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Critical Review

Evidence-based Review on the Use of Proton Therapy in Lymphoma From the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee

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Introduction

Proton therapy was first suggested in the management of lymphoma in 1974 as a way to spare the bone marrow when treating total nodal fields (1). However, interest in its use in lymphoma has grown only recently with the global growth in proton therapy centers, as well as with improvements in treatment delivery techniques. Hodgkin lymphoma (HL) is a rare malignancy, with approximately 8500 new cases annually in the United States, of which approximately 50% may ultimately receive radiation therapy (RT). A high proportion of HL cases occur in adolescents and young adults, and it is the most common malignancy among 15- to 19-year-old persons. Fortunately, HL is associated with excellent outcomes with standard therapy, with a 10-year survival rate of approximately 90%. In contrast to HL, non-Hodgkin lymphoma (NHL) is a more common disease, with approximately 66,000 cases diagnosed annually in the United States; 10% to 15% of these ultimately require RT as part of their treatment. NHL generally affects older patients, with most cases occurring at age $\geq$50 years and incidence rates increasing with age, but there are subtypes, such as primary mediastinal B-cell lymphoma, that are more commonly found in young adults aged between 20 and 40 years. Although the outcomes of NHL are not as favorable as those of HL, they are, in general, better than those of most solid tumors.

As such, lymphomas—especially HLs—represent malignancies with a high likelihood of long-term survival, allowing sufficient time for latent radiation injury from curative treatment to emerge and affect quality of life and, in some cases, life expectancy. Consequently, hematologist-oncologists are often willing to accept increased relapse rates and salvage therapy as a trade-off for omitting RT altogether. Proton therapy, however, offers an opportunity to maximize the increased initial cure rate offered by RT while minimizing the risk of late side effects historically associated with photon-based RT.

Currently, the cost of proton therapy is not covered by most private insurance plans, despite recommendations by the National Comprehensive Cancer Network Hodgkin and Non-Hodgkin Lymphoma Guidelines panels. The panels advocate for the RT modality that best spares the organs at risk (OARs) given the strong evidence of a radiation dose relationship with late organ toxicity. Often cited by insurance companies is the lack of endorsement by the American Society for Radiation Oncology, which failed to mention the use of proton therapy (either positively or negatively) for lymphoma in its proton guideline paper (2). The guidelines did, however, reference several articles on the use of proton therapy in the management of lymphoma as important additional reading. Furthermore, insurance companies will often cite recommended dose and/or volume limits proposed by QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) despite the limitations of those data, such as their disregard of RT-induced second cancers, their reliance on patient populations that do not reflect lymphoma survivors (eg, lung cancer patients are analyzed for pulmonary toxicity), and their expected modifications to the recommended dose and/or volume guidelines extracted from more recently published studies (3).

In an effort to draw attention to the use of proton therapy in lymphoma, and as a resource for future consideration of proton therapy coverage for lymphoma by other expert panels and insurance agencies, the Particle Therapy Cooperative Group (PTCOG) lymphoma subcommittee has developed an evidence-based review on the use of proton therapy in lymphoma. This report includes (*1*) the rationale for the use of proton therapy in the management of lymphoma, based on a review of the late morbidity associated with radiation dose, (*2*) a review of radiation dosimetry literature that compares proton therapy with photon irradiation, and (*3*) a review of the published clinical data.

Association of Late Morbidity With Radiation Dose

Second malignancies

Secondary cancers represent the most common cause of death among long-term survivors of HL (4). Radiation is a well-known carcinogen that increases the risk of second cancers as the dose increases and has a no-dose threshold (ie, no "safe dose"). Tables 1 and 2 summarize the major studies that have demonstrated the relationship between radiation dose and late effects (5-29). On the basis of this evidence, steps have been taken to reduce this risk by reducing the prescribed radiation dose, using smaller radiation fields, and using conformal radiation techniques.

Breast cancer

The breast tissue of young women is sensitive to ionizing radiation, and an increased incidence of breast cancers has been observed among survivors of HL (8, 30, 31). Several patient and treatment factors increase this risk, including larger radiation volumes (eg, mantle- vs mediastinal-field (31, 32) treatment including the axillae) (7), higher radiation doses (31), and younger ages at treatment (8, 30, 33). In a case-control study of 1-year female survivors of HL with a diagnosis at age $\leq$30 years, $\geq$4 Gy to the region of the breast where the subsequent cancer developed conferred a 3.2-fold increase (95% confidence interval [CI], 1.4-8.2) in breast cancer risk compared with patients receiving lower breast doses when no alkylating chemotherapy was used. The risk increased linearly (excess relative risk [ERR]/Gy, 0.15 [95% CI, 0.04-0.73]) to 8-fold (95% CI, 2.6-26.4) for breast tumors originating in regions of the breast that received $\geq$40 Gy (8).

The relative risk (RR) and absolute excess risk (AER) of breast cancer both decrease with increasing age at HL diagnosis (33), although both risks remain elevated

Table 1 Summary of literature describing risk of secondary cancers, cardiovascular disease, pulmonary toxicity, and endocrinopathies among Hodgkin lymphoma survivors treated with RT

Study	Cohort and treatment period	Outcome	Referent group	Risk (95% CI)	Evidence of linear relationship or cumulative incidence
Second cancers					
Aleman et al (5), 2003	The Netherlands (hospital based) N = 1261 Median age, 26 y (all <41 y) Treated 1965-1987	Fatal second solid tumors	General population	RT alone: SMR, 5.4 (3.4-8.2) RT and CT: SMR, 4.4 (2.0-8.3) Salvage Rx: SMR, 8.3 (6.1-11.2)	–
Castellino et al (6), 2011	United States (CCSS HL patients) N = 2742 Median age, 14 y (2-20 y) Treated 1970-1979	Fatal second malignant neoplasms	No RT	<30 Gy*: HR, 1.9 (0.4-8.7) ≥30 Gy*: HR, 7.4 (1.8-30.3)	–
Schaapveld et al (7), 2015	The Netherlands (hospital based) N = 3905 Treated 1965-2000	Incidence of second solid cancers	General population No RT	SIR, 4.2 (3.9-4.5) AER, 100.5 (91.3-110.2) HR for mantle RT, 2.6 (1.8-3.6)	30-y cumulative incidence, 28.5% (26.4%-30.5%)
Travis et al (8), 2003	International population based N = 3817 (105 cases and 266 controls) Median age, 22 y (all ≤30 y) Treated 1965-1994	Incidence of breast cancer	0-3.9 Gy†	4.0-6.9 Gy: RR, 1.8 (0-4.5) 7.0-23.1 Gy: RR, 4.1 (1.4-12.3) 23.2-27.9 Gy: RR, 2.0 (0.7-5.9) 28.0-37.1 Gy: RR, 6.8 (2.3-22.3) 37.2-40.4 Gy: RR, 4.0 (1.3-13.4) 40.5-61.3 Gy: RR, 8.0 (2.6-26.4) [≥4 Gy: RR, 3.2 (1.4-8.2)]	ERR/Gy, 0.15 (0.04-0.73)‡
Travis et al (9), 2002, and Gilbert et al (10), 2003	International population based N = 19,046 (227 cases and 455 controls) Median age, 50 y (9-81 y) Treated 1965-1994	Incidence of lung cancer	<5 Gy†	>0-4.9 Gy: RR, 1.3 (0.3-4.9) 5.0-14.9 Gy: RR, 4.1 (0.7-22) 15.0-29.9 Gy: RR, 2.5 (0.1-16.1) 30.0-39.9 Gy: RR, 8.6 (2.9-30) ≥40 Gy: RR, 7.2 (2.2-28) [≥5 Gy: RR, 5.9 (2.7-13.5)]	ERR/Gy, 0.15 (0.06-0.39)‡
Morton et al (11), 2014	International population registry N = 19,882 (36 cases and 71 controls) Median age, 34 y Treated 1943-1992	Incidence of esophageal cancer	<30 Gy and no RT†	≥30 Gy: RR, 4.3 (1.5-15.3)	ERR/Gy, 0.38 (0.04-8.17); P_{trend}<.001‡

(*continued on next page*)

Table 1 (*continued*)

Study	Cohort and treatment period	Outcome	Referent group	Risk (95% CI)	Evidence of linear relationship or cumulative incidence
Morton et al (12), 2013	International population registry N = 19,882 (89 cases and 91 controls) Median age, 30 y (11-83 y) Treated 1943-2003	Incidence of stomach cancer	0 Gy†	0.1-0.9 Gy: RR, 1.3 (0.4-4.1) 1.0-4.9 Gy: RR, 1.0 (0.3-3.5) 5.0-24.9 Gy: RR, 0.5 (0.1-2.7) 25.0-34.9 Gy: RR, 4.6 (1.2-20.5) 35.0-39.9 Gy: RR, 8.2 (2.6-29.7) ≥40 Gy: RR, 4.2 (1.2-15.6) ≥25 Gy vs <25 Gy: RR, 5.8 (3.0-12.3)	ERR/Gy, 0.09 (0.04-0.21); P_{trend}<.001‡
Dores et al (13), 2014	International population registry N = 19,882 (36 cases and 70 controls) Median age, 47 y (12-76 y) Treated 1943-2003	Incidence of pancreatic cancer	<10 Gy†	≥10 Gy: RR, 4.3 (1.7-15)	ERR/Gy, 0.098 (0.015-0.42); P_{trend} = .005‡
Cardiovascular					
Hancock et al (14), 1993	United States (Stanford) N = 2232 (88 deaths) Average age, 29 y (2-82 y) Treated 1960-1990	Cardiac death	General population	0-30 Gy*: SMR, 2.6 (0.4-8.7) >30 Gy*: SMR, 3.5 (2.7-4.3)	–
Aleman et al (5), 2003	The Netherlands (hospital based) N = 1261 (45 deaths) Median age, 26 y (all <41 y) Treated 1965-1987	Cardiovascular death	General population	RT alone: SMR, 7.2 (4.2-11.6) RT and CT: SMR, 5.5 (2.2-11.3) Salvage Rx: SMR, 5.9 (3.7-9.0)	–
Van Nimwegen et al (15), 2015	The Netherlands (hospital based) N = 2524 (1713 events) Median age, 27 y Treated 1965-1995	Incidence of any cardiac event	No RT	>0-29 Gy*: HR, 2.3 (1.3-3.8) 30-35 Gy*: HR, 3.1 (2.3-4.2) ≥36 Gy*: HR, 3.8 (3.0-5.0)	Patients treated with mediastinal RT had 40-y cumulative incidence of 54.6% (51.2%-57.9%)
Van Nimwegen et al (16), 2016	The Netherlands (hospital based) N = 2617 (325 cases and 1204 controls) Median age, 32 y (all <51 y) Treated 1965-1995	Incidence of MI and/or angina	No RT	>0-5 Gy†: RR, 1.14 (0.62-2.10) 5-14 Gy: RR, 2.14 (1.28-3.58) 15-19 Gy: RR, 2.76 (2.10-3.59) 20-24 Gy: RR, 2.79 (2.23-3.49) 25-34 Gy: RR, 3.21 (2.52-4.09) 35-45 Gy: RR, 2.54 (0.96-6.69)	ERR/Gy, 0.074 (0.033-0.148); P_{trend}<.001‡

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Table 1 (*continued*)

Study	Cohort and treatment period	Outcome	Referent group	Risk (95% CI)	Evidence of linear relationship or cumulative incidence
Cutter et al (17), 2015	The Netherlands (hospital based) N = 1852 (89 cases and 200 controls) All aged <41 y Treated 1965-1995	Incidence of valvular heart disease	No RT	≤30 Gy†: RR, 1.4 (0.5-3.8) 31-35 Gy: RR, 3.1 (1.7-5.6) 36-40 Gy: RR, 5.4 (3.9-7.7) >40 Gy: RR, 11.8 (4.9-28.5) P_{trend}<.001 (nonlinearity)	–
Van Nimwegen et al (18), 2017	The Netherlands (hospital based) N = 2617 (91 cases and 278 controls) Median age, 28 y (all <51 y) Treated 1965-1995	Incidence of congestive heart failure	No RT	1-15 Gy†: RR, 1.27 (0.86-1.89) 16-20 Gy: RR, 1.65 (0.98-2.77) 21-25 Gy: RR, 3.84 (1.97-7.47) ≥26 Gy: RR, 4.39 (2.00-9.65) P_{trend}<.001	–
Bowers et al (19), 2005	United States (CCSS HL patients) N = 1926 All aged <21 y Treated 1970-1986	Incidence of stroke	Siblings	Mantle RT: RR, 5.62 (2.59-12.25)	–
De Bruin et al (20), 2009	The Netherlands (hospital based) N = 2201 (96 cases) All aged <51 y Treated 1965-1995	Incidence of ischemic cerebrovascular disease (including TIA)	No RT	RT to neck and/or mediastinum: HR, 2.5 (1.1-5.6)	–
Pulmonary toxicity					
Ng et al (21), 2008	United States (DFCI/BWH) N = 52 Median age, 31 y (18-69 y) Treated 2001-2005	Decline in %DLCO	NA	MLD ≥13 Gy or V20 ≥ 33%: 60% persistently declined %DLCO	ERR/Gy, −0.96 (−1.79 to −0.14) at 1 y after treatment
Endocrinopathy					
Van Nimwegen et al (22), 2015	The Netherlands (hospital based) N = 2264 Aged <51 y 1965-1995	Diabetes	General population	≥36 Gy para-aortic and/or spleen: HR, 2.3 (1.54-3.44) ≥36 Gy para-aortic alone: HR, 1.82 (1.02-3.25)	HR/Gy mean dose to pancreatic tail, 1.017 (P<.001)
Cella et al (23), 2013	Italy (Naples) N = 53 (22 cases) Median age, 28 y (14-70 y) Treated 2001-2009	Hypothyroidism	NA	Cumulative risk (median follow-up, 32 mo): 11.5% for V30 ≤62.5% 70.8% for V30 >62.5%	–

Abbreviations: AER = absolute excess risk; BWH = Bringham Women's Hospital; CCSS = Childhood Cancer Survivor Study; CI = confidence interval; CT = chemotherapy; DFCI = Dana Farber Cancer Institute; %DLCO = percentage predicted carbon monoxide–diffusing capacity; ERR = excess relative risk; HL = Hodgkin lymphoma; HR = hazard ratio; MI = myocardial infarction; MLD = mean lung dose; NA = not applicable; RR = relative risk; RT = radiation therapy; Rx = treatment; SIR = standardized incidence ratio; SMR = standardized mortality ratio; TIA = transient ischemic attack; V20 = volume receiving ≥20 Gy; V30 = volume receiving ≥30 Gy.

* Prescribed dose.

† Estimated dose to location of late outcome.

‡ No evidence of departure from linearity.

compared with the general population even for women in whom HL is diagnosed at age ≥35 years (7). AER continues to increase with time from irradiation because of the baseline absolute risk increasing with age (33). The 30-year cumulative incidence among women with HL who have survived 5 years was 16.6% (95% CI, 14.1%-19.2%) (7). Reassuringly, in this cohort, breast cancer risk is significantly less in those women who receive axillary-sparing supradiaphragmatic RT compared with those treated with mantle RT (hazard ratio [HR], 0.37; 95% CI, 0.19-0.72), suggesting that techniques that reduce the volume of breast tissue irradiated may reduce breast cancer risk.

Lung cancer

The 30-year cumulative risk of lung cancer within a cohort of Dutch patients treated for HL was 6.4% (95% CI, 5.4%-7.6%) (7). A lung radiation dose ≥5 Gy to the area where the subsequent cancer developed has been associated with a 5.9-fold increase (95% CI, 2.7-13.5) in the RR of lung cancer; furthermore, the risk increased linearly with dose (ERR/Gy, 0.15 [95% CI, 0.06-0.39]; $P_{trend}<.001$) (9, 10). The RR of second lung cancer did not increase until 5 to 9 years after RT but persisted for >20 years. It is important to note that the risk of RT-associated lung cancer is multiplied by tobacco use: RR of 6 (no RT, moderate smoker) versus RR of 7.2 (≥5 Gy to the regions of the subsequent lung cancer, light smoker or nonsmoker) versus RR of 20.2 (≥5 Gy to the regions of the subsequent lung cancer, moderate smoker) (9). Given the poor outcomes in treating secondary lung cancer after thoracic RT (34), treatment techniques that reduce the lung radiation dose and therefore the lung cancer risk are expected to be beneficial.

Gastrointestinal cancer

The third greatest AER of second cancer in HL survivors is from gastrointestinal cancers, including esophageal cancer (11), stomach cancer (12), pancreatic cancer (13), and colorectal cancer (7). The ERR of these cancers has been demonstrated to increase linearly with radiation dose to the affected organ (Tables 1 and 2) (5-29). The risks of stomach and pancreatic cancer have been shown to increase synergistically by the combination of RT and procarbazine. Any treatment strategies that have the potential to reduce radiation dose to these organs are therefore of potential clinical benefit.

Other solid second cancers

The RRs of other solid cancers (eg, sarcoma and thyroid, salivary, skin, uterine, kidney, and bladder cancers) are also increased following treatment of HL (6, 7, 30, 35) and, when considered together, account for approximately 30% of the AER. Consistently, among all second cancers, the RR decreases with age at treatment, but as it remains persistently elevated with time from treatment (>35 years), the AER continues to increase owing to the increased background rate associated with aging (7). Not all increased secondary cancer risk is due exclusively to radiation exposure; chemotherapy exposure, genetic factors, and immunologic factors also play a role. However, radiation exposure has been clearly related to other cancers in populations of childhood cancer survivors (36), and secondary cancer risk has been related to the integral dose of radiation received (24). For all demonstrated dose-response relationships, with the exception of thyroid cancer (37), the cancer risk increases linearly with radiation dose; therefore, any reduction in integral radiation dose to normal tissues would have the potential to reduce the overall burden of second cancer incidence among HL survivors compared with those treated in the past.

Second cancers following NHL

While survivors of NHL are at increased risk of second malignancies (38, 39), no statistically significant difference in risk based on whether the patient received RT or not has been demonstrated, with few exceptions. Irradiated NHL patients had an excess risk of sarcoma, breast cancer, and mesothelioma compared with unirradiated survivors. Among young female patients (aged <25 years), the risk of breast cancer was increased 5-fold by irradiation (39), suggesting that there may be potential clinical benefits in reducing the integral radiation dose.

Cardiovascular

Cardiovascular mortality

Cardiovascular disease (CVD) is the most common nonmalignant cause of death among HL survivors (5, 6, 40). Within a Dutch cohort of patients with HL who were aged ≤40 years at diagnosis, the RR of CVD death was 6.3 times that of the general population with an AER of 17.8 per 10,000 person-years. The RR of CVD-related death is higher for patients treated before age 21 years (RR, 13.6) (5) and decreases with older age at treatment. However, it remains significantly elevated up to age 65 years, particularly for ischemic heart disease (41). Although RR decreases with age at treatment, AER increases with age because of an increasing background rate, and the absolute increase persists at and beyond 20 years after initial treatment (4, 6, 41).

Cardiovascular morbidity

In addition to death from CVD, nonfatal CVD results in a considerable burden of illness among survivors of HL (15, 42). In a hospital-based cohort, the cumulative incidence of cardiac disease at 40 years was 54.6% (95% CI, 51.2%-57.9%) for HL patients treated with mediastinal RT (15). Recent studies have estimated retrospectively the radiation dose to the heart and cardiac substructures using a variety of methods (16, 17, 43, 44). Despite the limitations of such studies, data from both HL and breast cancer radiation dosimetry studies converge on the same conclusion: a linear, no-threshold radiation dose−response relationship exists between mean heart dose and risk of CVD (16, 43, 44), with an estimated ERR of 7.4% per mean gray to the heart (95% CI, 2.9-14.5 among breast cancer patients and 3.3-4.8 among HL

Table 2 Summary of literature describing RT-associated risk of other secondary cancers and pulmonary toxicity among cancer survivors aged <21 years

Study	Cohort and treatment period	Outcome	Referent group	Risk (95% CI)	Evidence of linear relationship and cumulative incidence
Secondary cancer					
Tukenova et al (24), 2011	French-UK cohort* N=4590 Aged <17 y 1985	Death from secondary carcinoma	0-40 J	≥150 J: 5.2 (2.2-12.6)	–
		Death from secondary sarcoma		≥150 J: 12.5 (3.1-47.6)	–
Neglia et al (25), 2006	CCSS* N=14,361 Aged <21 y 1970-1986	Incidence of glioma	<1 Gy	1-9.9 Gy†: OR, 0.0 (0.0-5.17) 10-19.9 Gy: OR, 7.61 (1.49-38.8) 20-29.9 Gy: OR, 6.68 (1.47-30.3) 30-44.9 Gy: OR, 21.0 (3.11-142.3) >45 Gy: OR, 17.5 (2.86-107.5)	–
		Incidence of meningioma	<1 Gy	1-9.9 Gy†: OR, 0.0 (0.0-15.8) 10-19.9 Gy: OR, 12.0 (1.42-100.7) 20-29.9 Gy: OR, 21.6 (3.13-149.3) 30-44.9 Gy: OR, 96.3 (10.32-899.3) >45 Gy: OR, 58.0 (6.02-559.0)	–
Boukheris et al (26), 2013	United States (CCSS)* N=14,135 (23 cases) All aged <21 y Treated 1970-1986	Incidence of salivary gland tumors	0 Gy†	>0-2.9 Gy: RR, 2.1 (0.4-14.5) 3.0-11.4 Gy: RR, 5.7 (1.2-39.6) 11.5-80.4 Gy: RR, 7.2 (1.7-48.3)	ERR/Gy, 0.36 (0.06-2.5); P_{trend}=.005
Bhatti et al (27), 2010	United States (CCSS)* N=12,547 (115 cases) All aged <21 y Treated 1970-1986	Incidence of thyroid cancer	0 Gy†	>0 to <5 Gy: RR, 1.2 (0.6-2.5) 5 to <10 Gy: RR, 8.5 (3.2-22.6) 10 to <15 Gy: RR, 10.6 (4.5-24.9) 15 to <20 Gy: RR, 13.8 (6.3-30.3) 20 to <25 Gy: RR, 14.6 (6.8-31.5) RR less at doses >25 Gy (but still increased)	–
Tukenova et al (28), 2012	French-UK cohort* N=4568 Aged <17 y 1985	Incidence of digestive organ tumors	General population	RT alone: SIR, 1.0 (0.2-3.0) CT alone: SIR, 9.1 (2.3-23.6) RT and CT: SIR, 29.0 (20.5-39.8)	OR/Gy, 0.13 (0.05-0.32)
			No RT	0-9 Gy†: OR, 1.1 10-29 Gy: OR, 5.2 (1.7-16.0) ≥30 Gy: OR, 9.6 (2.6-35.2)	

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Table 2 (*continued*)

Study	Cohort and treatment period	Outcome	Referent group	Risk (95% CI)	Evidence of linear relationship and cumulative incidence
Pulmonary toxicity					
Dietz et al (29), 2016	United States (CCSS)* N = 14,316 Median age, 7 y (all <21 y) Treated 1970-1986	Pulmonary death (138 deaths)	No RT	10-15 Gy: RR, 4.4 (1.0-18.5) 15-20 Gy: RR, 7.7 (2.0-29.1) 20-25 Gy: RR, 5.2 (1.2-22.3) ≥25 Gy: RR, 15.7 (3.7-65.5) P_{trend}<.01	–
		Oxygen need	No RT	0-5 Gy: RR, 1.0 (0.8-1.2) 5-10 Gy: RR, 1.3 (0.9-1.9) 10-15 Gy: RR, 1.6 (1.1-2.3) 15-20 Gy: RR, 1.9 (1.3-2.8) 20-25 Gy: RR, 2.5 (1.7-3.8) ≥25 Gy: RR, 2.9 (1.8-4.7)	–
		Lung fibrosis	No RT	0-5 Gy: RR, 1.0 (0.6-1.7) 5-10 Gy: RR, 1.0 (0.4-2.7) 10-15 Gy: RR, 3.8 (2.1-7.0) 15-20 Gy: RR, 1.9 (1.3-2.8) 20-25 Gy: RR, 7.1 (3.7-13.7) ≥25 Gy: RR, 11.0 (5.4-22.0)	–
		Recurrent PNA	No RT	0-5 Gy: RR, 1.0 (0.6-1.5) 5-10 Gy: RR, 1.0 (0.4-2.3) 10-15 Gy: RR, 1.4 (0.7-2.9) 15-20 Gy: RR, 2.9 (1.5-5.9) 20-25 Gy: RR, 3.4 (1.6-7.1) ≥25 Gy: RR, 3.1 (1.3-7.6)	–
		Chronic cough	No RT	0-5 Gy: RR, 0.9 (0.7-1.0) 5-10 Gy: RR, 1.2 (0.9-1.7) 10-15 Gy: RR, 1.2 (0.9-1.6) 15-20 Gy: RR, 1.6 (1.2-2.2) 20-25 Gy: RR, 1.9 (1.4-2.8) ≥25 Gy: RR, 2.1 (1.3-3.2)	–

Abbreviations: CCSS = Childhood Cancer Survivor Study; CI = confidence interval; CT = chemotherapy; ERR = excess relative risk; OR = odds ratio; PNA = pneumonia; RR = relative risk; RT = radiation therapy; SIR = standardized incidence ratio.

In all studies, Hodgkin lymphoma survivors comprised a small minority of the cohort.

* Cohort also includes nonlymphoma patients.

† Prescribed dose.

patients) (16, 43). The ERR was highest within the youngest tertile of patients treated for HL (ERR, 20%/Gy [<27.5 years] vs 8.8%/Gy [27.5-36.4 years] vs 4.2%/Gy [36.5-50.9 years]), but this was not statistically significant (P = .149) (16). For valvular heart disease (17) and heart failure (18), the dose-response relationships exhibit a statistically significant curvature rather than a linear relationship (Tables 1 and 2). Taken together, these results suggest that although a reduction in the higher dose volume of irradiation to the heart may be of particular benefit for some cardiac diseases (valvular heart disease and heart failure), any possible reduction of heart dose may benefit lymphoma patients, regardless of age at treatment. As the background risk of CVD and the incidence of other cardiac risk factors tend to increase with age, it may be that AER—and hence any potential reduction with proton therapy—may actually be highest for older patients, at least in the first 20 years following treatment.

Stroke

Childhood (19) and adult (20) HL survivors are at an increased risk of stroke after treatment (Table 1). Among adults, stroke was more commonly ischemic (vs hemorrhagic) and attributed to large-artery atherosclerosis or cardioembolism (20), presumably owing to irradiation of the carotid and subclavian arteries and heart (valvular disease), respectively. Significant risk factors for this increased risk included neck and mediastinal RT (HR, 2.5; 95% CI, 1.1-5.6; reference: no supradiaphragmatic RT), younger age at treatment, and hypertension. The 30-year cumulative incidence of ischemic stroke or transient ischemic attack was 7%. Similar results were seen within the Childhood Cancer Survivor Study cohort (19). In this cohort, mantle-

field RT was associated with a higher RR (5.62; 95% CI, 2.59-12.25; reference: siblings) than in the Dutch adult study, potentially because of the younger age of HL patients treated and referent groups.

Pneumonitis and pulmonary late effects

Although mediastinal lymphoma is treated to lower doses than primary lung tumors, radiation pneumonitis (RP) has been well documented among lymphoma patients. The risk of RP development has been associated with mean lung dose, volume receiving ≥5 Gy ($V_{5\ Gy}$), and volume receiving ≥20 Gy ($V_{20\ Gy}$) (45, 46). The risk of grade 1 to 3 RP, even with the use of intensity modulated RT (IMRT), is approximately 10% after consolidation RT but is 25% to 35% among patients treated for refractory or relapsed disease (45, 46), likely given that these patients are heavily pretreated and many receive consolidation with high-dose chemotherapy with stem cell rescue.

On the basis of a comparison of childhood cancer survivors with their siblings, ≥5 years after diagnosis, thoracic RT was significantly associated with lung fibrosis (RR, 4.3; $P=.001$), recurrent pneumonia (RR, 2.2; $P=.001$), and supplemental oxygen use (RR, 1.8; $P<.001$) (47). Subacute changes have also been noted. Within a prospectively studied cohort of 52 patients with HL, mediastinal RT did not further reduce diffusion capacity (percentage predicted carbon monoxide—diffusing capacity [%DLCO]) compared with those treated with chemotherapy alone. However, it was associated with persistently decreased %DLCO up to 1 year after therapy (21); for every 1-Gy increase in mean lung dose, the estimated reduction in %DLCO at 1 year was 1%.

Endocrinopathies

Hypothyroidism

Hypothyroidism is one of the most common endocrine disorders after treatment, afflicting 25% to 50% of HL survivors (23, 48, 49). The range in reported incidence likely reflects the variability among study cohorts' demographic characteristics (age, sex), follow-up time, and definition of hypothyroidism. In general, diagnosis of hypothyroidism was based on thyroid stimulating hormone, free triiodothyroinine (free T3), and free thyroxine (free T4) values, regardless of whether symptoms were present. Supradiaphragmatic RT, but not chemotherapy, is a significant risk factor for hypothyroidism (48), with thyroid volume receiving ≥30 Gy ($V_{30\ Gy}$) being a strong dosimetric predictor; the risk of hypothyroidism was 11.5% with $V_{30\ Gy}$ ≤62.5% versus 70.8% with $V_{30\ Gy}$ >62.5% ($P<.0001$) among HL patients treated with combined-modality treatment (median dose, 32 Gy) (23).

Diabetes

The first report of abdominal RT and development of non—insulin-dependent diabetes mellitus (DM) was described among nephroblastoma patients, with a higher rate among those with left- versus right-sided tumors (50). An increased risk of DM has been noted among childhood cancer survivors treated with abdominal irradiation (odds ratio, 2.7; 95% CI, 1.9-3.8) compared with sibling controls, which was independent from body mass index or physical inactivity (51). DM risk increased with increasing radiation dose to the tail of the pancreas, where islets of Langerhans are concentrated (RR, 1.61 per 1 Gy; 95% CI, 1.21-2.68) (52). Damage to the insulin-producing islets of Langerhans cells and potentially peripancreatic microvascular tissue may result in reduced insulin levels.

Recently, increased DM risk has been documented among HL survivors (22). DM risk was evaluated by irradiated field (para-aortic lymph nodes [PAO], PAO with spleen, no PAO) among 2265 5-year HL survivors treated between 1965 and 1995; doses to the whole pancreas and subsites (head, body, tail) were also retrospectively estimated for a subset of patients based on measurements in water and anthropomorphic phantoms. DM risk was related in a dose-dependent and RT volume—dependent manner. Risk significantly increased with PAO RT doses ≥36 Gy (HR, 2.28; 95% CI, 1.53-3.38) versus none, as well as with increasing field extent: no PAO RT versus PAO without spleen (HR, 1.87; 95% CI, 1.12-3.13) versus PAO and spleen RT (HR, 2.28; 95% CI, 1.53-3.38). Increased risk with splenic RT was attributed to likely irradiation of the pancreatic tail. Risk of DM increased with increasing mean dose to the pancreatic tail (HR, 1.017/Gy) and was higher among patients treated before age 25 years (22).

Review of Dosimetric Studies and Specific OARs

Potential dose reduction to OARs with proton therapy

General

Fourteen studies evaluating a variety of lymphoma target volumes that have compared the OAR dose of a photon plan versus a proton plan are shown in Table 3 (53-67), and weighted average dose comparisons with the different OARs are shown in Table 4 and Tables E1-E6 (available online at www.redjournal.org). All of these studies compared standard-of-care radiation planning with 3-dimensional (3D) conformal RT planning, generally with anterior-posterior (AP)—posterior-anterior (PA) field arrangements; 13 also included sophisticated modern photon planning (modern RT [mRT]) with IMRT (7 studies), volumetric modulated arc therapy (VMAT) (4 studies), and/or TomoTherapy (TomoTherapy, Madison, WI) (3 studies). Proton therapy was delivered with passive-scatter techniques (8 studies) and/or pencil-beam scanning (PBS) (8 studies). Only the prospective study from the University of Florida (UF) included some patients treated with the breath-hold technique.

Clear details on plan arrangements have not been routinely described for either mRT or proton therapy. In

Table 3 Studies comparing proton therapy with photon RT

Study	No. of patients	Location	Field	Breath hold	3D RT	mRT	Protons	Heart	Lung	Breast	Thyroid	Esophagus	Body	Other
Hoppe et al 2012 (53), 2014 (54)	20	Mediastinum	ISRT	No	X	IMRT	PSPT	X	X	X	X	X	X	Cardiac substructures
Chera et al (55), 2009	9	Mediastinum	Residual	No	X	IMRT	PSPT	X	X	X	X		X	
Knausl et al (56), 2013	10	Mediastinum	ISRT		X	IMRT	PBS	X	X	X	X			Bones
Knausl et al (56), 2013	10	Mediastinum	Residual		X	IMRT	PBS	X	X	X	X			Bones
Cella et al (57), 2013	3	Mediastinum	mIFRT		X	fIMRT, IMRT, Tomo	PBS	X	X	X	X			Coronary vessels
Horn et al (58), 2016	14	Mediastinum	ISRT		X	Tomo	PSPT	X	X	X	X	X	X	
Andolino et al (59), 2011	10	Breasts	mIFRT		X		PSPT	X	X	X	X	X		Cord
Maraldo et al (60), 2014	37	Head and neck	INRT		X	VMAT	PBS				X			Neck muscles, larynx, pharynx, parotid, SM gland
Zeng et al (61), 2016	10	Mediastinum	ISRT		X	IMRT	PSPT, PBS	X	X	X				Cord
Maraldo et al (62), 2013	27	Mediastinum	INRT		X	VMAT	PBS	X	X	X				
Li et al (63), 2011	10	Mediastinum	ISRT	No	X		PSPT	X	X	X		X		Coronary vessels
Jørgensen et al (64), 2013	46	Esophagus	INRT		X	VMAT	PBS					X		
Toltz et al (65), 2015	20	Mediastinum	mIFRT		X	Tomo	PBS	X	X	X				
Sachsman et al (66), 2015	12	Subdiaphragm	ISRT		X	IMRT	PSPT							Stomach, liver, bowel, pancreas, kidney
Maraldo et al (67), 2013	46	Neck	INRT		X	VMAT	PBS							Carotids

Abbreviations: 3D = 3-dimensional; fIMRT = forward intensity modulated radiation therapy; IMRT = intensity modulated radiation therapy; INRT = involved-node radiation therapy; ISRT = involved-site radiation therapy; mIFRT = modified involved-field radiation therapy; mRT = modern radiation therapy; PBS = pencil-beam scanning; PSPT = passively scattered proton therapy; RT = radiation therapy; SM = submandibular; Tomo = TomoTherapy; VMAT = volumetric modulated arc therapy.

mRT, concerns have arisen that the best plans are not always selected, such as the use of equally spaced fields that may cause more of a low-dose bath in OARs that would not have been otherwise irradiated. However, in their study, Cella et al (57) did evaluate forward IMRT (fIMRT) plans that used AP-PA field arrangements. These primarily anterior and posterior oblique field arrangements, similar to the "butterfly technique" used at some centers (68), limit

Table 4 Weighted average difference in dose between 3D RT, mRT, and PT across studies for organs at risk

	No. of patients				
Organ	3D RT	mRT	mRT vs 3D RT	PT vs 3D RT	PT vs mRT
Body	43	43	0.49 Gy	3.15 Gy	2.66 Gy
Esophagus	100	80	1.4 Gy	3.9 Gy	1.8 Gy
Heart	123	103	1.44 Gy	3.57 Gy	2.24 Gy
Thyroid	99	103	−1.57 Gy	1.43 Gy	2.09 Gy
Breast	104	84	−1.09 Gy	1.47 Gy	2.45 Gy
Lungs	123	103	−0.39 Gy	2.81 Gy	3.28 Gy
Lung V_{20}	76	56	11%	9.10%	0%

Abbreviations: 3D RT = 3-dimensional radiation therapy; mRT = modern radiation therapy; PT = proton therapy; V20 = volume receiving ≥20 Gy.

the low-dose bath to the breast and lung but at the expense of slightly higher doses to the heart. Unfortunately, not enough detail is available in the other studies to understand whether the "best plan" was used in comparison planning. On the other hand, field arrangement is also very important in proton planning but can vary considerably depending on the distribution of disease. Many patients benefit from the use of anterior fields only, such as when disease drapes over the anterior aspect of the heart. However, some of the comparative dosimetric studies used an AP-PA field approach to treat these patients, which may not have maximized the benefit of protons. For example, Horn et al (56) and Cella et al (57) typically used AP-PA field arrangements for their proton plans whereas Andolino et al (59) used only posterior fields in a focused effort to restrict breast dose but may not have maximized cardiac dose sparing. Consequently, it is hard for this review to describe detailed evaluations of the fields used.

In addition, proton planning experience is important, especially for more advanced techniques such as PBS. Most of these studies were performed at centers without experience in planning or treating with proton therapy and generated comparative plans that may not have been as robust to the effects of setup and proton range uncertainty as an actual "deliverable" plan generated at an experienced institution.

Another consideration is the quality of the plans compared in the dosimetric studies. Studies from centers without proton delivery capabilities provide little to no information on dose uncertainties accounted for in their treatment plans. Current practice in proton lymphoma RT includes mitigation techniques for range uncertainties caused by both range calculation approximations and tissue density variations caused by setup errors and physiological motions. Range calculation uncertainties, mainly attributed to inaccuracies in Hounsfield units to stopping power conversion along the proton beam path, are commonly accounted for by adding a margin (generally 2.5%-3% of the range with or without 1-2 mm) along the beam path both distally and proximally to the target. The effects of density variations in the beam path to proton penetration depth in tissue for passive-scattering and uniform scanning deliveries are eased by range compensator "smearing" (thinning), which reduces distal conformity but ensures target coverage under setup errors and motion. For proton pencil-beam deliveries, robust optimization can be used to account for range uncertainties. Alternatively, a geometric expansion similar to the conventional PTV margin is used in combination with robustness evaluation. Robustness evaluation is the systematic dose recalculation of the treatment plan for numerous dose calculations and delivery error scenarios, as well as review of the resulting dose distributions. For treatments delivered by proton pencil beam, the interplay between the scanning beam and a moving target creates dose inhomogeneities within the target, degrading the dose distribution. Larger spots and dose repainting are used to maintain robustness of mediastinal lymphoma proton pencil-beam treatments (61). With the small cohorts in dosimetric studies comparing photon and proton lymphoma plans, it is difficult to discern if all plans are of deliverable quality, especially because some use the approach of simple geometric expansions as motion management without motion evaluation. Four-dimensional computed tomography scan for target and OAR delineation and dose calculation is commonly used for proton lymphoma RT. Breath-hold techniques for motion management and lung dose reduction during therapy are less common and not well-described in the literature (69).

Target volumes for the studies generally treated sites of initial involvement prior to chemotherapy as is performed with involved-site or involved-node RT (14 studies). In some instances, involved-field RT was described; however, 3D target volumes with a clinical target volume (CTV) and planning treatment volume (PTV) were always used. Two studies evaluated residual postchemotherapy sites of involvement (55, 56), one of which also evaluated pre-chemotherapy sites of disease (56). These studies are notable for observing less absolute dose reduction to OARs when comparing proton versus photon treatment plans, when just the residual disease was treated. This finding suggests that the differences in modality are less apparent with smaller field volumes, as was also reported in the review article by Lohr et al (70).

The vast majority of the dosimetric studies have focused on mediastinal sites (11 studies), evaluating the following OARs: heart, lung, breast, thyroid, esophagus, coronary vessels, and body dose. Two studies evaluated head and neck treatment and reported the dose to the carotids, neck muscles, larynx, pharynx, parotids, and salivary glands. Only one study evaluated subdiaphragmatic disease and included the stomach, liver, bowel, pancreas, and kidneys. Consequently, there are more robust dosimetric data for the use of proton therapy for mediastinal lymphoma than for other sites. The next section focuses on a review of the 11 studies of the mediastinal sites that evaluated dose to the thoracic OARs. It is interesting that the summary in Table 4 demonstrates that the dose reduction achieved by mRT for

any of the organs compared with 3D RT was smaller than the dose reduction achieved by proton therapy for the same organs compared with mRT.

Heart

Of the 9 published studies evaluating the dosimetric benefits of proton therapy on cardiac dose, 7 demonstrated improvements compared with photon techniques (53, 55-59, 61-63) (Table E1; available online at www.redjournal.org). Seven of these studies evaluated passive-scanning proton therapy, and 2 evaluated an active scanning technique. Among the 7 studies that showed improvement in cardiac dose with proton therapy, the largest improvement was seen in comparison with 3D RT. Hoppe et al (53) noted a decrease in mean cardiac dose of 7.6 Gy (relative biological effectiveness [RBE]) (RR, 46%) with proton therapy compared with 3D RT and 3.3 Gy (RBE) (RR, 27%) compared with IMRT. In a study by Horn et al (58), the mean cardiac dose was reduced with proton therapy: 11.4 ± 8.2 Gy for 3D RT versus 7.8 ± 5.8 Gy (RBE) for proton therapy ($P = .02$). Compared with TomoTherapy, proton therapy demonstrated an improvement in low-dose radiation levels, including both the volume receiving $\geq$4 Gy ($V_{4\ Gy}$) (RBE) (32.8% vs 46.2%) and volume receiving $\geq$10 Gy (RBE) ($V_{10\ Gy\ [RBE]}$) (25.4% vs 33.8%) ($P < .01$). Cella et al (57) noted an improved mean cardiac dose of 10.2 Gy (RBE) in patients treated to the whole mediastinum with proton therapy in comparison with either AP-PA (22 Gy), forward-planned IMRT (23.8 Gy), inverse-planned IMRT (17.2 Gy), or TomoTherapy (14.6 Gy). In addition, lower volumes of the heart were exposed to moderate-dose radiation levels: volume receiving $\geq$25 Gy (RBE) ($V_{25\ Gy\ [RBE]}$) of 7.3% (protons), 60.5% (3D RT), 67.5% (forward-planned IMRT), 22% (inverse-planned IMRT), and 8.7% (TomoTherapy). Knausl et al (56) compared 2 opposed 6-, 10-, or 15-megavolt photon fields, IMRT using 7 6-megavolt beams, and a single anterior proton field in 10 patients. Protons reduced the mean heart dose by approximately 3 Gy (RBE). Li et al (63) evaluated 10 consecutive patients with mediastinal lymphoma who were treated with proton therapy to a dose of 30.6 to 50.4 Gy (RBE); 7 patients had primary refractory disease, and 8 had HL. Proton therapy was associated with a lower mean dose to the heart (8.8 Gy [RBE] vs 17.7 Gy [RBE]) compared with conventional RT. Maraldo et al (62) evaluated 27 early-stage HL patients and compared 3D RT, VMAT, and proton therapy treatment plans for involved-nodal RT volumes. Similar conclusions were reached with better cardiac sparing allowed by proton therapy compared with other modalities. Zeng et al (61) evaluated proton plans (using a single anterior field with a double-scattering approach as well as PBS) in 10 patients planned for involved-site RT for HL by use of a prescription dose of 30.6 Gy (RBE). Compared with 3D RT and IMRT, proton therapy lowered the mean heart dose, $V_{30\ Gy\ (RBE)}$, $V_{20\ Gy\ (RBE)}$, $V_{10\ Gy\ (RBE)}$, and $V_{5\ Gy\ (RBE)}$.

Of the 9 studies, 2 did not demonstrate a dosimetric improvement in heart dose (55, 59). In 1 of the studies, priority was given to limiting the radiation dose to breast tissue (59). This analysis used a posterior proton beam technique with passive scatter, which allowed exposure of the heart with the beam's entrance dose. Therefore, the proton plans were not designed to be cardiac sparing. In comparison with other studies that included patients with various extents of mediastinal disease, the second study is the only study in which all patients had disease limited to the superior mediastinum (ie, no disease below the hila); therefore, because of disease location, there was no cardiac dose benefit with proton therapy (55).

Overall, the studies demonstrated an average dose reduction of 3.57 Gy (RBE) in mean heart dose compared with 3D RT and 2.24 Gy compared with mRT, while mRT only reduced the heart dose by 1.44 Gy compared with 3D RT. These dose differences appear to be important considering the emerging data showing that even the lowest cardiac doses are associated with increased cardiac complications, justifying an "as low as possible" approach. Given the potential for cardiac sparing in HL when there is mediastinal disease treated with proton therapy, there would be a lower expected risk of long-term cardiotoxicity (14-18).

Coronary vessels

Although the coronary vessels have not traditionally been contoured as OARs to evaluate during treatment planning, 2 studies have evaluated the coronary artery dose from proton therapy compared with 3D RT and one has compared it with IMRT (54, 63). The main differences in dosimetry between proton therapy and photon RT were focused on the left coronary arteries. In one study, proton therapy resulted in a relative dose reduction of 11% in $V_{5\ Gy\ (RBE)}$, 13% in $V_{10\ Gy\ (RBE)}$, 25% in $V_{20\ Gy\ (RBE)}$, and 28% in $V_{30\ Gy\ (RBE)}$. In the other study, comprising 20 patients, the mean doses to the left anterior descending artery (LAD), left circumflex artery, and right circumflex artery were reduced by 2, 15, and 2 Gy (RBE), respectively, compared with 3D RT and by 2, 7, and 1 Gy (RBE), respectively, compared with IMRT. Although the median dose difference may not have been remarkably different for the cohort as a whole, when 3D RT and proton therapy were compared, there was a difference in dose >5 Gy (RBE) to the LAD among 5 patients, to the left circumflex artery in 8 patients, and to the right coronary artery in 4 patients. When IMRT and proton therapy were compared, there was a difference >5 Gy (RBE) to the LAD in 2 patients, to the left circumflex artery in 6 patients, and to the right coronary artery in 3 patients. These differences indicate that, depending on disease distribution, there could be a considerable dose reduction to the coronary vessels using proton therapy.

A caveat to these published observations is that none of the studies evaluated the potential impact from the higher radiobiologically equivalent dose (RBE, 1.35-1.6) (71) at the distal edge (2 mm) of the spread-out Bragg peak with proton therapy, when beams end on the coronary vessels. Theoretically, this could put a much higher "hot spot" in the coronary vessels, which might place the patient at higher risk of a coronary vascular event. To address this, using multiple fields (2 or 3) that end at slightly different

locations is expected to reduce the unwanted concentrations of high linear energy transfer, which may correlate to higher RBE regions. An additional reduction in potential high RBE concentration is expected from cardiac motion, especially in relation to breathing motion, which blurs the region located in that higher RBE region.

Breast

Proton therapy has been compared with 3D RT in 10 studies, 8 of which also evaluated modern photon techniques (Table E2; available online at www.redjournal.org). Among the studies, one did not report actual dose to the breast tissue in Gy (RBE) but rather translated that dose into the risk of breast cancer development (65). In all of the studies, proton therapy lowered the mean radiation dose to the breast compared with 3D RT or mRT.

The average mean dose reduction compared with 3D RT ranged from 0.2 Gy (RBE) to 3.65 Gy (RBE), and when compared with IMRT, VMAT, and/or TomoTherapy, it ranged from 0.5 Gy (RBE) to 6.4 Gy (RBE). The largest dose difference for proton therapy compared with 3D RT was observed in a study that used only posterior fields to maximize sparing of the breast while ignoring the heart dose (59). On the other hand, the study that demonstrated the largest difference in dose compared with VMAT was by Maraldo et al (62), which analyzed young women with large bulky mediastinal disease. It is important to note that, when one is evaluating the breast dose with more modern photon treatment, field design is critical, as pointed out in the study by Cella et al (57), which evaluated a standard IMRT plan, an fIMRT plan that forcibly avoided the breasts, and a TomoTherapy plan. They found that the fIMRT plan was always better at reducing the radiation dose to the breasts compared with IMRT or TomoTherapy; however, the trade-off was a higher mean heart dose with the fIMRT plan compared with either the IMRT or TomoTherapy plan.

Something that was not well addressed in these publications but was observed among the average breast dose-volume histogram comparisons for 3D RT, IMRT, and proton therapy was that a higher volume of breast tissue receives low-dose RT (<12 Gy) while a smaller volume receives higher-dose RT (>15 Gy) when compared with proton therapy or 3D RT (53). Currently, no well-validated model is available to use and no perfect dose-volume histogram point has been established to help identify the risk of breast cancer for these different scenarios, leading us to ultimately base conclusions on the mean breast dose.

Proton therapy can lower the mean breast dose compared with photons; however, this benefit may be small (mean dose difference of 1.47 Gy [RBE] compared with 3D RT and 2.45 Gy [RBE] compared with mRT) in some cases and, depending on the proton therapy technique, not worth other OAR trade-offs (eg, heart dose). On the other hand, the magnitude of the benefit might be greater for patients with certain disease distributions, such as axillary disease or bulky lower mediastinal disease, that may put more of the breast tissue into the radiation field (72).

Lung

Ten distinct studies have evaluated the dose of radiation to the lung with proton therapy (53, 55-59, 61-63, 65) (Table E3; available online at www.redjournal.org). Of these studies, 6 compared proton therapy using a passive-scatter technique while 4 used PBS. In general, all of the studies demonstrated a significant mean dose reduction to the lungs using proton therapy, with larger benefits seen when compared with IMRT (mean difference, 3.28 Gy [RBE]) than when compared with 3D RT (mean difference, 2.81 Gy [RBE]). However, because of the higher conformality of mRT in the high-dose region, the $V_{20\ Gy\ (RBE)}$ with mRT was unchanged while there was a difference of 9.1% compared with 3D RT.

The 3 studies with the largest difference in mean dose to the lungs with proton therapy compared with 3D RT reported actual treatment with proton therapy (53, 61, 63). These studies may have seen larger differences in mean dose to the lungs owing to selection bias in that patients expected to benefit more from proton therapy, and because of large bulky mediastinal disease, might preferentially be referred for proton therapy. In addition, of all of the studies, these 3 are likely to have included the most objective and robust planning, which may have led to more optimal beam arrangements, as seen in the use of an AP field rather than an AP-PA or PA field arrangement to treat anterior mediastinal disease. An interesting finding is that in the study by Andolino et al (59), in which posterior fields were used to protect breast tissue, proton therapy did not help in sparing the heart or lung.

The 2 studies that evaluated the treatment of post-chemotherapy residual disease demonstrated the smallest differences in mean dose to the lung of 1.79 Gy (RBE) and 0.45 Gy (RBE). This is likely because of the smaller target volumes, which one would expect would lessen the absolute benefit in dose reduction when compared with the larger volumes. The dose reduction to the lungs seen across all of these dosimetric studies (with an average dose reduction of 2.81 Gy [RBE] when compared with 3D RT and 3.28 Gy [RBE] when compared with mRT) is expected to translate into lower rates of RP, fibrosis, pulmonary dysfunction, and risk of secondary lung cancer with proton therapy compared with photon therapy.

Thyroid

Seven studies evaluated the radiation dose delivered to the thyroid from proton therapy compared with 3D RT, 6 of which also evaluated mRT (Table E4; available online at www.redjournal.org). Most studies specified that treatment was delivered to at least the head and neck region plus the mediastinum for most patients. No significant difference in mean dose to the thyroid was found between proton and photon therapy in 5 of the 7 studies. One study showed a lower mean thyroid dose using protons compared with 3D

RT (15.8 Gy [RBE] vs 21.5 Gy [RBE], $P = .004$); this study used a posterior-only proton field, whereas an anterior approach was used in all other studies (59). One study, which was the only to use a formal thyroid dose constraint, resulted in the lowest thyroid $V_{30\ Gy\ (RBE)}$ being achieved with PBS (7%) compared with 3D RT (93.9%), IMRT (60%), and TomoTherapy (45%) (57). Important to note is that these results were achieved only when treatment of the bilateral supraclavicular regions and mediastinum was assumed; the thyroid $V_{30\ Gy\ (RBE)}$ was no lower with proton therapy compared with TomoTherapy if only one supraclavicular region and the mediastinum were treated. Collectively, these data imply that thyroid dose reductions may be achieved with proton therapy for patients with HL receiving RT to the neck and thorax depending on the proximity of the target volume to the thyroid, as well as the proton beam arrangement. However, the clinical implication of the dose reduction that may occur with an average mean dose difference of 1.43 Gy (RBE) compared with 3D RT and 2.09 Gy (RBE) compared with mRT may not significantly affect the risk of hypothyroidism or thyroid cancer, especially considering that thyroid cancer risk does not follow a linear dose-response curve.

Esophagus

Four dosimetric studies have evaluated the radiation dose to the esophagus with proton therapy (Table E5; available online at www.redjournal.org). The data demonstrate a meaningful reduction in esophageal exposure in 2 of the studies when proton therapy was compared with 3D RT (53, 63), while 2 studies that used posterior fields with and without anterior fields demonstrated little to no benefit with proton therapy. The data suggest that protons are particularly beneficial for esophageal sparing when anterior beams are used.

Jørgensen et al (64) compared 3D RT, VMAT, and proton therapy for 46 patients treated with involved-nodal RT to a prescription dose of 30.6 Gy (RBE). The mean esophagus dose with each technique was 16.4 Gy, 16.4 Gy, and 14.7 Gy (RBE), respectively ($P < .001$). The clinical effect of a difference in mean dose of approximately 2 Gy (RBE) and no difference in maximum dose is probably not substantial. Andolino et al (59) compared involved-field RT with 3D RT versus proton therapy in 10 women receiving 21 Gy (RBE). This study observed no difference in mean or maximum esophageal dose. For the proton therapy plans in these cases, priority was given to breast sparing and posterior beams were used in all cases. Li et al (63) compared 3D RT with proton therapy in 10 patients receiving between 30.6 Gy (RBE) and 50.4 Gy (RBE). They found a large difference in all dose-level exposures to the esophagus, including mean dose (9.5 Gy vs 22.3 Gy), $V_{5\ Gy\ (RBE)}$ (37% vs 63%), $V_{10\ Gy\ (RBE)}$ (34% vs 60%), and $V_{30\ Gy\ (RBE)}$ (15% vs 49%). No elective nodal irradiation was performed, and the PTV was essentially a 1-cm expansion from the gross tumor volume. Hoppe et al (53) compared 3D RT, IMRT, and proton therapy in 15 patients receiving involved-node RT as per the European Organisation for Research and Treatment of Cancer guidelines. This study found a significant difference in mean esophagus dose between the techniques (20.3 Gy, 16.4 Gy, and 13.4 Gy [RBE], respectively). Overall, that the weighted average dose reduction was 3.9 Gy (RBE) compared with 3D RT and 1.8 Gy (RBE) compared with mRT suggests that there might be instances in which proton therapy may help reduce the impact of esophagitis, which could be important in certain clinical situations.

Body

Three published dosimetry studies have compared the radiation dose received by the total body with 3D RT, IMRT, and proton therapy plans in patients with HL (Table E6; available online at www.redjournal.org). One study reported it by integral dose ([Body − CTV (in milliliters)] × Mean dose = Integral dose [in joules]), while the other two reported it as mean dose to the body that was used for planning. Each study concluded that proton therapy can significantly reduce the overall dose of radiation the body received during RT compared with a variety of photon therapy techniques. Investigators at UF compared the proton plans of 20 patients receiving involved-nodal irradiation on a clinical trial versus 3D RT and IMRT plans and found that the integral dose was reduced with proton therapy by an average of 69 J (relative reduction, 57%) compared with 3D RT and by an average of 50 J (relative reduction, 49%) with IMRT (53). Chera et al (55) reported the mean body dose, $V_{4\ Gy\ (RBE)}$, $V_{10\ Gy\ (RBE)}$, volume receiving ≥16 Gy (RBE) ($V_{16\ Gy\ [RBE]}$), volume receiving ≥24 Gy (RBE) ($V_{24\ Gy\ [RBE]}$), and $V_{30\ Gy\ (RBE)}$ for 3D RT, IMRT, or passive-scattering proton therapy plans in 9 patients (27 plans) with stage II HL. They found that proton therapy significantly reduced the mean total body dose ($P < .0001$) and $V_{4\ Gy\ (RBE)}$ to $V_{30\ Gy\ (RBE)}$ (all $P \leq .0003$) when compared with 3D RT and the mean dose ($P = .0002$) and $V_{4\ Gy}$ (RBE) ($P = .03$) when compared with IMRT. Similarly, in 14 patients with supradiaphragmatic HL, Horn et al (58) found that proton therapy significantly reduced the mean dose, $V_{4\ Gy\ (RBE)}$, $V_{10\ Gy\ (RBE)}$, volume receiving ≥15 Gy (RBE) ($V_{15\ Gy\ [RBE]}$), and $V_{20\ Gy\ (RBE)}$ compared with 3D RT (mean dose, 4.3 Gy vs 7.6 Gy [RBE]; $P < .01$) or helical TomoTherapy (mean dose, 4.3 Gy vs 7.2 Gy [RBE]; $P < .01$). It is important to note that all 3 dosimetric studies came to a similar conclusion that proton therapy results in a reduction in mean body and integral doses compared with photon-based techniques. This difference may be particularly important when considering the risk of second cancers, including rarer tumors such as sarcomas, which—although rare for an individual—can add up to substantial numbers in populations of long-term survivors of lymphoma.

Impact of breath-hold technique

As discussed earlier, only one of the dosimetric comparative studies included the breath-hold technique with

photons or protons. In the photon studies comparing IMRT with 3D RT techniques, use of deep-inspiration breath hold (DIBH) reduced the dosimetric advantages of IMRT over 3D RT (73). With DIBH, the dose reduction to OARs appears greater for patients whose disease is localized to the superior mediastinum (74). However, no standard approach exists for using DIBH in lymphoma, and challenges of reproducibility, especially when treatment requires multiple breath holds per fraction, are a concern without real-time imaging for confirmation. These uncertainties may pose an even greater problem in proton therapy, which is more sensitive to unanticipated setup issues than photon therapy.

Incorporating DIBH with photon techniques may decrease some of the observed dosimetric benefits of protons (when treating with free breathing), although this depends on the initial extent of disease. In patients with disease limited to the superior mediastinum (above the carina), DIBH with photons may be associated with similar doses to the heart compared with free-breathing proton therapy, especially with lower prescription doses (such as 20 Gy [RBE]); however, DIBH with IMRT would still lead to a much higher integral body dose than free-breathing proton therapy. Furthermore, when mediastinal disease extends below the carina (eg, cardiophrenic lymph nodes), DIBH may not provide as great of a dose reduction to the heart given that the target volume must extend inferiorly to the heart (69). In a small dosimetric study (n=7) comparing IMRT, intensity modulated proton therapy, and DIBH presented only in abstract form, the differences between intensity modulated proton therapy with free breathing and IMRT with DIBH were not statistically significant, aside from lower mean dose to the breast favoring protons (75). On the other hand, centers that have been treating patients with proton therapy have observed that, in patients with lower mediastinal disease that drapes in front of the heart and/or involves cardiophrenic nodes, free-breathing proton therapy remains superior to DIBH with IMRT for the heart and integral dose (Fig. E1; available online at www.redjournal.org) (69).

Review of Clinical Evidence for Proton Therapy

In light of conformal dose distributions with protons, coupled with modern treatment using smaller fields and lower radiation doses, some investigators have raised concerns about the potential of increased recurrences, in particular at the field edge. Studies have demonstrated excellent outcomes after passive scatter– and uniform scanning–based proton therapy that are comparable with historical controls. The first clinical outcomes were reported from UF. In its phase 2 study of 15 patients with stage I to III HL treated with consolidative involved-node proton therapy, the 3-year relapse-free survival rate was 93%, with 1 relapse both within and outside the target field (54). Recently, UF reported outcomes from 22 patients with pediatric HL (7 intermediate risk, 11 high risk, and 4 relapsed) treated to a median dose of 21 Gy (RBE). With a median follow-up of 36 months, there were 3 recurrences (2-year progression-free survival rate, 86%) that occurred exclusively within the high-risk group. One was an isolated in-field recurrence, while 2 were both in field and out of field (76).

Similar outcomes have been replicated at other academic- and community-based proton centers (77, 78) where consolidation proton therapy has primarily been used for young patients with mediastinal HL and bulky disease (78). Among 40 patients with HL treated with consolidation proton involved-site RT and prospectively followed up in the Proton Collaborative Group Registry, there were 3 recurrences (2-year relapse-free survival rate, 85%) in a cohort predominantly composed of patients with unfavorable stage I or II disease (45%) or stage III or IV disease (33%). Two recurrences were in field within bulky mediastinal disease treated to 21 Gy (RBE); one was superior to the CTV and would have been outside the photon field as well (77). In the largest study to date, comprising 135 patients prospectively followed up who had HL treated with protons (including 40 in the aforementioned Proton Collaborative Group Registry), the 3-year progression-free survival rate was 92% (78). In addition, Massachusetts General Hospital in Boston reported treating 46 patients with lymphoma (including both HL [n=34] and NHL [n=12] and patients with relapsed or refractory disease [28%]) and demonstrated, with a median follow-up of 50 months, a 5-year progression-free survival rate of 80% with no evidence of any significant proton therapy–related toxicities with the exception of hypothyroidism (79).

Investigators at UF also reported their outcomes with proton therapy for the management of a small cohort of NHL patients, which included patients with primary mediastinal B-cell lymphoma, orbital lymphoma, natural killer/T-cell lymphomas, and plasmablastic lymphoma (80). With a 38-month median follow-up, the 2-year local control rate was 91%, with an in-field recurrence developing at the completion of proton therapy in 1 patient with natural killer/T-cell lymphoma, while no grade 3 toxicities were observed within the rest of the cohort.

Proton therapy outcomes with PBS techniques are also beginning to emerge. Preliminary data from the University of Pennsylvania in Philadelphia have demonstrated promising results with PBS (81), which generally yields more conformal dose distributions but requires additional attention to motion management. Patients treated with PBS had limited motion in the orthogonal planes (<5 mm), and dose repainting was performed when only 1 field was used. With a relatively short follow-up period (median, 7.2 months), 1 out-of-field recurrence has occurred among the 12 adult patients. Similarly, the Proton Therapy Center of Prague recently reported its experience using PBS for mediastinal lymphoma (82). Among 35 patients treated thus far with a median follow-up period of 10 months, no grade 3 toxicities or grade 2 pneumonitis has been observed. Furthermore, only 2 patients had disease relapse and both of these occurred outside of the proton field.

Notably, across all studies, no proton-related grade 3 or higher acute or late complications have been observed. Acute grade 2 toxicities included esophagitis, dermatitis, and fatigue, as expected with photon therapy. At least a decade of follow-up is needed to realize the potential benefit of protons in reducing RT-associated late effects. Nonetheless, these early data provide reassurance that using more conformal treatment with protons is not associated with increased marginal recurrences and that excellent cure rates are still maintained as has been observed in a few IMRT series for HL (83-85).

Recommendations

In summary, substantial published data suggest important dose-response relationships with late toxicity in a number of organs of concern among survivors of lymphoma. Significant data exist from 14 radiation treatment planning studies demonstrating that proton therapy has reduced radiation exposure to the OARs compared with photon RT. Unsurprisingly, there are substantially different levels of predicted benefit based on individual patient age, sex, and disease distribution, as well as the specific methods used for photon and proton planning; indeed, the potential benefit regarding protons may vary by patient in the era of involved-site RT, given that the initial sites of involvement dictate the areas that need to be covered. In view of the fact that randomized clinical trial data will likely never exist to test the predicted benefits of proton therapy in reducing late toxicities in patients treated for lymphoma, as the necessity for at least a decade of follow-up and already low event rates render such a study extremely challenging, proton therapy should be reasonably considered in appropriately selected lymphoma patients when it can significantly decrease the dose to critical structures. Ideally, these patients should be enrolled on prospective clinical trials or with registries that gather patient outcomes and radiation dosimetry information for future research purposes, and they should be considered in the development of a model-based approach for identifying those who may benefit the most from proton therapy.

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