (ie, before or during puberty) and the number of courses of dexamethasone in the reinduction phase (ie, 1 or 2).

Immune system

The long-term decrease in immunity following splenectomy and/or functional asplenia (after RT) has been extensively documented, not only in the loss of opsonization, but also in alterations of the levels of serum immunoglobulins.

Second Malignancies

Second malignant neoplasms (SMNs) in childhood cancer survivors are caused by the carcinogenic effects of radiation, chemotherapy, or both. Risk of SMNs is related to cumulative doses of each. Genetic predisposition, such as mutation of the retinoblastoma (*Rb*) or *p53* (ie, Li-Fraumeni syndrome) gene, also plays an important role. Retinoblastoma was the most common primary cancer in several large studies of patients with SMNs, followed by Hodgkin disease and soft tissue sarcomas. The most common sites/types of SMNs include the brain, breast, thyroid, bone, and second leukemias. An estimated 50% of carriers of the *Rb* gene develop an SMN within 50 years from radiation; the risk to unirradiated carriers is less than or approximately 25%.

Secondary leukemia due to alkylating agents

- Mechanism is direct DNA damage.
- Risk is related to cumulative dose.
- Acute myelogenous leukemia (AML) following therapy with alkylating agents usually occurs 4-8 years after diagnosis of the primary cancer and is often preceded by myelodysplasia. Abnormality or loss of chromosome 5, 7, or both is common.
- Alkylating agents include nitrogen mustard, cyclophosphamide, ifosfamide, melphalan, and procarbazine.

Secondary leukemia due to epipodophyllotoxins

- Mechanism is inhibition of topoisomerase II, thus preventing repair of damaged DNA.
- Risk may be related to cumulative dose, dose scheduling (ie, once weekly or twice weekly), or both; data are not clear, but secondary AML following administration of these agents has been reported in as many as 12% of patients with acute lymphoblastic leukemia (ALL).
- AML usually develops 2-4 years after diagnosis of the primary cancer. No myelodysplastic phase occurs. As an SMN, AML is usually French-American-British classification (FAB) subtype M4 or M5 (ie, myelomonocytic or monocytic, respectively), with abnormalities of chromosome arm 11q23 (*MLL* gene).
- Almost no patients survive.
- Examples of epipodophyllotoxins are etoposide and teniposide.

Secondary solid tumors due to radiation therapy

- Risk is related to cumulative dose of radiation and age at time of treatment.
- Unlike the risk of developing secondary leukemia, the risk of secondary solid tumor after radiation continues to increase over time, with a latency of 10-20 years or longer.
- Most common SMNs include breast cancer (after mantle radiation for Hodgkin disease), brain tumors (after cranial radiation treatment [CRT] for ALL), soft tissue or bone sarcomas, thyroid cancer, and bladder cancer. The risk to a specific site may be related to the proliferative capacity of that tissue, eg, bone and breast during puberty.

Second Malignancies in Survivors of Childhood Cancer

Disease	Number of Patients	Cumulative Risk	Risk Factors	Reference
All cancers	13,581	3.2% at 20 y	...	Neglia, 2001
		2% at 20 y after leukemia, with brain tumors most common after ALL (especially if <5 y at diagnosis)	Almost every patient with ALL had CRT	
		2.1% at 20 y after CNS	...	
		7.6% at 20 y after Hodgkin disease	...	
ALL	1597	2.7% at 18 y	Most patients had CRT	Dalton, 1998
ALL	1612	1.4% incidence of brain tumors at 20 y*	...	Walter, 1998
Hodgkin	979	9% at 15 y	Radiation in development of solid tumors	Meadows, 1989
		4% at 15 y for leukemia/lymphoma	Dose-related risk of alkylators	
Hodgkin	499	7.7% at 15 y	Higher risk in adolescents and females, especially breast cancer	Beatty, 1995
Hodgkin	1380	7% at 15 y with breast cancer most common	...	Bhatia, 1996
		Almost 35% breast cancer by age 40 y	Solid tumor	
Wilms	5278	1.6% at 15 y	Abdominal RT potentiated by doxorubicin	Breslow, 1995
Rhabdomyosarcoma	1770	1.7% at 10 y with bone sarcomas most common, then AML	...	Heyn, 1993
Retinoblastoma	1604	51% at 50 y for hereditary retinoblastoma with sarcomas most	Potentiated by radiation	Wong, 1997

*Median latency 12.6 y

Prevention, Follow-up, and Monitoring

Young adult survivors of childhood cancer must be monitored closely in a comprehensive multidisciplinary long-term follow-up clinic. These clinics usually include oncologists, specialty physicians, oncology nurse specialists and nurse practitioners, social workers, rehabilitation specialists, and school liaisons. These specialists complement and support the primary caretaker, who is expected to carry more of the burden of follow-up in the current managed care environment. Only with continued efforts to collect data on long-term complications of childhood cancer and its therapy can interventional strategies be studied and modifications made in current therapy to lessen toxicity to future generations of cancer survivors.

Education of the patient and family concerning long-term effects must start before the institution of therapy. The patients have the right to understand, in accordance with their age, the long-term effects that treatment will have on growth and development, personal appearance, fertility, and other bodily functions. When infertility is a potential problem, males who are pubertal should be offered sperm banking as an option prior to the institution of therapy. In the future, females may be offered the same kind of cryopreservation service.

Prevention of toxicity

- Radiation therapy (RT) may be omitted (eg, as in most children with acute lymphoblastic leukemia [ALL] on current protocols) or delayed (eg, infants with brain tumors). In addition, techniques for limiting fields, including radiosurgery and conformal radiation, may lessen toxic effects on normal structures. For example, conformal radiation to the posterior fossa is being examined in children with medulloblastoma with the hope that the cochlea can be spared and ototoxicity lessened.
- Cumulative doses of alkylating agents, such as nitrogen mustard, cyclophosphamide, ifosfamide, and procarbazine, may be limited. Toxic effects of chemotherapy may be prevented or lessened with the use of chemoprotectants; for example, dexrazoxane may lessen both the cardiac toxicity of anthracyclines and the pulmonary toxicity of bleomycin.
- In a recent Dana Farber study, dexrazoxane was shown to decrease early cardiac toxicity in children with ALL who received doxorubicin. That study and several completed Pediatric Oncology Group studies showed no short-term adverse effects on survival. However, long-term results regarding the effectiveness of cardiac protection and disease-free survival await further follow-up. Current recommendations are to use dexrazoxane only in the setting of a controlled clinical trial.
- Amifostine (Ethyol) is also being studied as a potential protectant against cisplatin-induced acute bone marrow toxicity, nephrotoxicity, neurotoxicity (including ototoxicity), and radiation-induced damage to normal tissues. However, one small study in children with medulloblastoma, and another in children with germ cell tumors, did not show any protection against cisplatin-induced ototoxicity.
- Healthy dietary and lifestyle habits, such as exercise and avoidance of alcohol, sun, and tobacco should be promoted. Counseling regarding avoidance of risky behaviors, such as smoking and recreational drug use (cocaine especially in individuals who have cardiac risk factors) is recommended during follow-up visits with survivors.

Monitoring for late effects

- Musculoskeletal: Children receiving RT should have yearly physical examinations, including a scoliosis examination (especially if in pubertal growth spurt); obtain radiographs as needed.
- Breast: Girls receiving mediastinal RT should be taught self-breast examination. Beginning baseline mammograms at age 25-30 years or 10 years after RT in these patients has been recommended. Perform annual clinical examinations and repeat mammograms every 2-3 years depending on breast tissue.
- Brain: Children receiving CRT should undergo neurocognitive testing at baseline, then whenever the clinical need arises.
- Neuroendocrine: Monitor yearly growth curves in all children who received radiation. For children who receive RT to the hypothalamic-pituitary axis in doses greater than 2900 cGy, assess bone age around age 9 years. Perform growth hormone stimulation testing about 2 years after finishing therapy, sooner if growth starts to decelerate. Check luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone or estradiol, prolactin, and morning cortisol at baseline and then as needed. Perform thyroid function studies (ie, thyroid-stimulating hormone [TSH], free thyroxine, triiodothyronine) at baseline and then every 3-5 years as needed.
- Ovary: Girls who receive alkylating agents or abdominal or pelvic RT should have their menstrual histories monitored yearly after therapy; elevated LH and FSH and low estradiol may indicate ovarian failure if menses do not occur and if signs of premature ovarian failure are present. Hormone replacement therapy is necessary for girls who do not go through puberty or who have evidence of premature ovarian failure.
- Testes: In boys who receive alkylating agents or testicular or pelvic RT, check baseline LH, FSH, and testosterone once they reach the age of 12 years and then as needed. Passage through puberty is rarely affected; only large doses of alkylators and RT doses greater than 3500 cGy are likely to affect Leydig cells. Sperm analysis represents the criterion standard regarding fertility, although elevated gonadotropins and small testes are excellent indicators of potential infertility.
- Cardiac: Children who receive anthracyclines, high-dose cyclophosphamide, or mediastinal or spinal RT should undergo echocardiography ECHO and ECG at baseline, then every 3-5 years after treatment; perform these tests more often if abnormalities are present. Perform Holter ECG every 5 years and then as needed in children who receive high cumulative doses of anthracyclines. Perform stress ECHO or radionuclide angiography (RNA) or multiple gated acquisition (MUGA) as needed or if screening ECHO findings are abnormal.
- Pulmonary: Children who receive chest or mediastinal RT, bleomycin, or carmustine (BCNU) or lomustine (CCNU) should undergo pulmonary function tests (PFTs) at baseline, then every 3-5 years as needed. Strongly counsel these children regarding smoking and exposure to pulmonary toxins.
- Renal: Children who receive cisplatin, carboplatin, cyclophosphamide, ifosfamide, or abdominal RT should have creatinine and magnesium monitored every 1-2 years; measure creatinine clearance at baseline and then every 3-5 years as needed in patients who receive platinum-containing chemotherapy. Perform yearly urinalysis in all children who receive ifosfamide or abdominal RT. Children who receive ifosfamide also should have serum phosphate and urine glucose and protein monitored yearly for evidence of Fanconi syndrome.
- Bladder: After cyclophosphamide, ifosfamide, or bladder RT, patients should have yearly urinalysis to check for hematuria.
- Thyroid: Children who receive RT to the neck, mediastinum, or spine should have TSH, free thyroxine, and triiodothyronine checked yearly for 10 years. Obtain an ultrasound if a nodule or goiter is palpated.
- Liver: In children who have been treated with 6-mercaptopurine, methotrexate, actinomycin-D, or abdominal RT, liver function tests should be performed every 1-3 years. All survivors who received blood products, especially those who were treated prior to 1992, are at risk for hepatitis C and should be checked for all hepatitis viruses.

- GI: After abdominal K1, check stool yearly for occult blood because of the risk of secondary cancers. Malabsorption may be reflected in a history of diarrhea, lactose intolerance, or failure to thrive and should be investigated.
- Second cancers: Monitoring for second cancers varies by patient genetic predisposition and treatment. For an early diagnosis, the survivor and his/her family must be educated regarding the risks and they must understand that they can detect problems in the earliest stages. Annual visits to a health care provider serves the purpose of ongoing counseling and provides a baseline of health for the rational assessment of future signs and symptoms.

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- Relevant clinical guidelines include the following:
 - Long term follow up of survivors of childhood cancer: A national clinical guideline
 - Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Sections 1-2: Any cancer experience
 - Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Sections 3-5: Blood/serum products
 - Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Sections 38-91: Radiation
- Relevant clinical trials include the following:
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