Long-Term Survivors of Childhood Cancer: The Late Effects of Therapy

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ABSTRACT

The successful treatment of pediatric malignancy by multimodality therapy has improved the outcome for children with cancer. It has been estimated that 0.1% of individuals 20 years of age are survivors of childhood cancer. This represents a large cohort nationally who, with maturation, may be increasingly beset by the medical and social consequences of treatment.

The study of long-term effects of cancer chemotherapy has grown enormously in the past decade. Any side effect that does not resolve after the completion of therapy is a long-term effect of therapy. Side effects recognized during the therapeutic period are usually addressed by the treating physicians. More problematic are those effects of therapy that are subclinical at completion of therapy but manifest years later. These are the true late effects of therapy and are the focus of this review.

The cytotoxic effects on maturing tissues become apparent only with development. Thus physical, intellectual and pubertal development as well as reproductive potential may be impossible to assess for a decade or more, depending upon the age at the time of treatment. Nonetheless, the ability to predict the likelihood of a given adverse outcome is enormously helpful to the survivor and may allow for the mitigation of severe effects.

Organ injury may also be subclinical initially. With aging and additional stress, compensatory mechanisms may fail. The development of effective screening methodologies may be essential for early interventions. Lifestyle changes may reduce exposure to further toxins and mutagenic agents such as alcohol and cigarette smoke that may lead to secondary malignancy, particularly if compounded in some instances by genetic predisposition.

Programs for survivors of childhood cancer were developed within pediatric oncology. As the children become adults, the likelihood of continued care at the initial treating institution decreases. Oncologists and other health care professionals who become responsible for the health care of this maturing cohort will need to understand the risks engendered by childhood cancer therapy. The Oncologist 1999;4:45-54

INTRODUCTION

The success of three decades of effective multimodality therapy for the treatment of childhood cancer has brought a cohort of maturing individuals, pursuing the normal experiences of life. Of each 1,000 twenty-year-olds, one is a survivor of childhood cancer [1]. Although the study of late effects originally arose within the realm of pediatrics, concerns may surface throughout the life cycle. Effects of therapy on the maturing organs become manifest only with the developmental process that unmasks hitherto unseen injury to immature organs. The focus of clinical trials on three- or five-year event-free survival thus does injustice to the needs of patients for support and information long after the trial endpoints are reached.

For the patient, any side effect for which he or she must compensate during life is a long-term effect. Tissue damage noted during or at the end of therapy may remain stable or become progressive. Late effects refer specifically to those unrecognized toxicities that are absent or subclinical at the end of therapy but manifest later as a result of growth, development, increased demand, or aging. Compensatory mechanisms that initially maintain the function of injured organs may fail with general organ senescence. Afflicted patients may have to undergo major adjustments to a lifestyle for which they are unprepared. The genetics of familial cancer syndromes and the mutagenic effects of therapy independently or synergistically may result in a significantly increased risk for a second malignancy. Synergistic effects of
mutagenic agents (e.g., cigarette smoke) or toxins (e.g., alcohol) remain unknown.

This review will focus on types of tissue injury noted in long-term survivors. Rather than a comprehensive review of all described “late effects,” the goal will be to consider types of effects and time of presentation. Stratification of effects by the time of appearance is important in considering potential causality as well as clinical screening methods. Specific organ toxicities will be presented to illustrate these points. The extent of tissue injury must be evaluated in terms of the therapies and doses given during the treatment period.

The plateau of the survival curve is most prominent in survivors of childhood malignancy since few diseases unrelated to the tumor or its therapy will result in an early death. Although the survivors of modern childhood cancer therapy are beginning to enter their fourth decade of life, it may be another two decades before the effect of aging on such individuals becomes clinically apparent. This enlarging population, as well as the similar population of young adult survivors of cancer, will require considerable attention from internists and the medical community in the decades to come.

Development-Dependent Late Effects

A goal of childhood is to grow and develop into a healthy, capable adult. Therapy for the treatment of malignancy may interfere with development in terms of physical growth, neurocognitive growth, musculoskeletal growth (hypoplasia), and, ultimately, pubertal development. To patients, these effects can come as an unexpected reminder of the harsh therapy; a physically normal child at the end of therapy becomes clinically apparent. This enlarging population, as well as the similar population of young adult survivors of cancer, will require considerable attention from internists and the medical community in the decades to come.

Physical Growth

Children with active disease and those undergoing harsh therapies rarely grow at a normal rate. Causes for this include hypermetabolic states, the effects of chronic disease, and poor nutrition. After the completion of therapy, many children experience a growth spurt and a resumption of normal growth velocity. Specific therapies may interfere with this possibility.

Hypoplasia

Localized radiotherapy affects the musculoskeletal and integumentary growth directly. This form of growth impairment, known as hypoplasia, causes significant cosmetic concern in radiation-treated survivors. Asymmetric radiation fields resulting in differential growth of the radiated versus nonirradiated tissue cause the most prominent effects. Functional effects, such as muscle or back pain due to radiation induced scoliosis, can occur. Hypoplasia is not apparent at the end of therapy but becomes manifest with growth, particularly during the pubertal spurt. Many patients have considered themselves physically recovered, only to experience the emergence of scoliosis, for example, as an unexpected reminder of the past. Particular sensitivity of adipose tissue to radiation may lead to asymmetric fat distribution with weight gain any time in life. Weight control will mitigate this effect.

Breast asymmetry occurs after unilateral chest radiotherapy prior to maturity. Doses of 20 Gy may stop breast development completely, whereas 10 Gy to the breast bud may cause hypoplasia [2, 3]. The effect of asymmetric fields may become rapidly apparent with pubertal development, sometimes necessitating reduction mammoplasty. Lactation may not be possible for these young women [4]. Early counseling may lessen post-partum disappointment.

Linear Growth Effects

Cranial irradiation affects linear growth by its effect on the hypothalamic-pituitary axis. The effect is dose- and age-dependent. Patients treated with large doses of whole-brain radiotherapy, usually for brain tumors, are likely to have severe growth hormone deficiency necessitating hormone replacement. Those who have received \( \leq 24 \) Gy (e.g., for leukemia) may have normal baseline levels of growth hormone with abnormal response to stimulation [5] and atypical patterns of release, particularly during puberty [6]. Growth velocity after lower doses of radiotherapy thus may proceed at a low normal pace until puberty, at which time the classic “growth spurt” may be minimal [7].

Early onset of puberty is common after cranial radiation, further reducing ultimate height [7]. The younger the child at the time of radiation, the earlier the onset of puberty [8]. Higher body mass index, noted in survivors of childhood leukemia treated with cranial radiation [9], is inversely related to the age of puberty [10]. Final height SDS score in children with acute lymphoblastic leukemia was most prominently reduced in those who received 24 Gy, but was noted even in unirradiated patients [11].

After spinal radiotherapy, the effect of aberrant growth hormone release and early puberty may be compounded by
vertebral stature loss after T10-L5 irradiation. Dose and age of radiation profoundly affect ultimate stature loss [12].

These effects can only be mitigated prior to closure of the epiphyses. Close monitoring of growth is recommended but may not be sufficient. An early puberty with a sluggish growth spurt exerts its effect quickly, preventing successful interventions. Investigators have been assessing the role of growth hormone stimulation beginning shortly after completion of therapy, at which time growth velocity may be within normal ranges. Inhibition of the pubertal spurt may prolong the potential growth phase [8].

**Intellectual Development**

Intellectual outcome after the completion of therapy most accurately predicts the ultimate integration of a survivor of cancer into society. Central nervous system (CNS) radiotherapy or high-dose chemotherapy that achieves sufficient CNS levels for prevention of meningeal leukemia rarely results in severe mental retardation. Cognitive deficits are common, resulting in poor academic achievement. Difficulties in reading, language, and arithmetic may arise from impairment of attention capabilities, memory, and visual perceptual motor skills [13, 14]. Clinical experience suggests that brain tissue injury becomes increasingly apparent over the years after completion of therapy. Over time, intellectual growth begins to lag behind the expected course [15]. Cellular neuronal changes that are causative have not been well delineated.

The severity of the effect is determined by both dose of therapy and the time at which it was given. Those who receive higher doses (>36 Gy) for the treatment of brain tumors have significant deficits that virtually always require intensive educational efforts. High doses of radiation are deferred until after age two, if possible, for cognitive effects of radiation on infant development are profound.

Preschool children appear to be exceptionally sensitive to cranial radiotherapy. After 18-24 Gy of cranial radiotherapy, preschool children often require special educational resources to learn basic skills, while older children may have difficulties only with acquisition of complex systems such as a new language or high-level mathematics. These children treated with lower doses of radiation are likely to remain within the mainstream education efforts but should have services available to achieve maximal success. Similar effects may be seen after intense intrathecal and infusional chemotherapy [16].

Parental expectations and abilities to assist with learning have a major effect on ultimate educational attainment. Most survivors enter college at the same rates as siblings, except for those receiving ≥24 Gy (relative risk [RR] = 0.67) or treated as preschoolers (RR = 0.6) [17]. An overall enhanced need for special education or a “learning-disabled” classification (RR of 3.4 and 3.6 respectively) exists, and occupational success may not be equal to that of siblings [18].

**Pubertal Development**

During childhood it is virtually impossible to clinically assess the extent of treatment-induced gonadal damage, although anticipatory guidance can be given based upon prior experience. Monitoring throughout the pubertal process is essential. One early observation is insufficient since initial pubertal development may proceed (e.g., pubic hair) in the face of severe gonadal injury as a result of adrenal corticoid hormones. Long delays in assessment may have social consequences.

Sertoli cells are more sensitive than Leydig cells to radiation and to alkylating agents [19, 20]. Young boys without Leydig cell damage thus experience normal masculinization even in the face of azoospermia. Such sterile males, young or old, can usually be assured of potency and normal libido. For those receiving higher doses of therapy, testosterone levels as well as pubertal development should be assessed. During early adolescence, testosterone levels in the lower ranges of normal for an adult male are to be expected. By late puberty, testosterone deficiency should be treated in order to normalize libido and masculinization.

Ovaries are less sensitive than are testes to gonadotoxic agents. However, an affected female child may experience both pubertal delay and amenorrhea. Hormone therapy may be needed to initiate and maintain feminization. A secondary but potentially critical reason for treating estradiol deficiency is the prevention of osteoporosis and early coronary artery disease.

Cranial radiation can also result in secondary gonadal insufficiency by virtue of impairment in LH/FSH production and secretion. Patients treated with higher doses of cranial radiation may be affected. In those brain tumor patients receiving hypothalamic-pituitary axis radiation as well as alkylating agents (e.g., BCNU, CCNU), direct gonadal effects as well as secondary gonadal insufficiency may be noted.

**Organ-Specific Effects**

For those who have received the harsh therapies that are often used in the treatment of malignancy, the aging process is likely to be more profound than noted in an individual of similar age.

**Gonadal Toxicity in Adults**

Gonadal toxicity in adults expressed by amenorrhea or azoospermia may have its onset during therapy. Reversibility is dependent on dose of gonadal radiation or alkylating agents. Ovarian function is unlikely to recover long after the immediate treatment period, since long-term amenorrhea is commonly
due to loss of ova. The testis is more sensitive to cytotoxic therapies than the ovary, but late recovery (2-12 years after radiotherapy) has been reported [19]. The mechanism of this slow repair remains unclear.

Alkylating agents are the most notorious inducers of infertility; little gonadal toxicity is noted after the antimetabolites, vinca alkaloids, anthracyclines, bleomycin, or platinum derivatives. Combined effects of these agents with alkylating agents are not well documented. Prediction of fertility in an adult woman can usually be determined by evaluation of her menstrual cycle. The same dose of drug is more likely to affect an older woman than a younger one.

Cyclophosphamide at a dose of 5 g/m² is likely to cause amenorrhea in women over 40, while many adolescents will continue to menstruate after >20 g/m² [21]. Although young women may not become amenorrheic after cytotoxic therapy, the risk of early menopause is significant. Byrne has shown that female survivors (five years disease-free) of cancer diagnosed at age 13 to 19, who were menstruating at age 21 had a risk of menopause that was four times greater than that of controls during the time from ages 21 to 25 [22].

Direct radiotherapy to the ovaries also causes infertility. Oophoropexy is commonly performed to prevent infertility in women with Hodgkin’s disease whose ovaries would otherwise remain in the radiation field. Lower doses or even scatter of radiation within the small body of an infant or toddler may cause more profound effects. Oophoropexy is not useful since the small torso does not offer a sanctuary for the ovaries. Flank radiotherapy administered to young girls with Wilms’ tumor does not affect the ovaries, but may result in reduced fetal size by effects on uterine vasculature or on the ability of uterine muscle to grow with pregnancy [23, 24].

The testes are considerably more sensitive to the effects of both radiation and chemotherapy. Sterility is usual after approximately 10 g/m² of cyclophosphamide. The prepubertal state offers, at best, only limited protection to testes treated with cyclophosphamide. Ten percent of men will become sterile after one to two cycles of MOPP chemotherapy, while 80% to 100% are sterile after six courses [25]. Low doses (2-3 Gy) of radiotherapy result in azoospermia in all males, with late recovery noted occasionally after a period of years. Spermatozoa are much more sensitive to cytotoxic therapies than are the Leydig cells which produce testosterone. As a result, most males who are sterile after cytotoxic therapy continue to have normal masculinization and sexual function. Others can receive testosterone injections every three to four weeks.

The outcome for infertile or sterile survivors continues to improve with emerging reproductive technologies. The possible benefits of sperm banking are enhanced by the ability to inseminate ova with only minimal numbers of spermatozoa. Since this option is not currently available for prepubertal boys, artificial insemination remains the most frequently used approach for spouses of sterile male survivors of childhood cancer. Female survivors have more limited options, although ova from a surrogate donor can be implanted after fertilization by the spouse. Storage of ova is an ongoing goal of current research [26].

Deficient gonadotropin release from the hypothalamic-pituitary axis may impair fertility after cranial irradiation. Hyperprolactinemia is another easily treatable effect of hypothalamic-pituitary irradiation that may impair fertility as well as growth and libido [27]. After treatment with high-dose radiotherapy for CNS tumors not involving the hypothalamic-pituitary axis, 40% were found to have hyperprolactinemia. The risk was dose-dependent, with 82% of males and 50% of females affected after receiving >55 Gy [27]. Appropriate endocrinologic interventions with bromocriptine and similar dopamine agonists can be helpful. The relatively high frequency of this effect is often unrecognized as a result of the non-life-threatening nature of the problem. Nonetheless, appropriate therapy can markedly affect the quality of life.

Cardiac

Anthracyclines play a major role in the treatment of most childhood cancers. Unfortunately, cardiac damage is most pronounced after the anthracycline drugs, with additive effects of cyclophosphamide and radiation therapy. Anthracyclines cause myocardial cell death with a resulting diminution in myocyte number. Residual myocytes hypertrophy in a compensatory manner [28].

Cardiac injury manifesting during or shortly after completion of chemotherapy may progress, stabilize, or improve after the first year [29]. This improvement may be transient or last for a considerable length of time. Nonetheless, patients with reduced cardiac function within six months of completing chemotherapy are at increased risk for the development of late cardiac failure [30].

It is clear that myocardial injury can be detected with sensitive screening tests in virtually all anthracycline-treated patients, even after a cumulative dose of 45 mg/m² [31]. One such study noted that 86% of anthracycline-treated patients had abnormal findings with dobutamine stress echocardiography [33]. Initial improvement in cardiac function after completion of therapy appears to result, at least in part, from compensatory changes. With later stresses of life, compensation may diminish. In particular, myocardial depressants such as alcohol or increased afterload brought on by exercise, rapid growth, or pregnancy may induce late cardiac failure. Steinherz et al. have noted a significant incidence of late cardiac decompensation manifested by cardiac failure or lethal arrhythmia occurring 10 to 20 years after the
administration of these drugs [30]. Clinical response to diuretics and digoxin is only temporary. The patients ultimately die of cardiac causes. Improvement in cardiac function can be significant with afterload reduction [32]. It remains to be determined whether such an intervention can delay or even prevent late decompensation in patients at risk.

Evidence that there is a continuum of injury that will manifest itself throughout the lives of these patients is particularly worrisome [34]. Anecdotal evidence suggests that isometric exercise increases the risk for late cardiac failure, particularly in those who attempt to improve their masculine physique by weight lifting after neck or mantle radiotherapy [34]. Many pediatric cardiologists counsel patients to avoid excessive alcohol intake and isometric exercises such as weight-lifting (including high school or college football, where weight-lifting is an essential part of training). Since studies cannot ethically be performed to determine which patients might be at highest risk with aggressive programs of isometric exercise, physicians must be ready to counsel survivors of potential risk. One might surmise that those who have received the higher doses of anthracyclines should be counseled and monitored most closely.

Pregnancy, a time of increased cardiac demand, remains a risky period for anthracycline-treated women. Those who are contemplating a pregnancy or who already are pregnant should be evaluated by a cardiologist. Obstetricians should be made aware that these women may have limited ability to compensate for the increased blood volume and requisite increased cardiac output of pregnancy. Careful monitoring during pregnancy, particularly the postpartum period, is essential. Women with significantly limited cardiac reserve may best be advised that pregnancy may carry unacceptable risk.

Profound cardiac effects of radiation may be noted. The multiple risks include valvular damage, pericardial thickening, and ischemic heart disease [35]. Patients have a markedly increased relative risk of both angina and myocardial infarction years after radiotherapy for Hodgkin’s disease. Adult patients (4,665) treated for Hodgkin’s disease had a relative risk for myocardial infarction of 2.56 after mediastinal irradiation [36]. A similar study found a relative risk of 3.1 for a cardiac death in 2,232 consecutive patients with Hodgkin’s disease [37]. This risk was noted in those receiving >30 Gy of mantle irradiation and was greatest for those treated before 20 years of age. Blocking the heart reduced the risk of cardiac death due to causes other than myocardial infarction. These studies are relatively new, and the full impact of radiotherapy on life expectancy may not be noted for many years to come, especially in the younger population. Of great concern is that in patients treated before 21 years of age, the relative risk of myocardial infarction was found to be 41.5 [38]. Deaths occurred after 3-22 years, exclusively in those who had received 42-45 Gy. No deaths were noted in those treated with chemotherapy and lower mediastinal radiation doses. Techniques currently in use that may mitigate the effects include the avoidance of anteriorly weighted ports, reduction of total tumor dose to <40 Gy, reduction of daily fraction dose to <200 cGy, and cardiac shielding.

Pulmonary

Effects of cytotoxic therapies on the lungs that manifest acutely may be lethal or may subside over time. However, pulmonary function tests may not return to normal, and there may be an insidious onset of clinical pulmonary dysfunction. Long-term outcome will be determined by the severity of the acute injury, the possibility of tissue repair, the degree of compensation possible, and the likelihood of decompensation. In one study, 35% of children treated for brain tumors with nitrosourea and radiotherapy died of pulmonary fibrosis, 12% within three years and 24% after a symptom-free period of 7-12 years [39]. As a result, the recommended limit in children has been lowered from 1,500 to 750 mg/m². Long-term effects after the lowered dose are unknown. In addition to the effects of alkylating agents on lung parenchyma, oral cyclophosphamide has caused lethal restrictive lung disease by inhibition of chest wall growth, resulting in extremely thin anterior-posterior chest diameters. This effect may become clinically apparent as late as seven years after completion of therapy [40]. It has not been reported after modern intermittent intravenous cyclophosphamide regimens.

Patients treated with bleomycin may experience pulmonary insufficiency manifested by bilateral basilar rales with an interstitial pneumonitis characterized by a reticular or nodular pattern [41, 42]. Even after completion of therapy, the risk for overt decompensation remains for at least one year. Infection or exposure to increased intraoperative oxygen may precipitate such an event. Late pulmonary decompensation has not been described in this population, but some risk may remain. Studies suggest that discontinuing bleomycin when the DLCO is <50% minimizes the risk of clinical compromise in pulmonary function [43]. A recent study by Kung et al. has noted that 22% of Hodgkin’s disease patients with normal pulmonary function tests at the end of therapy (with either three cycles each of MOPP and ABVD or two cycles of each with 2,550 cGy of involved field radiotherapy) developed abnormalities with follow-up of one to seven years [44].

In long-term follow-up, pulmonary dysfunction is usually subclinical. Subconscious avoidance of exercise that has become difficult may be seen; it is rarely attributed to therapy or recognized by the patient himself. Patients who have been treated with pulmonary radiation and cytotoxic agents such as BCNU, CCNU, and bleomycin should undergo tests...
Genitourinary Tract

Tubular damage and hypertension associated with renal artery stenosis are the most commonly noted problems after radiation therapy, particularly with doses greater than 20 Gy [46, 47]. Children may be susceptible to lower doses. Chemotherapy may exert a synergistic effect, resulting in dysfunction after only 10-15 Gy [48]. Chemotherapy alone, particularly cisplatin (or high-dose carboplatin), is notorious for glomerular and tubular injury [49, 50]. Glomerular injury may show evidence of recovery over time, while tubular injury persists. Long-term follow-up remains limited. The nitrosourea may also affect glomerular function. Ifosfamide, which has been used extensively for only a short time, results in a renal Fanconi’s syndrome with glycosuria, phosphaturia, and aminoaciduria [51]. Hypophosphatemia may result in slow growth with possible bone deformity if untreated. Glomerular filtration may also be affected by ifosfamide. Although there appears to be limited improvement over time, it is premature to speculate on long-term outcome. For children with moderate renal dysfunction of any etiology, a concern remains that with growth, compensation for damage will become inadequate.

The bladder is also particularly susceptible to cytotoxic agents. Cyclophosphamide and ifosfamide have acrolein as a metabolic by-product. This may be the cause of the hemorrhage cystitis, fibrosis, and occasionally diminished bladder volume noted after these drugs [52, 53]. In addition, even asymptomatic patients who have received these agents are at increased risk of developing bladder cancer [54]. Any patient who has received one of these agents should have an annual urinalysis, with additional evaluation if hematuria is noted. Radiation also induces bladder fibrosis, diminishing capacity, and decreasing contractibility. The severity is proportional to dose and the proportion of the bladder irradiated [55]. Scarring may also diminish function of the urethra and ureter.

Thyroid Gland

Damage to thyroid is common after radiotherapy. Patients treated for Hodgkin’s disease in whom the thyroid was irradiated had a 47% actuarial risk of overt or compensated hypothyroidism at 26 years [56]. Initially, compensatory hypothyroidism is manifested by elevation in TSH, with normal T3 and T4. Although this effort initially maintains the euthyroid clinical state, further deterioration of thyroid function results in clinical symptomatology. Treatment with thyroid hormone is recommended with persistent evidence of compensated hypothyroidism. Although it remains unknown whether early use of thyroid hormone also prevents the cellular injury that may predispose to a secondary malignancy in humans, animal studies have shown that chronically elevated TSH levels in the presence of irradiated thyroid tissue can enhance tumor development [57, 58]. Other thyroid disorders can also be seen after thyroid irradiation. These include: benign nodules (3.3%), Graves’ disease (3.1%), thyroid cancer (1.7%), and Hashimoto’s thyroiditis (0.7%) [56].

Gastrointestinal/Hepatic

There are few studies describing long-term effects to this system. This may result from underdetection or from a longer latency period than for other organs. Hepatic effects may be difficult to attribute to specific components of care, since many chemotherapeutic agents as well as radiotherapy may be damaging. Transfusions increase the risk of viral hepatitis. Hepatitis C has been identified in increasing numbers of survivors, 119 of 2,620 tested [59]. Of these patients, 24 of 56 who agreed to participate in a longitudinal study underwent liver biopsy. Chronic hepatitis was noted in 83%, fibrosis in 67%, and cirrhosis in 13%.

Fibrosis and adhesions are known to occur after radiotherapy to the bowel. Even in the absence of any known increased susceptibility, it seems prudent to advocate for complete compliance with ACS colon cancer screening recommendations.

Surgical Effects

Surgical toxicities should also be remembered. Functional status after amputation may exert considerable effect on lifestyle. Those with a nephrectomy are advised to avoid sports traumas that may compromise the residual kidney. More silent and potentially life-threatening is splenectomy, now uncommonly a part of the staging procedure for Hodgkin’s disease. Such patients have an increased risk for sepsis with encapsulated bacteria. A pneumococcal vaccine prior to splenectomy and every five to seven years is recommended. Many physicians prefer that all such patients have penicillin or an alternative available to use by the patient for prophylaxis or for illness. Medical care should be sought and antibiotic coverage administered at first sign of fever. Vaccinations against h. influenza and n. meningococcus should also be considered prior to splenectomy.
SECONDARY MALIGNANCY

Within 20 years, survivors of childhood cancer have an 8%-10% risk of developing a second malignant neoplasm [60, 61]. This can be attributed to the mutagenic risk of both radiotherapy and chemotherapy, which is further compounded in patients with genetic predispositions to malignancy. The risk of secondary malignancy induced by cytotoxic agents is related to the cumulative dose of drug or radiotherapy.

The risk of malignancy with normal aging results from the risk of cumulative cellular mutations. Compounding the normal aging process by exposure to mutagenic cytotoxic therapies results in an increased risk of secondary malignancy, particularly after radiotherapy, alkylating agents, and podophyllotoxins. Commonly cited secondary malignancies include leukemia after alkylating agents and podophyllotoxins [62, 63]; solid tumors, including breast, bone, and thyroid cancer in radiation fields [56-64]; and bladder cancer after cyclophosphamide [54]. The leukemias tend to arise earlier, two to three years after podophyllotoxins and 5 to 10 years after alkylating agents. In contrast, the latent period for many of the solid tumors is 10-20 years or longer. Breast cancer in women treated with conventional-dose radiotherapy during the peripubertal period is of particular concern, with studies showing that more than half of these individuals are expected to be afflicted by the age of 40 years [65]. Older adolescents should be taught breast self-examination, while those in their twenties may benefit from mammograms or other tests that may be better screening tools in the glandular breast tissue of young women. Screening tests should be considered in other populations at high risk. Thus, an annual urine test for heme may allow for early detection of bladder cancer, and films of radiated areas every five years may facilitate identification of changes in the bone that may represent malignant evolution.

The genetic risk may be most prominent in patients with a constitutively abnormal retinoblastoma gene [66]. Children with hereditary retinoblastoma may have as high as a 60% risk of secondary malignancy by the age of 30-40 years [67]. Exposure to radiotherapy shortens the lag time from diagnosis of first to the second malignancy in this group. Patients with the Li-Fraumeni syndrome characterized by the presence of an abnormal p53 gene are also at increased risk. This gene limits a cell’s ability to stop proliferation in the face of chromosomal damage [66].

EVALUATION OF THE PATIENT

After completion of therapy, a survivor of childhood cancer is likely to return for follow-up at increasingly longer intervals. Screening tests often must be scheduled, and full review of the therapeutic course requires advanced planning. It is therefore recommended that cumulative doses of previously administered therapy are calculated in advance, with consideration given to potential risks. The patient’s age at diagnosis and at the scheduled visit should be reviewed to determine the likelihood that a particular effect might occur at some time (for counseling purposes), or might be manifest at the visit. Screening tests such as those outlined in Table 1 may help detect subclinical effects that could become clinically relevant in the future.

CONCLUSIONS

As our patients grow, the fields of pediatric and adult oncology must grow with them. Our job is not done when the cancer cells are gone, for the years of life may present challenges that may be recognized only in the context of the original treatment plan. It must be our goal to mitigate the effects when possible, and, if not possible, to understand the effects so that future treatment regimens can be designed with fewer risks to long-term health.

Emphasis on the acute treatment phase has resulted in remarkable successes. Our discipline must now set up the mechanisms to learn where therapies have failed those who are cured of their cancers. Only by continued, systematic follow-up of large cohorts of survivors will we know the full spectrum of damage caused by cytotoxic therapy and possible interventions that may mitigate the effects. At present it is suggested that these survivors, whose bodies have been subjected to harsh cytotoxic therapies, should be encouraged to protect their bodies from further injury using the preventive approaches known to be effective for the general population. These include abstinence from tobacco, limited exposure to alcohol, sun protection, reduced fat intake, and maximal intake of fruits and vegetables. At a minimum, the surveillance techniques for detecting cancer in the general population (breast self-examination, mammography, testicular examination, examination of stools for blood, and evaluations of the rectum and colon) should be performed regularly.

A dilemma exists for the practitioner who might someday find that one in 1,000 patients is a survivor of childhood cancer. This number is too high for a practitioner to be unaware of potential problems, but far too low for him or her to maintain an adequate knowledge base to provide optimal care. Nevertheless, the trend over recent years has been to return patients to the care of primary physicians. Ongoing methods for educating both the patient and the primary caretakers must be devised. We must set up programs to evaluate the survivors every one to three years to assess and care for chronic organ damage, providing the necessary support for the primary physician. This must not replace the primary caretaker, but rather complement good primary care with that of the specialist who can anticipate potential problems specific to cytotoxic therapy.
## REFERENCES


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