Cancer survivorship care from the Memorial Sloan Kettering Cancer Center

Cardiotoxicity and Breast Cancer as Late Effects of Pediatric and Adolescent Hodgkin Lymphoma Treatment

An evidence-based review of two common sequelae among HL survivors.

ABSTRACT
The American Cancer Society estimates that in 2014 nearly 16,000 U.S. children and adolescents developed cancer, and in roughly 1,200 of these cases the cancer was Hodgkin lymphoma (HL). The great majority of these patients will survive, joining the thousands who have been diagnosed and treated successfully in decades past. Nurses' familiarity with and attention to the late effects of the chemotherapy and radiation therapy used to treat HL, which include breast cancer as well as cardiotoxicity and its sequelae, are essential in helping these patients maintain their overall health.

Keywords: adolescent cancers, breast cancer, cancer survivorship, cardiotoxicity, Hodgkin lymphoma, late effects of treatment, oncology, pediatric cancers

In 1972, at the age of 13, Ann Rowland was a normal teenager who developed a mild swelling on her neck—perhaps, she thought, from a mosquito bite. (This case is a composite based on my clinical experience.) When the swelling failed to resolve and she developed a fever of 38.2°C (100.8°F), she was taken to her pediatrician and quickly admitted to a hospital, where she underwent a biopsy and was diagnosed with Hodgkin lymphoma (HL). Her workup included a chest X-ray, which revealed a mediastinal mass; a staging laparotomy with liver biopsy, which ruled out hepatic disease; and, as was routine at that time, a splenectomy. While under anesthesia, she underwent a bone marrow biopsy, which was negative. She and her parents were told she had stage IIB HL, meaning she had at least two sites of lymphoma on the same side of the diaphragm (stage II) and at least one of the "B" symptoms, indicating more advanced disease (see *Hodgkin Lymphoma Stages*[1]). Her treatment would consist of cobalt radiation to the mantle field, so called because the area resembles a mantle (a loose, sleeveless cloak) encompassing the submandibular, submental, cervical, supraclavicular, infraclavicular, axillary, mediastinal, and pulmonary hilar lymph nodes—that is, the upper body from the lower jaw to the 12th thoracic

vertebra.[2] The mantle radiation would be administered over the course of approximately five weeks until a total dosage of 4,500 cGy was achieved.

A little more than a year later, however, her disease recurred and required chemotherapy consisting of doxorubicin, vincristine, cyclophosphamide, prednisone, and procarbazine. She completed the chemotherapy, expecting that to be the end of the story. It would turn out to be only the beginning. Although Ms. Rowland has had a fulfilling life—she graduated from college, married, works in her chosen field, and enjoys many hobbies—she went on to develop both secondary breast cancer and significant cardiotoxicity, two of the most serious complications of the lifesaving treatment she received for HL as an adolescent. Today, at 58, she needs to be vigilant about her health in ways not necessarily required of other women her age.

This article discusses the late effects associated with the historical and current management of pediatric and adolescent HL. *Late effects* can be defined as therapy-related complications or adverse effects that may persist or arise after completion of treatment for a malignancy. Although the article focuses primarily on secondary breast cancer, the most common solid malignancy among female HL survivors who received mantle radiation therapy, and cardiotoxicity, the leading cause of noncancer death among HL survivors,[3-5] it also enumerates other late adverse effects and related issues nurses must consider when caring for patients with a history of HL treatment. A goal of the article is to raise awareness among nurses of residual risks associated with the various HL treatments, thereby promoting appropriate screening and, as needed, referral for specialty care.

The composite case presented here demonstrates the significant posttreatment morbidity that can accompany HL survival. While treatment modalities and methods have changed since the 1970s, many patients in today's health care system were, like Ms. Rowland, treated for HL during that era. They, as well as their younger counterparts, who may be at reduced risk for some adverse effects (having received less intensive therapies that use lower radiation doses and smaller fields), will require screening and observation for the development of late adverse treatment effects throughout their lives.

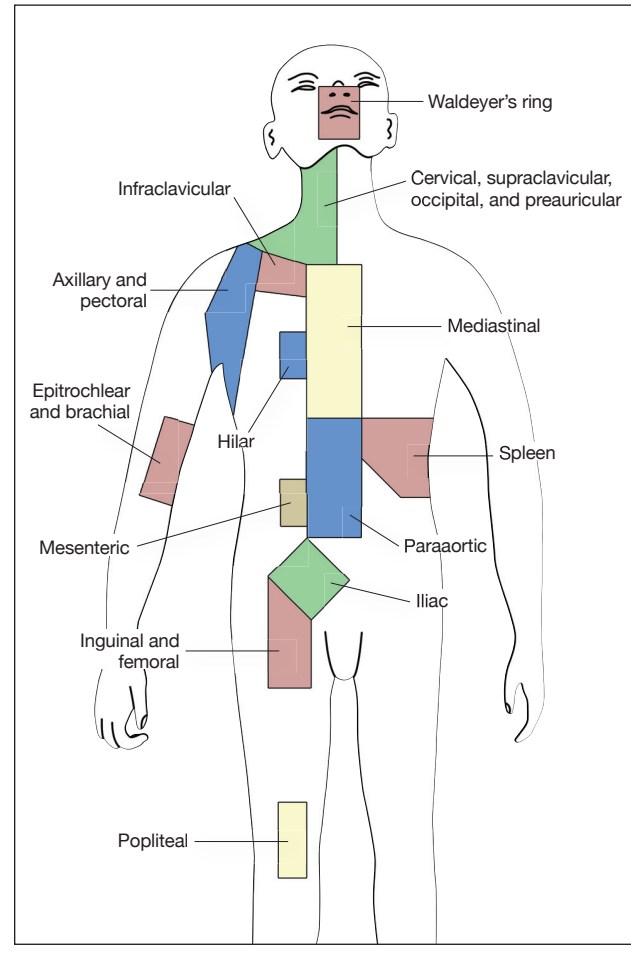


Figure 1. Anatomic Regions Used for the Staging of Hodgkin Lymphoma and to Guide Radiation Therapy

UNDERSTANDING HL: INCIDENCE AND ETIOLOGY

HL was first described in 1832 by Thomas Hodgkin,[6] but Carl Sternberg in 1898 and Dorothy Reed in 1902 were credited with describing its histopathology.[7] In classic HL, the Reed–Sternberg cell is a hallmark finding. This malignancy of the immune system is characterized by a proliferation of abnormal lymphocytes that initially cause localized disease, but can spread to contiguous lymphoid structures and, eventually, to nonlymphoid organs.

Incidence. Childhood cancers represent 1% of all new cancers diagnosed in the United States.[8] In 2014, an estimated 15,780 new cancer cases and 1,960 cancer deaths occurred among children and adolescents (from birth to 19 years of age).[8] According to the American Cancer Society (ACS), roughly one in 530 adults between the ages of 20 and 39 has survived a childhood cancer.[9] As of January 2010, there were an estimated 379,112 survivors of childhood and adolescent cancers, of whom 35,253 (9.3%) had been treated for HL.[9]

Formerly called Hodgkin's disease, HL accounts for 6% of all childhood cancers. In the United States, incidence is highest among adolescents ages 15 to 19—29 cases per million are diagnosed in this population each

year. The incidence rate among children ages 10 to 14, five to nine, and zero to four is estimated to be three times, eight times, and 30 times lower, respectively, than the adolescent incidence rate.[10]

Etiology. The causes of HL are unknown, but the prevalence of Epstein–Barr virus (EBV) antibody titers in a large proportion of newly diagnosed patients suggests that EBV infection may play a role in HL development. The great majority of children and young adults infected with EBV, however, do not develop HL. Immunodeficiency is believed to be another HL risk factor, as incidence is higher in people with primary immunodeficiencies, autoimmune lymphoproliferative syndrome, and HIV infection.[8, 10]

The risk of developing HL is greater among those whose parent or sibling has the disease.[11] In 2004, Goldin and colleagues published a comprehensive review of the Swedish and Danish cancer registry databases that showed a small but significant increased risk of HL development in relatives of patients who had the disease.[12] This risk was found to be greater in male relatives, and greater in siblings than in parents or offspring. The researchers concluded that, for those who have a relative with HL, the lifetime risk of developing HL increases from the observed risk of 0.24% (based on the National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER] data) to 0.69%. It is not clear whether the familial association in HL is due to shared genetics or to common environmental or infectious exposures. Since many HL survivors fear having a child with the disease, it is often reassuring for them to hear that the risk is low.

Presentation. Approximately 80% of patients who have HL present with painless supraclavicular or cervical lymphadenopathy; 35% of children and 75% of adolescents have mediastinal disease, which can cause cough, dyspnea, or orthopnea.[7, 10] In addition, many patients experience nonspecific constitutional symptoms, including fever, weight loss, night sweats, anorexia, and pruritus.[7] Another associated symptom is pain induced by alcohol ingestion, which usually occurs in areas of nodal enlargement. The mechanism by which alcohol ingestion induces pain is not understood, but the syndrome resolves with HL treatment.[7] Only three of these HL symptoms (fever, weight loss, and night sweats) are considered B symptoms and are correlated with poorer prognosis.[7] Since these signs and symptoms can present with many subsequent illnesses other than HL (including menopause), it's important for nurses to reassure HL survivors that they understand the concern and fear that such symptoms evoke. For some HL survivors, the fear of recurrence is lifelong.

HISTORICAL AND CURRENT HL TREATMENT

Before the 1980s, when clinicians began routinely using computed tomography (CT) to determine the extent of HL, disease stage was determined through the use of laparotomy, splenectomy, and lymphangiogram. The prevailing opinion was that the extent of splenic disease could not be assessed accurately without the spleen's total removal and pathologic examination, and the laparotomy allowed for a more thorough evaluation of lymph node involvement as well as an opportunity to perform liver and bone marrow biopsies. With the advent of improved imaging techniques and the demonstrated benefit of combined modality therapy (radiation therapy plus chemotherapy), the need for this surgery was obviated.[13, 14]

In the 1960s and 1970s, the treatment for pediatric and adolescent HL, based on the adult models, was high dose (3,500 to 4,500 cGy) radiation therapy delivered to the mantle field. With use of a partial transmission block, the heart and lungs would have received a lower dose.[15] Then, as now, in the case of disease below the diaphragm, radiation was delivered to the abdominal and pelvic lymph nodes in an inverted Y pattern (see Figure 1 for the anatomic regions used to guide radiation therapy in HL). This method was curative for a significant number of patients, but not for those with advanced disease (HL staged beyond IIA) or bulky disease (HL involving chest tumors at least one-third as wide as the chest or tumors outside the chest at least 10-cm across). Furthermore, it was associated with skeletal growth

Hodgkin Lymphoma Stages[1]

Hodgkin lymphoma is classified as follows:

- Stage I: Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
- Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE)
- Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or both (IIIES)
- Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement

Stages may also be assigned the letter "A" if symptoms are absent or "B" if any of the following symptoms occur:

- unexplained fever of 38°C (100.4°F) or higher
- unexplained loss of 10% or more of body weight within the six months preceding diagnosis
- drenching night sweats

abnormalities in children.[7, 13, 16] For those whose disease recurred, as it did in the case of Ms. Rowland, chemotherapy was required.

In the 1960s, a chemotherapy regimen known as MOPP (mechlorethamine [also known as nitrogen mustard], Oncovin [a now-discontinued brand name for vincristine], prednisone, and procarbazine) was introduced and evaluated in clinical trials with lower doses of radiation therapy. Together, the treatments produced remission in some patients with fewer skeletal abnormalities but were associated with treatment-related leukemias and gonadotoxicity.[17] There was an effort to limit or avoid the use of mechlorethamine because of these associated risks.[18, 19] In subsequent trials, cyclophosphamide, which is less myelosuppressive than mechlorethamine, was used in its place.[18]

In the mid-1970s, Bonadonna and colleagues developed the HL regimen commonly referred to as ABVD (Adriamycin [a brand name for doxorubicin], bleomycin, vinblastine, and dacarbazine).[20] Initially introduced in the adult population, ABVD was later adopted for the pediatric, adolescent, and young adult population. ABVD had superior antineoplastic activity to MOPP and preserved fertility, but it was not without adverse effects: the cardiotoxicity associated with doxorubicin, an anthracycline, and the pulmonary fibrosis that can result from bleomycin, both of which are exacerbated by the use of mantle radiation.[13] To reduce gonadal toxicity and enhance antineoplastic activity, etoposide was also incorporated into some regimens over the years in place of the alkylating agents cyclophosphamide and procarbazine.[21, 22]

Reductions in the dose (to 1,500 to 2,500 cGy) and field of radiation have also been associated with reduced late effects without compromising survival. Since the 1990s, clinicians have adopted a risk-adapted, response-based treatment approach in which radiation therapy, chemotherapy, or both are selected and titrated based on disease-related factors.[7, 13, 16] More recently, the efficacy of protocols that eliminate radiation therapy altogether has been tested in patients with favorable risk profiles.[23]

Although efforts to formulate treatment protocols that have the least potential to cause harmful late effects without compromising survival continue, all treatments for pediatric and adolescent HL, particularly those used in past decades, are associated with significant morbidity (see Table 1 for selected examples). Two of the most prevalent and life-threatening late effects are female breast cancer, secondary to chest radiation as well as to any underlying genetic tendencies, and cardiotoxicity and its sequelae, which are related to chest radiation that encompasses the heart and to the anthracycline component of chemotherapy.

BREAST CANCER

Breast cancer is the most common treatment-related solid malignancy in female HL survivors who received mantle radiation therapy.[24] Male breast cancer is no more prevalent in men who received mantle radiation therapy for HL than in the general population. An analysis of a large cohort of cancer survivors from the Childhood Cancer Survivor Study, which followed patients who survived more than five years after a childhood cancer diagnosis between 1970 and 1986, found that no men had reported breast cancer as of May 2002.[3]

Being less than 30 years of age at the time of radiation therapy for Hodgkin lymphoma is associated with having the highest risk of secondary breast cancer.

Female breast cancer as a late adverse effect of HL treatment was first described by Hancock and colleagues in a 1993 record review, which showed that women under the age of 30 who were treated for HL with radiation therapy had a marked increase in breast cancer risk, and that this risk increased dramatically more than 15 years after therapy.[25] In 2003 Bhatia and colleagues found that female patients who were treated for HL with an extended mantle field before the age of 16 had a cumulative incidence of breast cancer that approached 20% by age 45.[24] Other researchers have corroborated the finding that being less than 30 years of age at the time of radiation is associated with having the highest risk of breast cancer.[26, 27]

Even the lower-dose involved-field radiation therapy to the chest increases breast cancer risk in female patients.[27-30] The risk of breast cancer in women who undergo chest radiation therapy increases modestly if there is breast cancer in a close relative.[31, 32] It is, therefore, important to determine whether female patients with a history of HL treatment have a family history of breast cancer.

A highly significant linear relationship exists between radiation dose and breast cancer risk, with

Table 1. Selected Potential Late Effects of Hodgkin Lymphoma Treatment

Treatment Modality	Potential Late Effect
Splenectomy	• Lifetime risk of overwhelming sepsis of 2%–4% • Risk of encapsulated organisms (pneumococcus, *Haemophilus influenzae*, meningococcus), but also of *Escherichia coli*, *Klebsiella*, and other gram-negative pathogens, malaria, and tick-borne pathogens
Mantle radiation	• Dry mouth with risk of dental caries, periodontal disease, accelerated dental decay • Thyroid disease • Breast cancer • Pulmonary dysfunction • Cardiotoxicity • Radiation fibrosis with associated musculoskeletal problems • Osteoporosis
Paraaortic radiation	Secondary malignancy in the radiation field
Doxorubicin	Cardiotoxicity
Bleomycin	Pulmonary toxicity
Vincristine	Peripheral neuropathy
Mechlorethamine (Mustargen, Valchlor), cyclophosphamide, or procarbazine (Matulane)	Gonadal toxicity (infertility) or early menopause
Prednisone	• Osteoporosis • Cataracts • Avascular necrosis

doses of approximately 4,000 cGy associated with an 11-fold increased risk.[28] Some studies have shown that this risk is reduced in women who also received radiation therapy to the ovaries or alkylating chemotherapeutic agents, which decrease or ablate ovarian function.[28, 33] This protective effect is presumably due to suppressed estrogen stimulation of breast tissue.[33, 34] The attenuated risk associated with alkylating agents has not been seen in all analyses, however.[29] Both the patient's age at the time the alkylating agent or ovarian radiation is given and the dosage used are important factors in whether or not ovarian ablation occurs. Ablation is less likely to occur in younger women, who have a greater number of eggs and follicles, than in older women.[35]

Moskowitz and colleagues found that the cumulative risk of breast cancer by age 50 in female patients who underwent chest radiotherapy for HL during childhood is comparable to that of female patients with the *BRCA1* genetic mutation—about 35% and 31%, respectively. By comparison, among female patients with the *BRCA2* genetic mutation the risk is 10%.[29] This startling statistic puts into perspective the risk of breast cancer faced by women with a history of HL treatment.

Henderson and colleagues conducted a systematic review of studies of women treated for cancer as children or young adults (ages 30 or younger) between 1960 and 2000.[33] (Most of the studies focused on HL treatment in particular.) Of the more than 14,000 women in the studies, 7,000 had received chest radiation therapy and 422 had developed breast cancer. Among the women who had been treated with chest radiation therapy, the increased risk of breast cancer was apparent within eight years of therapy and continued to rise in follow-up studies.

As in the general population, the majority of breast cancers related to childhood or young adult cancer treatment are invasive ductal carcinomas; survival outcomes are similar within the two groups, with survival relative to stage at diagnosis.[33] The increased mortality rates observed in women whose breast cancer is secondary to prior cancer treatment speaks to both the late stage at which the breast cancer is diagnosed and the limited treatment options available to such women—owing to their need to avoid treatments that were used to manage their initial cancer.[33, 36, 37] The use of doxorubicin is generally limited to a lifetime cap of 550 mg/m^2, and the drug cannot

be used in women who have demonstrated cardiotoxicity. Radiation therapy options may also be limited by prior radiation exposures.

Treatment-related breast tumors in female cancer survivors are similar to breast tumors in the general population in terms of human epidermal growth factor receptor 2 (*HER2*) and hormone (estrogen and progesterone) receptor status.[33, 38] However, the incidence of bilateral breast cancer is higher among women previously treated with chest radiation therapy for cancer than in the general population. Bilateral disease may not be detected on imaging, but in some women who have opted for prophylactic bilateral mastectomy, disease has been found in what was believed to be the uninvolved breast. Among women treated with chest radiation, reported rates of bilateral disease range from nearly 13% to 17%, with 5% being synchronous (that is, occurring at the same time or within three months of the initial cancer) and up to 12% being metachronous (occurring at different points in time).[32, 33, 36, 39]

With breast cancer survival related to stage at diagnosis, the benefit of early detection in this young population cannot be sufficiently stressed. The current Children's Oncology Group (COG) guidelines recommend that, in addition to monthly breast self-exam and annual clinical breast exam, women and girls who received chest radiation for childhood cancer should begin screening with mammography and magnetic resonance imaging (MRI) every 12 months starting at age 25 or eight years after radiation therapy, whichever occurs last.[40] So, for example, a woman treated at age 21 would begin screening at age 29 (eight years after radiation therapy), while a woman treated at age 14 would begin screening at age 25. The ACS also recommends MRI as an adjunct to mammography for women who have a 20% or greater lifetime risk of breast cancer, which includes those who were treated with chest radiation therapy for HL.[41] COG and the ACS recommend screening with both imaging tools because many of these young women have dense breasts, which reduces the sensitivity of mammography.

Despite well-publicized benefits of such screening in this high-risk population, one study demonstrated that most women are not being screened in a manner consistent with guideline recommendations.[42] Only 37% of women ages 25 to 39 who were treated for a childhood cancer with chest radiation therapy reported receiving a screening mammogram in the past two years, and 47% had never had a mammogram. The most important predictor of having had a mammogram was the recommendation of a physician. Nurses who see high-risk women can teach them about the risks and the benefits of early detection. A depiction of the same breast as observed with both mammography and MRI can be a powerful tool to teach patients about the benefits of dual screening (see Figure 2).

Breast MRI is performed in the prone position with the dependent breasts visible through two cutouts in the table. For some women, particularly those with radiation damage to the musculature of the neck and shoulders, this position is uncomfortable. To promote adherence, be sure to explain to the patient the importance of the test.

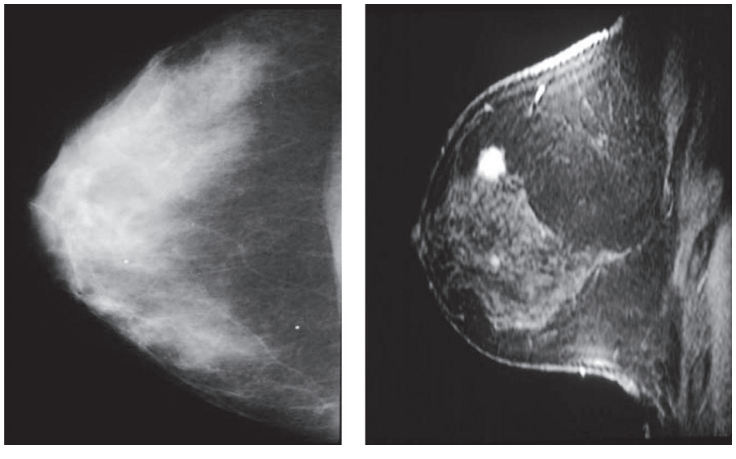
The radiation risks associated with mammography, though minimal, as well as the physical and emotional toll a false-positive finding on either mammogram or breast MRI may take on the patient need to be considered. It is reasonable to explain, however, that on the basis of current evidence, testing carries significant benefit and in many cases may be lifesaving.

CARDIOTOXICITY

Both chest radiation therapy, which encompasses the heart, and chemotherapeutic regimens that include an anthracycline are associated with significant morbidity. When these therapies are used in combination, the risks associated with each are increased.

In 1995, our composite case, Ms. Rowland, developed congestive heart failure (CHF) and complete heart block, requiring a pacemaker. The high-dose mantle radiation she had received at age 13 significantly elevated her risk of coronary artery disease (CAD) and cardiomyopathy. Close monitoring of her cardiac status with stress echocardiogram and visualization of her coronary arteries using coronary CT angiography is ongoing. She has been taught to report such warning signs as chest pain, discomfort, or pressure; indigestion; shortness of breath; pedal edema; fatigue; and reduced exercise tolerance. She maintains close communication with her cardiologist,

Figure 2. Detection of an Occult Cancer: Mammogram vs. MRI



A mammogram (left) and a magnetic resonance imaging (MRI) scan of the same breast in a 44-year-old woman with a nonpalpable mass. The mammogram was read as normal, but the MRI clearly shows the mass. Images courtesy of Virgilio Sacchini, MD, Memorial Sloan Kettering Cancer Center.

her long-term follow-up providers, and her primary care provider. To reduce cardiac risk, she takes a daily aspirin as an antithrombotic therapy (aspirin dosages vary among patients depending on their specific needs) and maintains a low-density lipoprotein cholesterol level of less than 100 mg/dL.

The anthracycline family of chemotherapeutic agents includes doxorubicin (the only anthracycline used in the treatment of HL), daunorubicin, epirubicin (Ellence), idarubicin (Idamycin PFS), and mitoxantrone. These are among the most effective agents used to combat pediatric and adult malignancies. They have long been associated with cardiotoxicity, however, and clinicians have undertaken efforts to balance efficacy and safety, using the lowest possible dosages without sacrificing benefit.

Cardiotoxicity rarely presents at the time of anthracycline administration or within the first year following treatment, but usually many years later.[43-45] Anthracyclines damage the heart muscle in a dose-dependent way, so the higher the cumulative dose, the higher the risk of toxicity. However, toxic effects can be seen in some patients at lower doses, and other patients can tolerate much higher doses.

Since cardiovascular disease is the leading cause of noncancer death among HL survivors, it's essential to provide adequate screening, identification of patients at risk, and early intervention.[3-5] In 1991 Steinherz and colleagues reported on a cohort of 201 survivors of pediatric malignancies who had been treated with a median 450-mg/m^2 anthracycline dose, 51 of whom had also been treated with mediastinal radiotherapy.[46] Of the 201 patients, 47 (23%) had late cardiac abnormalities, nine had dysrhythmia and cardiac failure, and three had sudden death.

Cardiovascular disease in this population can manifest as CHF resulting from cardiomyopathy, CAD and myocardial infarction (MI), valvular disease, cerebrovascular accidents, or combinations thereof.[7, 34, 46-51] Because these problems can develop in patients who are significantly younger than those in the general population with similar age-related abnormalities, screening is key to early detection and management. Since cardiac disease can be asymptomatic, clinical examinations alone may be insufficient to detect abnormalities. Patients with a history of HL treatment should be screened in accordance with COG guidelines (see Figure 3 at http://links.lww.com/AJN/A71).

Heart failure. Anthracyclines are associated with dilated cardiomyopathy, a form of CHF that can be asymptomatic as it progresses over many years. Anthracycline-induced CHF is not clinically distinguishable from other forms of CHF, and serious arrhythmias and sudden cardiac death have been seen in both symptomatic and asymptomatic patients with late cardiomyopathy.[43] The risk of heart failure increases with higher cumulative doses of anthracyclines,[43] concurrent cardiac-directed radiotherapy,[43] female sex,[43] preexisting heart disease,[43] hypertension,[43] increased time interval from therapy, and younger age at treatment. Studies have also suggested that there may be genetic factors related to the development of anthracycline-induced cardiomyopathy.[52, 53]

Anthracycline-induced left ventricular dysfunction is common, although varying study methodologies have made it difficult to quantify the incidence.[42] In a landmark 1979 study, von Hoff and colleagues demonstrated a continuum of increasing risk in left ventricular dysfunction as anthracycline dosage increased.[54] A 2007 Dutch study of 1,474 five-year survivors of HL, all diagnosed between 1965 and 1995 and before the age of 41, showed that after a median follow-up of 18.7 years, the risks of CHF and MI were greatly elevated in the HL survivors compared with the general population.[48] Investigators observed higher incidence rates of CHF, MI, and angina pectoris in patients treated at a younger age, especially those treated before age 20, suggesting that immature cardiovascular tissue may be more vulnerable to radiation and chemotherapy. When left ventricular failure is diagnosed, referral to a cardiologist experienced in the treatment of anthracycline-induced cardiomyopathy should be considered, if feasible.

It is imperative to remember that conditions that stress the heart, like infection, pregnancy, and childbirth, place the HL survivor at risk, and attention must be paid to cardiac function during such periods of increased cardiac workload. COG guidelines recommend that patients who received an anthracycline dosage greater than or equal to 300 mg/m^2 or less than 300 mg/m^2 plus chest radiation receive a cardiac evaluation if pregnant or planning to become pregnant. The evaluation should include an echocardiogram before and periodically during pregnancy (especially during the third trimester). In addition, owing to their risk of cardiac failure, these patients should be monitored during labor and delivery.[40]

An infrequent but important outcome of anthracycline therapy, observed on electrocardiography, is prolongation of the QT interval, which places a patient at risk for ventricular arrhythmias.[44, 55] Since certain psychotropic, antibiotic, antifungal, and antidepressant medications can further prolong the QT interval, patients should be made aware of this risk so they can inform their health care providers and medication prescriptions can be safely tailored.

Valvular heart disease. Because chest radiation encompasses the heart, it can damage the heart valves. Valvular heart disease secondary to chest radiation predominantly involves the left side of the heart, with an incidence of approximately 6% at 20 years.[50] In a study of 415 patients treated for HL between 1962 and 1998, the most common valvular lesion was aortic stenosis.[50] Patients with a treatment history of chest radiation need to receive regular clinical examinations and to follow COG screening guidelines, which call

for a specific schedule of echocardiography to detect these abnormalities based on age at treatment. Since perioperative morbidity in this population is higher than in the general population, surgeons familiar with the late effects of chest radiation therapy on the cardiac structures and the chest wall should be consulted whenever possible.

CAD. Cardiac-directed chest radiation can cause direct injury to the proximal coronary arteries, accelerating atherosclerotic plaque formation and leading to CAD and MI, the most common adverse cardiac outcomes following chest radiation therapy. This exposure puts patients in a very different risk category from patients who have not received radiation therapy, and traditional risk calculators, such as those from the Framingham Heart Study or the American College of Cardiology/American Heart Association, may not be applicable in this population.

After 20 years following mantle radiation therapy, the actuarial cumulative risk of symptomatic CAD has been estimated to be more than 21%,[56] and after 30 years, the cumulative incidence of MI is about 13%.[48] While more modern radiation techniques reduce the radiation dose to the total heart, the proximal coronary arteries, including the left main and left anterior descending arteries, remain in the field. It is therefore imperative for patients with this treatment history to be screened and taught about the benefits of altering modifiable risk behaviors. While it is important to teach patients to report anginal signs and symptoms, nurses should also take note when patients report less typical cardiac symptoms—such as dizziness, lightheadedness, excess fatigue, indigestion, decreased endurance or exercise performance—keeping in mind that many patients have asymptomatic disease, perhaps owing to altered pain perception following radiation.[57]

Heidenreich and colleagues studied 294 young adults with a history of HL treatment and no known CAD.[58] Most were asymptomatic and all had been judged to be free of cardiac disease during clinical evaluations prior to screening; however the incidence of cardiovascular disease was significant. At rest, 63 (21.4%) patients had abnormal echocardiographic images and, with stress testing, 54 (18.4%) patients developed perfusion deficits, wall motion abnormalities, or ST-segment changes. Coronary angiography demonstrated stenosis of 50% or more in 22 patients (7.4% of those screened and 55% of those who underwent angiography). Seven patients underwent bypass graft surgery following screening.

These data underscore the substantial risk of cardiovascular disease in adults with a history of chest radiation therapy, with or without anthracycline therapy. When any young adult presents with this treatment history and chest discomfort, angina secondary to radiation-induced CAD should be considered and the appropriate screening undertaken.

MODIFIABLE RISK FACTORS

It is crucial to address modifiable risk factors in all patients at risk for negative cardiac outcomes, and nurses play an essential role in education and follow-up. Armstrong and colleagues evaluated more than 10,000 childhood cancer survivors (12.8% of whom had been treated for HL) to determine the relative contribution of modifiable cardiovascular disease risk factors (such as diabetes, dyslipidemia, or obesity) to the development of major cardiac events.[59] They found that hypertension significantly increased the risk of CAD, heart failure, arrhythmia, and valvular disease. The combination of chest radiation therapy and hypertension potentiated this risk, and hypertension was independently associated with risk of cardiac death. While the risk of a cardiac event increased with the number of cardiovascular disease risk factors, risk factor combinations that included hypertension were associated with the greatest risk. It is essential for nurses to address modifiable risk factors (such as smoking, excessive alcohol use, and illicit drug use) with HL survivors, while encouraging physical activity, a heart-healthy diet, and aggressive management of diabetes and dyslipidemia.

SURVIVORSHIP TREATMENT SUMMARY AND CARE PLAN

In 2006, the Institute of Medicine made the following recommendation: "Patients completing primary treatment should be provided with a comprehensive care summary and follow-up plan that is clearly and effectively explained. This 'Survivorship Care Plan' should be written by the principal provider(s) who

How to Determine Potential Risks and Recommended Screening in HL Survivors

If your patient has a history of Hodgkin lymphoma (HL) and does not have a treatment summary, you can ask the following questions to determine potential risks and recommended screening protocols:

- How old were you when diagnosed with HL?
- Where were you treated? Can records be obtained?
- Do you know the stage of your disease?
- What treatments did you have? Surgery? Chemotherapy? Radiation? A combination of these?
- Do you have your spleen?
- If you had radiation therapy to the chest, have you had any breast imaging?
- Does anyone in your extended family have breast cancer?
- If you had radiation therapy to the chest or a chemotherapy called doxorubicin ("the red medicine"), have you had any cardiac screening?

Questions of this nature, coupled with an assessment of current symptoms, can serve as the basis for a comprehensive, risk-based care plan.

Figure 4. Treatment Summary and Care Plan Developed for Ms. Rowland[a]

TREATMENT SUMMARY AND CARE PLAN			
Name: Ann Rowland		**Date of Birth:** 10/22/58	
Cancer Diagnosis: Hodgkin lymphoma, Stage IIB			
Date of diagnosis: 7/1972 Age at diagnosis: 13 years Date of relapse: 10/1973 Location of relapse: chest wall Date of completion of therapy: 8/8/75			
Surgery			
Date		**Procedure**	
7/1972		Laparotomy and splenectomy	
Radiation Therapy			
Date Start	**Date Stop**	**Field**	**Dose (cGy)**
8/2/72	9/13/72	Mantle	4,500 (Cobalt)
Chemotherapy			
Drug Name		**Dose (units or mg/m^2)**	
Vincristine			
Cyclophosphamide		11 g/m^2	
Prednisone			
Doxorubicin (Adriamycin)		450 mg/m^2	
Procarbazine			
Potential Late Effects		**Screening Recommendations**	
• Cardiovascular problems • Lung problems • Thyroid problems • Musculoskeletal problems • Fertility problems/early menopause • Osteopenia/Osteoporosis • Infection secondary to asplenia • Second cancers		• Complete physical exam every year • Echocardiogram annually[b] • Electrocardiogram at baseline and as clinically indicated[b] • Annual mammogram and breast magnetic resonance imaging[c] • Bone density at baseline and as clinically indicated • Pulmonary function test at baseline and as clinically indicated • Annual blood work: complete blood count, comprehensive panel, thyroid-stimulating hormone, 25-hydroxyvitamin D, fasting lipids • Rapid evaluation for fever >100.4°F • If asplenia, immunizations per recommendations from the Centers for Disease Control and Prevention	
Cancer Diagnosis: Ductal carcinoma in situ, right breast			
Date of diagnosis: 1997 Age at diagnosis: 38 years Date of completion of therapy: 1997			
Surgery			
Date		**Procedure**	
4/1997		Right lumpectomy	
Cancer Diagnosis: Invasive breast cancer, left breast			
Date of diagnosis: 5/2009 Age at diagnosis: 50 years Date of completion of therapy: 2009			
Surgery			
Date		**Procedure**	
5/2009		Left modified radical mastectomy and right [prophylactic] total mastectomy and left axillary node dissection	
Hormonal Therapy			
Arimidex (anastrozole)		Since 6/2009	

[a]This care plan incorporates recommendations for a woman who has received therapy similar to the therapy Ms. Rowland received for HL. Because Ms. Rowland went on to develop cardiac disease and breast cancer, the screening recommendations are replaced by therapeutic interventions.
[b]These recommendations exist until the development of cardiac disease, after which therapeutic interventions are instituted.
[c]This recommendation exists until the diagnosis of a secondary breast cancer.

coordinated oncology treatment."[60] The oncology community has increasingly moved in the direction of following this recommendation, though it should be noted that the treatment summary usually describes only cancer treatment, not treatment for cardiac disease or other conditions even if these conditions are treatment related.

When caring for a patient with a history of cancer, it is important to ask whether she or he has a treatment summary—particularly when the treatments may have late effects. The treatment summary and care plan should be provided to patients as they finish cancer treatment to alert them and their future health care providers to potential risks and late adverse effects associated with the treatments they received and the need for appropriate screening. The document lists potential risks (based on exposures) and screening recommendations. It is important for clinicians to bear in mind that some adverse effects may not become evident for 10 to 20 years or more after the completion of cancer treatment.

At the time Ms. Rowland was initially treated, the provision of a treatment summary and care plan was not the standard protocol. Clinicians caring for a patient with a history of HL who has no treatment summary should make every effort to obtain medical records from the treating facility. In addition, it's important to ask patients the appropriate questions (see *How to Determine Potential Risks and Recommended Screening in HL Survivors*). Based on the answers to these questions and a thorough patient history, a nurse can develop a treatment summary and care plan for such a patient (see Figure 4 for an example of a care plan for Ms. Rowland).

RESOURCES

It is well understood by those involved in long-term follow-up care of childhood cancer survivors that their needs are unique and until recently were not well addressed in the academic preparation of health care providers. Programs caring for childhood cancer survivors can provide clinical expertise and work with primary care providers to provide patient follow-up.

COG's *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* offers complete exposure-related, risk-based clinical practice guidelines for the screening and management of late effects resulting from treatment of pediatric malignancies.[40] The most recent update of the guidelines, version 4.0, was released in October 2013 and is available at www.survivorshipguidelines.org. The guidelines include "Info Links" and "Health Links," which describe the risks associated with each exposure, the personal precautions patients should consider taking, and the screening recommendations to be followed. Recognizing the unique health care needs of patients treated for HL in childhood or adolescence will help nurses to best meet their needs. ▼

For 127 additional continuing nursing education activities on cancer topics, go to www.nursingcenter.com/ce.

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