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Survivorship in Hodgkin Lymphoma

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1. Introduction

Hodgkin lymphoma (HL), formerly called Hodgkin's disease, is a malignancy of mature B-cell lineage (germinal or post-germinal center), with over 8,000 new cases diagnosed annually in the United States.[1] HL has historically been characterized by many histologic subtypes with the finding of Reed-Sternberg cells unify the diagnosis. HL is well known to have a bimodal distribution of incidence, occurring most frequently in two distinct age groups: young adults (age 15-35) and those ages greater than 55 years old. For the purpose of this chapter, we will focus on the young adults treated for and cured of HL with radiation therapy (RT), chemotherapy, or combined modality therapy (CMT).

HL remains in many ways the archetype within oncology with regards to incremental improvements, established through well-performed clinical trials, turning an incurable and universally fatal illness into one that is, more often than not, cured with first-line therapy. The need for an understanding of how best to care for survivors of HL is predicated upon patients being cured of their HL. This was first achieved in the 1960's when HL was shown to be a curable disease, first with high-dose extended field RT,[2] and subsequently with multi-agent chemotherapeutic regimens such as MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone).[3] Increasingly intensive treatments, however, were handcuffed to increasing toxicity.[4] As the likelihood of cure started to plateau in the 1990's at approximately 80%, the toxic consequences of these intensified treatment regimens – acute as well as late effects – increasingly came into focus.[5] As HL is largely a disease of young, functional, and fertile, with survivors often living long lives (with whatever impairment resulting from disease and treatment), the need to better understand the medical needs of survivors of HL began to receive significant attention from the medical community. Additionally, investigators began to pursue improvement in HL therapy from a very different perspective – seeking not to identify further intensifications of therapy, but rather to attempt to delineate how treatment toxicities could be limited without sacrificing the excellent outcomes gained over the past decades. Accordingly, improvements in radiation delivery have led to preferential use of smaller fields (involved field radiation therapy, and now even involved nodal field radiation in select circumstances.[6, 7] Efforts in the development of systemic chemotherapy for HL have been focused upon not only

intensification of therapy, but in the selective application of such treatment. Currently, the management of HL is driven by patient- and disease-specific characteristic including age and gender, stage, bulk, location, and risk models specific for early or advanced stage disease.[8-12] Early-stage patients, particularly those with bulky disease (most often defined as a mass greater than 10 cm in long-axis diameter or encompassing more than a third of the intrathoracic diameter) are commonly treated with combined modality approaches of varying intensity.[13] Advanced disease is frequently treated with chemotherapy alone with consolidation radiation therapy to sites of bulk [14], although here, intensity of treatment is often dictated by risk prediction. The next generation of clinical trials seeks more individualized and specific ways to tailor treatment intensity, particularly using response-adapted strategies with early restaging functional imaging with 18-fluorodeoxyglucose (FDG) positron emission tomography (PET). As treatments continue to emerge, and evolve, the needs of survivors will of course develop in kind. Nonetheless, there exist over 160,000 patients living after being cured of HL; having received treatments with long-term effects, and it is the optimal care of these patients that is the focus of survivorship efforts.[15]

2. Importance of post-treatment care

During the first 10 years following diagnosis of HL, relapse remains the leading cause of death. [16] However, by 15-20 years following diagnosis, risk of death due to causes other than HL will have surpassed those due to the lymphoma itself.[17, 18] By risk stratification, those with early stage disease are more likely to have secondary malignancy and cardiovascular disease when compared to those with advance disease, an observation attributable to improved prognosis as well as effects from RT, more often a component of therapy for early stage disease. As the risk of relapse diminishes after treatment the subsequent quality of life altering comorbidities become apparent and accelerated.[19] Although second primary malignancy and cardiovascular disease are the most frequent causes of non-lymphoma mortality among patients with HL, they are far from the only medical conditions for which they are at risk. Pulmonary, musculoskeletal, endocrine, neurologic, and psychiatric illness all occur at increased frequency among HL survivors, typically as direct sequelae of the disease or its treatment. Tellingly, a single-institution series investigating the global effects of late morbidity found that, among survivors an average of 21 years post-treatment, 94% reported at least one morbidity of any grade severity, 50% at least one morbidity of grade 3 or greater (according to a modification of the Common Terminology Criteria for Adverse Events, version 3), and 23% two or more morbidities of grade 3 or greater.[18] In order for a physician to offer optimal care for survivors of HL, such care should be built upon an understanding of these risks, both individually and collectively.[20]

3. Second primary malignancy

Unfortunately, among those cured of HL, second primary malignancy remains the leading cause of mortality 15 years after disease-free survival.[21] For instance, a risk model approximated that those diagnosed at the age of 30 with HL will have a 30 year cumulative risk of second primary malignancy for men and women at 18% and 26%, respectively, compared to age-matched risks of 7% and 9%.[22, 23] The latency of the various second

malignancies seen following therapy for HL varies by histology. Risk for myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) peak at three to five years after therapy and return to population baseline, or at most remain minimally elevated, by 10 years after.[24-26] The inverse is true for solid tumor malignancies, where increased risk only first becoming appreciable by 10 years after the completion of therapy.[27]

4. Hematologic malignancies

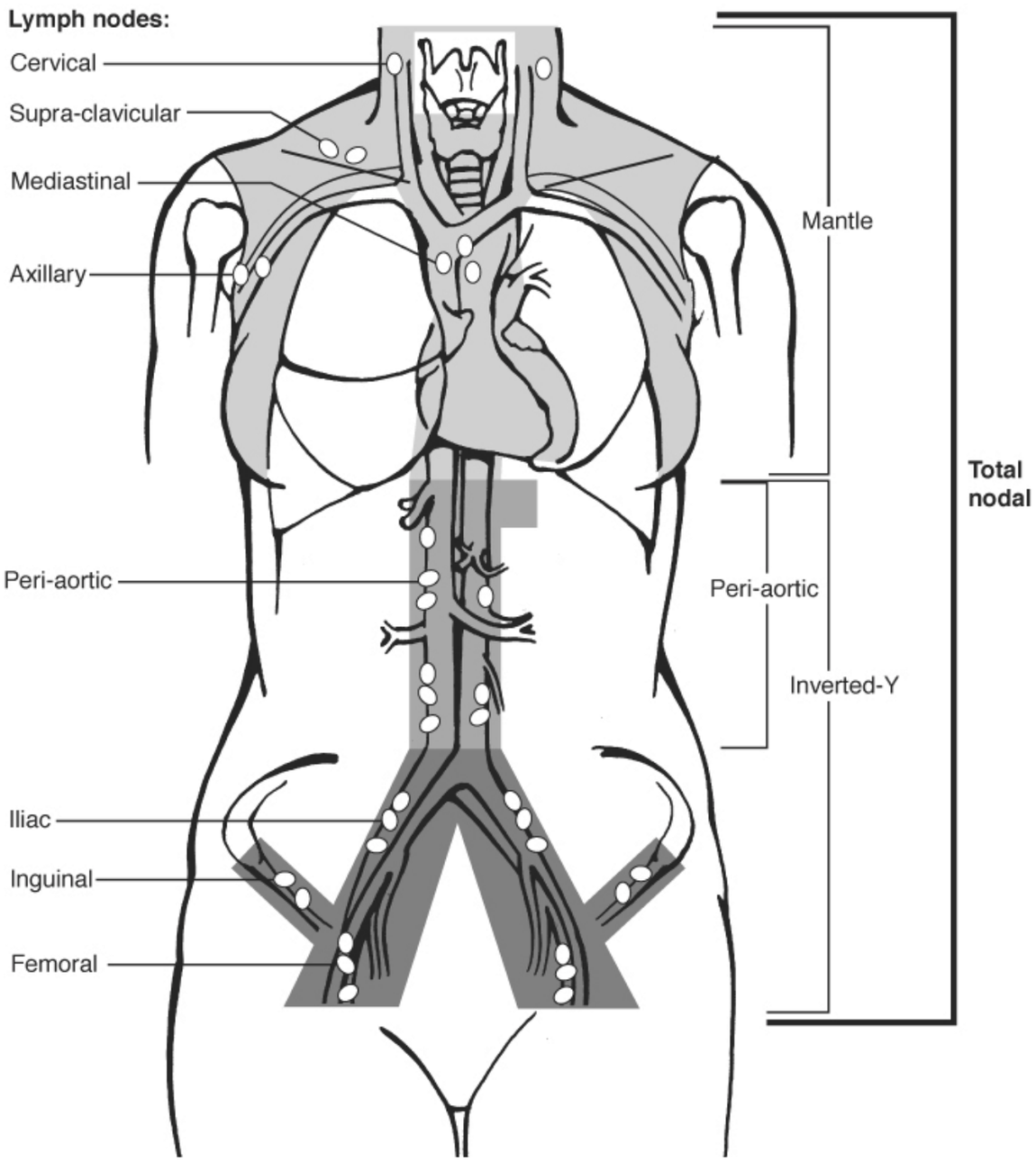
Already survivors of one hematologic malignancy, the fact that they are at heightened risk for the development of additional hematologic malignancies – particularly MDS, AML, and non-Hodgkin lymphoma (NHL) – are a source of frustration to doctors and patients alike. Treatment-induced MDS or AML is a well-established risk of HL therapy; the relative risk of acute leukemia among patients cured of HL is 80 times greater than the general population, although the absolute excess risk is low.[28] The risk of MDS/AML is largely predicated upon the treatment delivered, as the cumulative dose of potent alkylating chemotherapy (e.g., mechlorethamine) or topoisomerase inhibitors (e.g., doxorubicin or etoposide) and the delivery of radiotherapy account for much of this increased risk.[24, 29] Despite ongoing advancements in the treatment of the acute leukemias, treatment-related AML remains profoundly dangerous, with median survival measured in months.[28] Indeed, it was in part the leukemogenicity of the older MOPP regimen that helped fuel the ascendance of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as the chemotherapeutic standard of care for average-risk HL. The absolute excess risk of AML following treatment with ABVD is between 0 and 0.4%, whereas with MOPP was 2.8% (and with MOPP and radiotherapy as CMT, 5.5%).[25, 30, 31] The modern intensified regimen, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), and is associated with a risk of AML of 3.2%. This observation has largely led to the selective use of this highly effective regimen only in high-risk patients – patients in whom the risk of poor outcomes with ABVD merit exposure to more leukemogenic therapy.[32] The risk of secondary acute leukemia in patients receiving consolidative RT for HL appears to be more closely related to the field of therapy than to the delivered dose.[27] This contribution to leukemia risk has been somewhat mitigated, as modern RT strives to limit therapeutic exposure, preferring involved fields to extended fields, although these efforts are not expected to entirely obviate the contribution to risk of leukemia from radiotherapy.

In addition to acute myelogenous leukemia, HL survivors are also at increased risk for the subsequent development of non-Hodgkin lymphoma (NHL).[21, 33, 34] The risk appears to be influenced by the selection of treatment, with alkylator therapy and radiotherapy emerging as the likely causes of oncogenesis. Estimates of the relative risk of NHL among survivors of HL are varied across reports, ranging from 2 to 22, but the absolute risks are low: The 25-year cumulative risk of NHL is less than 4%, and the absolute excess risk (AER) of NHL is less than 10 cases per 10,000 person-years.[21]

5. Solid tumor malignancies

Although the development of a second primary hematologic neoplasms following curative treatment for HL is a potentially life-threatening event, and one for which survivors are at far greater risk than age-matched controls, solid tumors collectively comprise a much greater risk for survivors – 75% of second primary malignancies will not be AML or NHL,

but rather will be of solid organ origin, and unlike the risk of AML, the risk (and excess risk) of solid organ malignancy has no apparent plateau among HL survivors. Unlike AML, however, much of the risk of solid tumors arising from treatment of HL is attributable to local genotoxic damage due to radiation therapy; each routine involved field of radiotherapy is associated with potential solid-tumor risks within the given field (Figure 1).



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Fig. 1. Radiation therapy fields in the treatment of classical Hodgkin lymphoma.

6. Lung cancer

HL survivors are at increased risk for developing lung cancer; with a relative risk of 7 and an AER of 7 per 10,000 person-years, lung cancer represents a serious cause of morbidity and mortality.[22, 35-39] This risk is mediated by the volume and dose of lung tissue exposure to ionizing radiation, cumulative dose of alkylating chemotherapy, and environmental factors.[22] HL patients who had a positive smoking history and received radiation therapy as a part of their management have a markedly higher incidence of lung cancer when compared to HL who non-smokers and received radiation therapy, with relative risks as high as 50 times that of the general population.[40] Interestingly, regardless of smoking history, incident lung cancers develop within the radiation-exposed lung parenchyma. HL survivors who develop lung cancer have a median survival of less than a year [41, 42], and recently have been shown to have a 60% less chance of survival than cases of stage-matched *de novo* lung cancer.[43] We continue to adamantly recommend smoking cessation (with the support of a smoking cessation clinic) to patients at the time of diagnosis given the interaction between cigarette smoking and therapy in augmenting the subsequent risk of lung cancer. Whether to screen at-risk patients with a history of HL, and if so, how best to do so, remain unanswered questions. National Comprehensive Cancer Network (NCCN) guidelines recommend annual chest imaging (either X-ray or CT scan) for all patients except those who were treated without alkylator therapy, mediastinal RT, and who have no other risk factors.[44] The recommendation of screening CT has been supported by cost modeling, showing it to be cost effective, particularly in smokers.[45] However, perhaps the greatest impetus, albeit indirect, for lung cancer screening in HL survivors comes from the National Lung Screening Trial.[46] This large randomized trial of non-cancer patients with strong smoking histories demonstrated that, with annual low-dose CT scans of the chest for three consecutive years, lung cancer-specific and overall survival could be improved. How best to extrapolate these findings to the HL survivor population is unclear, and the duration and intensity of screening will require further clarification, but an annual low-dose chest CT scan in at-risk survivors may well emerge as the de facto standard of care, and given the current body of data should be discussed with patients at risk.

7. Breast cancer

After 15 years of follow-up, women treated with mantle field radiation before the age of 20 had a 40-fold increased risk of developing breast cancer compared to age-matched controls.[47] In a retrospective study of HL survivors treated with more modern radiation dose and delivery, doses as low as 4.0Gy to the breast were associated with a 3.2 fold cancer risk compared to women who were treated with lower doses of radiation. This risk increased to 8-fold for women treated with >40 Gy to the breast. Age at radiation dominates the risk assessment for second primary breast neoplasia; in one study, for instance, the actuarial risks of breast cancer for patients receiving mantle radiation by 25 years after treatment were 34%, 22%, and 3.5% for patients under age 20, age 20-30, and over age 30, respectively; radiation therapy to patients over the age of 30 appears to confer at most a minimal risk of subsequent breast cancer.[48] Concomitant use of alkylating agents or pelvic radiation can have protective effects against development of breast cancer, presumably due to the low-estrogen state induced by premature ovarian failure.[47, 49] The question of how best to monitor patients who have received treatment likely to increase breast cancer risk remains unanswered, and an area of active research.

Guidelines for the screening of women for breast cancer continue to evolve, as do recommendations for screening high-risk patients, such as those with hereditary risk for breast cancer due to the inheritance of BRCA1 or BRCA2.[52] Unfortunately, many female HL survivors will also be at an increased risk for subsequent breast cancer, risk that is associated with exposure of breast tissue to ionizing radiation when contained in RT fields. For instance, women treated with mantle radiation under age 20 have a 40-fold increased risk of developing breast cancer compared to age matched controls at a median of 15 years follow-up.[21] Developmental age of breast tissue also strongly influences the risk of radiation induced carcinogenesis, as in patients who received mantle RT under the age of 20, age 20-30, and over 30 the risk of breast cancer was 34%, 22.3%, and 3.5% respectfully at 25 years post treatment.[48] Given the many changes that have taken place in the delivery of RT in the treatment of HL (extended fields giving way to more limited involved fields; efforts at limiting dose; and improved simulation techniques, to name but three), it is hoped that risks of breast cancer following RT may be lower for patients treated in the current era. Nonetheless, recent data suggest that modern radiotherapy techniques may not in fact lead to reductions in second malignancy;[53] estimating risks of breast cancer will require ongoing reassessment so as to permit the most appropriate screening approach for individual patients given their individual risk profiles. Interestingly, concomitant use of alkylating agents or pelvic radiation can have protective effects against development of breast cancer, thought to be related to decreased estrogen production induced by treatment-related ovarian suppression or premature ovarian failure.[54] If efforts at fertility preservation with administration of gonadotropin releasing hormone agonists prove successful, as may be the case in breast cancer therapy[55], it is possible this benefit may be either abrogated or nullified.[56]

The optimal surveillance strategy for patients placed at increased risk for breast cancer by their HL therapy remains a subject of investigation, but standards of care are beginning to emerge. The National Comprehensive Cancer Network (NCCN) and the American Cancer Society (ACS) have recommended that, for those who received mediastinal radiotherapy before the age of 30, breast cancer surveillance should begin between eight and ten years following treatment.[50, 51] Mammography remains an important modality for breast cancer screening in this patient population, although the addition of an annual breast magnetic resonance imaging is reasonable for high-risk patients (particularly those with dense breasts on mammography, a finding that limits the sensitivity of mammography for early detection); the use of MRI in screening is extrapolated from a comparable risk group, women with BRCA1 mutation, in whom breast MRI has been validated as a useful element in screening programs.

Many other types of solid tumor malignancies remain overrepresented in HL survivors. Papillary thyroid carcinoma is the most notable among them and is clearly associated with radiation therapy, although the risk of thyroid cancer decreases with doses above 30 Gy, consistent with increased cell kill of normal thyroid tissue.[58] Other radiation-associated cancers can be seen as well, including gastrointestinal carcinomata and soft tissue sarcomata, as well as a strong association with non-melanoma skin cancer, both basal and squamous cell histologies.[22] Given these risks, surveillance for second primary malignancy should take such risks into account, including modification of colorectal

screening for patients receiving infradiaphragmatic radiation, and special attention to skin examination in radiation fields.

8. Cardiovascular toxicities

While secondary malignancies remain the leading cause of mortality in long-term HL survivors, death due to cardiac causes places second and cardiovascular morbidity and mortality is far more common among HL survivors than among comparable untreated individuals. The specific cardiovascular toxicities for which HL survivors are at increased risk can include coronary artery disease (CAD), valvular heart disease, congestive heart failure (CHF), pericardial disease, electrical conduction abnormalities, and cerebrovascular disease.[59]

9. Coronary artery disease

HL survivors who receive radiotherapy to the mediastinum are at increased risk of early onset CAD. A British cohort of HL survivors was found to be 3.2 times more likely to suffer a myocardial infarction (MI) than population controls. [60] In Dutch HL survivors treated with mediastinal radiation, the 20-year cumulative risk of myocardial infraction was 21.2%.[61] In a similar cohort Aleman et al. reported the risk of development of a myocardial infarction at 30 years post-radiation was 12.4%.[62] The selection of chemotherapy, including the use of anthracyclines, does not appear to definitively impact risks of CAD among survivors. Classical CAD risk factors (hypertension, diabetes, cigarette smoking, and hyperlipidemia) continue to play a role in promoting atherosclerosis in HL survivors, necessitating optimal medical management.[63] At present, there have only been two prospective studies of cardiac screening in HL survivors. Heidenreich et al. [64] reported an abnormal stress test (echocardiogram and/or radionucleotide myocardial perfusion scan) in 21% of asymptomatic HL survivors fifty percent of those with an abnormal functional study demonstrated an obstructive lesion at the time of definitive coronary angiography. Furthermore, Kupeli et al. [65] use CT angiogram to detect subclinical CAD in survivors of childhood HL, and found a 6.8 times greater post-radiation HL survivors. CT angiography is felt to represent the non-invasive gold standard for detection of CAD, with sensitivity and specificity of 94% and 97%, respectfully, compared to fluoroscopic angiography.[66] Whether screening CT angiography is appropriate for adult HL survivors remains an open question, and indeed no standard of care yet exists for the surveillance for subclinical CAD in HL survivors.

10. Valvular heart disease

The risk of subsequent valvular heart disease is significantly increased among HL survivors treated with mediastinal RT, again believed due to direct toxic effects on the valve apparatus. Investigators have observed a seven- or eight-fold increase in the likelihood of experiencing significant valvular heart disease among irradiated survivors, risks that appear not to be mediated by chemotherapy agents or dosages.[62, 67] The aortic valve is the most commonly affected, and female gender appears to predispose to disease.[68] Echocardiographic surveillance to assess valvular competence is often included as an

element of routine follow-up of HL survivors treated with mediastinal radiation, although as of yet no guidelines for adult survivors have been developed.

11. Congestive heart failure

Although the most common cause of congestive heart failure (CHF) in HL survivors is ischemic cardiomyopathy, significant concerns remain about the risk of late non-ischemic cardiomyopathy. While cumulative dose of anthracycline is associated with risks of CHF, currently the maximum cumulative dose of doxorubicin would not exceed 400 mg/m^2 and typically would not exceed 300 mg/m^2, the dose exposure from 6 cycles of ABVD, dose levels that would be expected to be associated with low risks of cardiomyopathy.[69, 70] Doxorubicin is not the only therapeutic agent for HL associated with CHF; It has long been recognized that mediastinal RT can predispose to CHF as well.[71] The impact of therapy on risk of subsequent CHF has been convincingly elucidated in patients treated as children for HL; data from the Childhood Cancer Survivor Study estimate a hazard ratio of 6.8 in HL survivors, with young age (<10y), female gender, higher doses of doxorubicin, and mediastinal RT all contributing to risk in multivariate modeling.[72] Subclinical LV dysfunction in survivors of childhood HL appears also to be common, although estimates of cumulative incidence are heterogeneous, ranging from 0 to 57% in 25 studies using traditional echocardiographic metrics (studies that were themselves heterogeneous in how subclinical LV dysfunction was defined).[73] Among patients treated for adult HL, long-term survivors are at increased risk for developing CHF, with one set of estimates (among patients who largely did not receive anthracycline-based chemotherapy) of absolute excess risk ranging from 16-35 cases/10,000 person-years.[74] Furthermore, while mediastinal RT appears contributes to the increased cardiac morbidity in HL survivors treated as adults,[59] how this risk interacts with the risk attributable to anthracycline-based chemotherapy has not been well described. How best to monitor the LV function, or even to identify early or subclinical LV dysfunction, in HL survivors needs to be more rigorously investigated if evidence-based screening guidelines are to be developed.

12. Pulmonary toxicity

Beyond the risk of lung cancer (discussed above), therapy for HL has the potential of causing both acute and chronic lung disease. The three most common first-line regimens for HL – ABVD, Stanford V, and BEACOPP – all contain bleomycin, an agent with a well-described association with pneumonitis. Baseline pulmonary function prior to initiation of bleomycin-containing therapy is standard, both to select a group of patients for whom such therapy is inappropriate as well as to establish baselines against which future tests (either routine surveillance in the absence of symptoms or testing to delineate the cause of dyspnea or cough) can be compared. Such complaints are common; as many as 30% of HL survivors will report the symptom of dyspnea during or after treatment.[19] Acute bleomycin pneumonitis is a serious, and potentially life-threatening condition, with mortality rates reported as high as 27%.[75] Patients who experience bleomycin pneumonitis, even when having survived and recovered from the acute episode, are more likely to report chronic fatigue and dyspnea than unaffected patients. Furthermore, when fields include pulmonary parenchyma, radiation therapy can also lead to acute pneumonitis or, later, pulmonary fibrosis, conditions that can compound the damage from bleomycin exposure. Given these

risks, many experts will elect to monitor PFT's serially both during treatment as well as periodically among survivors.

13. Endocrinopathies

Endocrine systems are typically characterized by homeostatic balance supported by positive and negative feedback. The organs involved in such systems may be susceptible to damage or disruption from cytotoxic chemotherapy or ionizing radiation, and indeed survivors of HL are at risk for dysfunction of several hormonal systems. Therapy for HL can be toxic to the thyroid and the gonads, resulting in hypothyroidism and compromised fertility, respectively.

14. Thyroid disease

Hypothyroidism is a potential long-term consequence of radiotherapy involving the thyroid bed. Unlike papillary thyroid cancer, an uncommon late sequela of thyroid irradiation, hypothyroidism is seen in at least half of HL survivors who are more then 10 years from treatment cancer having undergone RT involving the thyroid.[76] Risk factors associated with higher rates of hypothyroidism in HL survivors in addition to dose and field of radiation include female gender, treatment with combined-modality therapy, and duration of time since radiation. [77] There is no consensus on the optimal frequency of thyroid stimulating hormone screening or the value at which to initiate thyroid hormone replacement in the absence of symptomatic hypothyroidism, but treatment with thyroid hormone replacement is routine and effective at minimizing the impact of hypothyroidism.

15. Gonadal dysfunction

Given the epidemiology of the disease, survivors of HL are often young, functional, and potentially fertile.[78] Unfortunately, treatments for HL may lead to temporary infertility, primary gonadal failure (azoospermia or primary ovarian failure), or subfertility (dysspermatogenesis or early onset of menopause). Given high cure rates among patients who will often go on to want to have children, investigators have sought to understand the impact of treatment on fertility, as well as how best to safeguard fertility prospectively. While a full discussion of fertility preservation is beyond the scope of this chapter, choice of chemotherapeutic agents, total dose of chemotherapy, radiation field and dose, and age at treatment are influence the outcomes with regards to fertility. The selection of therapy, including alkylating chemotherapy and pelvic radiation, has the potential to impact fertility in both men and women.[79, 80] In male patients, semen cryopreservation when possible should be encouraged before commencing chemotherapy so as to preserve fertility should azoospermia result from treatment, although some patients will be incapable of banking adequate semen, presumed to be due to the cytokine milieu caused by the underlying lymphoma. While ABVD chemotherapy results in temporary azoospermia in approximately one third of patients, permanent azoospermia is rare. This stands in contrast to more intensified regimen using bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (baseline or escalated BEACOPP), which typically leads to durable azoospermia.[81]

In female patients, risk of infertility or subfertility is thought to be influenced by delivered therapy, intensity of therapy (number of cycles), and perhaps age at treatment. The leading cause of infertility is related to premature ovarian failure as a result of chemotherapy, radiation or combined modality therapy.[82] While egg preservation is commonly discussed at the time of consultation prior to proceeding to definitive treatment, not infrequently the pace of the disease, financial constraints, or patient choice are barriers to fertility preservation for women. For those who have been treated and subsequently attempt natural pregnancy, the data support optimism regarding likelihood of conception. In females who had received ABVD without pelvic radiation therapy and had no evidence of relapsed at three years were surveyed on their experience on fertility. Hodgson et al. found that of those that attempted to become pregnant 70% were successful with a median time to pregnancy of 2 months.[83] Interestingly, in this report the age at diagnosis or the number of cycles of chemotherapy did not demonstrate an increase risk of subfertility compared to controls. Further data is emerging with patients with aggressive disease by prognostic modeling warranting initial intense treatment with BEACOPP, a regimen felt by most to be significantly more pituitary-gonadal axis. Dann et al. [84] reported that in patients younger than 40 with locally unfavorable or advanced HL whom underwent up to 4 cycles of initial BEACOPP therapy an astounding 94% of had preserved cyclic ovarian function. Furthermore, they reported numerous successful pregnancies in this cohort up to 7 years after commencement of BEACOPP. While this data is encouraging egg preservation or other options to facilitate preservation of fertility in an imperative part of the treatment plan. Recent research into ovarian suppression with gonadotropin releasing hormone agonists prior to initiation of chemotherapy has shown promise, with a recent large randomized clinical trial in women with breast cancer showing a statistically significant decrease in rates of amenorrhea 12 months after completion of adjuvant therapy from 26% to 9%.[55] More definitive efforts at preservation of female fertility include cryopreservation of fertilized embryos or, more recently, unfertilized ova elective oophorectomy with cryopreservation and re-implantation after therapy; and transposition of the ovary outside of pelvic radiotherapy fields.[56] For the survivor of HL, however, pre-treatment fertility preservation is something that was, or was not, done, and there are no established interventions to promote or restore fertility in the post-treatment setting. Recently, however, investigations into the use of anti-Müllerian hormone (AMH) levels to predict both the ability to conceive as well as the likelihood of early menopause in cancer survivors, have offered future promise for a more individualized assessment of fertility prospects and guidance regarding family planning.[85]

16. Health related quality of life

In addition to the medical morbidities that survivors of Hodgkin lymphoma may experience due to their disease and its treatment, there exist significant risks as well of impaired quality of life, with fatigue, anxiety and depression, and impaired vocational success having been well described among HL survivors. An understanding of the global well-being of survivors requires incorporation of psychosocial support into the delivered multi-disciplinary care.

Health related quality of life (HRQOL) encompasses a patient's perception of physical, psychological, and social well-being. In a 10-year follow-up of survivors of early stage HL in

Europe, women tended to have a lower HRQOL and higher symptoms scores than did men. Regardless of gender, younger age was associated with higher functioning and lower symptom severity score, and emotional suffering was generally reported to be more severe than physical symptoms.[86] Of note, results in this study did not demonstrate a relationship between type of treatment and HRQOL outcomes. In a study out of the Southwest Oncology Group in the United States, a comparison of HRQOL in patients treated with either EFRT or CMT found persistent fatigue reported by survivors of each treatment modality, but again without differences according to treatment.[87] Effects seem to wane as length of time post-treatment increases; HL survivor 10 years from treatment continue to report lower general health scores, but many specific QOL domains no longer differ between treated patients and age-matched controls.[88, 89]

17. Chronic fatigue

A common theme among investigations into the quality of life of survivors of HL has been the impact of persistent and pervasive fatigue.[86, 87, 90] Chronic fatigue is three times more likely in HL survivors than in age matched controls, and is less likely to be associated with poor mental health than in untreated patients who experience chronic fatigue.[89, 91] Retrospective studies have attempted to characterize pre-existing risk factors that can predict post-treatment chronic fatigue, and reports have implicated B symptoms at diagnosis, social isolation, and presence of treatment-related pulmonary toxicity.[91, 92] The underlying cause of chronic fatigue in HL survivors remains incompletely understood, although ongoing research suggests a link between chronic fatigue in cancer survivors and inappropriate elevation of proinflammatory cytokines.[93-95] At this time, however, the interventions that have been shown to impact chronic fatigue in HL survivors the most favorably are cognitive behavioral therapy and structured aerobic exercise.[96-98]

18. Psychiatric morbidity

An extensive literature exists describing the frequency and severity of psychological and psychiatric morbidity among cancer survivors in general, and recent investigations have attempted to characterize the impact on mental health resulting from diagnosis and treatment of Single-institution data has found that, at a median follow-up of 21 years, 17% of HL survivors reported having being diagnosed with major depression, and of these 90% had been prescribed one or more anti-depressant medications; an additional 12% denied depression but reported significant anxiety in the post-treatment period.[99] In an analysis of survivors of HL in Norway, both anxiety and depression were overrepresented, and risk of mental illness was associated with lower economic status, having received combined-modality therapy (as opposed to radiation alone), and having had a prior history of a psychiatric diagnosis.[100] It appears the peak risk of depression is at 2 years post diagnosis with a gradual decline thereafter, but the risk of depression, anxiety, and post-traumatic stress disorder can be lifelong and requires collaboration with mental health professionals in the delivery of multi-disciplinary care to HL survivors.[101-103]

19. Occupational outcomes

For many patients diagnosed with HL, symptoms from the illness, time for testing and treatment, and the resultant acute and chronic toxicities from therapy can significantly

disrupt careers and limit employment opportunities post-treatment. Several factors including limit the ability to continue working or return to work include disease characteristics at the time of diagnosis (site, stage, treatment, and disease response), patient characteristics (age, gender, comorbidity, socioeconomic status), and work-related factors (physical workload, stress, and social support).[104] Younger patients with good disease control and higher educational attainment are more likely to return to pre-diagnosis socioeconomic stature.[102, 104] Among HL survivors 20 years from treatment, 18% reported that treatment for their HL interfered with their career 11% that it prevented subsequent full-time employment, and 9% that they were incapable even of routinely completing household chores.[99] While employment status in the United States is closely linked to both health and life insurance, HL survivors often suffer a negative impact on their insurance status, even after prolonged remissions.[105] Collectively, these challenges may ultimately disrupt the family support network, but interestingly, despite these challenges HL survivors who were married at the time of diagnosis do not appear to experience higher divorce rates than the general population in either the United States nor the Netherlands, to name but two examples.[102, 106]

20. Future research in the care of survivors

As clinical research in the management of HL continues to develop, with reduction in radiation fields, further limitation of chemotherapy dosages, response-adapted therapy, and possibly eliminating or replacing the most offensive agents in current multi-agent chemotherapeutic programs, opportunities for understanding and discovery in the field of HL survivorship will endure. With the recent FDA approval of brentuximab vedotin in the treatment of relapsed CD30+ HL – the first drug specifically approved for HL – this agent is now be tested earlier in the course of therapy, potentially replacing bleomycin in ABVD.[107] Many additional classes of agents have shown promise in HL, including immunomodulatory agents, histone deacetylase inhibitors, inhibitors of the mammalian target of rapamycin (mTOR), and phosphoinositide-3 kinase (PI3K) inhibitors, to name but four. In this era of rapidly expanding armamentarium of therapeutics, it is imperative that prospective protocols employ thoughtful correlative studies that ask and are powered to answer not only the question regarding acute toxicity, but also late medical morbidity and impact upon quality of life. Also sorely needed are guidelines to aide physicians in monitoring their patients for the myriad late effects associated with therapy – and the data to inform such guidelines. And as HL survival continues to improve (and as oncologists become an increasingly limited resource), models of efficient and effective multi-disciplinary care for survivors of HL need to be developed, tested, and propagated.[108]

21. Conclusion

Survivors of Hodgkin lymphoma represent a unique group of patients who, despite having been cured of an aggressive and life-threatening malignancy, continue to suffer from late medical and psychosocial morbidities associated with their diagnosis, treatment, and the sequelae thereof. Risks of second primary malignancy, cardiovascular disease, pulmonary disease, and endocrine dysfunction are influenced by patient characteristics such as age and gender, and treatment characteristics, such as selected chemotherapy and the inclusion, dose, and field of radiotherapy. Psychosocial challenges appear to be less treatment-

dependent, but represent no less of a challenge to well-being among survivors. As treatments continue to evolve, and as our understanding of these risks – who is at risk, how best to identify or screen for them, and even how best to prevent them – evolves as well, the need will only become greater for evidence-based management guidelines. With the appropriate tools, engaged physicians can become all the more capable of promoting and preserving health among patients with, and survivors of, Hodgkin lymphoma.

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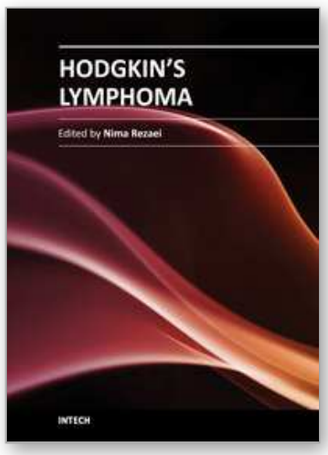
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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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