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Caring for Survivors of Hodgkin Lymphoma

An evidence-based review of common late effects of HL treatment.

ABSTRACT: Hodgkin lymphoma (HL) is a highly curable cancer. Advances in diagnosis and treatment have resulted in excellent cure rates, producing an ever-increasing number of HL survivors who live decades beyond their initial cancer treatment. These survivors, however, are at risk for late effects secondary to the cancer treatments they received years earlier, most notably, subsequent primary cancers, cardiovascular disease, pulmonary toxicity, and endocrine dysfunction. Monitoring and managing such late treatment effects may significantly challenge survivors' long-term health care providers, who may need to take on increased survivorship care. For physicians and nurses working outside of oncology settings, who are increasingly called upon to collaborate with oncologists when caring for HL survivors, understanding the late treatment effects and potential risk factors facing this growing patient population is essential to the provision of comprehensive long-term care. The authors provide an overview of HL, review the most commonly encountered late adverse effects of treatment, and discuss current recommendations for survivor surveillance and screening.

Keywords: Hodgkin lymphoma, late effects, oncology, treatment

Hodgkin lymphoma (HL) treatment has come a long way since its discovery by Thomas Hodgkin in 1832. Formerly known as Hodgkin's disease, HL is a highly curable cancer with a five-year survival rate of nearly 87% overall and greater than 92% for localized (stage 1) disease.[1] An estimated 208,805 Americans were living with HL in 2015.[1] HL is considered a rare cancer and its incidence is stable, with roughly 8,500 new cases diagnosed annually. Diagnostic and treatment advances have greatly increased the number of HL survivors, many of whom live for decades after initial diagnosis. Secondary to their previous cancer treatment, however, long-term survivors often experience serious late effects that may manifest as subsequent primary cancers, cardiovascular disease, pulmonary toxicity, or endocrine dysfunction.[2] Such treatment effects may occur as late as 40 years after initial treatment.[3,4]

With more than 40% of new HL cases diagnosed in children and young adults ages zero to 34,[1] long-term, risk-based monitoring is essential, as most of this patient population will live well into adulthood. Late treatment effects pose lifelong concerns for HL survivors and significantly challenge their health care providers. Knowledge of HL treatment risks and signs of late treatment effects is critical to the effective care of survivors—a matter of concern given projections that by 2025 the oncology workforce will be insufficient to respond to the growing demand for oncology services.[5] To ensure the sustainability of survivorship care, the American Society of Clinical Oncology has recommended expanding the use of advanced practice providers and promoting collaboration between oncologists and primary care providers,[5] a suggestion that echoes ideas expressed in the 2006 Institute of Medicine report *From Cancer Patient to Cancer Survivor: Lost in Transition*.[6] Nurses are tasked with providing supportive and preventive care to HL survivors to help them maintain health and quality of life.

This article reviews the classification, etiology, and diagnosis of HL and discusses both past and current

treatment approaches for early-stage disease, the late effects associated with each, and the follow-up care recommended for HL survivors by the National Comprehensive Cancer Network (NCCN) and the Children's Oncology Group (COG).

OVERVIEW OF HODGKIN LYMPHOMA

HL, a cancer of the lymphoid system, is classified into one of two major types: classical HL, which accounts for roughly 95% of cases and is distinguished by the presence of Reed–Sternberg cells, and nodular lymphocyte predominant HL, which accounts for about 5% of cases, contains no Reed–Sternberg cells, and is characterized by lymphocyte predominant, or "popcorn," cells.[7] Disease progression and treatment options differ for these two types of HL, and the survival rate is somewhat better for patients with the nodular lymphocyte predominant type.[8] Here we focus on the more common classical HL.

Etiology. Despite extensive research into HL, its etiology is not completely understood. Associations between classical HL and such viruses as Epstein–Barr[9] and HIV,[10] as well as other immunosuppressive conditions, have been identified. However, the fact that HL does not necessarily develop in patients with these conditions and often develops in the absence of these conditions suggests that other factors are involved in oncogenesis. Other viral infections, such as measles, appear to be inversely associated with HL and may be protective.[11] Familial clustering of HL suggests that genetic predisposition may be a risk factor as well.[12]

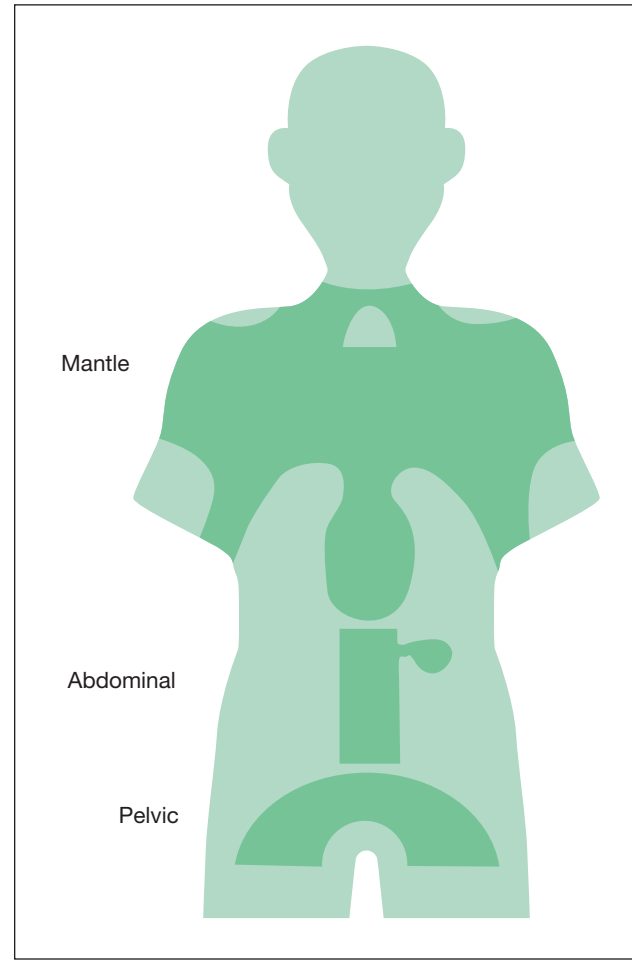
Presentation. Patients typically present with painless and rubbery lymphadenopathy involving the cervical, supraclavicular, or axillary lymph nodes. Chest pain, shortness of breath, and cough are common symptoms for patients with significant mediastinal lymphadenopathy. Patients may also develop fatigue, high fevers, night sweats, anorexia, and weight loss—signs and symptoms that are associated with poorer prognosis.[13]

Diagnosis. NCCN guidelines recommend using excisional lymph node biopsy to diagnose HL.[7] Disease staging includes radiographic evaluation with contrast-enhanced computed tomography (CT) and fluorodeoxyglucose positron emission tomography (PET)/CT.[7] Diagnostic precision is crucial in determining proper treatment with the least potential for acute and long-term late effects. HL survivors are more likely to die from late treatment effects than from HL.[14]

HL TREATMENT MODALITIES: PAST AND PRESENT

High-dose radiation therapy was the mainstay of HL treatment before the 1980s. This therapy often included mantle field radiation, which delivered radiation to lymph nodes in the neck, chest, and armpits and provided limited shielding of vital organs (see Figure 1). Although this is no longer the standard of treatment, patients treated with such high-dose radiation above the diaphragm may experience subsequent primary malignancies, radiation-induced cardiovascular disease, pulmonary toxicity, and endocrine dysfunction months to years after treatment.[7] In recent years, with advances in radiation treatment precision, it has become possible for clinicians to significantly reduce both the dose and field of radiation exposure.[15]

Figure 1. Common Radiation Fields Used in the Treatment of Hodgkin Lymphoma



Chemotherapy. As early as the 1940s, nitrogen mustard was used to treat HL as a single-agent alkylating chemotherapy.[16] Single-agent chemotherapy, however, was not successful in curing HL. Chemotherapy didn't gain acceptance until the 1970s, after the adoption of multiagent regimens that were

often able to cure HL in the absence of radiation therapy.[16] But as the number of chemotherapeutic agents increased, so too did the number of adverse treatment effects and long-term sequelae. As with radiation, these included subsequent primary cancers, cardiovascular disease, pulmonary toxicity, and endocrine dysfunction.[16] (See Table 1.[17])

The contemporary chemotherapy protocols favor the response-adapted approach to treat early-stage HL. Radiation therapy is considered in patients with inadequate early response, with the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) protocol the regimen most commonly prescribed for adults, and the doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) regimen the most commonly prescribed for pediatric patients. (The "A" in these protocols represents "Adriamycin," the now-discontinued brand name for doxorubicin.) The modern protocols are designed to cure HL while limiting the number of toxicities, though they still carry risks of late effects. Since many of today's survivors were treated with older protocols that may have more significant late effects, adult and pediatric survivorship guidelines highlight the need to monitor, identify, and treat these late effects to prevent morbidity and mortality. While ABVD has a more favorable toxicity profile than older regimens, it too is associated with significant late effects, including cardiotoxicity and pulmonary fibrosis.

SECONDARY MALIGNANCIES

With the recognition of treatment-associated late sequelae, radiation fields have been narrowed, dosing of radiation and chemotherapy have been titrated based on patient response and disease characteristics, and new chemotherapy regimens have been developed. Even with enhanced treatment precision, HL survivors remain at risk for second primary malignancies—the leading cause of death among HL survivors—for decades after initial treatment (see Figure 2).[14] A cohort study involving 3,905 HL survivors who received treatment between 1965 and 2000 found that at 30 years following treatment the cumulative incidence of a second solid cancer was 33.2%, compared with a 9.6% cumulative incidence of cancer in the general population, and at 40 years it was 48.5%, compared with 19% in the general population.[3]

Breast cancer is one of the most commonly occurring second cancers among women treated for HL,[3] with risk substantially higher among patients who receive extended field radiation therapy.[7] For patients with early-stage disease and favorable risk factors, the NCCN treatment guidelines recommend a multiagent chemotherapy regimen in conjunction with involved site radiation therapy, which is directed only at lymph node sites shown to have lymphoma involvement on PET scanning. However, for younger patients who are in complete response after two to four cycles, as documented by CT or PET scanning, chemotherapy alone may suffice.[7] For female HL survivors with a history of chest irradiation, the NCCN recommends annual clinical breast examination, mammography, and breast magnetic resonance imaging beginning eight to 10 years after completion of treatment or at age 40, whichever occurs first, in addition to monthly breast self-examination.

Lung cancer development after HL treatment is associated with both radiation therapy and alkylating agents, with the risk from radiation therapy directly related to radiation dosage. Patients who receive chest

Table 1. Chemotherapy Agents Used in Hodgkin Lymphoma Treatment and Their Associated Late Effects[17]

Drug Class	Drugs	Late Effects of Concern
Antitumor antibiotics	Doxorubicin (an anthracycline)[a, b, c, d] Bleomycin[a, b, c, d]	Cardiac toxicity (including cardiomyopathy) Pulmonary toxicity (including interstitial pulmonary fibrosis)
Vinca alkaloids	Vinblastine[a, d] Vincristine[b, c, d, e]	Peripheral neuropathy
Epipodophyllotoxins	Etoposide[b, c, d]	Second malignancy (including leukemia)
Alkylating agents	Dacarbazine[a] Procarbazine[c, e] Cyclophosphamide[b, c] Mechlorethamine[d, e]	Second malignancy, possible gonadal damage
Corticosteroids	Prednisone[b, c, d, e]	

[a]Used in the ABVD chemotherapy regimen, which is in current use.
[b]Used in the ABVE-PC chemotherapy regimen, which is in current use.
[c]Used in the BEACOPP chemotherapy regimen, which is in current use.
[d]Used in the Stanford V chemotherapy regimen, which is in current use.
[e]Used in the MOPP chemotherapy regimen, which was replaced by ABVD in the early 1990s.

radiation of 30 Gy or more have been found to have a seven-to-nine-fold greater risk of lung cancer than those who receive less than 5 Gy.[14] Cigarette smoking has additive detrimental effects on HL survivors. Travis and colleagues found that, among patients classified as current cigarette smokers (at diagnosis or in follow-up data) and treated with an alkylating chemotherapy or radiation therapy, smoking increased the risk of lung cancer 20-fold; among patients classified as moderate-to-heavy smokers and treated with both radiation therapy and an alkylating chemotherapy, lung cancer risk increased 49-fold.[18] Screening HL survivors for lung cancer is controversial. For patients who received chest radiation therapy, some experts suggest the judicious use of low-dose CT scanning, especially among current or former smokers,[19] while others recommend performing a thorough history and annual physical examination over the use of CT imaging in the absence of suggestive signs and symptoms.[20]

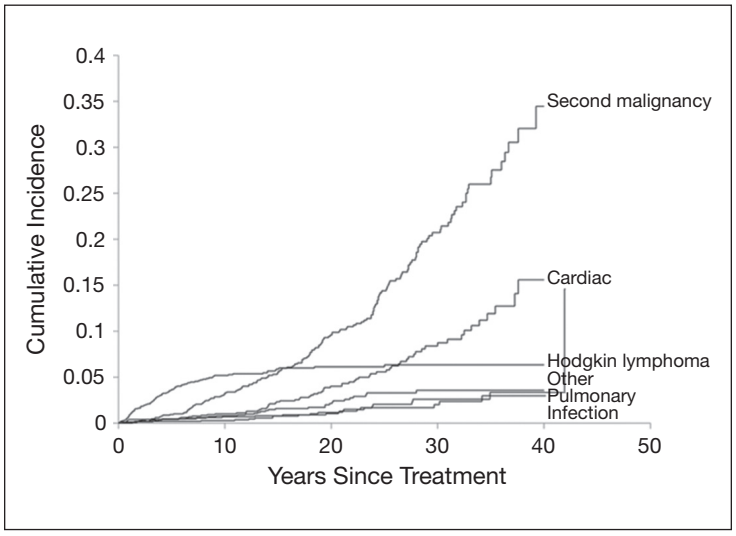
Current NCCN guidelines recommend following the routine screening guidelines of the American Cancer Society to detect lung cancer in HL survivors.[7] Additional emphasis should be placed on smoking cessation counseling, along with cognitive behavioral therapy and pharmacologic assistance, for those who demonstrate readiness to quit smoking.[7]

CARDIOVASCULAR DISEASE

Cardiovascular disease secondary to cancer treatment is the leading noncancer-related cause of death among HL survivors.[21] A study that included more than 200,000 cancer survivors, who were diagnosed at ages 15 to 39 between 1971 and 2006 and followed until 2014, found that nearly 30% of excess deaths among HL survivors over age 60 were directly linked to cardiovascular disease, with ischemic heart disease accounting for 74% of those deaths.[22] Independently, radiation therapy and anthracycline chemotherapy, such as doxorubicin, can cause left ventricular dysfunction, cardiomyopathy, coronary artery disease, and arrhythmias. A critical component of managing the late cardiovascular effects of HL treatment is evaluating the extent of injury each treatment exerts.

Radiation-induced cardiotoxicity. When directed at the chest, radiation can cause direct tissue damage, chronic inflammation, and the production of free radicals, resulting in myocardial fibrosis. The fibrotic changes can structurally damage the vasculature, valves, and chambers of the heart, leading to a myriad of cardiovascular disorders, with risk of radiation-induced cardiovascular disease being proportional to the radiation dose delivered to the heart.[21] In a retrospective, case–control study in the Netherlands, van Nimwegen and colleagues reported that HL survivors who had received chest irradiation that exposed the heart to a mean dose of 20 Gy had a 2.5-fold increased risk of coronary heart disease and a 7.4% excess relative risk per Gy.[23]

Figure 2. Cumulative Incidence of Cause-Specific Mortality Among Long-Term Hodgkin Lymphoma Survivors



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The cardiotoxicity of anthracycline drugs is attributed to their binding to myocardial DNA, which damages the DNA, impairs the body's natural DNA repair process, and produces reactive oxygen species that continually damage the myocardium.[24] Significant risk factors for developing cardiovascular late effects of anthracycline therapy include cumulative doses of 500 mg/m^2 or more, younger age, and female gender.[25]

Combined treatment with anthracyclines and chest irradiation is associated with an even higher risk of cardiovascular disease. Spewak and colleagues found that survivors of childhood cancer treated with a cumulative anthracycline dose of 300 mg/m^2 or more and total chest irradiation of 30 Gy or more were seven times more likely to have an abnormal echocardiogram during routine follow-up than those treated with the anthracycline chemotherapy alone.[26] Armstrong and colleagues found that HL survivors with hypertension were more than 19 times more likely to develop heart failure than their siblings.[27] Traditional cardiac risk factors, such as hypercholesterolemia, hypertension, diabetes mellitus, and smoking appear to significantly elevate the risk of cardiovascular disease among HL survivors.[23,28]

Cardioprotective agents. No drugs are currently approved by the U.S. Food and Drug Administration to reverse the cardiotoxicity associated with HL treatment, but the use of antioxidants, such as amifostine,[29] melatonin,[30] and selenium,[31] to suppress the oxidative stress and inflammatory processes seen in HL survivors has shown promise in animal and in vitro studies. Furthermore, a prospective study of

Table 2. Provider Guidelines for Posttreatment Hodgkin Lymphoma Follow-Up[7, 17]

Timing[a]	NCCN Guidelines	COG Guidelines
At follow-up visits	• Patient education and aggressive management of cardiovascular risk factors • Counseling: reproduction, psychosocial, health habits, skin cancer risks, breast self-exam, smoking cessation, and diet and exercise • Consider routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer as per ACS guidelines.	• Patient education and counseling in general health maintenance • Smoking cessation counseling • Immunization per CDC guidelines • Baseline and as clinically indicated: o ECG o ECHO o PFT o Testosterone (males: baseline at age 14, then as clinically indicated) o Semen analysis (periodic upon patient request) • FSH (in sexually mature men if unable to obtain semen sample), LH, estradiol (females: baseline at age 13, then as clinically indicated)
Every 6 months	• Lipid profile	• Dental exam and cleaning
Every year	• Review of systems and physical exam • Blood pressure check • CBC, chemistry profile, fasting glucose • Influenza vaccine • TSH, if patient had received neck irradiation • Breast cancer screening (for women who received chest or axillary irradiation) o Initiated 8 to 10 years after end of therapy, or starting at age 40, whichever comes first o Clinical breast exam o Mammography and MRI for females who received radiation therapy between ages 10 and 30	• Review of systems and physical exam • Blood pressure counseling • TSH, free T4 • Pulmonary exam • ECHO if o < age 5 at treatment and received radiation to chest o < age 1 at treatment and received anthracycline dosed at ≥ 200 mg/m^2 o ages 1 to 4 at treatment and received anthracycline dosed at ≥ 300 mg/m^2 o age 5 or older at treatment and received anthracycline dosed at ≥ 300 mg/m^2 with or without radiation o serial decline in cardiac function is detected • Ophthalmologic exam • Dermatologic exam • Breast cancer screening (≥ 20 Gy radiation with exposure to the breasts) o Yearly clinical breast exam at onset of puberty, then every 6 months starting at age 25 o Yearly mammogram and breast MRI initiated 8 years after radiation or at age 25, whichever occurs later • Lung cancer screening o Pulmonary exam yearly, especially for patients with history of respiratory symptoms o Discuss benefits and risks of CT scan to screen for lung cancer • Psychosocial assessment for depression, anxiety, PTSD, suicidal ideation
Every 2 years	—	• Fasting glucose or HbA_{1c} and lipid profile • ECHO if o < age 1 at treatment and received anthracycline dosed at < 200 mg/m^2 o ages 1 to 4 at treatment and received anthracycline dosed at ≥ 100 to < 300 mg/m^2 o age 5 or older at treatment and received anthracycline dosed at ≥ 200 to < 300 mg/m^2 and no radiation o < age 5 at treatment and received any amount of radiation to the chest o age 5 or older at treatment and received combined radiation and anthracycline dosed at < 300 mg/m^2 o age 5 or older at treatment and received ≥ 30 Gy of radiation to the chest

Table 2. Continued

Every 5 years	• Pneumococcal, meningococcal, and *Haemophilus influenzae* revaccination for patients treated with splenic radiation therapy or splenectomy	• ECHO if o age 5 or older at treatment and received < 30 Gy of radiation to the chest o age 1 to 4 at treatment and received anthracycline dosed at < 100 mg/m^2 o age 5 or older at treatment and received anthracycline dosed at < 200 mg/m^2
Every 10 years	• Stress test and ECHO • Carotid ultrasound if patient had received neck irradiation	—

ACS = American Cancer Society; CBC = complete blood count; CDC = Centers for Disease Control and Prevention; COG = Children's Oncology Group; CT = computed tomography; ECG = electrocardiography; ECHO = echocardiography; FSH = follicle-stimulating hormone; HbA_{1c} = glycated hemoglobin; LH = luteinizing hormone; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PFT = pulmonary function testing; PTSD = posttraumatic stress disorder; T4 = thyroxine; TSH = thyroid stimulating hormone.
[a]Follow-up begins 5 years after treatment.

226 patients who developed cardiotoxicity after receiving anthracycline-containing therapy found that angiotensin-converting enzyme (ACE) inhibitors and β-blockers could improve left ventricular ejection fraction within one year of treatment.[32] No data are available on the use of ACE inhibitors and β-blockers in patients with late cardiovascular effects, and no trials investigating the efficacy of these agents in protecting patients against the late effects of chest irradiation and anthracycline-based therapy are underway.

Nonpharmacologic interventions to reduce risk of cardiovascular disease in HL survivors has been studied by Jones and colleagues.[33] In this retrospective cohort study with longitudinal follow-up, 1,187 survivors of childhood HL completed questionnaires about their participation in vigorous exercise, defined as at least 20 minutes of intense exercise three days per week, as well as follow-up questionnaires collecting sociodemographic and health information, including cardiovascular events. Investigators found that regular vigorous exercise was associated with a 51% reduced risk of any cardiovascular event among the adult survivors. They believe that regular aerobic exercise can suppress systemic inflammation and engage the body's natural antioxidative response. While it's well known that regular exercise can mitigate various risk factors for cardiovascular disease in the general population, this study suggests that it may serve an even greater purpose for HL survivors.

Early detection and treatment. The NCCN recommends that cardiovascular testing, including stress testing, echocardiography, and carotid ultrasound (if the neck was irradiated), be performed at 10-year intervals beginning at the completion of HL treatment.[7] The COG provides risk-adapted screening guidelines that call for yearly echocardiograms for those at higher risk, based on the potential impact of radiation to the heart and the anthracycline dose.[17]

While it's well known that regular exercise can mitigate various risk factors for cardiovascular disease in the general population, a recent study suggests that it may serve an even greater purpose for HL survivors.

Screening for coronary artery disease. For patients treated with mediastinal radiation therapy, van Leeuwen-Segarceanu and colleagues recommend that screening for coronary artery disease begin as early as five years after treatment if the patient was age 45 or older at diagnosis, or if the patient was younger at diagnosis but has two or more coronary artery disease risk factors, such as hypertension and hyperlipidemia.[34] For patients diagnosed at a younger age who do not have coronary artery disease risk factors, screening should start 10 years after mediastinal radiation therapy.

While coronary angiography is considered the best method for assessing coronary vasculature, it is invasive and expensive. Though less accurate than coronary angiography, coronary artery calcium scores, which are calculated from CT scans of the heart, have shown promise in detecting coronary artery disease in asymptomatic HL survivors.[34] For this reason, van Leeuwen-Segarceanu and colleagues propose that serial coronary artery calcium scores be used to screen patients at low-to-intermediate risk of developing coronary artery disease after HL treatment.[34]

Lifestyle management. It's strongly recommended that health care providers caring for HL survivors take steps to detect and manage dyslipidemia, hypertension, metabolic syndrome, obesity, and diabetes.[27] The NCCN emphasizes preventive strategies, such as closely monitoring traditional risk factors, recommending annual blood pressure measurement, and biannual lipid studies.[7] General health promotion recommendations include a balanced diet, physical activity, and smoking cessation.

Resources for Clinicians and Hodgkin Lymphoma Survivors

Academy of Nutrition and Dietetics: www.eatright.org

American Cancer Society (ACS): www.cancer.org

- ACS: Stay Away from Tobacco: www.cancer.org/healthy/stay-away-from-tobacco.html

American Society of Clinical Oncology (ASCO) Survivorship Compendium: www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/survivorship/survivorship-compendium

- ASCO Fertility Preservation Guidelines: www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2018-fertility-preservation-summary-table.pdf
- ASCO Cancer Treatment and Survivorship Care Plans: www.cancer.net/survivorship/follow-care-after-cancer-treatment/asco-cancer-treatment-and-survivorship-care-plans

American Society for Reproductive Medicine: www.asrm.org

Cancer Care: www.cancercare.org

Cancer Legal Resource Center: http://cancerlegalresources.org

Cancer Control P.L.A.N.E.T.: https://cancercontrolplanet.cancer.gov/planet/index.html

Centers for Disease Control and Prevention Cancer Survivors: www.cdc.gov/cancer/survivors/index.htm

Children's Oncology Group, Survivorship Guidelines: www.childrensoncologygroup.org/index.php/survivorshipguidelines

Journey Forward: www.journeyforward.org

LIVESTRONG: Becoming a Parent After Cancer: www.livestrong.org/we-can-help/livestrong-fertility

- LIVESTRONG: Your Survivorship Care Plan: www.livestrong.org/we-can-help/healthy-living-after-treatment/your-survivorship-care-plan

Memorial Sloan Kettering Cancer Center: Living Beyond Cancer: www.mskcc.org/experience/living-beyond-cancer

National Cancer Institute (NCI) Office of Cancer Survivorship: https://cancercontrol.cancer.gov/ocs

- NCI: Facing Forward Series: https://cancercontrol.cancer.gov/ocs/resources/ffseries.html

National Coalition for Cancer Survivorship: www.canceradvocacy.org

National Comprehensive Cancer Network Guidelines: www.nccn.org/professionals/physician_gls/default.aspx#survivorship

Oncology Nursing Society: www.ons.org

The Samfund: Support for Young Adult Cancer Survivors: www.thesamfund.org

U.S. Department of Agriculture: ChooseMyPlate: www.choosemyplate.gov

Young Survival Coalition: www.youngsurvival.org

Cognitive-behavioral strategies have long been recognized by the American Heart Association as effective interventions in changing lifestyle behaviors to improve health.[35] Nurses can successfully incorporate such strategies as motivational interviewing into their practice to increase patient commitment and adherence to health-promoting behaviors.

PULMONARY TOXICITY

Treatment-associated pulmonary toxicity, categorized as restrictive lung disease, may become chronic.[25] For patients treated with chest irradiation doses above 20 Gy, the odds of pulmonary function decline over time were 24 times greater than in age- and sex-matched healthy controls.[36] Pneumonitis, which is typically evident two to three months after chest irradiation, can cause long-term fibrotic changes that manifest as chronic cough or shortness of breath.

Cytotoxic agents, such as bleomycin, may produce interstitial pneumonitis and, eventually, pulmonary fibrosis, resulting in similar symptoms.[25] When treatment modalities are combined, dose reduction is often necessary to reduce the risk of pulmonary toxicity. Caution must be exercised when administering supplemental oxygen to patients with a history of bleomycin exposure, as these patients may be vulnerable to lung injury.[21, 37] HL survivors with treatment-associated pulmonary toxicity may benefit from the support of a pulmonology specialist.[38]

ENDOCRINE DYSFUNCTION

Hypothyroidism among HL survivors is associated with neck irradiation. Up to 50% of HL survivors develop some form of thyroid dysfunction, with hypothyroidism representing 90% of cases.[19] Hypothyroidism usually develops within five years of treatment, but a 1991 record review of 1,787 patients with HL who were treated with radiation therapy alone, radiation therapy and chemotherapy, or chemotherapy alone found that thyroid abnormalities may occur as late as 26 years after treatment.[39] Signs and symptoms of hypothyroidism include fatigue, weight gain, cold intolerance, weakness, cardiac dysfunction, cognitive difficulties, and depression. Since symptoms vary widely and may overlap with those of other late treatment effects or acute disease processes, nurses must conduct a thorough review of systems to provide appropriate patient education and counseling.

A retrospective study of 61 consecutive patients undergoing chemotherapy and radiation therapy for HL identified two critical factors that predicted the risk of hypothyroidism: dose of radiation and the percentage of thyroid gland exposed.[40] When 62.5% or less of the thyroid gland was exposed to radiation at a dose of 30 Gy or more, the risk of hypothyroidism was 11.5%; the risk increased to 70.8% when the percentage of thyroid gland exposed exceeded 62.5% at the same radiation dose. Annual monitoring of thyroid-stimulating hormone and free thyroxine along with a review of systems and physical examination are recommended.[7]

Infertility. While lymphoma itself may reduce sperm quality,[41, 42] both male and female patients who received chemotherapy or radiation therapy for HL may experience posttreatment fertility complications; these may be temporary or permanent, depending on treatment type, dose, and age at the time of treatment. Because those with HL are generally diagnosed and treated when young, many will explore fertility preservation options prior to the start of treatment. Providers, therefore, should not assume that HL survivors are infertile.

Pregnancy complications. In published studies, the percentage of women becoming pregnant following HL treatment varies widely, from less than 10% to more than 50%.[43] Women with a history of pelvic or abdominal irradiation for HL should be closely monitored during pregnancy and childbirth as they may be at risk for preterm birth, miscarriage, stillbirth, or postpartum hemorrhage.[43] Such HL treatments as the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP; the "o" represents Oncovin, the discontinued brand name for vincristine) and ABVD regimens may have harmful effects on sperm that may impede healthy reproduction. Therefore, following the completion of HL treatment, men are advised to use barrier contraception for two years.[41]

Premature menopause. In female patients, abdominal irradiation may cause ovarian suppression and damage, although menstruation can remain normal; if ovarian damage is severe, it may result in premature menopause. In one British study, risk of premature menopause increased 20-fold with pelvic radiation or alkylating chemotherapy and increased 36-fold with combination therapy.[44]

Nurses can use motivational interviewing to increase patient adherence to health-promoting behaviors.

SURVIVORSHIP CARE PLANS

All HL survivors should be provided with a treatment summary and survivorship care plan to promote

awareness of and adherence to follow-up guidelines (see Table 2[7, 17]). These should be provided in writing or electronically to patients and primary care providers at or before the transition to survivorship care. They should include the following[45]:

- cancer diagnosis and date
- cancer stage
- all related treatments, including
  - chemotherapy agents and doses
  - surgeries (procedures and dates)
  - radiation therapy (start date, stop date, fields, and dosage)
  - hormonal therapy (agent and treatment period)

The documents should list potential late effects along with secondary malignancy and cardiovascular surveillance and screening recommendations.

A 2015 Dutch study revealed that most HL survivors in the Netherlands were not routinely screened for cardiovascular disease.[4] Surveys of primary care providers and childhood cancer survivors suggest that such findings may reflect a lack of preparedness on the part of primary care providers to evaluate and manage long-term effects of childhood cancer treatments as well as the survivors' lack of knowledge of their childhood diagnosis and treatment.[46, 47] In another study, 1,124 family physicians in the United States and Canada were surveyed regarding proper follow-up care for cancer survivors. Only 16%, 10%, and 74% correctly identified the recommended surveillance guidelines for breast cancer, cardiovascular disease, and hypothyroidism, respectively, in HL survivors.[48] The same study found that 85% of the family physicians surveyed preferred to provide care in collaboration with an oncologist or a formal survivorship program, and of those who had cared for one or more survivors, only 48% had ever received a treatment summary in advance of the patient's first visit. Oeffinger and colleagues found that primary care physicians' adherence to surveillance recommendations increased when survivors were provided with these documents.[49]

Nurses play a critical role in caring for cancer survivors in a variety of health care settings. As such, they need to be familiar with challenges the HL survivors face and knowledgeable about strategies that promote survivors' health and mitigate toxicity (see *Resources for Clinicians and Hodgkin Lymphoma Survivors*). ▼

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