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Scientific Article

Does the Incidence of Treatment-Related Toxicity Plateau After Radiation Therapy: The Long-Term Impact of Integral Dose in Hodgkin's Lymphoma Survivors

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Abstract

Background: Conventional radiation therapy (RT) has produced unprecedented cure rates in patients with Hodgkin's lymphoma (HL) but exposed large volumes of nontargeted tissue to radiation (integral dose).

Objective: Our goal was to report the effects of integral radiation dose on health outcomes in patients with at least 20 years of potential follow-up time.

Methods and Materials: We reviewed the medical records of 365 patients who were treated with RT for HL between 1965 and 1995. All patients were confirmed to have received primary RT with curative intent at our institution for de novo HL. Serious adverse events were classified as HL progression or death, grade $\geq$3 treatment- or staging-related acute or late effects, second malignancies, or cardiovascular events.

Results: The minimum potential follow-up time was 20 years, and the actual median follow-up time 22 years (range, <1-49 years) for all patients and 27 years (range, 5-49 years) for surviving patients. The overall survival rates at 5, 10, 20, 30, and 40 years were 86%, 76%, 64%, 44%, and 27%, respectively. The observed-to-expected ratio for second malignancy was 3.6 (95% confidence interval, 2.9-4.4). Grade $\geq$3 cardiovascular events occurred in 31% of all patients (n = 112). At the time of the most recent follow up, serious adverse events occurred in 70% of the entire cohort (n = 256) and 58% (n = 103), 77% (n = 103), and 93% (n = 50) among those with a potential 20, 30, and 40 years of follow up, respectively.

Conclusions: With increased survivorship, the long-term impact of the integral radiation dose may result in clinically significant adverse events, which suggests the importance of surveillance and affirms advances in both chemotherapy and RT that minimize the integral dose in future patients with HL.

Disclosures: Dr. Bradford S. Hoppe is a scientific consultant for Merck & Co., Inc, and Bristol-Myers Squibb.

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Introduction

With a 10-year survival rate that exceeds 80%, patients treated for Hodgkin's lymphoma (HL) are well suited for the study of late toxicities of oncologic intervention.[1] Historically, conventional x-ray-based radiation therapy (RT) with or without adjuvant chemotherapy has been delivered in moderate-to-high radiation doses to clinically involved areas and complementary fields at risk for subclinical disease.[2] With only 2-dimensional imaging to delineate targets and verify treatment-targeting accuracy, treatment fields were generous to avoid geographic or marginal misses. Furthermore, x-ray–based therapy resulted in substantial entrance and exit doses beyond the targeted areas. These factors led to the deposition of substantial, low-to-moderate, integral radiation doses in nontargeted tissues compared with modern radiation techniques that use 3-dimensional imaging for target definition, daily image guided treatment delivery, and conformal radiation techniques that redistribute or reduce the radiation dose to nontargeted tissues.

With increasing survivorship, the late effects of these early treatment successes have emerged and include an increased risk of secondary malignancies and cardiovascular morbidity.[3-19] The purpose of this paper is to review the long-term outcomes of patients with at least 20 years of minimum potential follow-up time after RT for HL.

Methods and Materials

With institutional review board approval, our study population included 365 patients who were evaluated at the University of Florida (Gainesville) for RT for HL between 1965 and 1995, and received primary RT with curative intent for de novo HL. Patient and tumor characteristics are shown in Table 1. Data were collected from patient medical records, and direct contact was made with survivors within 12 months of the analysis when feasible.

A total of 122 patients were alive and without evidence of disease at the time of the analysis, and 32 patients were alive and without evidence of disease before being lost to follow up. The remaining 211 patients were deceased. The minimum potential follow-up time was 20 years, and the actual median follow up 22 years (range, <1-49 years) for all patients and 27 years (range, 5-49 years) for surviving patients. The median age at the time of the initial RT was 25 years (range, 3-82 years).

^{60}Co gamma ray teletherapy 2-dimensional planning and delivery techniques were used in this group of patients until 1978; thereafter, patients increasingly were treated with linear accelerators until 1995 when linear accelerators were used exclusively. Three-dimensional imaging was introduced in 1984. Some patients received involved-field RT (IFRT), which was defined as all lymph nodes within the same region as the clinically involved node, but most patients received extended-field RT (EFRT), subtotal irradiation (STNI), or total nodal irradiation (TNI), which included involved nodes plus clinically uninvolved contiguous nodal regions. STNI involved a mantle field (including the neck, supraclavicular fossae, axillae, and mediastinum), the spleen or splenic pedicle, and paraaortic nodes. TNI additionally included the pelvic nodes.

The treatment volumes were IFRT, EFRT, mantle, STNI, and TNI in 11, 25, 34, 149, and 146 patients, respectively. Overall, 160 patients received RT alone; 205 received either adjuvant chemotherapy (3-6 cycles of mustargen, oncovin, procarbazine, and prednisone or adriamycin, bleomycin, vinblastine, and dacarbazine) or salvage chemotherapy for recurrence after RT. Acute treatment toxicities were recorded and graded using the Common Terminology Criteria for Adverse Events, version 3.[20] Causes of death were classified as related to disease, treatment, or staging for HL; second malignancy; cardiovascular late toxicity; pulmonary late toxicity; or intercurrent disease not known to be related to either HL or treatment for HL.

Disease progression, second malignancies, and other late effects were classified as in field (within RT volume), marginal (within 5 cm of RT volume), or out of field. Cardiovascular disease was defined as coronary artery disease (CAD), which included myocardial infarction; coronary artery bypass graft surgery; percutaneous coronary intervention; or >75% stenosis on coronary angiogram or autopsy, cardiomyopathy, or valvular heart disease. Clinically significant valve dysfunction was defined as moderate or severe stenosis or insufficiency on echo- or angiogram or dysfunction resulting in surgical repair. The only noncoronary atherosclerotic disease included was >40% stenosis of the carotid or clinical outcomes, such as transient ischemic attack or stroke. Otherwise, noncarotid atherosclerotic disease included >40% stenosis of the subclavian, renal, or celiac arteries by ultrasound or angiogram; vascular surgery on the involved vessel; or clinical outcomes, such as subclavian steal syndrome or renal atrophy. Nonmalignant thyroid disease was defined as clinical hypothyroidism that required pharmacologic replacement or multinodular thyroid requiring resection.

Serious adverse events (SAEs) were classified as HL progression or death, grade ≥3 treatment- or staging-related acute or late effects, second malignancies, or cardiovascular events. Overall survival (OS) counted death from any cause; cause-specific survival (CSS) counted deaths from HL or SAEs related to treatment or staging; and progression-free survival (PFS) counted only HL progression. The expected incidence of relevant outcomes in the general population was obtained from the Surveillance, Epidemiology, and End Results (SEER) database.

Table 1 Patient and tumor characteristics of 365 patients with Hodgkin's lymphoma treated with definitive radiation therapy

Characteristics	No. of patients
Ann Arbor stage at initial treatment	
I	93
II	152
III	95
IV	25
Systemic B symptoms	
Yes	88
No	277
Histology	
Mixed cellularity	76
Nodular sclerosis	232
Lymphocyte predominant	24
Lymphocyte depleted	4
Hodgkin's lymphoma unclassified*	29
Sex	
Male	220
Female	145

* No specific histologic subtype assigned.

Most statistical computations were performed using SAS and JMP software (SAS Institute, Cary, NC). The Kaplan-Meier product limit method was used to estimate OS, PFS, and CSS. The observed-to-expected ratio (OER) was the observed number of malignancies in this sample, divided by the sex- and age-stratified expected values. Available person-years of follow up for each patient were distributed into both sex and 5-year age bins. Subsequently, an expected value for each bin was attained by multiplying the total person-years by the corresponding malignancy rate in the general U.S. population.

The overall expected value was the summation of these sex- and age-stratified values (Surveillance Research Program, National Cancer Institute SEERStat software, version 7.1.0, Bethesda, MD). Fisher exact test was used to construct confidence intervals (CIs) for the resulting OER via the OpenEpi online calculator. The multivariate analysis was conducted evaluating the following 3 covariates: age at RT (<30 years; >30 years), received chemotherapy (yes/no), and field size (TNI vs EFRT/STNI vs mantle/IFRT).

Results

Patient outcomes

Figure 1 shows the OS, PFS, and CSS survival curves. The OS rates at 5, 10, 20, 30, and 40 years were 86% (95% CI, 81.8%-89.0%), 76% (95% CI, 70.8%-80.0%), 64% (95% CI, 58.8%-68.8%), 44% (95% CI, 38.1%-49.6%), and 27% (95% CI, 21.0%-34.3%), respectively, with 154 patients (42%) still alive at the time of the analysis. The causes of death were HL (n = 40) and acute complications of treatment (n = 14, including 6 patients with persistent HL at the time of the complication). Grade 5 acute events included infection (n = 8), pneumonitis (n = 3), pancytopenia (n = 2; both patients received chemotherapy), and stroke (n = 1).

All patients who died of infection had either chemotherapy or splenectomy, and both patients who died of pancytopenia received chemotherapy. Thirty-one percent of deaths (n = 49) were from a second malignancy, 27% (n = 42) from cardiovascular disease, 15% (n = 23) from unknown causes, 5% (n = 8) from pulmonary disease, 8% (n = 13) from infection, 4% (n = 7) from myelodysplatic syndrome or bone marrow failure, 3% (n = 5) from traumatic injury, 5% (n = 8) from comorbid disease, and 1% from myelitis (n = 1) or renal disease (n = 1).

Patterns of recurrence

Initial treatment failed to control disease in 24% of patients (n = 86), and most patients had either marginal misses or distant progression (74%). Forty-nine percent of patients with HL progression (n = 42) ultimately died of HL. One-quarter of patients with disease progression required >1 salvage regimen, but more than one-half with HL progression were eventually salvaged.

Chemotherapy was delivered as a component of salvage therapy in 77% of patients with disease progression (n = 66). The rate of treatment failure within the first 1, 2, 5, and 10 years were 33%, 54%, 79%, and 93%, respectively.

Serious adverse events

At the time of the most recent follow up, SAEs had occurred in 70% of the cohort (n = 256) and in 58% (n = 103), 77% (n = 103), and 93% (n = 50) of those with a potential 20, 30, and 40 years of follow up, respectively.

Acute toxicity

There were 16 grade 4 SAEs, including thrombocytopenia (n = 8), pulmonary embolism (n = 3), infection (n = 2), myelitis resulting in paraplegia (n = 1), leukopenia (n = 1), and pericarditis (n = 1). There were 34 grade 3 toxicities, including leukopenia (n = 14), thrombocytopenia (n = 6), nausea or emesis (n = 6), pneumonitis (n = 3), myelitis (n = 1), dysphagia (n = 1), skin necrosis (n = 1), pericarditis (n = 1), and anemia (n = 1). Two patients had a fetal abortion, which is not characterized by the Common Terminology Criteria for Adverse Events, version 3.

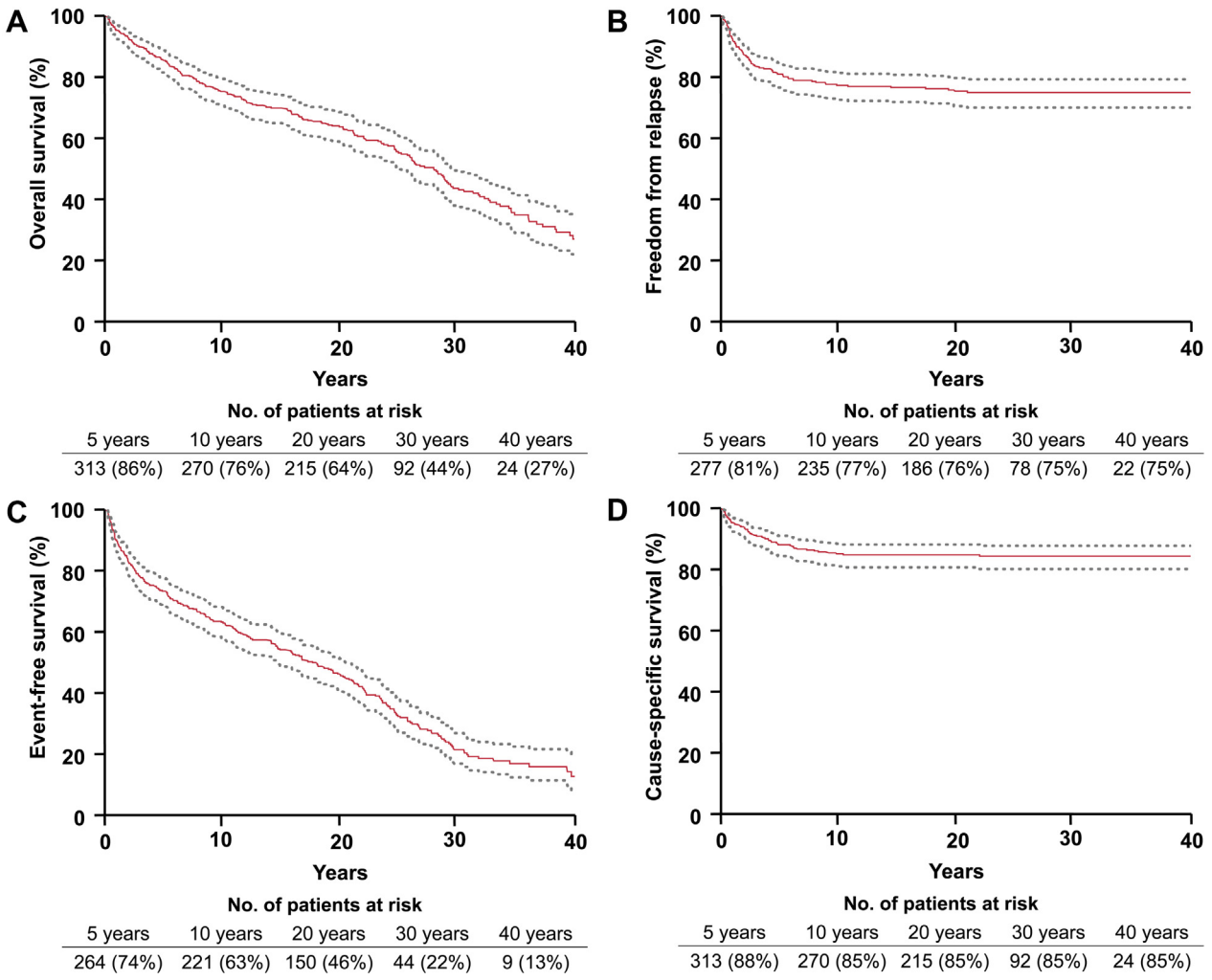

Figure 1 Kaplan-Meier curves for 365 patients with 95% confidence intervals shown as dotted lines: (A) Overall survival, (B) freedom from relapse, (C) event-free survival, and (D) cause-specific survival.

Second malignancy

A total of 113 malignancies occurred in 89 patients, causing 49 deaths. Figure 2A shows the rates of freedom from second malignancy. The incidence of second malignancy in our study group was 89 cases in 7561 age- and sex-stratified patient-years, resulting in an OER of 3.6 (95% CI, 2.9-4.4; $P < .001$). The second malignancy rates at 20, 30, and 40 years were 17% (95% CI, 13%-22%), 34% (95% CI, 28%-41%), and 49% (95% CI, 39%-58%), respectively, with a median latency to the first malignancy of 20 years (range, 1-49 years). The median age at the start of RT was 25 years (range, 4-70 years), and at the time of diagnosis of the second malignancy 49 years (range, 21-82 years).

The most frequent in-field malignancy (excluding nonmelanomatous skin cancer) was breast cancer, with 30 cases of invasive breast cancers and 5 of ductal carcinoma in situ occurring in 26 patients at a median latency time to the first breast cancer diagnosis of 22 years (range, 11-40 years). Among patients who developed secondary breast cancers, the median age at the time of RT for HL was 20 years (range, 11-52 years). Six patients died of breast cancer during the study period. None of the 6 women who died of breast cancer were followed at our clinic or had routine mammographic screening; however, all who were followed at our clinic had routine breast cancer screening, and those who developed breast cancer were diagnosed with node-negative disease and treated successfully. The OER for breast cancer for patients age <30 years was 11.9 (range, 6.7-17.1; $P < .0001$) and 2.4 (range, 0.3-4.4; $P = .128$) for those age >30 years.

Lung cancer was noted in 14 patients. The smoking history was unknown in 4 patients, negative in 3 patients, and >15 pack-years in 7 patients. The OER for lung cancer was 4.0 (95% CI, 1.9-6.1; $P < .001$). All 14 patients died of lung cancer.

Eight patients (2%) developed acute myelocytic leukemia, and all had received chemotherapy, constituting a

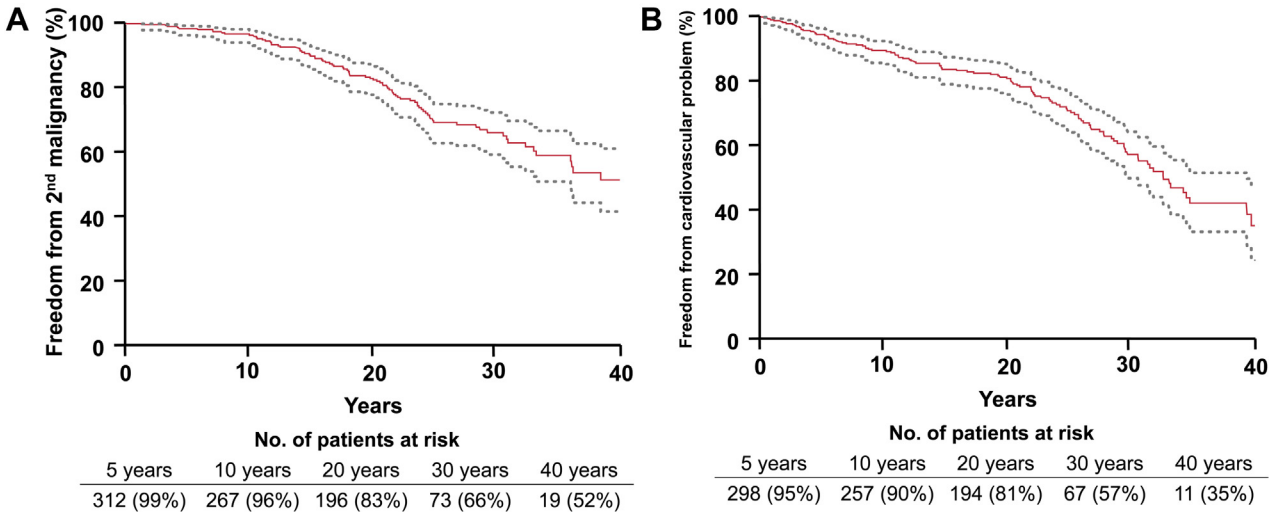

Figure 2 Kaplan-Meier curves with 95% confidence intervals shown as dotted lines for (A) freedom from second malignancy and (B) freedom from grade ≥3 cardiovascular toxicity.

4% rate of leukemia in patients treated with combined RT and chemotherapy. All 8 patients expired. No patient who received RT alone developed leukemia. In-field nonmelanomatous skin cancers were numerous and likely underrecorded. Basal cell carcinomas occurred in at least 8% of patients (n = 29). There were also 2 out-of-field and 2 in-field melanomas, and 1 from an unknown primary site.

Cardiovascular events

Freedom from grade ≥3 cardiovascular events is shown in Figure 2B. The median age at the time of the first cardiac event was 53 years for valve disease, 53 years for ischemic heart disease, 57 years for carotid artery pathology, and 52 years for cardiomyopathy. The incidence and prevalence of cardiovascular disease increased over time with 37 events in 33 patients (9%) at 10 years, 70 events in 56 patients (15%) at 20 years, 132 events in 95 patients (26%) at 30 years, and 157 events in 109 patients (30%) at 40 years of follow up. Furthermore, 47% of 91 patients with >30 years of follow up and 74% of 23 patients with >40 years of follow-up experienced at least 1 cardiovascular event.

Coronary atherosclerotic disease was diagnosed in 81 patients (54 men and 27 women), and all but 5 received mediastinal irradiation. Grades 3, 4, and 5 ischemic events occurred in 3%, 13%, and 6% (n = 12, 47, and 22) of patients, respectively. The smoking history was >15 pack-years in 25 patients, negative in 30 patients, and unknown in 26 patients. Thirty-one patients (8%) developed clinically significant valve dysfunction, and all but 6 patients required valvuplasty or replacement. Four patients had grade 5 cerebrovascular events related to carotid pathology. Eleven patients had at least unilateral endarterectomies, and 17 had a grade 3 carotid artery toxicity, including a cerebrovascular accident, transient ischemic attack, or stenosis. There were 14 patients with grade 4 cardiomyopathies and 9 patients with grade 5. One patient developed grade 5 constrictive pericarditis.

Noncoronary atherosclerotic disease was noted in 21 patients involving 10 renal arteries, causing renal insufficiency; 2 celiac arteries leading to mesenteric angina; and 9 subclavian or common iliac arteries with >40% occlusion. All 14 subdiaphragmatic events occurred in patients who received abdominal or pelvic radiation (4%).

Other late effects

Nonmalignant thyroid dysfunction that manifested as either hypothyroidism requiring pharmacologic replacement or multinodular thyroid requiring resection was noted in 51% of patients (n = 160) who were alive or dead of intercurrent disease. Other late grade 4 events included infection (n = 5), pulmonary events (n = 3), or hematologic events (n = 4).

A multivariate analysis was conducted. For both secondary malignancy and cardiotoxicity, only age >30 years was significant for both endpoints (P = .02 and < .01, respectively). Both the factors of receiving chemotherapy (P = .2180 and .9637, respectively) and field size (P = .96 and .61, respectively) were not statistically significant.

Discussion

Most HL survivors who were treated ≥20 years ago have experienced SAEs, particularly second malignancies and cardiovascular events. The OER for a second malignancy in our study was 3.6 (95% CI, 2.9-4.4; P < .001). Second malignancy has been reported by others as the leading cause of morbidity and mortality

among long-term survivors of HL.[4,5,10-13,21-26] In fact, Oeffinger et al demonstrated that among a cohort of >10,000 childhood cancer survivors, HL survivors developed the highest cumulative incidence of severe, life-threatening, and fatal complications (grades 3-5), particularly secondary malignant neoplasia and cardiac toxicity.[23] Our results showed that the second malignancy rates at 20, 30, and 40 years were 17% (95% CI, 13%-22%), 34% (95% CI, 28%-41%), and 49% (95% CI, 39%-58%), respectively, with a median latency to first malignancy of 20 years (range, 1-49 years). As shown in prior SEER database studies, the median age at the time of the first malignancy is 67 years, but the median age at the time of the second malignancy in our series was 49 years, which suggests that chemotherapy and RT may not only increase the relative risk of secondary malignancy but also accelerate its onset.[27]

Perhaps the most well-described topic in the literature is the significantly higher risk of breast cancer in female HL survivors. Most studies have demonstrated an increased risk of breast cancer starting 10 to 15 years after treatment.[13,19,22,23] A recent meta-analysis of breast cancer in 24,505 female HL survivors found a median latency after RT of 17.7 years and a relative risk of 8.23.[19] Others have reported mean latencies of 18 years and a 3.2-fold increased risk with RT doses that exceed 4 Gy to the breast.[10] Breast cancer was the most common second malignancy in our series with 30 cases of invasive breast cancers and 5 cases of ductal carcinoma in situ in 26 patients with a median latency to the first diagnosis of breast cancer of 22 years (range, 11-40 years). Only 6 patients died of breast cancer; however, their prognosis is likely related to surveillance intensity.

Interestingly, the OER for breast cancer was 11.9 (range, 6.7-17.1; $P < .0001$) for patients treated for Hodgkin's disease age <30 years and 2.4 (range, 0.3-4.4; $P = .128$) for those age >30 years. However, there was a statistically significant higher risk of a second cancer diagnosis in patients age >30 years. This finding suggests that although the relative risk related to treatment is higher in patients who are younger at the time of treatment, the integral dose reduction may also be important even in older individuals given the competing increased risk of malignancy secondary to advancing age.

The risk of lung cancer (second most-frequent malignancy in our study) is reportedly the highest among smokers treated with chest RT and alkylating agents at ages >40 years.[11,18,24] Lung cancer was noted in 14 patients in our series, including 7 patients who smoked >15 pack-years, 3 patients who had never smoked, and 4 patients whose smoking status was unknown. The OER for lung cancer was 4.0 (95% CI, 1.9-6.1; $P < .001$). In contrast to secondary breast cancers in our experience, secondary lung cancers were universally fatal.

An increased risk of late cardiovascular morbidity and mortality (including valvular dysfunction, pericardial disease, and carotid disease, subclavian disease, and CAD) after mediastinal RT has been well established.[5,6,9,28,29] Valve dysfunction and CAD occurred in 8% (n = 31) and 22% (n = 81) of our patients, respectively. In an earlier report from our institution with a shorter median follow up of 11 years, Hull et al identified valvular dysfunction and CAD in 6% and 10% of patients, respectively.[29]

Our current findings suggest that the risk for cardiovascular does not plateau but continues to increase with time: 47% of patients with >30 years of follow up and 74% of patients with >40 years of follow up experienced at least 1 cardiovascular event. Similar to the accelerated onset with secondary malignancies, the results show that the median age at the time of the first cardiac event was 53 years for valve disease, 53 years for ischemic heart disease, 57 years for carotid artery pathology, and 52 years for cardiomyopathy. As noted by the American Heart Association, the average age at the time of the first cardiac event is mid-60s for men and early 70s for women, which suggests that chemotherapy and RT also hasten onset.[30]

A major strength of the present study is that all 365 patients have a minimum potential follow up of 20 years with a median actual follow up of 27 years in survivors; therefore, the long-term outcomes are largely known rather than projected.[3,4] We found that, over time, 70% of patients experienced at least 1 SAE after HL, and 93% of the cohort with a potential 40 years of follow up experienced at least 1 SAE. Finally, although the types of SAEs affecting HL survivors are similar to those in patients without a history of HL (ie, cancer and heart disease), the sites of SAE in HL survivors suggest that radiation exposure of nontargeted tissues, such as the heart, heart valves, blood vessels, and soft tissues, may accelerate the development of these events. Although this study confirms the long-term efficacy of RT with or without chemotherapy in HL survivors, the results also underscore the importance of reducing the integral dose to nontargeted tissues in patients who receive RT for the management of HL, and even in patients >30 years of age because the risk of a secondary event in absolute terms increases with age. As several studies have shown, a promising strategy for integral dose reduction may be limiting the field size and dose of radiation both through the use of adjuvant chemotherapy and highly conformal methods of radiation delivery, such as proton therapy.[8,14,16,31,32]

Conclusions

With increased survivorship, integral radiation doses result in increasing clinically significant adverse events, which suggests the importance of long-term surveillance and reaffirms advances in chemotherapy and RT that

minimize the integral dose in patients with HL who receive RT.

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