Late effects of cancer treatment in children

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Over the past two decades remarkable advances have been made in treating childhood malignancies. Survival rates of children with cancer in the 1940s and 50s were in the 10–20% range, whereas today they have escalated to 60–70%.[1] Based on this current trend, by the year 2000, one in 900 young adults (15–45 years of age) will be a survivor of childhood cancer.[1] But survival is not without cost: antineoplastic therapy does not discriminate between tumor and normal tissue, and this, in turn, may lead to a significant incidence of delayed sequelae.[2] Such late effects include a spectrum of complications from minor symptomatology to major morbidity and mortality.

Acute toxicity induced by chemotherapy can be related to the proliferation kinetics of individual cell populations. Thus, the most susceptible structures are tissues or organs with a high cell turnover rate such as the oral and intestinal mucosa, bone marrow, hair follicle, testis, and liver. Least susceptible are cells that replicate slowly or not at all, i.e. neuron, muscle, connective tissue, and bone. Notable exceptions are the effects induced on nerve tissue by methotrexate, the vinca alkaloids, cisplatin, and high-dose cytosine arabinoside and the effects on cardiac muscle inflicted by the anthracyclines.

In addition to these factors, damage to tissues and organs with a low repair potential often results in deficits that are prolonged or permanent. Thus, children may appear to tolerate acute toxicities of cancer therapy more easily than adults, but the long-lasting effects are often more devastating, particularly if growth, fertility, neuropsychologic function, and cardiac reserve are compromised.

This communication will review — by system — delayed sequelae encountered in long-term survivors of childhood cancer. A long-term survivor is defined as an individual in whom cancer was diagnosed before age 16 who is free of malignant disease 5 years after diagnosis and initiation of treatment. In such individuals, delayed sequelae may occur as a consequence of the cancer or its therapy.

Central nervous system

Long-term survivors of childhood malignancies who require treatment of the central nervous system (CNS) are at substantial risk to develop adverse neuropsychologic sequelae. This generally involves patients with brain tumors and acute lymphocytic leukemia.[3–10] Particularly important are learning difficulties following treatment with cranial radiation (1,800–2,400 cGy) and intrathecal methotrexate.[6,7] Younger children are at greatest risk for developing the most severe cognitive disabilities, especially with radiation therapy.[6] Qualitative assessments of intelligence in children with brain tumors treated with high-dose radiation also show that they are clearly more impaired than those treated with neurosurgery alone.[3]

Neuropsychologic testing at the pediatric department at the University of Texas M.D. Anderson Cancer Center and others has demonstrated that of all the therapies used to combat or prevent CNS disease, radiation is the most

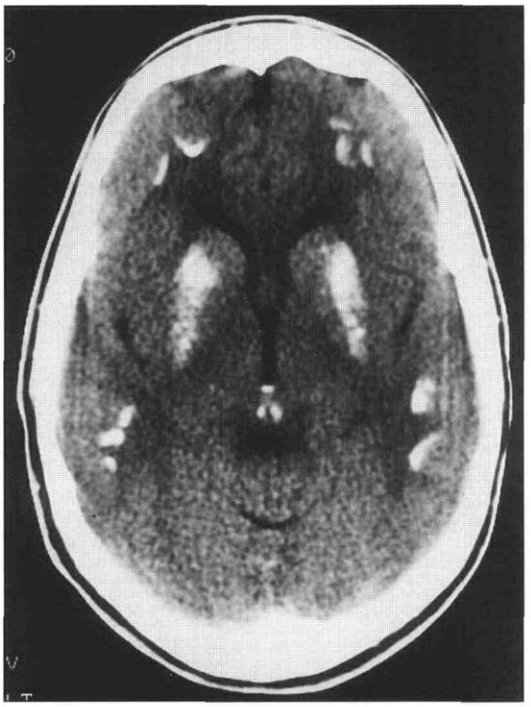


Fig 1. Treatment-related leukoencephalopathy. Contrast-enhanced CT scan demonstrates symmetrical bilateral changes of the periventrical white matter (arrows). There is no mass effect or contrast enhancement. These changes represent demyelination as a result of radiation and chemotherapy.

likely to contribute to learning difficulties.[5-7] Patients receiving 2,400 cGy cranial radiation exhibit cognitive impairment in mathematics, memory (especially spatial memory), attention, concentration, and fine motor speed and coordination. A lower dose of cranial radiation (1,800 cGy) and significantly intensified systemic and intrathecal methotrexate produce comparable adverse neurotoxicity.[8] Recent investigations also have demonstrated that girls developed more severe and global IQ depression than boys after receiving IV methotrexate.[9] The abnormalities produced by cranial radiation and methotrexate also may be observed on computerized axial tomography (Fig 1) and nuclear magnetic resonance.[10-13]

Leukoencephalopathy may result from treatment with cranial radiation and methotrexate alone or in combination.[10] Histopathologically, leukoencephalopathy is characterized by reactive astrocytosis, gliosis, and demyelination. Clinically, the syndrome may manifest as dementia, dysarthria, dysphagia, ataxia, spasticity, seizures, and coma.[10] Radiologic studies may reveal intracerebral calcification, dilatation of the ventricular and subarachnoid space, and white matter hypodensity.[11-13] Other reported neurologic sequelae include radiation-induced optic nerve damage and posterior capsular cataracts (the latter may also be steroid induced).[14] Hearing deficits have occurred following treatment with radiation therapy and cisplatin.[15]

Endocrine system

The endocrine system may be subjected to multiple, long-term sequelae from antineoplastic therapy. Thus, the pituitary gland may be injured by radiation therapy resulting in isolated growth hormone deficiency, or less frequently, panhypopituitarism. These long-term sequelae may not be evident until many years after therapy.[16] One of the major sequelae produced by radiation damage to the hypothalamic pituitary axis is a deficiency in growth hormone. Shalet et al. found that 90% of children who receive > 3,000 cGy to the cranium and 50% who receive 2,400 cGy have evidence of growth hormone deficiency within 2 years.[17]

The thyroid gland is also sensitive to radiation therapy: dysfunction may manifest as hyper- or hypothyroidism, but most commonly appears as compensated hypothyroidism. Reported abnormalities have been detected from 6 months to 7 years after therapy completion.[18] Although a patient with compensated hypothyroidism may be asymptomatic, exogenous hormone usually is administered to suppress persistently elevated thyroid-stimulating hormone levels and to inhibit chronic stimulation of the thyroid gland.[19] The intent is to prevent later development of thyroid malignancy.

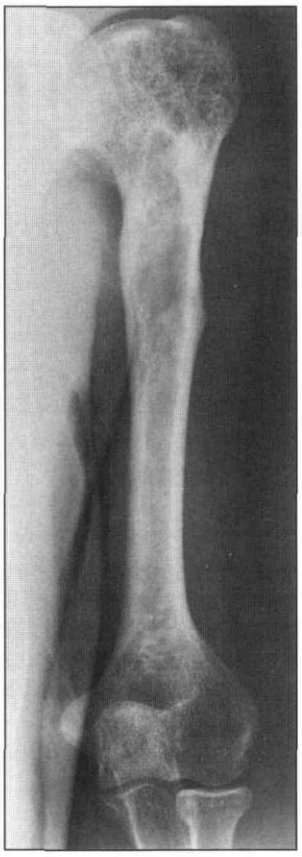
Gonadal function may be impaired by surgical procedures, radiation therapy, or chemotherapy. Surgical removal may be necessary when a tumor is present in either the ovary or testis. The damaging effect of radiation therapy on the ovaries is directly related to the dose of radiation and the age at the time of treatment.[20] Women older than 40 years of age experience ovarian failure after only 400–700 cGy, whereas comparable doses in younger women are less devastating: normal menstruation and pregnancy have followed abdominal doses up to 2,000 cGy.[21] Some prepubertal children, particularly girls, treated with cranial radiation are at increased risk for precocious puberty and short stature.[22] This is considered to be because of premature activation of the hypothalamic pituitary-gonadal axis and early closure of the epiphyseal plate.

Prepubertal females, as opposed to postpubertal females, appear less likely to experience gonadal injury following therapy with cytotoxic agents. In the former population, normal pubertal development, ovarian function, and successful pregnancies have followed treatment with most chemotherapy regimens, although cyclophosphamide, MOPP (nitrogen mustard, vincristine, prednisone, and procarbazine), and the nitrosoureas occasionally have been implicated as a cause of gonadal damage.[23,24] Postpubertally, advancing age correlates with increasing ovarian sensitivity to damage by chemotherapy: alkylating agents are particularly harmful to this age group.[25] Although women may not immediately experience ovarian failure following chemotherapy or radiotherapy, they may later develop early menopause.

Prepubertal boys treated for leukemia, Wilms' tumor, and Hodgkin's disease have been found to be sterile and/or exhibit elevated gonadotrophins and low testosterone levels as a result of direct or scatter testicular radiation in doses of 146–2,500 cGy.[26,27] They also have demonstrated a high risk for delayed sexual maturation. In the postpubertal age, radiation also may produce severe damage to the testis. The effect is dose dependent: 100 cGy may produce transient azoospermia and 600 cGy irreversible sterility.[26,28]

The prepubertal testis, while apparently more resistant to damage by chemotherapy than the older testis, still appears somewhat sensitive, especially to alkylating agents. Doses of cyclophosphamide exceeding 400 mg/kg/dose were found to produce gonadal abnormalities in up to 30% of prepubertal boys.[29] Prepubescent boys treated with six or more courses of MOPP chemotherapy also demonstrated evidence of testicular failure.[26] This was detected by elevated FSH levels, depletion of germinal epithelium on testicular biopsy, and increases in LH levels with low testosterone levels. Gynecomastia as a complication of BCNU, MOPP, and cyclophosphamide has been attributed to a decrease in the testosterone level.[30,31]

Postpubertally, the testis appears very sensitive to alkylating agents[30-32] and the nitrosoureas.[33] Damage is related to dose and duration of treatment. The majority of postpubertal males will be sterile after five to six cycles of MOPP chemotherapy. DaCunha demonstrated that three cycles of MOPP represent the maxi-



◀ **Fig 2. Postradiation Ewing's sarcoma left humerus. Lytic lesion with permiative pattern in proximal diaphysis of humerus complicated by pathologic fracture.**

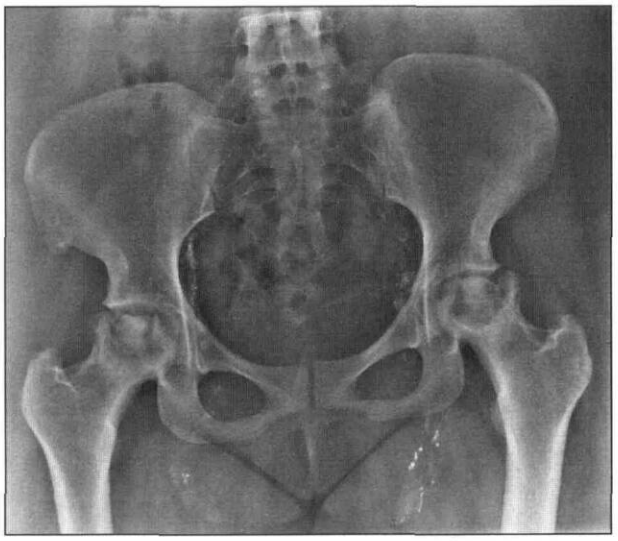


Fig 3. Postradiation aseptic necrosis of femoral epiphysis. Bilateral collapse and shortening of femoral heads with multiple defects and narrowing of joint representing aseptic necrosis. Notice hypoplastic change of iliac bones secondary to radiation. ▶

mum exposure compatible with recovery of spermatogenesis.[31] Pryzant also found that postpubertal males receiving > 9.5 gm/m^2 of cyclophosphamide were at high risk of permanent sterility.[32] Bone marrow transplant regimes for children containing high-dose cyclophosphamide and total body irradiation also carry a significant risk for testicular or ovarian failure.[34]

Musculoskeletal system

Linear growth may be adversely affected by antineoplastic treatment. Despite the fact that some degree of catch-up growth may occur following therapy completion, in some instances short stature is permanent. Growth arrest may be the result of one or more of a combination of factors, such as the tumor itself, surgery, spinal radiation, malnutrition, corticosteroids, and/or radiation damage to the hypothalamic pituitary axis. The effects of antineoplastic therapy are generally dose dependent.

As outlined earlier, radiation damage to the hypothalamic axis may result in a deficiency in growth hormone and, ultimately, linear growth.[17] Final adult height also may be affected by radiation to the spine, abdomen, and extremities.[35,36] The extent of the deformity is related to dosage, schedule, age at time of treatment, epiphyseal injury, and arrest of chondrogens.[35–37] Radiographic abnormalities in the vertebrae appear as end-plate irregularities, anterior beaking, "bone-within-bone effect", flattening, and asymmetry of vertebral bodies.[38]

Growth also may be affected by spinal deformities such as scoliosis and kyphosis. This may result from asymmetric exposure of the spine to radiation therapy. In the past, the portal of radiation therapy, as for example in Wilms' tumor, or neuroblastoma, usually was confined to the site of origin of the tumor producing a 40–70% incidence of scoliosis.[35] Current radiation practices accommodate the entire vertebral body into the radiation field, thereby significantly decreasing the incidence of scoliosis. Nevertheless, patients should be monitored closely for this complication — especially as they enter the adolescent growth spurt — since treatment still may be associated with inhomogeneity of dose.

Inhibition of vertebral growth also has been observed in patients with brain tumors following radiation therapy to the entire spinal column in doses > 3,500 cGy.[39,40] The abnormalities are exaggerated if radiation is administered during periods of active growth. The deficits manifest as a reduction in sitting height and radiographic changes in the vertebrae as described above.

Radiation damage to other long bones and soft tissues manifests as hypoplasia, widening and fraying of the metaphyseal plate, sclerosis, and abnormal trabeculation (Fig 2). In addition, there may be functional limitation, shortening of the extremity, osteonecrosis, increased susceptibility to fracture, and poor healing. Avascular necrosis of the femoral neck and slipped capital femoral epiphysis may follow pelvic radiation[41] (Fig 3). Steroids also have been incriminated in avascular necrosis of the femoral head.[42] Long-term administration of methotrexate and corticosteroids may result in profound osteoporosis and growth arrest.[43]

Radiation therapy to the head and neck in a growing child may cause significant deformity of bone and soft tissue hypoplasia. The teeth also are susceptible to radiation injury. Defects include root shortening, rampant caries, abnormalities in mandibular alignment, malocclusion, loss of enamel, root agenesis, micrognathia, trismus, and delayed or arrested tooth devel-

Fig 4A – 4B. Anthracycline cardiotoxicity.

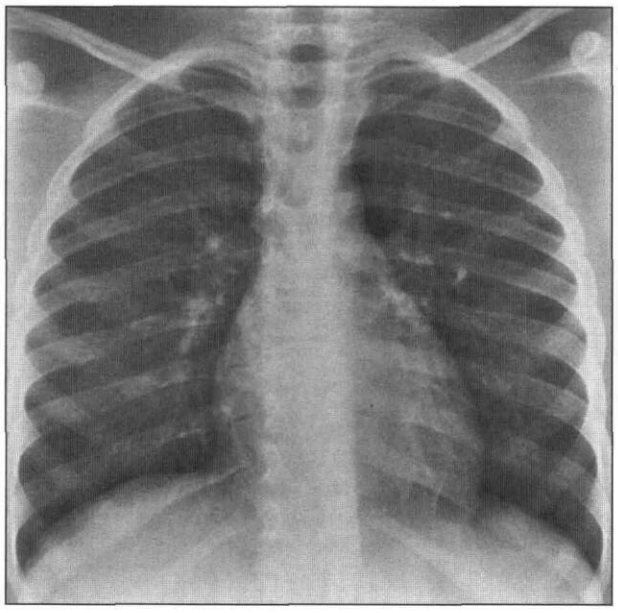


Fig 4A. Normal chest radiograph — 12 years post doxorubicin. Total cumulative dose 480 mg/m².

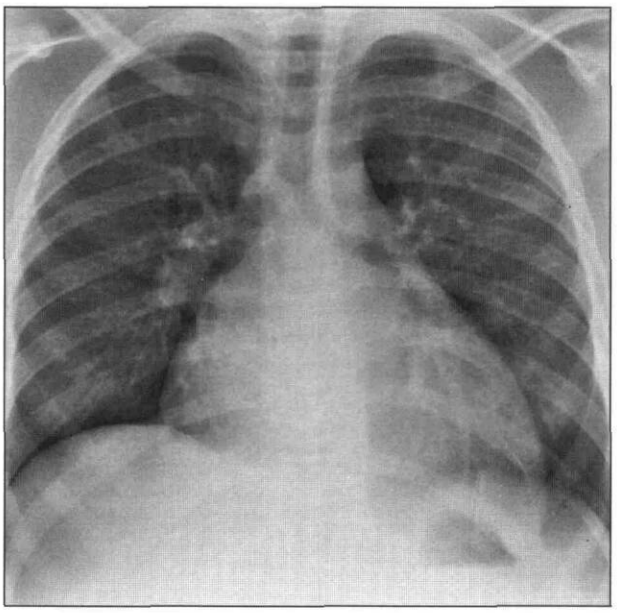


Fig 4B. Chest radiograph — 11 months later. Cardiac enlargement with pulmonary congestion compatible with congestive heart failure.

opment.[44] Radiation alters the character of saliva and renders the teeth more sensitive to injury and caries. Severity of the dental and maxillofacial deformity induced by radiation varies inversely with age at the time of treatment. Dental abnormalities possibly also may be caused by chemotherapy and include growth failure of and/or abnormal development of teeth, small crown hypoplasia, shortening and thinning of premolar dental roots, and tapering and shortening of the incisors.[44]

Cardiac system

The heart is susceptible to damage by radiation therapy[45] and certain chemotherapeutic agents.[46–49] Radiation-induced cardiotoxicity most often manifests as a pericardial effusion or constrictive pericarditis, sometimes associated with pancarditis. The threshold for inducing damage appears to be 4,000 cGy, although pericarditis has been reported after as little as 1,500 cGy.[45] Cardiac damage may be silent and only detected by specific imaging studies. Symptoms may not develop for some years following therapy; in symptomatic patients, pericardiocentesis or a pericardial window may be required to improve cardiac function.

The anthracyclines (daunorubicin and doxorubicin) may cause acute cardiac toxicity during therapy; however, they may also cause cardiac damage that only becomes apparent many years after therapy completion[47](Fig 4). Late cardiac effects manifest as left ventricular dysfunction, congestive cardiac failure, coronary artery disease, arrhythmias, or sudden death. Anthracycline cardiotoxicity is dose related; the incidence of cardiomyopathy is 30% with doses > 600 mg/m² and less than 1% with doses < 500 mg/m².[46] The potential to develop cardiac failure may be exacerbated by chemotherapeutic agents such as cyclophosphamide, dactinomycin, mithramycin, DTIC, and/or mediastinal radiation.[48]

The anthracyclines cause direct damage to cardiac myocytes by reducing the number of residual cells to a critical level. This, in turn, does not allow appropriate concomitant myocardial growth with the increase in age. Histologic examination in patients with late cardiac dysfunction reveals myofibrillar loss, hypertrophic changes of the myocytes, mitochondrial swelling and focal interstitial fibrosis.[46] Lipshultz reported increased afterload and decreased contractility, or both, on echocardiography in 65% of 115 children treated for acute lymphoblastic leukemia with doxorubicin. The dose in his study was in excess of 228 mg/m² and the abnormality was detected at a median of 6.4 years after completion of therapy.[49] Cumulative dose of doxorubicin and therapy on patients younger than 4 years were considered significant risk factors.

Children treated with anthracyclines need long-term followup. Steinherz documented an increase in the incidence of abnormal echocardiograms with doses > 500 mg/m² 10 years after treatment.[47] The true incidence of long-term survivors with subclinical, postanthracycline myocardial damage remains to be determined. The majority of patients with abnormal cardiac findings are asymptomatic, although congestive cardiac failure may occur as late as 6–10 years after drug exposure.[47]

Pulmonary system

Pulmonary radiation may damage the elastic properties of the lungs. Long-term effects manifest as loss of lung volume and compliance and a reduction in dif-

fusing capacity of carbon monoxide. These abnormalities have been reported following treatment with 1,100–1,400 cGy and are more prone to occur in children younger than 3 years old.[50]

The lungs are also susceptible to significant latent toxicity from chemotherapy. Agents associated with pulmonary toxicity include bleomycin,[51] BCNU,[52] cyclophosphamide,[53] busulfan,[54] chlorambucil,[55] and methotrexate.[56] The incidence of pulmonary toxicity with bleomycin in adults increases as the total dose exceeds 400–450 mg; however significant pulmonary toxicity in children generally is seen with as little as 60 mg/m^2.[51] Toxicity manifests as nodular infiltrates in a diffuse or basilar distribution on radiographic examination of the chest (Fig 5). Pulmonary fibrosis caused by BCNU may develop several years after receiving the drug. O'Driscoll described six deaths secondary to lung fibrosis among 17 survivors of childhood brain tumors treated 2 to 13 years previously with BCNU.[52] All the remaining survivors had small lung volumes, restrictive lung disease, and decreased carbon monoxide diffusion capacity.

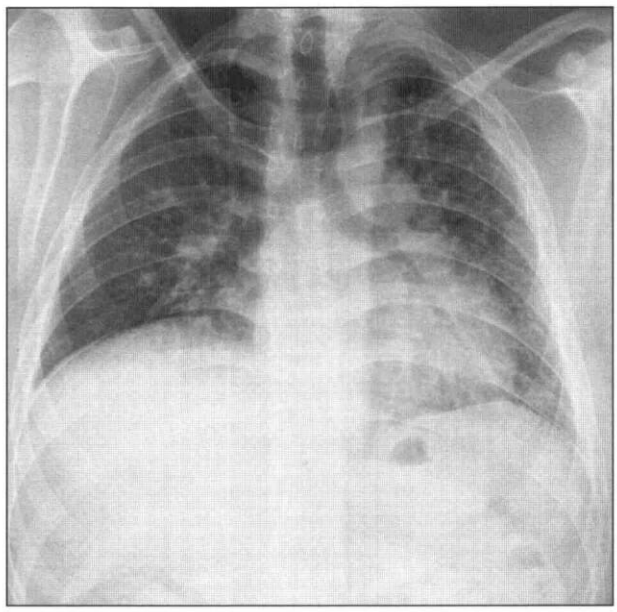


Fig 5. Bleomycin pulmonary toxicity. CT scan demonstrates bilateral reticulonodular infiltrate consistent with bleomycin toxicity.

Gastrointestinal tract

Radiation to the gastrointestinal tract involving any site from esophagus to rectum may result in fibrosis or stricture.[57] Obstruction, ulceration, and malabsorption syndromes may occur. The incidence and severity of these problems may be compounded by radiomimetic chemotherapy and surgery, which may be required to treat the primary malignancy or obstruction.

Radiation to the liver may cause acute or chronic damage, including chronic hepatic fibrosis.[58] The threshold dose, above which a steep rise in liver complications may occur, is 3,000 cGy. The potential to develop long-term sequelae is enhanced if radiation is administered in combination with dactinomycin or doxorubicin and if juxtaposed to hepatic resection. Methotrexate[59] and 6-mercaptopurine[60] also are associated with long-term liver damage. Long-term, low-dose chemotherapy appears to carry a greater risk of liver damage than a high-dose intermittent schedule. Chronic hepatic damage is most often insidious and symptomless. Liver function tests and size remain normal until extensive fibrosis and cirrhosis develop. This usually appears concurrently and is not infrequently associated with the symptomatology of chronic hepatitis. Also of concern is the possibility of chronic damage, which may result from hepatitis B and hepatitis C contracted via blood product transfusions — often required to treat myelosuppression during cancer therapy.

Urinary tract

Late sequelae attributed to the effects of antineoplastic therapy on the kidney and bladder also may be encountered. Radiotherapy to the kidney may cause chronic nephritis. Onset of symptoms is variable and may develop after only a few months or as long as 13 years after therapy: Symptoms may occur *de novo* or following acute nephrotoxicity.[61] Damage can occur directly from radiation to the kidney and also from radiation-induced retroperitoneal fibrosis with urethral obstruction.[62] Whole- or hemi-abdomen radiation therapy has been reported to retard compensatory hypertrophy of the remaining kidney after unilateral nephrectomy.[63]

Delayed renal failure attributable to chemotherapy generally does not occur unless associated with acute toxicity or complications appearing with initial exposure to treatment. Major nephrotoxic agents include cisplatin, methotrexate, BCNU, and ifosfamide. The effects of these agents may be potentiated by the aminoglycosides, vancomycin, or amphotericin. Late effects of ifosfamide include chronic tubular dysfunction. This may manifest as Fanconi's syndrome and clinical rickets.[64]

Radiation to the bladder may cause hematuria and/or chronic cystitis. These effects may be aggravated by dactinomycin, the anthracyclines, or cyclophosphamide. The latter and its analog ifosfamide may induce direct toxic effects on the urothelium of the bladder.[64, 65] Cyclophosphamide as a cause of hemorrhagic cystitis has been implicated in 4–36% of its recipients; the complication may occur acutely or many years after therapy.[65] Twenty-five percent of children treated with doses of cyclophosphamide in excess of 6 gm/m^2 were documented to develop fibrosis of the bladder.[65] The latter can lead to vesicoureteral reflux, chronic cystitis, and damage to the upper renal tract. The use of MESNA (2-mercaptoethanesulfonate sodium), a sulfhydryl agent that binds the active (toxic) metabolites of

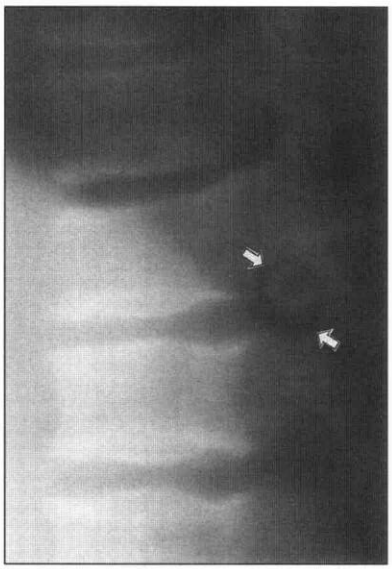


Fig 6. Benign bone tumor. Osteochondroma of apophysis of L1, (arrows), 12 years postirradiation with 45 Gy (4,500 rad) for Wilms' tumor at age 5 years. Notice also changes in the vertebrae.

Fig 7. Malignant bone tumor. Malignant fibrous histiocytoma of medial clavicle 7 years postmantle irradiation with 40 Gy (4,000 rad) for Hodgkin's disease, IIIA, at age 17 years.

cycylophosphamide and ifosfamide, may minimize the acute toxicity and possibly prevent chronic damage.[64] In addition to chronic cystitis, invasive carcinoma of the bladder following cyclophosphamide therapy also has been reported.[66, 67]

Miscellaneous late sequelae

Radiation in sufficient dose will adversely affect the normal development of virtually any organ or structure in the body. Hyperpigmentation, capillary telangiectasia, and atrophy are manifestations of radiation damage to the skin. Radiation therapy to the male pelvis may result in impotence and erectile dysfunction. If the prepubertal female breast bud is in the radiation field, atrophy or maldevelopment of the breast may occur. Radiation therapy administered to the abdomen for Hodgkin's disease may result in unilateral or bilateral hydroceles.[68] Cranial and peripheral neuropathies may develop as a consequence of radiation-induced nerve damage.[69]

Mutilating operations may on occasion be required to achieve cure. Procedures may include orbital exenteration or amputation. Less extensive operations that may have equally devastating effects on long-term survivors include diversionary procedures for cancer of the genitourinary or gastrointestinal tract. Radical retroperitoneal node resection may cause retrograde ejaculation and splenectomy may significantly alter humoral immunity.

Second malignant neoplasms

Over the past three decades, an increasing number of second malignant neoplasms have been documented in survivors of childhood cancer. The reported incidence varies from 3–20% with a 10- to 20-fold risk compared with age-matched controls, depending on the type of original tumor and the period of latency between the primary and second malignancy.[70–76] However, the overall lifetime risk for developing a second tumor is unknown, since most survivors presently are in the 20- to 40-year age group. In general, susceptibility to the development of a second neoplasm is related to type of primary tumor, biology, treatment administered, and genetic and other predisposing factors. These factors, and an outline of the second malignant neoplasms detected in long-term childhood survivors at the University of Texas M.D. Anderson Cancer Center, are discussed below in greater detail.

Radiation therapy is a major component of treatment; it is a known oncogene. Its effect is believed to be a consequence of genetic mutation(s). This risk of inducing malignant change with radiation therapy depends on age at treatment and type, dose, rate, and frequency of radiation. Rapidly proliferating cells, as for example in the bone or thyroid gland of a child, appear to be more susceptible to radiation injury than those of adults.[75] Also, orthovoltage radiation, with its greater absorption in bone, is more commonly associated with carcinogenicity as opposed to the megavoltage form.[76] As a general rule, the oncogenic effect of radiation is directly proportional to the dose delivered: the higher the dose the more likely the induction of oncogenesis. However, there are exceptions to this generalization. Thus, low-dose or scatter radiation to the head and neck in children has been incriminated both in the development of thyroid cancer[71–79] and benign thyroid nodules.[78] Further, benign bone tumors, (osteochondromas, Fig 6) as opposed to malignant bone tumors (Fig 7) also have been reported.[80]

Chemotherapeutic agents most commonly associated with the induction of second malignant neoplasms comprise the alkylating agents:[81] procarbazine,[82, 83] nitrosoureas,[84] and epipodophyllotoxins.[85] The alkylating agents and procarbazine are major components of MOPP; this combination and the nitrosoureas are used extensively to treat Hodgkin's disease and frequently are implicated in causating second malignant neoplasms in survivors of this and other malignancies.[81–86]

Bone sarcomas, soft tissue sarcomas, and thyroid cancer are the most common second malignancies re-

ported by the Late Effects Study Group[71] and the Intergroup Rhabdomyosarcoma Study.[74] Brain tumors, breast cancer, skin cancer, and a variety of other malignant tumors were noted less frequently. Kushner, at the Memorial Sloan Kettering Cancer Institute, reported that after 10 years, the risk for developing second malignancies, particularly nonlymphocytic leukemia and bone sarcoma following MOPP therapy was 6% and 5%, respectively.[82] At 15 years, the risk rose to 18.7%. It appears that the risk for acute nonlymphocytic leukemia was greatest in the first decade after therapy, whereas for solid tumors it was more common in the second decade. In contrast, Sullivan failed to detect any case of acute leukemia among 228 patients treated for pediatric Hodgkin's disease with a median followup of 13 years.[83]

Pui reported that the incidence of acute myeloid leukemia following treatment for acute lymphocytic leukemia was 2–5%.[85] The second malignant neoplasm was considered to be due to the prior administration of an epipodophyllotoxin. Neglia recently reported that brain tumors were the most commonly occurring second tumors in childhood cancer survivors followed by leukemia and lymphoma.[86] The tumors developed predominantly in children who received cranial radiation as prophylactic treatment to prevent development of leukemia in the central nervous system.

In addition to radiation therapy and chemotherapy, several familial and genetic factors are associated with an increased risk for developing malignant tumors. Among these are the genetic form of retinoblastoma, neurofibromatosis, nevoid basal cell carcinoma syndrome, xeroderma pigmentosa, familial adenomatous polyposis, and immunologic deficiency states. A sibling of a patient with cancer also has a slightly increased risk for developing a malignancy.

Retinoblastoma is an uncommon childhood tumor, but it is the most common initial neoplasm preceding a second tumor.[87] Davesa estimated the incidence of the tumor to be 11 new cases per million per year in children younger than 5 years of age; 20–30% of these will present as the genetic bilateral form of the disease.[87] Abramson reported that the risk for a second malignant tumor in such children after radiation was 10% at 10 years, 50% at 20 years, and 90% at 30 years. In nonradiated patients the risk was 10% at 10 years, 30% at 20 years, and 68% at 32 years.[88,89] A lower incidence was noted by Draper: 4.2% at 18 years among all patients and 84% in those with the genetic form of the disease.[90]

Osteosarcoma and soft tissue sarcomas are the most common second malignancy in retinoblastoma patients. Most osteosarcomas arise within radiated areas. The other tumors, though occurring less frequently, arise in locations well outside the radiated port. Neoplasms that arise in the radiated areas have a shorter latency period than those in nonradiated sites. Recent reports indicate that the locus of the retinoblastoma and osteosarcoma gene is on chromosome 13.[91,92] This association most probably accounts for the high incidence of osteosarcoma in patients with the genetic form of retinoblastoma.

Malignancies in long-term survivors may also be linked to other genetic factors. Li and Fraumeni first reported a familial cancer syndrome characterized by a high incidence of sarcomas, early breast cancer, and other neoplasms including brain tumors, leukemia, and adrenocortical tumors. The tumors generally occurred in individuals in their fifties who were closely related to the patients.[93,94] Birch et al. and Strong et al. later reported a high familial incidence of similar tumors in relatives of children with second malignancies.[95,96] This suggested a familial association in the risk of developing a second malignant tumor in long-term pediatric survivors with soft tissue sarcoma.

During the past several years, increased emphasis has further been placed on the genetic changes that may occur in neoplasia. This may have a relationship to the development of second malignant neoplasms in long-term survivors. In 1990, Malkin reported p53 germline mutations in five families representative of the Li-Fraumeni syndrome.[97] Subsequently, data on 57 children with second malignant tumors who were not representative of Li-Fraumeni syndrome also were published.[98] Only four of the patients exhibited a p53 germline mutation. Later, Toguchida also reported p53 germline mutations in 8 of 196 patients (4%) with sarcomas.[99] Five of the eight patients stemmed from families with a high incidence of cancer, particularly osteosarcoma. Thus, although provocative, the inheritance of p53 mutation does not necessarily presage development of a malignant tumor. Some family members with the mutation who are in their fifties have yet to develop cancer. It is also possible that radiation and/or chemotherapy could increase the predisposition for individuals with the p53 germline mutation to develop a second carcinogenic event.[100]

The pediatric department of the University of Texas M.D. Anderson Cancer Center has registered 782 long-term childhood cancer survivors over the past 34 years. During this period, 62 patients developed second primary tumors. This represents an overall incidence of 7.9%. The age of the patients at initial diagnosis varied from 0.23 to 17 years (median 11.5) and the interval to development of the second malignant neoplasms varied from 1.7 to 24.8 years (median 11.8). The primary diagnoses comprised Hodgkin's disease (24), rhabdomyosarcoma (7), osteosarcoma (5), leukemia (6), brain tumor (6), neuroblastoma (2), and miscellaneous (12). Thirty-two patients, including all patients with thyroid cancer, were rendered free of disease after therapy for the second tumors (51%).

Forty-eight second malignant neoplasms occurred in an involved or contiguous radiated field in which doses varying from 500 cGy to 6,400 cGy were administered. Forty-nine of the 62 patients also received alky-

lating agents. An outline of the dose intensity of alkylating agents (total dose over unit time) administered to patients with second malignant neoplasms is depicted in the Table. Because of small numbers of patients in each category and wide variation in dosage, it is not possible to determine the cumulative alkylating dosage and dose intensity that may be implicated in the induction of second malignant tumors. It is also possible that simple alkylating agent exposure (probably in association with other factors), rather than cumulative dosage or dose intensity may be the trigger point for developing second malignant neoplasms. Thus, despite the fact that alkylating agents have been implicated in the etiology of second malignant neoplasms, additional data are needed to define their exact role.

Overall there is incontestable evidence that the potential to develop second malignant neoplasms in long-term survivors of childhood cancer represents a constant threat. However, as depicted earlier, a reasonable number of patients who develop second malignant neoplasms may still be rendered free of disease. It is hoped that with improved methods of radiation treatment and better understanding of the carcinogenic effects of chemotherapy, the hazards of this complication will be reduced. Exploration of the genetic risks also may be helpful. Close surveillance of childhood cancer survivors throughout life is also of major importance.

TABLE. SECOND MALIGNANT NEOPLASMS AND ALKYLATING DOSE INTENSITY

		Total Dose (gm/M2)			*Duration (days)*			*Dose/Total (days)*		
Alkylating Agent	*Pts*	*Med*•	*Min*†	*Max*‡	*Med*	*Min*	*Max*	*Med*	*Min*	*Max*
Nitrogen mustard	13	0.055	0.015	0.159	150	60	894	0.00033	0.000033	0.004
Procarbazine	14	6.10	0.072	20.000	180	60	894	0.02800	0.0012	0.102
Cyclophosphamide	19	11.25	0.560	75.000	420	90	826	0.02300	0.0044	0.1068
Chlorambucil	2									
CCNU	1									

• Median; † Minimum; ‡ Maximum.

Psychosocial effects

The diagnosis of cancer and its treatment during childhood or adolescence can interfere significantly with normal growth and development. At each milestone and stage of achievement, objectives may be stunted or reversed. Forced dependency, academic interruptions, physical changes, and disruption in family and peer relationships may have an adverse lifetime effect. Many investigators have attempted to evaluate the psychosocial status of survivors of childhood cancer with results that are as varied as the number of studies. Overall, however, the outlook is possibly encouraging.

A majority of the studies found no increased incidence of major psychiatric disorders among long-term survivors, only difficulties in adjustment.[101-108] There are a few notable exceptions. An early study by Koocher and O'Malley found 59% of survivors had at least mild psychiatric symptomatology manifesting as ineffective socialization and self-help skills.[106] Lansky and Chang reported that long-term survivors, when compared with their siblings, had a higher incidence of prior episodes of depression, anxiety, alcoholism, and/or suicide attempts.[107, 108] Lansky also noted that 87% of long-term survivors encountered difficulties in school attendance and 28% reported academic problems due to absenteeism. Forty-six percent reported that their academic plans were disrupted while 38% indicated that their career goals were changed because of the cancer and therapy.[107] Similarly, Mulhern identified 30–40% of survivors at risk for school-related problems, with a 3- to 4-fold increased risk for this complication in those who received cranial radiation.[109]

Several studies of childhood cancer survivors also examined achievement goals as a reflection of adaptation. Despite some discrepancies, most of the studies found a higher percentage of rejection from military service for males and females when compared with siblings or matched peer controls. Further, although the percentage of rejection in employment was not as high as that in the military, it was significant, and appeared to be higher in males than females.[110, 111] However, the overall unemployment rate in long-term survivors was not greater than U.S. norms. Phillips reported that half of childhood cancer survivors had lower-level jobs than did their siblings.[112] Most long-term employed survivors, while able to obtain health insurance, experienced difficulties in doing so. Also, the percentage who obtained life insurance was significantly lower than that of the general U.S. population.

Hays noted differences in long-term survivors of childhood cancer in the 30- to 50-year age category as opposed to those 20 to 29 years old.[113] Those in the older age group were not significantly different in their economic achievement and insurability compared with peer-matched controls. For survivors 20 to 29 years old, there were significant differences between them and controls in acceptance to the military, attaining life insurance, education achievement, employability, work place interrelations and health insurance.[112] Many obtained health insurance that excluded cancer or any cancer-related problem.

Relationships of long-term survivors also have been examined as another indicator of life-goal achievement. Lansky reported that more than 50% of the long-term survivors observed disruption in peer relations.[107] Other investigators noted that survivors left home later than siblings and also married later than siblings or matched controls. Whether survivors marry in equal numbers or have a higher divorce rate than controls is uncertain.[105, 107, 110]

Two recent studies examined the general and emotional attitudes of long-term survivors. Gray found that long-term survivors on the whole were well adjusted. They had a more positive affect, higher intimacy motivation, greater perception of personal control, and greater satisfaction in regulating life situations compared with age-matched controls.[102]

Chesler noted that about 75% of survivors felt that they were different from their peers.[101] The most commonly noted differences were positive — being more advanced or mature and knowing more about life and their purpose. Both studies commented that the survivors' positive attitude was a highly effective coping mechanism. This would have been regarded as "Pollyannaish" had the survivors not also been realistic regarding their overall concerns. These comprised their physical health and abilities, possible development of second malignancies, fertility, and dissatisfaction with relationships.

Several studies also have evaluated predictors of post-therapy adjustment.[114, 115] Rait found a perceived lack of family cohesion and adaptability related to poor adaptation skills after therapy, and Fritz noted that communication patterns during therapy predicted post-therapy adjustment. Some investigators also noted that long-term survivors struggled with increased health worries, fear of a second malignancy, and concerns relative to fertility and health of offspring.[101, 102, 105, 116, 117]

In conclusion, it would appear that long-term survivors generally do not suffer from major psychiatric disorders. Although they may experience difficulties in personal relationships, academic pursuit, employment, acceptance into the military, insurance coverage, and may have health concerns (particularly second malignant neoplasms), overall they appear to have developed into adequately functioning individuals and productive members of society.

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