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Clinical Investigation

Predictors of Radiation Pneumonitis in Patients Receiving Intensity Modulated Radiation Therapy for Hodgkin and Non-Hodgkin Lymphoma

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Summary

Threshold lung doses associated with radiation pneumonitis (RP) are not well established for patients receiving modern mediastinal radiation for lymphoma. This review found that 14% of patients who received intensity modulated radiation therapy for lymphoma developed grade 1 to 3 RP.

Purpose: Few studies to date have evaluated factors associated with the development of radiation pneumonitis (RP) in patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), especially in patients treated with contemporary radiation techniques. These patients represent a unique group owing to the often large radiation target volumes within the mediastinum and to the potential to receive several lines of chemotherapy that add to pulmonary toxicity for relapsed or refractory disease. Our objective was to determine the incidence and clinical and dosimetric risk factors associated with RP in lymphoma patients treated with intensity modulated radiation therapy (IMRT) at a single institution.

Methods and Materials: We retrospectively reviewed clinical charts and radiation records of 150 consecutive patients who received mediastinal IMRT for HL and NHL from 2009 through 2013. Clinical and dosimetric predictors associated with RP according to Radiation Therapy Oncology Group (RTOG) acute toxicity criteria were

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All dosimetric parameters predicted RP risk, but low doses to large lung volumes was a particularly strong predictor. Patients undergoing salvage chemotherapy for relapsed or refractory disease who undergo peritransplant mediastinal RT are at the greatest risk of RP.

identified in univariate analysis using the Pearson χ^2 test and logistic multivariate regression.

Results: Mediastinal radiation was administered as consolidation therapy in 110 patients with newly diagnosed HL or NHL and in 40 patients with relapsed or refractory disease. The overall incidence of RP (RTOG grades 1-3) was 14% in the entire cohort. Risk of RP was increased for patients who received radiation for relapsed or refractory disease (25%) versus those who received consolidation therapy (10%, $P = .019$). Several dosimetric parameters predicted RP, including mean lung dose of >13.5 Gy, V_{20} of >30%, V_{15} of >35%, V_{10} of >40%, and V_5 of >55%. The likelihood ratio χ^2 value was highest for V_5 >55% ($\chi^2 = 19.37$).

Conclusions: In using IMRT to treat mediastinal lymphoma, all dosimetric parameters predicted RP, although small doses to large volumes of lung had the greatest influence. Patients with relapsed or refractory lymphoma who received salvage chemotherapy and hematopoietic stem cell transplantation were at higher risk for symptomatic RP.

Introduction

Consolidative radiation after initial systemic therapy has been shown to improve event-free survival rates in both Hodgkin lymphoma and non-Hodgkin lymphoma (1-5). Furthermore, for patients with relapsed or refractory disease, radiation therapy (RT) can offer meaningful local disease control (6, 7). An ongoing concern, however, is acute and chronic toxicity related to RT. For patients with Hodgkin lymphoma, most of whom receive bleomycin, concern has been expressed about superimposing lung damage from radiation on pulmonary toxicity from bleomycin.

Radiation pneumonitis (RP) is one of the main dose-limiting toxicities among patients receiving thoracic RT. Classic RP presents at 1 to 6 months after RT as a dry cough, dyspnea (with exertion or at rest), low-grade fever, and pleuritic chest pain. Often, evidence of damage within the radiation field, such as ground glass opacities or consolidative change, appears on radiography. In mild cases (ie, in Radiation Therapy Oncology Group [RTOG] grade 1 RP criteria), cough and dyspnea on exertion are mild and self-limited (8). In more serious cases, severe cough and dyspnea at rest can require steroid therapy (RTOG grade 3) or continuous O_2 therapy (RTOG grade 4).

Identification of dosimetric predictors of RP was initially established in the treatment of non−small-cell lung cancer, when Graham et al (9) reported the percentage of lung volume receiving 20 Gy (V_{20}) and the mean lung dose (MLD) were correlated with RTOG grade 2 or higher RP in 99 patients treated with 3-dimensional (3D) conformal RT (9). Numerous groups subsequently endorsed these findings (10-12). Fewer publications, however, have addressed whether lung dose-volume metrics can predict RP in patients with lymphoma.

Koh et al (13) found a low incidence of RP of 3% among 64 patients with Hodgkin lymphoma who received involved-field RT with 3D planning between 2003 and 2005. They identified V_{20} of 36% and MLD of 14 Gy as predicting rates of RTOG grade 2 RP exceeding 11%. Fox et al published the largest study to date among patients with Hodgkin lymphoma treated to the mediastinum and found that MLD of 13.5 Gy or greater and V_{20} of ≥33.5% predicted RP in 92 patients treated with 3D conformal involved-field RT between 2003 and 2007 (14). Of particular interest was the increased risk of more severe RP among peritransplantation patients, 35% of whom had RTOG grade 3 RP.

As intensity modulated RT (IMRT) is increasingly being used for patients with lung cancer, new dosimetric predictors of RP have emerged. The volume of lung that receives lower doses of radiation, such as 5 to 10 Gy, seems to correlate more closely with risk of RP than conventionally accepted V_{20} values (15, 16). To our knowledge, no report of dosimetric predictors for RP among patients with lymphoma who receive IMRT has been published. The objective of the current study, therefore, was to determine the incidence of RP among such patients and to review clinical and radiation-dosimetric factors potentially associated with the development of RP.

Methods and Materials

Patients

After approval by the appropriate institutional review board, we identified 165 consecutive patients with Hodgkin or non-Hodgkin lymphoma treated to the mediastinum with IMRT at our institution between January 2009 and November 2013. Fifteen of these patients were excluded for lack of follow-up, leaving 150 for the current analysis. Clinical notes, radiographic studies, laboratory results, and pulmonary function test results were reviewed retrospectively. Pulmonary function testing was done immediately before RT in most cases. Dose-volume histogram data were obtained from electronic radiation treatment planning documents.

Treatment planning

Treatments were simulated while patients were immobilized in the supine position with customized Vac-lock cradles. Most female patients were positioned on a 10°- to 15°-inclined board to minimize dose to the breasts (17). The breath-hold technique had been used only sporadically before 2012 but was used routinely after 2012. For patients who did not hold their breath during treatment planning, 4D computed tomography (CT) was used to account for respiration-induced motion of the target within the thorax. For patients who achieved a complete response after chemotherapy, radiation was delivered to involved sites with the goal of targeting prechemotherapy sites of disease involvement, with appropriate setup margin used according to recent guidelines from the International Lymphoma Radiation Oncology Group (18, 19). For patients with gross disease at the time of radiation, the fields were more generous and included the gross tumor and prophylactic coverage of adjacent mediastinal nodal stations.

A commercial treatment planning system was used to develop the IMRT plans. A 5-beam anterior-posterior weighted "butterfly" beam arrangement was used for treatment planning with coplanar 6-MV photon beams (20). Tissue heterogeneity corrections were applied to the final dose distribution. Normal structures, including the lungs, were delineated on the planning simulation scan. The total normal lung volume did not exclude the target gross tumor volume, clinical target volume, or planning target volume from the lung parenchyma. According to institutional standards for treating the thorax for hematologic malignancies, the pulmonary goals for planning were to keep the MLD to <14 Gy, V_{20} to <35%, V_{10} to <50%, and V_5 to <60%. When these dosimetric constraints could not be achieved, approval of the plan was at the discretion of the treating physician. IMRT was delivered with step-and-shoot multileaf collimation. For most patients treated with breath-hold technique to the mediastinum, 5 to 7 beams were used. The average patient performed 20-second breath-holds throughout the treatment. Each beam generally required 1 to 2 breath-holds to complete treatment for each field. Image-guided RT was based on either daily kV imaging or low-dose daily CT-on-rails (Varian Medical Systems, Palo Alto, CA).

Follow-up evaluations

Follow-up evaluations took place 1 to 3 months after completion of RT and then at 3- to 6-month intervals thereafter, with interval history and physical examination, basic laboratory studies, and CT scans with or without positron-emission tomography (PET)-CT.

RP was scored according to RTOG acute radiation morbidity scoring criteria for pneumonitis (8). We considered all grades of RP to be significant. Charts were reviewed by a board-certified radiation oncologist. The diagnosis of RP was based on the appropriate clinical symptoms with corresponding radiographic changes within the radiation field occurring within 12 months of completion of radiation therapy without evidence of other competing diagnoses (eg, infectious causes). The time to RP was defined relative to the final day of RT.

Statistical analysis

We examined the following clinical factors for potential association with RP: ethnicity, sex, age, lymphoma histology, disease stage, axillary involvement requiring radiation, type of initial chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine [ABVD] vs other regimens), number of chemotherapy cycles, number of bleomycin cycles, history of bleomycin toxicity, history of salvage chemotherapy before RT, peritransplant RT, bulky disease (>10 cm), history of smoking, history of asthma or chronic obstructive pulmonary disease (COPD), preradiation pulmonary function test values, and use of breath-hold during treatment. Dosimetric factors considered were total lung dose, lung V_{25}, V_{20}, V_{15}, V_{10}, and V_5, and MLD.

Pearson's χ^2 test was used to assess measures of association in frequency tables. The equality of group medians was assessed with nonparametric tests for equality. Receiver operating characteristic (ROC) analysis and logistic regression were done to assess whether dosimetric factors could predict the development of RP. Threshold doses for RP risk and doses corresponding to the optimal point of the ROC curve were determined. Multivariate logistic models identified independent predictors of pneumonitis. Additionally, individual logistic models, each testing for a difference dosimetric parameter, were tested. For each model, the likelihood ratio χ^2 values were obtained and tested for significance against the baseline model including all covariates except the dosimetric parameter. P values of $\leq$.05 were considered statistically significant. Statistical tests were based on a 2-sided significance level. All data analyses were done with Stata/MP version 13.0 software (StataCorp, College Station, TX).

Results

Characteristics of the 150 patients included in the study are listed in Table 1, and treatment details are shown in Table 2. Of 150 patients, 40 had relapsed or refractory disease and received salvage chemotherapy. Of these 40 patients, 37 underwent autologous stem cell transplantation (n = 30) or allogeneic stem cell transplantation (n = 6) or both (n = 1).

Twenty-one patients (14% of the entire group) developed pneumonitis at a median 2.04 months after completion of RT (range: 0.33-9.18 months). RP was grade 1 in 9 cases, grade 2 in 2 cases, and grade 3 in 10 cases (Table 3). No patient had grade 4 or 5 RP. The incidence of severe (grade 3) RP was 6.7% for all patients. Among the 110

Table 1 Baseline characteristics of 150 patients who received mediastinal radiation therapy for Hodgkin or non-Hodgkin lymphoma

Characteristic	Value or no. of patients (%)
Age	
Median, years (range)	33.0 (16.6-78.1)
Sex	
Female	88 (58.7)
Male	62 (41.3)
Ethnicity	
White	109 (72.7)
African-American	12 (8.0)
Hispanic	18 (12.0)
Asian	5 (3.3)
Other	6 (4.0)
Tumor histology	
Hodgkin lymphoma	110 (73.3)
Non-Hodgkin lymphoma	40 (26.7)
Disease stage	
I	16 (10.7)
II	106 (70.7)
III	11 (7.3)
IV	17 (11.3)
Bulky disease (>10 cm)	
Yes	87 (58)
No	63 (42)
Smoking history	
Yes	36 (24)
No	114 (76)
Asthma/COPD	
Yes	7 (4.7)
No	143 (95.3)
% of pre-RT FVC	
Median	94.0
Range	45-136
% of pre-RT FEV1	
Median	94.5
Range	28-134
% of corrected pre-RT DLCO, corrected	
Median	81.5
Range	31-130

Abbreviations: COPD = chronic obstructive pulmonary disease; pre-RT DLCO = preradiation diffusion lung capacity for carbon monoxide; Pre-RT FEV1 = preradiation forced expiratory volume in 1 second; Pre-RT FVC = preradiation forced vital capacity.

patients who received mediastinal RT as consolidation after initial chemotherapy, the incidence of any RP was 10%. Among the 40 patients with relapsed or refractory disease who received salvage chemotherapy, the incidence of RP was significantly higher at 25% ($P = .019$).

For the 21 patients who developed RP, the median MLD was 12.9 Gy (range: 8.2-16.3 Gy) compared with 10.3 Gy (range: 3.8-16.0 Gy) among patients who did not develop RP. The corresponding V_5 was 58% for those who had RP (range: 38%-66%) versus 49% for those who did not (range: 23%-64%). Other dosimetric parameters analyzed are listed in Table 4.

Dosimetric and clinical factors potentially predictive of RP are listed in Table 5. For all dosimetric parameters examined (V_{25}, V_{20}, V_{15}, V_{10}, V_5, and MLD), cutoff values were identified that were significantly associated with RP. ROC were generated to identify the predictive abilities of the dosimetric variables found to be significant on paired t tests by using the areas under the ROC. Based on these

Table 2 Treatment characteristics for 150 patients given mediastinal radiation therapy for Hodgkin or non-Hodgkin lymphoma

Characteristic	Value or no. of patients (%)
ABVD	
Yes	109 (72.7)
No	41 (27.3)
Cycles of chemotherapy	
Median (range)	6 (0-8.5)
Cycles of Bleomycin	
Median (range)	4 (0-8.5)
Bleomycin toxicity	
Yes	17 (11.3)
No	133 (88.7)
Salvage chemotherapy pre-RT	
Yes	40 (26.7)
No	110 (73.3)
Transplant	
Yes	37 (24.7)
Autologous	30
Allogeneic	6
Both	1
No	113 (75)
RT before transplant	13 (35)
RT after transplant	24 (64.9)
Radiation dose	
Median	30.6
Range	20-44.6
≤30.6 Gy	90
>30.6 Gy	60
Axilla treated	
Yes	23 (15.3)
No	127 (84.7)
Breathhold	
Yes	70 (46.7)
No	80 (53.3)
V_{25}	
Median (range)	18 (0-34)
V_{20}	
Median (range)	24 (4-40)
V_{15}	
Median (range)	30.0 (10-45)
V_{10}	
Median (range)	37.0 (15-59)
V_5	
Median (range)	50 (23-66)
Mean lung dose	
Median (range)	10.6 (3.8-16.3)

Abbreviation: ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine.

Table 3 Radiation pneumonitis according to the purpose of radiation therapy

Pneumonitis	No. of patients (%)		
	All patients (n=150)	Consolidative RT patients (n=110)	Patients with relapsed or refractory disease (n=40)
None	129 (86)	99 (90)	30 (75)
Any	21 (14)	11 (10)	10 (25)
Grade 1	9 (6)	6 (5.5)	3 (7.5)
Grade 2	2 (1.3)	0 (0)	2 (5.0)
Grade 3	10 (6.7)	5 (4.5)	5 (12.5)

findings, the following most rigorous cutoff values for dosimetric parameters were identified as being significantly associated with the development of any RP (grades 1-3): MLD of ≥13.5 Gy ($P<.001$), V_{25} of >23% ($P=.001$), V_{20} of >30% ($P=.002$), V_{15} of ≥35% ($P<.001$), V_{10} of ≥40% ($P=.001$), and V_5 of ≥55% ($P<.001$). RP developed in 9 of 18 patients (50%) with an MLD of >13.5 Gy versus 12 of 130 patients (9.2%) with an MLD of ≤13.5 Gy; 12 of 40 patients (30%) with V_{25} of >23% versus 9 of 110 patients (8.2%) with V_{25} of <23%; 8 of 23 patients (34.8%) with V_{20} of >30% versus 13 of 127 patients (1.2%) with V_{20} of <30%; 11 of 34 patients (32.4%) with V_{15} of <35% versus 10 of 116 patients (8.6%) with V_{15} of <35%; 13 of 47 patients (27.7%) with V_{10} of >40% versus 8 of 103 patients (7.8%) with V_{10} <40%; and 14 of 40 patients (35%) with V_5 of >55% versus 7 of 110 patients (7.0%) with V_5 <55%. The only clinical factors found to predict the development of RP was history of relapsed or refractory disease, for which transplantation or salvage chemotherapy (or both) was given. Race, disease stage, sex, age, type of chemotherapy, number of chemotherapy cycles, history of bleomycin toxicity, disease bulk, history of smoking, history of asthma or COPD, and pre-RT pulmonary function test values did not predict RP (Table 5). Among the patients who received peritransplant RT, no significant differences were found between rates of RP for patients who received RT before or after transplantation ($P=.501$) (Table 5). On logistic regression, dosimetric dose-volume and MLD parameters remained significant (Table 6). History of salvage chemotherapy (odds ratio [OR] = 3.00, 95% confidence interval [CI]: 1.16-7.75, $P=.023$) and transplantation (OR = 2.71, 95% CI: 1.04-7.07, $P=.042$) remained independent predictors of RP on univariate analysis.

In separate multivariate models testing each possible dosimetric threshold, every cutoff from V_5 to V_{25} was

Table 4 Dosimetric predictors of radiation pneumonitis

Parameter	No pneumonitis	Any pneumonitis	*P* value
Mean lung dose, Gy			
Median (range)	10.3 (3.8-16.0)	12.9 (8.9-16.3)	.018
% receiving V_{25}			
Median (range)	18.0 (0-34)	24.0 (14-32)	.254
% receiving V_{20}			
Median (range)	23.0 (4-40)	30.0 (20-37)	.228
% receiving V_{15}			
Median (range)	28.0 (10-45)	36.0 (23-43)	.022
% receiving V_{10}			
Median (range)	36.0 (15-59)	44.0 (28-51)	.051
% receiving V_5			
Median (range)	49.0 (23-64)	58.0 (38-66)	.008

Table 5 Clinical and dosimetric factors potentially associated with radiation pneumonitis

Factor*	No. of patients (%)		
	Patients with no pneumonitis (n=129)	Patients with any pneumonitis (n=21)	*P* value
Mean lung dose			
>12 Gy	34 (26.4)	12 (57.1)	.005
>13 Gy	17 (13.2)	10 (47.6)	<.001
>13.5 Gy	9 (7.0)	9 (42.9)	<.001
>14 Gy	5 (3.9)	6 (28.6)	<.001
V_5			
>50%	49 (38.0)	15 (71.4)	.004
>55%	26 (20.2)	14 (66.7)	<.001
>60%	10 (7.8)	5 (23.8)	.023
V_{10}			
>30%	94 (72.9)	20 (95.2)	.026
>35%	66 (51.2)	16 (76.2)	.033
>40%	34 (26.4)	13 (61.9)	.001
>45%	12 (9.3)	7 (33.3)	.002
V_{15}			
>25%	83 (64.3)	20 (95.2)	.005
>30%	54 (41.9)	15 (71.4)	.012
>35%	23 (17.8)	11 (52.4)	.001
>40%	5 (3.9)	2 (9.5)	.255
V_{20}			
>25%	52 (40.3)	13 (61.9)	.064
>30%	15 (11.6)	8 (38.1)	.002
>33%	8 (6.2)	5 (23.8)	.008
>35%	3 (2.3)	2 (9.5)	.088
V_{25}			
>20%	46 (35.7)	13 (61.9)	.022
>23%	28 (21.7)	12 (57.1)	.001
>25%	13 (10.1)	7 (33.3)	.004
History of bleomycin toxicity	16 (12.4)	1 (4.8)	.306
History of smoking	28 (21.7)	8 (38.1)	.103
Bulky disease (>10.0 cm)	75 (58.1)	12 (57.1)	.932
Relapsed or refractory disease	30 (23.2)	10 (47.6)	.019
Use of breathhold	60 (46.5)	10 (47.6)	.925
Peritransplant radiation	28 (21.7)	9 (42.9)	.037
Before transplant	9 (69.2)	5 (20.8)	.501
After transplant	19 (79.2)	4 (30.8)	

* Factors in boldface type represent the most significant cutoff points for RP according to receiver operating characteristic curves.

significant. However, the likelihood ratio χ^2 value was largest for the model including the V_5 dosimetric factor, where V_5 was >55% (likelihood ratio χ^2 = 19.37), highlighting the strength of this dosimetric parameter for predicting the variance in pneumonitis risk (Table E1; available online at www.redjournal.com). MLD was also a strong predictor (likelihood ratio χ^2 = 15.17). In contrast, the lowest likelihood ratio χ^2 value was for V_{20} of >30% (likelihood ratio χ^2 = 8.33).

Table 6 Univariate analysis of potential clinical and dosimetric factors associated with radiation pneumonitis

Parameter	Odds ratio	95% CI	*P* value
Mean lung dose			
Continuous	1.46	1.17-1.83	.001
>12 Gy	1.91	1.19-3.07	.008
>13 Gy	2.43	1.47-3.99	<.001
>13.5 Gy	3.14	1.81-5.43	<.001
>14 Gy	3.12	1.63-5.99	.001
V_5			
Continuous	1.12	1.05-1.20	.001
>50%	4.08	1.48-11.22	.006
>55%	7.92	2.90-21.63	<.001
>60%	3.72	1.13-12.27	.031
V_{10}			
Continuous	1.12	1.04-1.20	.002
>35%	3.05	1.06-8.83	.039
>40%	4.54	1.73-11.90	.002
>45%	4.88	1.65-14.42	.004
V_{15}			
Continuous	1.13	1.05-1.22	.002
>25%	11.08	1.44-85.28	.021
>30%	3.47	1.27-9.53	.016
>35%	5.07	1.93-13.34	.001
>40%	2.61	0.47-14.43	.271
V_{20}			
Continuous	1.12	1.03-1.21	.005
>25%	2.41	0.93-6.21	.07
>30%	4.68	1.67-13.13	.003
>33%	4.73	1.38-16.22	.014
>35%	4.42	0.69-28.20	.116
V_{25}			
Continuous	1.12	1.03-1.21	.005
>20%	2.93	1.13-7.59	.027
>23%	4.81	1.84-12.56	.001
>25%	4.46	1.53-13.05	.006
Pre-RT FVC	1.00	0.97-1.03	.999
Pre-RT FEV1	1.00	0.97-1.03	.882
Pre-RT DLCO (corrected)	1.00	0.96-1.03	.869
Radiation dose			
Continuous	1.13	1.03-1.24	.012
>30.6 Gy	2.19	0.86-5.59	.1
History of bleomycin toxicity	0.35	0.04-2.81	.326
History of smoking	2.22	0.84-5.89	.109
Bulky disease (>10.0 cm)	0.96	0.38-2.44	.932
Relapsed/refractory disease	3.00	1.16-7.75	.023
Use of breath-hold	1.05	0.42-2.63	.925
Peritransplant RT	2.71	1.04-7.07	.042

Abbreviations: Pre-RT DLCO = pre-radiation diffusion lung capacity for carbon monoxide; Pre-RT FEV1 = pre-radiation forced expiratory volume in 1 second; Pre-RT FVC = pre-radiation forced vital capacity.

Discussion

To our knowledge, this is the first study to specifically examine the incidence of and risk factors associated with the development of RP among patients with lymphoma treated with IMRT. The overall incidence of any RP (RTOG grades 1-3) was 14% among the entire group. However, patients who received salvage chemotherapy or transplantation for relapsed or refractory disease were at greater risk: the incidence of RP among those patients was 25% versus 10% among those who received consolidative RT for newly diagnosed disease. These numbers are strikingly similar to the incidence of RP in a large series of patients treated with anterior-posterior 3D conformal RT for Hodgkin lymphoma reported by Fox et al (14). In their study, RP developed in 14% of patients (13 of 92 patients), 10% for those with newly diagnosed disease versus 35% for those with relapsed and refractory lymphoma who received peritransplantation RT. These findings suggest that the risk of RP is greatest in patients treated for relapsed and refractory disease, and the overall risk of RP is comparable. However in the current series, we observed higher rates of grade 3 RP among patients who were treated with consolidative IMRT after initial chemotherapy. In the series by Fox et al (14), only 1 of 75 patients with newly diagnosed disease (1.3%) developed grade 3 RP compared to 5 of 110 patients in our study (4.5%). This suggests that when IMRT is used in this setting, even despite the use of low to moderate prescription doses, close adherence to pulmonary dose constraints should be maintained to limit the potential for grade 3 toxicity. Conversely, the rate of grade 3 RP was higher among relapsed and refractory patients treated with 3D conformal RT (4 of 17 patients [23.5%]) compared with IMRT in the current study (5 of 40 patients [12.5%]). This may be partially explained by the need to escalate doses in this patient population and the enhanced ability to modulate higher RT doses out of normal pulmonary tissue with IMRT.

In contrast to 3D conformal RT, distinct dosimetric parameters should be considered in IMRT planning and plan assessment. For patients treated with 3D conformal RT, the volume of lung receiving 20 Gy has consistently been found to predict the risk of symptomatic RP. In the study by Fox et al (14), a V_{20} of 33.5% was the threshold value. Koh et al (13) found that a V_{20} of 36% predicted RP among 64 patients with Hodgkin lymphoma who received 3D conformal RT to the thorax. Similarly, another study found that the volume of lung receiving 20 Gy predicted RP risk among 99 pediatric patients with Hodgkin lymphoma treated with 3D conformal RT (21). In the current study, in which IMRT was used exclusively for RT delivery, the V_{20} did predict RP risk; however, the volume of lung receiving

lower doses of radiation, especially V_5, was the most powerful predictor of RP. This finding has been endorsed in other studies evaluating the ability of dosimetric parameters to predict RP in the treatment of primary lung cancer with IMRT (15, 16). This result may reflect the conformality of the higher doses of radiation, in which the lower volumes being exposed to high doses become less clinically relevant. In turn, increases in the volume of lung that receives lower doses becomes more clinically meaningful with regard to pulmonary injury. This mechanism of lung damage would not be evident in patients treated with anterior-posterior 3D conformal RT plans because the volume of lung that would receive 5 Gy is typically no higher than the volume that receives 20 Gy. Therefore, from a clinical standpoint, evaluation of IMRT plans to the mediastinum must carefully consider not only the volume of lung receiving higher doses of radiation, because the V_{25}, V_{20}, and MLD were also predictive of RP in our patients, but also lower doses. Indeed, Fox et al (14) reported that an MLD of >13.5 Gy predicted RP, a finding consistent with the current study.

Use of IMRT in Hodgkin lymphoma has been questioned because of concern for the low-dose bath associated with use of multiple IMRT beams in a concentric beam arrangement. This raises concern for an increase in risk of secondary malignancy, particularly for young patients who often have an excellent long-term prognosis. To mitigate this concern, we used an anterior-posterior weighted IMRT beam arrangement with limited numbers of beams (typically 5) (20). This practice allows additional conformality around critical cardiac structures (the coronary arteries and left ventricle in particular) while it minimizes the low-dose exposure to the uninvolved thorax. We also used a breath-hold technique to minimize respiration-based motion and reduce lung exposure to radiation, although in this study, use of breath-hold was not associated with reduced risk of RP (22-24).

Bleomycin-induced lung injury requiring cessation of this drug is not uncommon among patients with Hodgkin lymphoma (25-27). Concern has been expressed about the safety of mediastinal RT after bleomycin pulmonary toxicity; however, we did not find RP to be associated with a history of bleomycin toxicity. Our findings endorses those of previous studies that mediastinal RT is not contraindicated after bleomycin lung injury (14, 28).

The risk of pneumonitis among patients who receive salvage chemotherapy and peritransplantation RT should not be taken lightly. High-dose chemotherapy followed by hematopoietic stem cell transplantation is associated with an inherent risk of pneumonitis, even in the absence of thoracic RT (29, 30). However, when peritransplantation RT is administered, the risk of pneumonitis increases, as shown in several studies (14, 31-33). One such study showed that RT given in the pretransplantation setting increased mortality among patients with Hodgkin lymphoma (33). Another group found that pretransplantation RT was significantly associated with grade 3 RP (57% vs 0% for post-transplantation RT, $P = .015$) (14). No patient in either of these 2 series experienced fatal RP. At our institution, preferred practice is for RT to be given after a stem cell transplantation; however, in circumstances where disease control cannot be achieved with salvage chemotherapy, RT is given before transplantation. Indeed, in the current study, RT was given before transplantation to 13 patients (35%) and after transplantation to 24 patients (74.9%). Overall, peritransplantation RT was associated with increased risk of RP (RP rate of 24% in peritransplantation patients vs 10.6% in newly diagnosed patients), but no differences in RP were found between patients who received RT before versus those who received transplantation afterward. The increased overall risk for RP among patients with relapsed or refractory disease highlights the need to carefully scrutinize IMRT plans to be given to patients receiving RT after salvage chemotherapy and in the peritransplantation period. It is plausible that a history of salvage chemotherapy alone, in the absence of transplantation, independently increases the risk relative to the transplant; however, we could not evaluate this point in the current study because almost all patients who received salvage chemotherapy went on to undergo autologous or allogeneic stem cell transplantation. Also important is that in the current study, the lung volume used did not exclude any target volumes, a point to be considered if the threshold values identified in this report are used.

Conclusions

In conclusion, MLD and low-dose parameters such as V_5, V_{10}, and V_{15} are valuable predictors for the development of RP in patients with lymphoma treated with IMRT. Patients with relapsed or refractory disease who receive salvage chemotherapy and undergo hematopoietic stem cell transplantation are at particularly high risk of RP. Regardless, when >55% of the total lung receives 5 Gy in the treatment of Hodgkin or non-Hodgkin lymphoma with IMRT, the risk of RP approaches 35%.

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