Long-term survivorship at a price: late-term, therapy-associated toxicities in the adult Hodgkin lymphoma patient

David J. Straus

Abstract: There have been an increasing number of survivors of successful treatment of Hodgkin lymphoma (HL) over the past 30 years. Although these survivors may be cured of their HL, long-term morbidity and mortality are associated with late toxicities of treatment. Identification of these late complications will lead to strategies to manage them when they occur and hopefully to decrease the risk of their development. Second malignancies followed by cardiovascular disease are the leading causes of late morbidity and mortality. Musculoskeletal difficulties, endocrine abnormalities including sterility and thyroid disease, heart and lung damage, persistent fatigue and psychosocial distress have also been seen. The subjects of this review are the late complications of primary treatment of HL and autologous stem cell transplantation, usually for relapsed disease.

Keyword: Hodgkin lymphoma long-term survivorship

Introduction

Cures have been achieved in a significant proportion of patients with Hodgkin lymphoma (HL) for many years. The long-term morbidity and mortality of treatment has become of increasing concern in these patient populations. Guidelines for surveillance to identify late toxicities and to optimize their management as early as possible are necessary. Strategies to minimize late toxicity with modifications of current or new treatments will also be informed by the identification and characterization of these late toxicities. The subject of this review will be the emerging literature on the late morbidity and mortality of patients successfully treated for HL.

Second malignancies

The risks of secondary leukemias and myelodysplastic syndromes have been decreased with the current standard ABVD (i.e. doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy regimen compared with the older alkylating agent-containing chemotherapy regimens of the MOPP (i.e. nitrogen mustard, vincristine, procarbazine, and prednisone) type. In a report of 1659 patients from Italy, the 15-year actuarial risk of acute leukemia was 4.2%. Risk of leukemia after radiation therapy (RT) alone was 0.3%,

2.8% after MOPP-containing regimens, 5.48% after MOPP-containing regimens + RT, and no leukemias were seen after ABVD alone. There were no acute leukemias after the 12th year of follow up [Brusamolino *et al.* 1998]. In a population-based report on registries in Europe and the USA of 35,511 HL survivors, the excess absolute risk of acute leukemia was highest in the first 10 years of follow up, and remained slightly elevated after 15 years [Schonfeld *et al.* 2006]. An increase in acute myeloid leukemias, possibly partly related to etoposide, has been reported at 10 years with the BEACOPP regimen (i.e. bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), in both the standard-dose (1.5%) and escalated (3.0%) versions compared with COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/ABVD (0.4%) [Engert *et al.* 2009].

The rate of second malignancies following RT with or without chemotherapy for HL is approximately 1% per year [Dores *et al.* 2002; Green *et al.* 2000]. Among 18,862 5-year HL survivors in cancer registries from the USA and Europe, the 30-year cumulative relative risks for secondary solid tumors was 18% for women and 30% for men, and the risks of breast and colorectal

Correspondence to:
David J. Straus, MD
Memorial Sloan-Kettering
Cancer Center, 1275 York
Avenue, Box 406, New
York, NY 10065, USA
strausd@mskcc.org

cancers were elevated 10–15 years before the age when routine screening is recommended [Hodgson *et al.* 2007]. The most common second malignancies were breast cancer, gastro-intestinal cancers, lung cancer, thyroid cancer, soft tissue and bone sarcomas, and acute leukemia [Metayer *et al.* 2000; Swerdlow *et al.* 2000; Van Leeuwen *et al.* 2000]. The risk of developing breast cancer following RT increased with length of follow up [Travis *et al.* 2005]. Addition of alkylating agent-containing chemotherapy of the MOPP type seemed to reduce this risk, probably because of effects on the ovaries to reduce estrogen production. The risk was also increased with chest wall radiation with doses above 40 Gy [Travis *et al.* 2003; Van Leeuwen *et al.* 2003]. The size of the RT volume was also important [De Bruin *et al.* 2009]. The risk of breast cancer was higher with full mantle compared with mediastinal irradiation alone. The incidence of poor-prognosis breast cancer may be increased compared with breast cancer with favorable risk factors following RT. The incidence of estrogen receptor-negative/progesterone receptor-negative breast cancer was nine times increased, while that of estrogen receptor-positive/progesterone receptor-positive breast cancer was five times increased after RT [Dores *et al.* 2010]. Despite guidelines that recommend annual mammograms starting approximately 8 years after chest irradiation or at least by age 25 years for pediatric patients, compliance with screening recommendations has been poor [Taylor and Taylor, 2009; Diller *et al.* 2002]. Among solid tumors, only alkylating agent-based regimens are associated with an increased risk of lung cancer [Travis *et al.* 2002]. Second malignancies are the leading cause of late morbidity and mortality [Oeffinger *et al.* 2006; Aleman *et al.* 2003].

Cardiovascular disease

Cardiovascular damage is the second most frequent cause of late mortality and morbidity [Oeffinger *et al.* 2006; Aleman *et al.* 2003], following RT with or without chemotherapy for HL. Carotid stenosis risk is increased after cervical RT, and the relative risk of stroke is increased 5–6 times after mantle RT [Bowers *et al.* 2005; Hull *et al.* 2003].

Overall there appears to be a 3–5 times increased incidence of cardiovascular disease with long follow up of HL survivors treated with RT including the chest alone or chest RT combined with chemotherapy compared with the general population. The diseases seen with increased frequency among 1474 5-year survivors of treatment of HL with a median follow-up time of 18.7 years, reported from the Netherlands, were valvular disorders, angina pectoris, myocardial infarction, and congestive heart failure [Aleman *et al.* 2007]. Significant heart valve abnormalities, presumably related to fibrosis, were found in 42.6% of 47 patients screened with echocardiography who received chest RT for HL at a median of 14.3 years after diagnosis [Adams *et al.* 2004]. In another series, clinically important valvular disease was found in 6% of patients 20 years after receiving RT for HL. Valve replacement surgery was required in 47% of patients with dysfunctional aortic valves and 27% of those with dysfunctional mitral valves [Hull *et al.* 2003]. More subtle abnormalities, such as restrictive cardiomyopathy and conduction abnormalities, have also been reported following mediastinal RT [Adams *et al.* 2004]. Anthracyclines appear to increase the risk of congestive heart failure and valvular disease beyond that seen with mediastinal RT [Aleman *et al.* 2007]. The risk for hospitalization for cardiac events for HL survivors treated with doxorubicin and mediastinal RT may be higher than that for survivors treated with mediastinal RT without doxorubicin [Myrehaug *et al.* 2010]. Recently, a high incidence of coronary artery abnormalities (16%) was reported among survivors of pediatric HL at a median follow-up time of 14 years from diagnosis as determined by computed tomography angiography, a minimally invasive technique that visualizes blood flow and is a candidate to replace conventional angiography. In multivariate analysis patients receiving mediastinal RT to a dose of greater than 20 Gy had a 6.8 times increased risk for coronary artery abnormalities compared with patients who received lower doses or no mediastinal RT [Küpeli *et al.* 2010].

Pulmonary and pericardial abnormalities [Abratt *et al.* 2004], due to fibrosis, are less common late complications of RT for HL with modern radiation therapy techniques.

Musculoskeletal abnormalities

Neck muscle wasting causing difficulty with neck extension ('neck drop') is common following RT to the neck and may cause discomfort [Portlock *et al.* 2003]. In the Childhood Cancer Survival Study (CCSS), an increased rate of osteonecrosis of 6.7, most commonly of the hips followed by the shoulders and knees, was found among

survivors of HL compared with matched siblings, probably related to corticosteroid exposure and RT to the affected joint [Kadan-Lottick *et al.* 2008]. Brachial plexopathies rarely occur as a result of fibrosis but are extremely difficult to manage [Schierle and Winograd, 2004].

Thyroid disease
In the CCSS, the incidence of hypothyroidism 20 years after a diagnosis of HL following neck RT to 3500–4999 cGy was 30% and 50% for patients receiving at least 4500 cGy. There was also an increased rate of hyperthyroidism (relative risk [RR] 8), thyroid nodules (RR 27), especially among females, in the population of adult survivors of childhood HL compared with matched siblings, and the RR of thyroid cancer was 18.3 compared with the general population [Sklar *et al.* 2000]. Secondary hypothyroidism is usually manageable with thyroid replacement therapy.

Fertility
Almost all men will develop azoospermia following alkylating agent-containing chemotherapy such as MOPP, MOPP variants or BEACOPP in both standard and escalated forms of the regimen, and only a minority will have recovery of viable sperm. Up to one third of men treated with ABVD will have transient azoospermia, but most will have full recovery of spermatogenesis [Sieniawski *et al.* 2008; Anselmo *et al.* 1990]. Sperm cryopreservation is recommended in men treated with alkylating agent chemotherapy of the MOPP or BEACOPP type who may wish to have children, although dysspermia prior to treatment was found in 77% of patients with advanced HL in a study of the German Hodgkin Study Group [Sieniawski *et al.* 2008]. In contrast, 90% of men prior to treatment in early stage HL trials conducted by the European Organization for Research and Treatment of Cancer and the Groupe d'Étude des Lymphomes de L'Adulte had good or intermediate sperm quality. B symptoms and elevated erythrocyte sedimentation rate, a surrogate for inflammation, were predictive of poor quality sperm [Van Der Kaaij *et al.* 2009]. Recently, sperm DNA damage was demonstrated for up to 24 months after completion of chemotherapy for HL and testicular cancer. This may lengthen the time in current recommendations that men should not attempt to procreate for 12–18 months after completion of cytotoxic chemotherapy to allow for full sperm recovery and minimize

the risks for adverse reproductive outcomes [O'Flaherty *et al.*, 2010].

Women treated with MOPP or MOPP variants had a cumulative risk of menopause by age 40 years of 48% in a cohort of patients with HL reported from the Netherlands [De Bruin *et al.* 2008]. At a median of 3.2 years following eight cycles of escalated BEACOPP, 51.4% of women had continued amenorrhea [Behringer *et al.* 2005]. In contrast, female fertility is well preserved following ABVD [Brusamolino *et al.* 2006]. There were no differences in pregnancy rates in women attempting to become pregnant between women treated ≥3 years previously with ABVD and normal controls. Use of oral contraceptives may have shortened the length of amenorrhea in women treated with a MOPP variant or BEACOPP [Behringer *et al.* 2005]. The effectiveness of gonadotropin-releasing factor agonists in protecting ovarian function following alkylating agent-containing chemotherapy is controversial [Oktay *et al.* 2009; Blumenfeld *et al.* 2008]. A randomized trial oral contraceptives or a gonadotropin-releasing factor antagonist (goserelin acetate) in women receiving escalated BEACOPP for advanced HL was terminated early because neither treatment resulted in ovarian follicle preservation as measured by anti-Mullerian hormone levels [Behringer *et al.* 2010]. *In vitro* fertilization with cryopreserved embryos has resulted in successful pregnancies following this type of chemotherapy and experimental approaches, such as oocyte or ovarian tissue cryopreservation and implantation, also show promise [Demeestere *et al.* 2007; Meirow *et al.* 2007].

Overall health status in long-term survivors
There are limited data on the overall health status of long-term HL survivors. The CCSS looked at frequencies of chronic conditions in 10,397 survivors of childhood cancer and 3034 siblings [Oeffinger *et al.* 2006]. A severity score was designed based on the Common Terminology Criteria for Adverse Events (version 3), which graded conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). Among 1876 adult survivors of childhood HL, the RR of a grade 3 or 4 chronic ailment was 10.2 (8.3–10.5). The cumulative incidence of a grade 3–5 chronic condition was approximately 40% between 20 and 25 years. Similar results were found in a Dutch retrospective cohort study of 1362 survivors of childhood cancer at a

median follow-up time of 17 years. For all cancers, grade 3 or 4 adverse events were observed in 55% of survivors who received RT only and 15% of survivors treated with chemotherapy only [Geenen *et al.* 2007].

We conducted a survey-based cohort study of patients treated as adults on first-line therapy protocols for HL at our center from 1975 to 2000 [Matasar *et al.* 2009]. The protocols included five combined-modality trials of chemotherapy + RT and one that included a chemotherapy-only arm. Of the 746 patients for whom follow up was available, 519 were alive, and survey data were available for 233 patients. One hundred and seven had died due to HL and 100 due to other causes. Ninety-four per cent of patients reported at least one late morbidity, 48% at least one grade 3–4 morbidity, and 21% at least two grade 3–4 morbidities. The most common late condition was second malignancy followed by cardiovascular disease.

Psychological and quality-of-life issues

We also assessed quality of life, fatigue, fears of recurrence, and mood in our HL survivor population using SF-12, FACIT-fatigue, Fears of Recurrence Questionnaire, and Hospital Anxiety and Depression Scale. A surprisingly high number of responders reported depression (17%), 90% of whom were on psychotropic medications, or anxiety (12%). Approximately one third of the responders rated their quality of life (physical and mental functioning) as fairly low. Over 80% of responders reported fears of recurrence or second cancers [Ford *et al.* 2008].

Improvement of quality of life was found 2 years after completion of treatment for early stage HL treated by the Southwest Oncology Group compared with 1 year following treatment, but fatigue persisted. Follow up of patients treated in EORTC-GELA trials for early stage HL demonstrated that health-related quality of life improved after 3 years with median follow up of 7.5 years, but that higher scores for fatigue following treatment were predictive of subsequent persistent fatigue [Heutte *et al.* 2009]. At a median follow-up time of 16 years following treatment, 30% of HL survivors reported chronic fatigue compared with 11% of the general population [Hjermstad *et al.* 2006]. A role of pro-inflammatory cytokines in cancer-related fatigue has been suggested by studies in breast cancer survivors.

There are less data on the psychological and social status of HL survivors. On the self-reported Brief Symptom Inventory, 22% of HL survivors treated on protocols conducted by the Cancer and Leukemia Group B met criteria for a psychiatric diagnosis [Kornblith *et al.* 1992]. At a median follow-up time of 9 years following treatment, 37% of HL survivors reported an unsatisfactory return of energy (fatigue) that was associated with depression. Moderately high divorce rates (32%), difficulty with fertility (18%), and decreased interest in sexual activity (20%) were also reported [Fobair *et al.* 1986]. HL survivors have also reported difficulties obtaining health and life insurance and loans [Mols *et al.* 2006; Joly *et al.* 1996; Kornblith *et al.* 1992]. On a post-traumatic stress disorder inventory, 32% of 44 HL and non-HL survivors reported two or three of the three defining symptoms: arousal ('reliving' the event that interferes with daily activity), avoidance, and hyper-arousal (distractibility, hypervigilance, outburst of anger, sleep difficulties), similar to a control population exposed to other external emotionally traumatic events [Geffen *et al.* 2003].

There is an emerging literature on interventions for psychological and quality-of-life issues. In a pilot study, a home-based exercise program improved fatigue, physical functioning, and maximal aerobic capacity among nine HL survivors identified with chronic fatigue [Oldervoll *et al.* 2003]. In a randomized trial for lymphoma patients receiving treatment and survivors, a 12-week program of supervised aerobic exercise resulted in improvements in patient-related physical functioning, overall quality of life, happiness, depression, general health, cardiovascular fitness, and lean body mass compared with a matched group who received usual care [Courneya *et al.* 2009]. A systematic and meta-analysis of interventions to relieve cancer-related fatigue in active patients and survivors including 57 randomized controlled trials of psychological interventions *versus* exercise demonstrated that both approaches were effective without significant differences. Multimodal exercise and walking programs, restorative approaches, supportive-expressive, and cognitive-behavioral therapy (CBT) were all helpful in relieving cancer-related fatigue [Kangas *et al.* 2008]. Psychostimulants, most often methylphenidate, have been found to lessen fatigue in patients with active cancer, but data are lacking for long-term cancer survivors [Breitbart and Alici, 2010]. Addition of

CBT to an exercise program did not improve cancer survivors' quality of life or physical activity compared with exercise alone in a randomized trial [May *et al.* 2009]. CBT was also found to improve chemotherapy-related cognitive change ('chemo brain') in long-term breast cancer survivors [Ferguson *et al.* 2007]. Fear of progression was decreased in cancer patients in two inpatient rehabilitation facilities with both brief CBT and supportive-experiential group therapy [Herschbach *et al.* 2010]. Further research on effective interventions for persistent fatigue and psychological and social distress is clearly needed.

Late mortality

Mortality rates for the cohort in our HL database followed a curve with two linear phases, an earlier steep phase representing death due to HL, and a second phase beginning at 6 years postdiagnosis, primarily due to causes other than HL. At 22 years, deaths due to other causes exceeded those due to HL led by second malignancies and cardiovascular events. Similar results were reported for cause-specific survival from two cancer centers in the Netherlands for 1261 patients with HL treated before age 41 years between 1965 and 1987 [Aleman *et al.* 2003]. In that study, deaths from other causes exceeded those due to HL after 20 years from start of treatment. Second malignancies followed by cardiovascular events were also the most common causes of deaths not due to HL.

Limitation of radiation therapy

The causes of late morbidity and mortality were the same, and most have been associated with RT in the literature. In our HL survivor study, this was despite limitations of RT field size and dose by contemporary, although not necessarily by current standards with respect to field size. Long-term follow up of patients with pediatric HL treated with combined-modality therapy of chemotherapy and low-dose RT at Stanford University was recently reported. The doses of RT were 15.0–25.5 Gy extended-field RT with an optional boost of 10 Gy to bulky sites. The cumulative incidence of second malignancies was 17% at 20 years and 29.4% at 30 years, similar to those seen with more standard higher doses [O'Brien *et al.* 2010].

Some data suggest a decreased second malignancy rate with smaller RT fields of treatment. In a cohort study of HL patients treated in five centers in the Netherlands between 1965 and 1995, while the RR of breast cancer was increased 2–8-fold in patients receiving any RT to the mediastinum, there was an additional 2.7-fold higher risk in women who had received full mantle RT compared with women who received only mediastinal RT [De Bruin *et al.* 2009]. Follow-up time was shorter for patients who receive mediastinal RT only than those who received mantle RT, and further follow up will be necessary to see if this difference holds up.

In recent years attempts have been made to decrease toxicity by further reducing the size of RT fields and reducing the number of cycles of chemotherapy. The HD10 study of the German Hodgkin Lymphoma Study Group randomized very favorable stages I and II HL patients with one or two sites of involvement to two or four cycles of ABVD followed by involved-field RT to either 20 or 30 Gy. The 5- and 8-year progression-free survivals were in excess of 90% and similar in all four arms of the study. At a median follow-up time of 7.5 years there was a 4.6% second malignancy rate, with no significant differences between the four arms. Of 57 deaths (4.8%), 10 were due to HL, 11 to second malignancies, 9 to cardiovascular events, and 7 and 5 to toxicities of primary and salvage treatments, respectively [Engert *et al.* 2010]. Little long-term data are available with this approach, but follow up beyond 15 years (median of 10 years) was reported by an Italian group for treatment of IA and IIA nonbulky HL with four cycles of ABVD and limited RT in most patients (extended field 23%, involved field 77%) [Brusamolino *et al.* 2006]. The reported projected 15-year event-free and overall survivals were 78% and 86%, respectively. However, even with limited treatment, the 5- and 12-year risks of second malignancies were 4% and 8%, and for cardiovascular events, 5.5% and 14%. This is a cause for concern regarding involved-field RT in combined-modality programs for early stage HL, although current involved fields may be even more limited than those employed in the past. Further follow up of more contemporary combined-modality programs will be necessary to see if late toxicities will be reduced [Sieniawski *et al.* 2007].

Autologous stem cell transplantation

Extensive discussion of the late results with autologous stem cell transplantation (auSCT) is beyond the scope of this review. However, a few

observations seem relevant. In the Bone Marrow Transplant Survivor Study (BMT-SS), late mortality was assessed in 854 patients who survived 2 years or more following auSCT for hematologic malignancies. Median follow-up time was 7.6 years. Relapse of primary disease was the cause of late death in 56%, second malignancies in 25%, cardiac toxicity in 6%, pulmonary complications in 5%, and other causes in 13.5%. Acute myelocytic leukemia (AML)/myelodysplastic syndrome (MDS) accounted for 65% of the late deaths due to second malignancies [Bhatia *et al.* 2005].

The prevalence of self-reported late effects among survivors was also investigated in the BMT-SS. Compared with siblings, at a median follow-up time of 6 years, survivors of auSCT reported a significantly higher frequency of cataracts, dry mouth, hypothyroidism, osteoporosis/avascular bone necrosis, congestive heart failure, dyspnea with exertion, neurosensory impairments, inability to attend school or work, and poor overall health. Females reported significantly higher frequencies of osteoporosis, congestive heart failure, and neurologic conditions. Patients who had received total body irradiation (TBI) as part of their conditioning regimen reported significantly higher frequencies of cataracts and dry mouth [Majhail *et al.* 2007]. In the European Bone Marrow Transplant registry, 9% of 693 patients developed a second malignancy of 7 years following auSCT for follicular B-cell lymphoma. AML/MDS accounted for 39 out of 64 (61%) of these second malignancies, and 34 of the 39 had received TBI as part of the conditioning regimen. The overall survival of patients who received TBI was significantly shorter after 5 years than those who did not receive TBI [Montoto *et al.* 2007].

Tentative recommendations for follow up
A truly data-derived set of follow-up guidelines awaits further analysis of studies such as ours on the overall outcome of long-term HL survivors. Guidelines for follow up of HL patients in our clinic are consistent with the National Comprehensive Cancer Network (NCCN) *Practice Guidelines in Oncology* v.2.2010 for HL (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). The same schedule is used for patients after primary treatment and after auSCT. We generally see patients every 3–4 months for the first year after completion of treatment, every 4–6 months for the second and third years, and every 6 months for the fourth and fifth years with either computed tomography or chest X-ray imaging, complete blood count, blood chemistries, erythrocyte sedimentation rate, thyroid-stimulating hormone and free thyroxine levels in patients who received neck irradiation. Since late effects of treatment as well as relapses are rare after 5 years for patients treated with chemotherapy only, we feel that these patients can be safely referred back to their primary care physicians after 5 years of follow up. We continue to follow the patients who received RT annually after 5 years with blood studies and chest X-ray. We start annual mammograms at 8–10 years or age 40 years, whichever comes first, in women who received mediastinal irradiation. We consider breast magnetic resonance imaging if clinically appropriate (women who receive mediastinal irradiation between ages 10 and 30 years). After 10 years of follow up, we have recently also begun to obtain carotid ultrasound for patients who received neck irradiation and coronary artery screening with stress testing, often with a nuclear medicine myocardial perfusion scan, for patients who received mediastinal RT. We also encourage aggressive management of hyperlipidemia and hypertension for these individuals.

Conclusion
Late complications related to treatment are an increasingly recognized problem as follow up increases of patients cured of their HL. Second malignancies and cardiovascular events are the most frequent causes of late serious morbidity and mortality, and are mostly associated with RT. Cardiomyopathies with anthracycline use and sterility and MDS/AML with alkylating agents and etoposide are the major problems seen with chemotherapy. Bone wasting also seems to be increased in older patients receiving chemotherapy. Late effects of treatment on quality of life and psychosocial functioning have also been recently identified. Use of less-toxic therapies, in particular limitation of the use of RT, may make a major contribution to reducing late morbidity and mortality of lymphoma survivors. Further research into the overall health status and quality of life of lymphoma survivors is necessary. Guidelines for follow up of HL survivors should be developed on the basis of real comprehensive data along with strategies to address preemptively anticipated potential medical and psycho-social problems.

Conflicts of Interest Statement

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References

Abratt, R.P., Morgan, G.W., Silvestri, G. and Willcox, P. (2004) Pulmonary complications of radiation therapy. *Clin Chest Med* 25: 167–177.

Adams, M.J., Lipsitz, S.R., Colan, S.D., Tarbell, N.J., Treves, S.T., Diller, L. *et al.* (2004) Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol* 22: 3139–3148.

Aleman, B.M., Van Den Belt-Dusebout, A.W., De Bruin, M.L., Van't Veer, M.B., Baaijens, M.H., De Boer, J.P. *et al.* (2007) Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 109: 1878–1886.

Aleman, B.M., Van Den Belt-Dusebout, A.W., Klokman, W.J., Van't Veer, M.B., Bartelink, H. and Van Leeuwen, F.E. (2003) Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 21: 3431–3439.

Anselmo, A.P., Cartoni, C., Bellantuono, P., Maurizi-Enrici, R., Aboulkair, N. and Ermini, M. (1990) Risk of infertility in patients with Hodgkin's disease treated with ABVD vs MOPP vs ABVD/MOPP. *Haematologica* 75: 155–158.

Behringer, K., Breuer, K., Reineke, T., May, M., Nogova, L., Klimm, B. *et al.* (2005) Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: A report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 23: 7555–7564.

Behringer, K., Wildt, L., Mueller, H., Mattle, V., Ganitis, P., Van Den Hoonaard, B. *et al.* (2010) No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a Phase II Trial from the German Hodgkin Study Group. *Ann Oncol* 21: 2052–2060.

Bhatia, S., Robison, L.L., Francisco, L., Carter, A., Liu, Y., Grant, M. *et al.* (2005) Late mortality in survivors of autologous hematopoietic-cell transplantation: Report from the Bone Marrow Transplant Survivor Study. *Blood* 105: 4215–4222.

Blumenfeld, Z., Avivi, I., Eckman, A., Epelbaum, R., Rowe, J.M. and Dann, E.J. (2008) Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. *Fertil Steril* 89: 166–173.

Bowers, D.C., McNeil, D.E., Liu, Y., Yasui, Y., Stovall, M., Gurney, J.G. *et al.* (2005) Stroke as a late treatment effect of Hodgkin's Disease: A Report from the Childhood Cancer Survivor Study. *J Clin Oncol* 23: 6508–6515.

Breitbart, W. and Alici, Y. (2010) Psychostimulants for cancer-related fatigue. *J Natl Compr Canc Netw* 8: 933–942.

Brusamolino, E., Anselmo, A.P., Klersy, C., Santoro, M., Orlandi, E., Pagnucco, G. *et al.* (1998) The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher aft [see bined modality programs than after chemotherapy alone and is correlated with the extent of radiotherapy and type and duration of chemotherapy: A case-control study. *Haematologica* 83: 812–823.

Brusamolino, E., Baio, A., Orlandi, E., Arcaini, L., Passamonti, F., Griva, V. *et al.* (2006) Long-term events in adult patients with clinical stage Ia-IIa nonbulky Hodgkin's lymphoma treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and adjuvant radiotherapy: A single-institution 15-year follow-up. *Clin Cancer Res* 12: 6487–6493.

Courneya, K.S., Sellar, C.M., Stevinson, C., McNeely, M.L., Peddle, C.J., Friedenreich, C.M. *et al.* (2009) Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol* 27: 4605–4612.

De Bruin, M.L., Huisbrink, J., Hauptmann, M., Kuenen, M.A., Ouwens, G.M., Van't Veer, M.B. *et al.* (2008) Treatment-related risk factors for premature menopause following Hodgkin lymphoma. *Blood* 111: 101–108.

De Bruin, M.L., Sparidans, J., Van't Veer, M.B., Noordijk, E.M., Louwman, M.W., Zijlstra, J.M. *et al.* (2009) Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. *J Clin Oncol* 27: 4239–4246.

Demeestere, I., Simon, P., Emiliani, S., Delbaere, A. and Englert, Y. (2007) Fertility preservation: Successful transplantation of cryopreserved ovarian tissue in a young patient previously treated for Hodgkin's disease. *Oncologist* 12: 1437–1442.

Diller, L., Medeiros Nancarrow, C., Shaffer, K., Matulonis, U., Mauch, P., Neuberg, D. *et al.* (2002) Breast cancer screening in women previously treated for Hodgkin's disease: A prospective cohort study. *J Clin Oncol* 20: 2085–2091.

Dores, G.M., Anderson, W.F., Beane Freeman, L.E., Fraumeni Jr, J.F. and Curtis, R.E. (2010) Risk of breast cancer according to clinicopathologic features among long-term survivors of Hodgkin's lymphoma treated with radiotherapy. *Br J Cancer* 103: 1081–1084.

Dores, G.M., Metayer, C., Curtis, R.E., Lynch, C.F., Clarke, E.A., Glimelius, B. *et al.* (2002) Second malignant neoplasms among long-term survivors of Hodgkin's disease: A population-based evaluation over 25 years. *J Clin Oncol* 20: 3484–3494.

Engert, A., Diehl, V., Franklin, J., Lohri, A., Dorken, B., Ludwig, W.D. *et al.* (2009) Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 Years of follow-up of the GHSG HD9 study. *J Clin Oncol* 27: 4548–4554.

Engert, A., Plutschow, A., Eich, H.T., Lohri, A., Dorken, B., Borchmann, P. *et al.* (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 363: 640–652.

Ferguson, R.J., Ahles, T.A., Saykin, A.J., McDonald, B.C., Furstenberg, C.T., Cole, B.F. *et al.* (2007) Cognitive-behavioral management of chemotherapy-related cognitive change. *Psychooncology* 16: 772–777.

Fobair, P., Hoppe, R.T. and Bloom, J. (1986) Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol* 4: 805–814.

Ford, J.S., Schwartz, J., McCallen, L.N., Matasar, M.J., Butos, J.N., Reidel, E.R. *et al.* (2008) Psychosocial functioning in survivors of Hodgkin lymphoma (Hl) treated during adulthood. *J Clin Oncol* 26(Suppl): abstract 9592.

Geenen, M.M., Cardous-Ubbink, M.C., Kremer, L.C., Van Den Bos, C., Van Der Pal, H.J., Heinen, R.C. *et al.* (2007) Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 297: 2705–2715.

Geffen, D.B., Blaustein, A., Amir, M. and Cohen, Y. (2003) Post-traumatic stress disorder and quality of life in long-term survivors of hodgkin's disease and non-Hodgkin's lymphoma in Israel. *Leuk Lymphoma* 44: 1925–1929.

Green, D.M., Hyland, A., Barcos, M.P., Reynolds, J.A., Lee, R.J., Hall, B.C. *et al.* (2000) Second malignant neoplasms after treatment for Hodgkin's disease in childhood or adolescence. *J Clin Oncol* 18: 1492–1499.

Herschbach, P., Book, K., Dinkel, A., Berg, P., Waadt, S., Duran, G. *et al.* (2010) Evaluation of two group therapies to reduce fear of progression in cancer patients. *Supportive Care Cancer* 18: 471–479.

Heutte, N., Flechtner, H.H., Mounier, N., Mellink, W.A., Meerwaldt, J.H., Eghbali, H. *et al.* (2009) Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10-year follow-up of the EORTC-GELA H8 randomised controlled trial. *Lancet Oncol* 10: 1160–1170.

Hjermstad, M.J., Oldervoll, L., Fosså, S.D., Holte, H., Jacobsen, A.B. and Loge, J.H. (2006) Quality of life in long-term Hodgkin's disease survivors with chronic fatigue. *Eur J Cancer* 42: 327–333.

Hodgson, D.C., Gilbert, E.S., Dores, G.M., Schonfeld, S.J., Lynch, C.F., Storm, H. *et al.* (2007) Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol* 25: 1489–1497.

Hull, M.C., Morris, C.G., Pepine, C.J. and Mendenhall, N.P. (2003) Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA* 290: 2831–2837.

Joly, F., Henry-Amar, M., Arveux, P., Reman, O., Tanguy, A., Peny, A.M. *et al.* (1996) Late psychosocial sequelae in Hodgkin's disease survivors: A French population-based case-control study. *J Clin Oncol* 14: 2444–2453.

Kadan-Lottick, N.S., Dinu, I., Wasilewski-Masker, K., Kaste, S., Meacham, L.R., Mahajan, A. *et al.* (2008) Osteonecrosis in adult survivors of childhood cancer: A Report from the Childhood Cancer Survivor Study. *J Clin Oncol* 26: 3038–3045.

Kangas, M., Bovbjerg, D.H. and Montgomery, G.H. (2008) Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull* 134: 700–741.

Kornblith, A.B., Anderson, J., Cella, D.F., Tross, S., Zuckerman, E., Cherin, E. *et al.* (1992) Hodgkin disease survivors at increased risk for problems in psychosocial adaptation. *Cancer* 70: 2214–2224.

Küpeli, S., Hazirolan, T., Varan, A., Akata, D., Alehan, D., Hayran, M. *et al.* (2010) Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. *J Clin Oncol* 28: 1025–1030.

Majhail, N.S., Ness, K.K., Burns, L.J., Sun, C.L., Carter, A., Francisco, L. *et al.* (2007) Late effects in survivors of Hodgkin and non-Hodgkin lymphoma treated with autologous hematopoietic cell transplantation: A report from the Bone Marrow Transplant Survivor Study. *Biol Blood Marrow Transplant* 13: 1153–1159.

Matasar, M.J., McCallen, L.N., Reidel, E.R., Ford, J.S., Oeffinger, K.S. and Straus, D. (2009) Late mortality and morbidity of patients with Hodgkin lymphoma treated in adulthood. *J Clin Oncol* 27(Suppl): abstract 8547.

May, A.M., Korstjens, I., Van Weert, E., Van Den Borne, B., Hoekstra-Weebers, J.E.H.M., Van Der Schans, C.P. *et al.* (2009) Long-term effects on cancer survivors' quality of life of physical training versus physical training combined with cognitive-behavioral therapy: Results from a randomized trial. *Supportive Care Cancer* 17: 653–663.

Meirow, D., Baum, M., Yaron, R., Levron, J., Hardan, I., Schiff, E. *et al.* (2007) Ovarian tissue cryopreservation in hematologic malignancy: Ten years' experience. *Leuk Lymphoma* 48: 1569–1576.

Metayer, C., Lynch, C.F., Clarke, E.A., Glimelius, B., Storm, H., Pukkala, E. *et al.* (2000) Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol* 18: 2435–2443.

Mols, F., Vingerhoets, A.J.J.M., Coebergh, J.W., Vreugdenhil, G., Aaronson, N.K., Lybeert, M.L.M. *et al.* (2006) Better quality of life among 10-15 year survivors of Hodgkin's lymphoma compared to 5-9 year survivors: A population-based study. *Eur J Cancer* 42: 2794–2801.

Montoto, S., Canals, C., Rohatiner, A.Z., Taghipour, G., Sureda, A., Schmitz, N. *et al.* (2007) Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: An EBMT Registry Study. *Leukemia* 21: 2324–2331.

Myrehaug, S., Pintilie, M., Yun, L., Crump, M., Tsang, R.W., Meyer, R.M. *et al.* (2010) A population-based study of cardiac morbidity among Hodgkin lymphoma patients with preexisting heart disease. *Blood* 116: 2237–2240.

O'Brien, M.M., Donaldson, S.S., Balise, R.R., Whittemore, A.S. and Link, M.P. (2010) Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. *J Clin Oncology* 28: 1232–1239.

Oeffinger, K.C., Mertens, A.C., Sklar, C.A., Kawashima, T., Hudson, M.M., Meadows, A.T. *et al.* (2006) Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 355: 1572–1582.

O'Flaherty, C., Hales, B.F., Chan, P. and Robaire, B. (2010) Impact of chemotherapeutics and advanced testicular cancer or Hodgkin lymphoma on sperm deoxyribonucleic acid integrity. *Fertil Steril* 94: 1374–1379.

Oktay, K., Sonmezer, M., Barad, D. and Gleicher, N. (2009) Trying to reduce ovarian damage in patients with hodgkin lymphoma using gnrh agonists? *Fertil Steril* 91: 298–299.

Oldervoll, L.M., Kaasa, S., Knobel, H. and Loge, J.H. (2003) Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors − results from a pilot study. *Eur J Cancer* 39: 57–63.

Portlock, C.S., Boland, P., Hays, A.P., Antonescu, C.R. and Rosenblum, M.K. (2003) Nemaline myopathy: A possible late complication of Hodgkin's disease therapy. *Hum Pathol* 34: 816–818.

Schierle, C. and Winograd, J.M. (2004) Radiation-induced brachial plexopathy: Review. Complication without a cure. *J Reconstr Microsurg* 20: 149–152.

Schonfeld, S.J., Gilbert, E.S., Dores, G.M., Lynch, C.F., Hodgson, D.C., Hall, P. *et al.* (2006) Acute myeloid leukemia following Hodgkin lymphoma: A population-based study of 35,511 patients. *J Natl Cancer Inst* 98: 215–218.

Sieniawski, M., Franklin, J., Nogova, L., Glossmann, J.-P., Schober, T., Nisters-Backes, H. *et al.* (2007) Outcome of patients experiencing progression or relapse after primary treatment with two cycles of chemotherapy and radiotherapy for early-stage favorable Hodgkin's lymphoma. *J Clin Oncol* 25: 2000–2005.

Sieniawski, M., Reineke, T., Nogova, L., Josting, A., Pfistner, B., Diehl, V. *et al.* (2008) Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: A report of the German Hodgkin Study Group (GHSG). *Blood* 111: 71–76.

Sklar, C., Whitton, J., Mertens, A., Stovall, M., Green, D., Marina, N. *et al.* (2000) Abnormalities of the thyroid in survivors of Hodgkin's disease: Data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 85: 3227–3232.

Swerdlow, A.J., Barber, J.A., Hudson, G.V., Cunningham, D., Gupta, R.K., Hancock, B.W. *et al.* (2000) Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: The relation to age at treatment. *J Clin Oncol* 18: 498–509.

Taylor, A.J. and Taylor, R.E. (2009) Surveillance for breast cancer after childhood cancer. *JAMA* 301: 435–436.

Travis, L.B., Gospodarowicz, M., Curtis, R.E., Clarke, E.A., Andersson, M., Glimelius, B. *et al.* (2002) Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 94: 182–192.

Travis, L.B., Hill, D.A., Dores, G.M., Gospodarowicz, M., Van Leeuwen, F.E., Holowaty, E. *et al.* (2003) Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 290: 465–475.

Travis, L.B., Hill, D., Dores, G.M., Gospodarowicz, M., Van Leeuwen, F.E., Holowaty, E. *et al.* (2005) Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 97: 1428–1437.

Van Der Kaaij, M.A.E., Heutte, N., Van Echten-Arends, J., Raemaekers, J.M.M., Carde, P., Noordijk, E.M. *et al.* (2009) Sperm quality before treatment in patients with early stage Hodgkin's lymphoma enrolled in EORTC-GELA Lymphoma Group Trials. *Haematologica* 94: 1691–1697.

Van Leeuwen, F.E., Klokman, W.J., Stovall, M., Dahler, E.C., Van't Veer, M.B., Noordijk, E.M. *et al.* (2003) Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst* 95: 971–980.

Van Leeuwen, F.E., Klokman, W.J., Veer, M.B., Hagenbeek, A., Krol, A.D., Vetter, U.A. *et al.* (2000) Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol* 18: 487–497.