Physical Late Effects in Adult Cancer Survivors

July 01, 2008 | Myelodysplastic Syndromes [1], Survivorship [2]
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Today there are nearly 12 million individuals living in the United States who have ever received a diagnosis of cancer.[1] This number is growing, having just been recently updated to approximately 11.9 million from a previous estimate of about 10.8 million cancer survivors.[2] One half of all men and one in three women will be diagnosed with cancer in their lifetime, with the largest burden being during later life; one in seven Americans 65 years of age and older has a past or present cancer diagnosis.[3]

Despite the traditional definition of a cancer survivor as an individual “from the time of diagnosis, through the balance of his or her life,”[4] cancer survivorship is increasingly recognized as a distinct phase of cancer care that follows primary treatment and is fraught with distinct physical and psychosocial hazards.[3] Consequences of cancer and its treatment present a tremendous challenge to survivors, their families, and their health-care providers. Oncology nurses have a critical role in educating survivors about physical and psychosocial effects and intervening to prevent and minimize their impact on individuals’ lives.

Long-term and late effects are broadly defined as consequences of cancer and its treatment that manifest either during or after cancer treatment and persist beyond the end of treatment.[3] This article focuses on manifold physical late effects, which range from specific sequelae such as radiotherapy-induced cataracts to multisystem consequences of chemotherapy-induced premature menopause, including menopausal symptoms, bone loss, and potential cardiovascular effects. This article provides a practical approach to late physical effects by focusing on 1) cancer treatment exposures (ie, surgery, chemotherapy, radiotherapy, etc) and 2) their effects on body systems, while considering modifying factors such as age, comorbidity, and cancer diagnosis. Although scant research and guidelines on screening, prevention, and management of late effects remain significant barriers to optimal cancer survivorship care, strategies for integrating the best available evidence into nursing practice are highlighted.

**POTENTIAL LATE EFFECTS BY BODY SYSTEM**

**Cardiovascular System**
The cardiovascular system provides an exemplar for understanding potential effects by cancer treatment, especially chemotherapy and radiotherapy, which can both lead to cardiovascular late effects. One of the most serious late effects of anthracycline and cisplatin chemotherapy is cardiac toxicity, which typically presents as cardiomyopathy, with clinical signs of congestive heart failure.[5,6] Cumulative dose, administration schedule, concurrent mediastinal irradiation, pre-existing cardiac disease, female gender, and young (< 18 years) or old (> 70 years) age increase risk.[7,8] Cumulative doses of 550 mg/m2 are associated with cardiac toxicity in adults.[9] Patients treated with cisplatin and bleomycin for testicular germ cell tumors are at risk for developing hypertension, increased weight, and an elevated lipid profile.[7,10] Radiotherapy to a field encompassing the heart, such as mediastinal radiation, confers risk for cardiotoxicity, which is usually delayed and can manifest as pericardial, valvular, myocardial, or coronary heart disease years after treatment.[8] Acceleration of coronary artery disease may also occur, resulting in angina and myocardial infarction. A recent evidence review suggests ways to monitor and treat cardiopulmonary late effects from cancer treatment in adults.[8]

**Pulmonary System**
Pneumonitis and pulmonary fibrosis are the most common pulmonary late effects. Lung injury may result from chemotherapy, radiotherapy, and recurrent respiratory infections in immunosuppressed patients, especially bone marrow transplant survivors.[10,11] Alkylating agents (primarily busulfan), nitrosoureas (eg, lomustine and carmustine), and bleomycin are associated with pulmonary fibrosis. Pulmonary fibrosis is the most common type of lung damage resulting from radiation therapy, although obstructive lung disease also occurs. Lung damage is more likely with higher radiation doses and larger lung fields.[8] Radiation therapy can potentiate long-term toxicity induced by chemotherapy.[12] Benign pleural effusions have been reported years after mantle radiation therapy.[13]

**Endocrine System**

Potential endocrine effects of cancer and its treatment include damage to the hypothalamic pituitary (HPA) axis, gonadal toxicity, and hypothyroidism. Radiation to the cranium or nasopharynx can damage the HPA, causing secondary gonadal failure. Subnormal levels of luteinizing hormone, follicle-stimulating hormone, and prolactin inhibiting factor have been found in males and females treated for head and neck tumors with 4,000–7,800 cGy of radiation, leading to irregular menses, low testosterone, reduced libido, and impotence.[14,15]

Gonadal toxicity may result from surgery, radiotherapy, chemotherapy, and/or hormonal therapy. Bilateral oophorectomy in premenopausal women leads to abrupt onset of menopause and its associated consequences, including infertility, rapid onset of bone loss, and menopausal symptoms, typically more severe than with natural menopause.[16] Pelvic radiotherapy and ovarian ablation with luteinizing hormone releasing hormone agonists have similar consequences.

Chemotherapy also has gonadotoxic effects, especially alkylating agents such as cyclophosphamide. Higher alkylating agent dose and advancing age at time of treatment are the greatest risk factors for chemotherapy related amenorrhea (CRA) and premature menopause.[16,17]

CRA is prevalent in premenopausal women with breast cancer, and algorithms are available to help predict risk based on age and chemotherapy regimen.[18] Guidelines are available for the assessment and management of both infertility and bone health in cancer survivors, two of the most clinically significant consequences of hypogonadism in both men and women.[19,20]

In men, damage to the germinal epithelium of the testis may result from alkylating agents or radiation. Leydig cell damage is unusual; thus, testosterone production and pubertal development are usually not affected.[21] Testicular damage with azoospermia is most frequent after mechlorethamine, cyclophosphamide, cytosine arabinoside, and high-dose cisplatin and etoposide.[22,23] Cumulative cyclophosphamide doses > 7.6 grams to 9 grams are associated with the highest risk of infertility.[24] The testis is extremely sensitive to radiation. The threshold dose required to damage germinal epithelium is as low as 3–4 Gy.[25,26] Finally, men treated with androgen-deprivation therapy for prostate cancer experience symptoms of hypogonadism including bone loss, and should be monitored for osteopenia or osteoporosis.[27]

**Table 1: Chemotherapy-Related Peripheral Neurotoxicity, Ototoxicity (incl. tinnitus, hearing loss)**

<table>
<thead>
<tr>
<th></th>
<th>Platinum Compounds</th>
<th>Antimitotics (taxanes, ixabepilone [Ixempra])</th>
<th>Vinca Alkaloids</th>
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<tbody>
<tr>
<td>Ototoxicity (incl. tinnitus, hearing loss)</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Sensory Neuropathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Motor Neuropathy (weakness, foot drop, gait disturbance)</td>
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<tr>
<td>Cranial Neuropathy (vocal cord paralysis, jaw pain, optic neuropathy)</td>
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<tr>
<td>Optic Neuropathy</td>
<td>X</td>
<td></td>
<td>X (rare)</td>
</tr>
<tr>
<td>Autonomic Neuropathy (postural hypotension, constipation, bladder dysfunction)</td>
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Neuromuscular System
A variety of neuromuscular late effects may result from cancer treatment. These include musculoskeletal and pain syndromes, as further described below, as well as peripheral and central neuropathies, which are some of the most common long-term complications of treatment (see Table 1). Chemotherapy and biologics such as interferon alfa may cause peripheral neurotoxicity, especially platinum compounds (cisplatin, carboplatin), vinca alkaloids (vincristine, vinblastine), and antimitotics (docetaxel [Taxotere], paclitaxel, ixabepilone [Ixempra]), although incidence and prevalence estimates vary widely.[28] Table 1 summarizes peripheral neurotoxicity associated with each class.
Peripheral neuropathy is most common, but autonomic neuropathy (ie, postural hypotension, cardiac conduction abnormalities, and constipation), retinal toxicity, and optic nerve damage may occur. Neurotoxicities typically develop during active treatment, but may not be fully reversible, and resulting pain and sensory abnormalities may persist indefinitely.[29]
Peripheral neuropathy includes both sensory and motor neuropathy. Sensory neuropathy is more common, and manifests with either positive (ie, paresthesias or dysesthesias) or negative symptoms (ie, sensory loss; reduced vibratory sensation, proprioception, or balance; and loss of deep tendon reflexes).[28] Motor neuropathy includes weakness, foot drop, and gait disturbance. Risk factors for neurotoxicity include increasing age, greater cumulative drug dose, combination therapy (especially platinums plus taxanes), infusion rate, and possibly pre-existing or hereditary neuropathies.[28] Treatment of neuropathy centers on pain management using opioids, anticonvulsants, and tricyclic antidepressants, improvement of function through physical and occupational therapy and exercise, and promotion of safety through patient education.[28,29] Nutritional supplements and topical analgesics are not consistently effective, and there are no clear preventative treatments.
Cognitive Function
Although neuropsychological consequences of childhood cancer treatment were among the first late effects to be identified,[30] cognitive effects in adults have only recently received increasing attention, with a national workshop convened in 2003 to address this issue,[31] and enough research to warrant a meta-analysis in 2003.[32] Both support key conclusions further substantiated by subsequent research,[33–35] that 1) cognitive dysfunction is greater in cancer patients who receive chemotherapy compared with both those who do not and healthy controls, 2) effects occur in a portion of the cancer patient population, and 3) effects are typically subtle but may have a profound impact on perceived function and quality of life.
Deficits are most consistently observed in executive functioning, verbal memory, information processing speed, attention, and learning, with similar domains affected by hormonal therapy for breast and prostate cancer.[36] Higher chemotherapy dose is a risk factor for cognitive impairment,[37] and genetic predisposition may play a role.[38] Cognitive sequelae of cranial radiotherapy can be more profound, especially delayed effects occurring > 6 months after treatment that range from symptoms of diffuse white matter injury (ie, mild fatigue, significant memory loss, or dementia) to focal necrosis with seizure, increased intracranial pressure, and neuroanatomical effects.[39]
Assessment of cognitive function is challenging,[31,36] with no clearly effective interventions for prevention or treatment. Several are promising, including remediation and compensatory strategies for strengthening the affected skill and facilitating adaptation, and psychostimulants improve attention, reaction time, and learning in other settings.[36]
Musculoskeletal Effects and Pain Syndromes
Surgery and radiotherapy may both lead to musculoskeletal late effects. Postmastectomy pain syndrome (PMPS) and post-thoracotomy pain syndrome are common postsurgical effects, and lead to long-term chronic pain in approximately 20% and 30% of individuals who undergo these respective procedures,[29] although rates are variable.[40] PMPS may also occur after lumpectomy and axillary dissection.[41]
If symptoms have a delayed onset, consider disease recurrence. Both conditions lead to neuropathic pain in the skin surrounding the surgical scar, but often extend to the arm, axilla, and shoulder.[29,40] Other phenomena (eg, breast phantom sensations, frozen shoulder) can result from surgery and/or radiotherapy.[40] Risk factors for PMPS include preoperative psychosocial distress and reconstructive surgery.[40] Treatments include topical capsaicin and lidocaine, tricyclic and other antidepressants (venlafaxine), gabapentin, opioid analgesics, and physical therapy.[29,40]
Lymphatic System
Lymphedema is an abnormal accumulation of protein-rich fluid causing locoregional symptoms of fullness and pain, clinically apparent swelling, and reactive inflammation and fibrosis.\[41\] It results from cancer treatments that damage the lymphatic system (surgery and radiotherapy), and onset may be delayed for years after diagnosis. Lymphedema is most common after axillary dissection or radiotherapy for breast cancer (rates of 4% to 49%), but also occurs following inguinal node dissection and/or radiotherapy and after neck dissection and/or radiotherapy.\[41\]

Lymphedema manifests in the limb or body part drained by affected lymph nodes, eg, the arm, axilla, or breast/chest wall after axillary dissection. Risk factors include obesity, trauma or infection, combined radiotherapy and surgery, and more extensive surgery; therefore, sentinel node procedures may decrease risk.\[42,43\] Risk reduction centers on avoidance of injury and infection of the affected body part, as detailed by the National Lymphedema Network (NLN).\[44\] Early identification of lymphedema is crucial, and individuals complaining of limb heaviness, aching, numbness, or swelling should be referred for evaluation. Complete decongestive therapy is the mainstay of treatment and consists of multilayer bandaging, lymphatic massage, exercise, and maintenance with a compression garment.\[41\] The NLN website lists certified lymphedema therapists.

**Genitourinary Effects**

Chemotherapy or radiotherapy may result in long-term toxicity to the urinary tract. Damage to the nephrons and bladder may occur with cyclophosphamide, ifosfamide, and cisplatin.\[45\] Cystitis; reduced bladder capacity and contractility; fibrosis of the ureters, bladder, and urethra; and nephritis are most frequently reported.\[46–48\] Hemorrhagic cystitis with cyclophosphamide may persist after treatment, and risk is compounded by concurrent ifosfamide or pelvic radiation. Symptoms of genitourinary effects include frequent urination, urgency, stress, and other incontinence. Clinical manifestations of nephritis include proteinuria, hypertension, anemia, and progressive renal failure, and can also occur as a result of radiation, especially with doses greater than 2,000 cGy and concurrent administration of radiation-enhancing drugs.\[49\] Rates of bladder dysfunction following radiotherapy or surgery for prostate cancer are highly variable but may occur in more than half of men, as may ejaculatory and erectile dysfunction.\[50,51\] Retroperitoneal lymph node dissection may also cause ejaculatory dysfunction.\[52\]

**Gastrointestinal Effects**

Radiation and radiation-enhancing chemotherapeutic agents can have significant long-term effects on the gastrointestinal (GI) tract.\[53\] When in the radiation field, damage to the esophageal wall can lead to mucosal ulcerations and gastroesophageal reflux disorder.\[53\] Malabsorption due to vascular abnormalities and altered digestive activity may result from radiation. Intestinal injury following abdominal and pelvic radiation usually occurs within 2 to 5 years but can present many years later, leading to increased bowel activity, decreased bile production and vitamin B12 and fat absorption, GI bleeding, abdominal or pelvic pain, fistula formation, and obstruction.\[54,55\]

While chemotherapy can augment acute GI radiation toxicity, its effects on late toxicity remain poorly established. Proton pump inhibitors show promise for prophylaxis and treatment of mucosal damage caused by cancer treatment.\[54\] Less common GI late effects include hepatic fibrosis, cirrhosis, portal hypertension, and veno-occlusive liver disease.\[56,57\]

**Head and Neck**

Visual defects and hearing loss can occur following central nervous system treatment.\[56\] Cataracts have been associated with cranial irradiation and long-term corticosteroid therapy. Retinopathy can occur following radiation to the eye, orbit, nasal cavity, paranasal sinus, or nasopharyngeal area, and first manifest with diminished vision.\[57\] Chemotherapy and concurrent illness, such as diabetes, may increase the risk. Chemotherapy can cause reversible and irreversible ocular effects. Conjunctivitis, keratitis, retinopathy, retinal hemorrhage, optic neuritis, and blurred vision are most frequently reported.\[58\]

Hearing loss, especially in the high tone range, is most common with cisplatin.\[59,60\] Combination with cranial radiation or concurrent ifosfamide increases the risk, as does cumulative cisplatin dose greater than 600 mg/m2.\[61,62\] Recurrent otitis media, ototoxic antibiotics, and history of noise exposure also elevate risk.

**SECONDARY MALIGNANT NEOPLASMS**

Cancer survivors who have received radiation or chemotherapy, especially alkylating agents, are at increased risk for developing secondary malignant neoplasms.\[63\] In addition to the type and dose of treatment received, risk depends on predisposing factors including environmental exposures (tobacco, diet), hormonal exposures, and genetic predisposition. Acute nonlymphocytic leukemia due
to alkylating agents is the most common chemotherapy-related second malignant neoplasm, although acute lymphocytic leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome also occur.[64] Bone and soft tissue sarcomas are the most common second malignant neoplasm after radiotherapy.[65] The latency period can be as short as 5 months, but incidence peaks at 15–20 years, and they can occur after doses ranging from 1,000–8,000 cGy.[65]

<table>
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<th>Table 2: Selected Guidelines and Resources for Monitoring and Management of Cancer Treatment Late Effects</th>
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<tr>
<td><strong>Author/Organization</strong></td>
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<tr>
<td>American Cancer Society (ACS)</td>
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<td>ASCO</td>
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<td>Oncology Nursing Society (ONS)</td>
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Other solid tumors are linked to radiotherapy, including skin cancer.[64,66] A slightly excessive number of tumors of the bladder, rectum, uterus, bone, and connective tissue has been reported in women who received radiation for gynecologic cancer. One study of Hodgkin’s lymphoma found a 17% cumulative risk of second cancers 20 years post-treatment, with 77% occurring in or adjoining the radiation field, and thyroid, lung, and breast cancers being most common.[67] Breast cancer is the most common solid tumor in women treated with mantle radiotherapy before age 30, and younger age and higher dose confer increased risk.[68] The American Cancer Society recently
released guidelines for breast MRI screening that include women treated with chest radiotherapy between the ages of 10 and 30 years.[69]

Implications for Nursing Practice
The diversity of potential late effects of cancer treatment can seem overwhelming, but a systematic approach can facilitate clinical assessment and intervention. By first identifying what treatments an individual has received, and then considering the potential effects on each body system, nurses can identify potential late effects, providing a foundation for patient education and clinical assessment, prevention, and management.

For example, a 38-year-old woman with breast cancer treated with lumpectomy, axillary dissection, left breast radiotherapy, and anthracycline-based chemotherapy is at greatest risk for late effects in the cardiovascular, endocrine, lymphatic, and musculoskeletal systems, as well as secondary malignancies (sarcoma, skin cancer) in the radiotherapy field. Risk of chemotherapy-related amenorrhea should lead the nurse to assess for and educate about menopausal symptoms, bone health, and fertility concerns.

Surgery confers risk for musculoskeletal effects and lymphedema, which should guide patient education and nursing assessment, with referral to physical therapy as indicated. Risk for anthracycline-related and potential radiotherapy-related cardiotoxicity should lower the threshold for evaluating cardiac symptoms, and the nurse should educate the survivor about preventive strategies (ie, diet, exercise, lipid control) for cardiovascular health.

Although the evidence base for late effects monitoring and intervention is limited, a number of resources are available to help guide clinical practice (see Table 2), many being consensus-based guidelines from expert panels. The Children’s Oncology Group guidelines organize late effects by treatment exposure and recommend strategies for evaluation and health counseling, accounting for risk factors.[70]

Although few adult survivorship guidelines exist, resources have grown over the past 5 years. Web-based tools can assist nurses in educating survivors about risk of late effects, such as the OncoLife Survivorship Care Plan,[71] as can the growing availability of treatment summaries.[72]

Conclusions
Potential late effects of cancer treatment are numerous, but related knowledge is limited by a dearth of longitudinal studies examining incidence, prevalence, correlates, risk factors, and course over time. Further, few randomized trials have addressed best approaches to monitoring and management of late effects in cancer survivors. Clinicians must typically rely on best judgment and, where available, consensus-based guidelines to guide practice. Nurses play a pivotal role in this process through patient education, early identification and management of late effects, and referral to appropriate specialists and disciplines.

This article is reviewed here:
Review of “Physical Late Effects in Adult Cancer Survivors”

Disclosures: Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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