Original Article

Radiation for Diffuse Large B-Cell Lymphoma in the Rituximab Era: Analysis of the National Comprehensive Cancer Network Lymphoma Outcomes Project

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BACKGROUND: The role of consolidation radiotherapy was examined for patients with diffuse large B-cell lymphoma who were treated at institutions of the National Comprehensive Cancer Network during the rituximab era. **METHODS:** Failure-free survival (FFS) and overall survival (OS) were analyzed in terms of patient and treatment characteristics. Potential associations were investigated with univariate and multivariate survival analysis and matched pair analysis. **RESULTS:** There were 841 patients, and most (710 or 84%) received 6 to 8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); 293 (35%) received consolidation radiation therapy (RT). Failure occurred for 181 patients: 126 patients (70%) who did not receive RT and 55 patients (30%) who did. At 5 years, both OS and FFS rates were better for patients who had received RT versus those who did not (OS, 91% vs 83% [$P = .01$]; FFS, 83% vs 76% [$P = .05$]). A matched pair analysis (217 pairs matched by age, stage, International Prognostic Index [IPI] score, B symptoms, disease bulk, and response to chemotherapy) showed that the receipt of RT improved OS (hazard ratio [HR], 0.53 [$P = .07$]) and FFS (HR, 0.77 [$P = .34$]) for patients with stage III/IV disease, but too few events took place among those with stage I/II disease for meaningful comparisons (HR for OS, 0.94 [$P = .89$]; HR for FFS, 1.81 [$P = .15$]). A multivariate analysis suggested that the IPI score and the response to chemotherapy had the greatest influence on outcomes. **CONCLUSIONS:** There was a trend of higher OS and FFS rates for patients who had received consolidation RT after R-CHOP (especially for patients with stage III/IV disease), but the difference did not reach statistical significance. ***Cancer* 2015;121:1032-9.** © *2014 American Cancer Society.*

KEYWORDS: consolidation, early stage, radiation, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

INTRODUCTION

Over the past 2 decades, recognition of the complexity of diffuse large B-cell lymphoma (DLBCL) has led to considerable changes in the recommended treatment, as reflected in guidelines from the US National Comprehensive Cancer Network (NCCN). A variety of pathologic, laboratory, and cytogenetic factors are now used to predict individual patients' responses to therapy and subsequent clinical outcomes.[1-5] In addition, response-adapted therapy based on changes in ^{18}F-fluorodeoxyglucose uptake on positron emission tomography is being introduced into the NCCN guidelines as findings on individually tailored chemotherapy become mature.[6-11] The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy became standard therapy in the early 2000s on the basis of available scientific evidence.[12] On the other hand, whether radiation therapy (RT) has a role in the treatment of DLBCL continues to be the subject of an ongoing controversy,[13] which partly reflects and is an extrapolation of the late side effects that

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developed in patients treated for Hodgkin's several decades ago when both radiation techniques and fields were rudimentary in comparison with the technology available today. In addition, conflicting evidence has come from both randomized and single-institution studies.[4,10,14-20] In view of these developments and technological advances in the planning and delivery of RT, we chose to examine the effects of using modern-day RT techniques for DLBCL at NCCN institutions on outcomes.

For this analysis, we used the NCCN outcomes database, which includes comprehensive, prospectively collected data on clinical characteristics, treatment factors, and outcomes for patients being treated for non-Hodgkin lymphoma. We sought to determine whether RT influenced failure-free survival (FFS) and overall survival (OS) in patients with newly diagnosed DLBCL of any stage who had been treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy.

MATERIALS AND METHODS

Patients

We identified patients with newly diagnosed DLBCL presenting at 1 of 7 member institutions of the NCCN from January 1, 2001 through December 31, 2008. The 841 patients in this analysis had a confirmed diagnosis of DLBCL that had been treated with R-CHOP with or without consolidation RT (defined as RT received within the first 90 days after the completion of chemotherapy). Patients were excluded if they had experienced disease relapse or progression during first-line therapy (including RT) or their therapy had been protocol-directed. The following characteristics were retrieved: age at diagnosis, sex, race, Ann Arbor disease stage, revised International Prognostic Index (IPI) score based on rituximab-era data,[15] presence of B symptoms and bulky disease (defined as $\geq$10 cm in the maximum dimension), site of disease (nodal vs extranodal; patients who had any extranodal site were grouped as extranodal), type and number of cycles of chemotherapy, response to chemotherapy, type of imaging used to assess the response, use of radiation, site of failure (with respect to radiation fields), and disease and vital status at the last follow-up (with cause of death if applicable). The 5-year FFS and OS rates were calculated as described later.

Pathology specimens (excisional and core-needle biopsy samples) were handled at each NCCN institution; no central review was done.

RT was recommended at the discretion of the treating medical oncologist; the radiation fields were involved-field. Unfortunately, the radiation dose was not provided so we could not perform a dose-response analysis.

Statistical Analysis

The definitions of response used in the NCCN database were as follows. Complete remission (including undetermined complete remission) was defined as the complete disappearance of all detectable clinical and radiographic evidence of disease and all disease-related symptoms if they were present before therapy and the normalization of biochemical abnormalities (lactate dehydrogenase) attributable to non-Hodgkin lymphoma lasting at least 4 weeks. Partial remission was defined as a $<$50% response as indicated by images obtained at the end of therapy. Bulky disease was $\geq$10 cm in the maximum dimension. For the purposes of this study, FFS was defined as the time from the completion of treatment to relapse; OS was defined as the time from the time of diagnosis to the date of last follow-up or the date of death. Baseline demographic and clinical characteristics were compared between subgroups with chi-square tests (for categorical variables) or Wilcoxon rank sum tests (for medians). Univariate logistic regression analysis was used to assess the potential factors that influenced 5-year OS and freedom from progression. Factors with a P value $\leq$ .25 were tested in a multivariate model. Cox proportional hazards regression was used to build the multivariate model. All statistical analyses were performed with Stata/SE 2011 (StataCorp, College Station, Texas).

We also assessed FFS and OS by using a matched cohort analysis as follows. Patients were paired according to whether they had or had not received RT, and they were matched for known prognostic factors, including age, sex, disease stage, IPI score, the presence of B symptoms or bulky disease, the number of chemotherapy cycles delivered, and the response to chemotherapy. Patients who had received RT were exactly matched (without placement) to R-CHOP–only patients to the third decimal place (thousandths) of the propensity score on a 1:1 basis. Cox proportional hazards regression was performed with stratification on the propensity score (rounded to the tenth place) to account for the matching nature of the data.

RESULTS

Clinical characteristics are summarized in Table 1. The median follow-up time was 4.5 years (range, 0.5-10.7 years), and the median age at diagnosis was 57.1 years (range, 18-91 years). Four hundred fifty-five patients (54%) were male, 689 (82%) were Caucasian, and 402

TABLE 1. Patient Characteristics

Characteristic	Treatment Group			*P*
	All	R-CHOP	R-CHOP+RT	
Patients, n (%)	841	548 (65.2)	293 (34.8)	
Age at diagnosis, median (range), y	57.1 (17.9-90.7)	58.3 (17.9-90.7)	54.1 (18.1-89.4)	<.0001
Sex, n (%)				
Male	455 (54.1)	286 (52.2)	169 (57.7)	.13
Female	386 (45.9)	262 (47.8)	124 (42.3)	
Race/ethnicity, n (%)				.81
Caucasian/non-Hispanic	689 (81.9)	447 (81.6)	242 (82.6)	
Hispanic	51 (6.1)	31 (5.7)	20 (6.8)	
African American, non-Hispanic	37 (4.4)	27 (4.9)	10 (3.4)	
Asian, Pacific Islander, non-Hispanic	38 (4.5)	24 (4.4)	14 (4.8)	
American Indian, non-Hispanic	1 (0.2)	1 (0.2)	0	
Other non-Hispanic	5 (0.6)	3 (0.55)	2 (0.7)	
Unknown	20 (2.4)	15 (2.7)	5 (1.7)	
Disease stage at diagnosis, n (%)				<.0001
I	218 (25.9)	86 (15.7)	132 (45.0)	
II	184 (21.9)	99 (18.1)	85 (29.0)	
III	137 (16.3)	119 (21.7)	18 (6.1)	
IV	302 (35.9)	244 (44.5)	58 (19.8)	
IPI score, n (%)				<.0001
0	186 (22.1)	89 (16.2)	97 (33.1)	
1-2	446 (53.0)	282 (51.5)	164 (55.8)	
3+	209 (24.8)	177 (32.3)	32 (10.1)	
Chemotherapy cycles, n (%)				<.0001
<6 cycles	131 (15.6)	49 (8.9)	82 (28.0)	
6-8 cycles	710 (84.4)	499 (91.1)	211 (72.0)	
Complete response to therapy, n (%)	633 (75.1)	441 (80.4)	192 (65.5)	<.0001
B symptoms at presentation, n (%)				.03
Unknown	6 (0.7)	4 (0.7)	2 (0.7)	
No	595 (70.7)	371 (67.7)	224 (76.4)	
Yes	240 (28.5)	173 (31.6)	67 (22.9)	
Bulky disease, n (%)				.0005
No	649 (77.2)	443 (80.8)	206 (70.3)	
Yes	192 (22.8)	105 (19.2)	87 (29.7)	
Presentation, n (%)				<.0001
Extranodal	221 (26.3)	109 (20.0)	112 (38.2)	
Nodal	620 (73.7)	439 (80.1)	181 (61.8)	

Abbreviations: IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiation therapy.

(48%) had stage I or II disease. One hundred eighty-six (22%) had an IPI score of 0, and 446 (53%) had an IPI score of 1 or 2; 240 (29%) had B symptoms at presentation, and 192 (23%) had bulky disease at presentation (including 88 patients with stage I/II disease). Six hundred twenty patients (74%) presented with nodal disease. Most patients (710 or 84%) had 6 to 8 cycles of R-CHOP (74% of those with stage I/II disease and 94% of those with stage III/IV disease), and 101 (12%) received intrathecal methotrexate; 293 (35%) received consolidation RT (217 had stage I/II disease [64 with bulky disease], and 76 had stage III/IV disease [23 with bulky disease]). In terms of disease response, 633 (75%) had a complete response. Most of the patients with bulky stage I/II disease (73%) had received RT, whereas 22% of the patients with bulky stage III/IV disease had.

Patients who received radiation, in comparison with those who did not, were significantly younger (54 vs 58 years, $P < .0001$), were more likely to have stage I-II disease (74% vs 38%, $P < .0001$), were more likely to have a lower IPI score (89% vs 68%, $P < .0001$), were more likely to have bulky disease (30% vs 19%, $P = .0005$), were more likely to have extranodal disease (38% vs 20%, $P < .0001$), and were more likely to receive abbreviated chemotherapy (28% vs 9%, $P < .0001$). The response to treatment, evaluated within 2 months of therapy completion, was assessed with computed tomography in 219 patients (26%: 143 in the R-CHOP–only group and 76 in the R-CHOP+RT group), with positron emission tomography in 145 patients (17%: 97 in the R-CHOP–only group and 48 in the R-CHOP+RT group), and with positron emission tomography/computed

TABLE 2. Causes of Death

Coded Cause of Death	Treatment Group		
	All	R-CHOP	R-CHOP+RT
All deaths, n (%)	119	88 (73.9)	31 (26.0)
Missing, n (%)	3 (2.5)	2 (2.3)	1 (3.2)
Unknown, n (%)	22 (18.5)	17 (19.3)	5 (16.1)
Other, n (%)	18 (15.1)	14 (15.9)	4 (12.9)
Progressive disease, n (%)	66 (55.5)	49 (55.7)	17 (54.8)
Excessive toxicity, n (%)	3 (2.5)	2 (2.3)	1 (3.2)
Secondary malignancy, n (%)	6 (5.0)	3 (3.4)	3 (9.7)
Accidental death, n (%)	1 (0.8)	1 (0.8)	0

Abbreviations: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiation therapy.

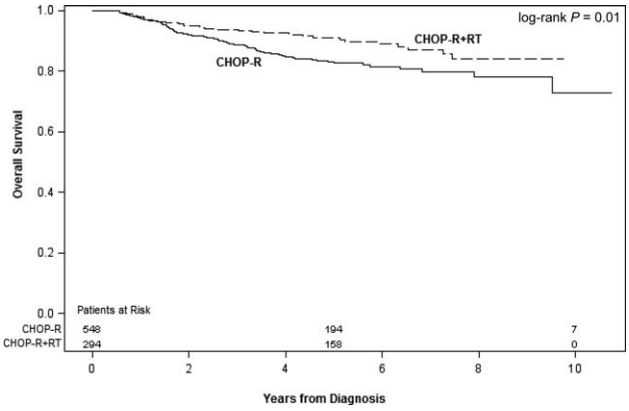

Figure 1. Five-year overall survival rates for patients who received RT and patients who did not. CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; R, rituximab; RT, radiation therapy.

tomography in 327 patients (39%: 217 in the R-CHOP–only group and 110 in the R-CHOP+RT group). Most patients (633 or 75%) experienced complete remission after R-CHOP; 192 of those patients had received RT. Another 187 patients (22%) experienced partial remission, and 93 of these patients had received RT; 6 patients had stable disease; and 15 could not be evaluated. At the time of this analysis, 119 patients had died (88 in the R-CHOP–only group and 31 in the R-CHOP+RT group); notably, a majority (66 or 55%) had died of progressive disease (Table 2).

Factors Contributing to OS and FFS

The 5-year OS and FFS rates were significantly higher for patients who had received RT (OS, 91%; FFS, 83%) versus those who did not (OS, 83% [$P = .05$]; FFS, 76% [$P = .01$]; Figs. 1 and 2). A univariate analysis revealed that the following factors influenced both 5-year OS and FFS (Table 3): age (OS for $\leq$60 years, 90%; FFS for

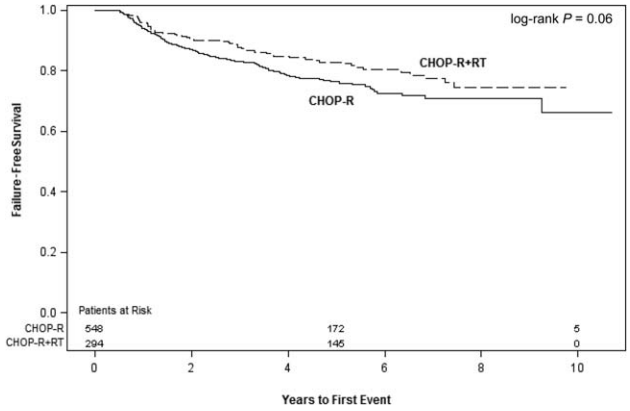

Figure 2. Five-year failure-free survival rates for patients who received RT and patients who did not. CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; R, rituximab; RT, radiation therapy.

$\leq$60 years, 83%; OS for >60 years, 80%; FFS for >60 years, 73% [$P = .0006$]), disease stage at diagnosis (OS for I/II, 93%; FFS for I/II, 89%; OS for III/IV, 79%; FFS for III/IV, 69% [$P < .0001$]), IPI score (OS for a score of 0, 98%; FFS for a score of 0, 95%; OS for a score of 1-2, 87%; FFS for a score of 1-2, 79%; OS for a score $\geq$ 3, 73%; FFS for a score $\geq$ 3, 64% [$P < .0001$]), B symptoms (OS for no symptoms, 91%; FFS for no symptoms, 74%; OS for symptoms, 84%; FFS for symptoms, 67%; [$P < .0001$]), and bulky disease (OS for no disease, 88%; FFS for no disease, 81%; OS for disease, 77%; FFS for disease, 70% [$P = .0003$]). Having extranodal disease at presentation was associated with FFS (85% vs 76% for nodal disease only, $P = .008$) but not with OS. Finally, a response to therapy was also associated with both OS and FFS (OS with a complete response, 88%; FFS with a complete response, 81%; OS without a complete response, 79%; FFS without a complete response, 72% [$P = .0003$]).

In multivariate analyses, the use of RT was associated with a nonsignificant trend toward a lower risk of death (hazard ratio [HR], 0.67) and failure (HR, 0.86). The response to therapy and the IPI score had the greatest influences on both OS and FFS; patients with an IPI score > 3 had HRs of 9.9 and 6.4 for death and failure, respectively ($P < .0001$ for both), and those who achieved a complete remission had an HR of 0.50 for death ($P = .0009$) and an HR of 0.57 for failure ($P = .001$). The presence of B symptoms and bulky disease and the receipt of <6 cycles of chemotherapy also influenced both OS and FFS ($P = .01$; for details, see Table 4).

To further examine influences on FFS and OS, we undertook a matched pair survival analysis using

TABLE 3. Univariate Analysis of Overall and Failure-Free Survival at 5 Years: All Patients

Variable	5-Year Overall Survival			5-Year Failure-Free Survival		
	Survival Estimate	95% CI	Log-Rank *P*	Survival Estimate	95% CI	Log-Rank *P*
Age at diagnosis						
≤60 years	0.90	0.87-0.92	<.0001	0.83	0.79-0.86	.0006
>60 years	0.80	0.75-0.84		0.73	0.67-0.78	
Sex						
Female	0.86	0.82-0.90	.71	0.80	0.75-0.84	.59
Male	0.85	0.81-0.88		0.78	0.73-0.81	
Race						
Other	0.82	0.73-0.88	.47	0.76	0.67-0.83	.63
Caucasian	0.86	0.83-0.89		0.79	0.76-0.82	
Stage at diagnosis						
I/II	0.93	0.89-0.95	<.0001	0.89	0.86-0.92	<.0001
III/IV	0.79	0.75-0.83		0.69	0.64-0.73	
IPI score						
0	0.98	0.94-0.99	<.0001	0.95	0.90-0.98	<.0001
1-2	0.87	0.83-0.90		0.79	0.75-0.83	
3+	0.73	0.66-0.79		0.64	0.56-0.70	
Chemotherapy						
<6 cycles	0.79	0.69-0.86	.08	0.75	0.65-0.82	.88
6-8 cycles	0.87	0.84-0.89		0.79	0.76-0.82	
B symptoms						
No	0.91	0.88-0.93	<.0001	0.84	0.80-0.87	<.0001
Yes	0.74	0.67-0.79		0.67	0.60-0.73	
Bulky disease						
No	0.88	0.85-0.91	<.0001	0.81	0.78-0.84	.0003
Yes	0.77	0.71-0.83		0.70	0.63-0.76	
Response to therapy						
Other	0.79	0.73-0.84	<.0001	0.72	0.65-0.78	.0003
Complete	0.88	0.85-0.90		0.81	0.77-0.84	
Lymph node involvement at initial site						
No	0.88	0.82-0.92	.45	0.85	0.79-0.90	.008
Yes	0.85	0.81-0.88		0.76	0.72-0.80	
Receipt of radiotherapy						
No	0.83	0.79-0.86	.01	0.76	0.72-0.80	.05
Yes	0.91	0.87-0.94		0.83	0.78-0.87	

Abbreviations: CI, confidence interval; IPI, International Prognostic Index.

propensity scores to estimate the effects of RT and observed covariates (age, disease stage, IPI score, number of chemotherapy cycles, B symptoms, bulky disease, and response to therapy) on OS and FFS (Table 5). There were 201 total matched pairs: 125 had stage I/II disease, and 76 had stage III/IV disease. This analysis showed that the use of RT seemed to reduce the risk of death (HR, 0.76) and failure (HR, 0.92) among all patients and particularly among patients with stage III/IV disease (HR for death, 0.53; HR for failure, 0.77), but these effects were not statistically significant (Table 5). Surprisingly, the use of RT for patients with stage I/II disease seemed to be associated with a higher failure rate (HR, 1.81), although the *P* value for this comparison was also not significant.

The rather illogical finding of higher failure rates for patients given RT for stage I/II disease led us to perform the following subset analyses. The first of these subset analyses separated patients with stage I/II disease into 1 of 2 subgroups: those who had received abbreviated chemotherapy (<6 cycles of R-CHOP, n = 103) and those who had received the full 6 to 8 cycles of R-CHOP (n = 296). For patients who received <6 cycles of R-CHOP, the receipt of RT (vs no RT) was associated with a nonsignificant trend of higher OS (HR, 0.4 [*P* = .19]) and FFS (HR, 0.44 [*P* = .24]). On the other hand, patients who received RT after the standard full course of R-CHOP had worse OS (HR, 2.06 [*P* = .22]) and FFS (HR, 3.27 [*P* = .01]) than those who did not receive RT (Table 4). Other attempts to evaluate OS and FFS in terms of disease bulk and nodal-only presentation versus extranodal presentation also showed no statistically significant associations (data not shown).

In the second and final subset analysis, we looked at sites of failure with respect to the receipt or nonreceipt of RT (Table 6). In that comparison, we found that the total number of failure sites was 126 (70%) among patients who did not receive RT versus 55 (30%) among those who did receive RT; moreover, failure appeared at the

TABLE 4. Multivariate Analyses of Overall and Failure-Free Survival by the Number of Cycles of R-CHOP

	Patients Receiving < 6 Cycles of R-CHOP (n = 103)						Patients Receiving 6-8 cycles of R-CHOP (n = 296)					
	Overall Survival			Failure-Free Survival			Overall Survival			Failure-Free Survival		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex			.09			.03		Dropped			Dropped	
Female	1.0			1.0								
Male	0.32	0.08-1.19		0.22	0.06-0.84							
Race			.02			.005		Dropped			Dropped	
Other	1.0			1.0								
Caucasian	0.21	0.06-0.74		0.17	0.05-0.59							
IPI score			.28			.24			.09			.26
0	1.0			1.00			1.0			1.0		
1-2	5.55	0.67-46.01		6.12	0.74-50.56		3.52	0.97-12.79		1.90	0.84-4.27	
3+	NE			NE			8.47	0.85-84.31		2.67	0.33-21.40	
B symptoms			.52			.98			.93			.82
No	1.0			1.0			1.0			1.0		
Yes	1.59	0.38-6.59		0.98	0.24-3.96		1.07	0.29-3.93		1.12	0.42-3.00	
Bulky disease			.50			.07			.58			.73
No	1.0			1.0			1.0			1.0		
Yes	1.65	0.39-6.95		3.57	0.90-14.11		1.38	0.44-4.39		0.86	0.37-2.01	
Response to therapy			.50			.97			.55			1.0
Other	1.0			1.0			1.0			1.0		
Complete	0.63	0.16-2.42		0.97	0.26-3.58		1.5	0.40-5.58		1.0	0.41-2.42	
Radiotherapy			.20			.22			.30			.01
No	1.0			1.0			1.0			1.0		
Yes	0.42	0.11-1.59		0.44	0.12-1.64		1.85	0.58-5.95		3.08	1.25-7.58	

Abbreviations: CI, confidence interval; HR, hazard ratio; IPI, International Prognostic Index; NE, could not be estimated; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE 5. Matched Pair Analyses for Overall and Failure-Free Survival by Disease Stage

	All Patients (201 Matched Pairs)			Stage I/II Patients (125 Matched Pairs)			Stage III/IV Patients (76 Matched Pairs)		
Variable	Survival Estimate	95% CI	Log-Rank *P*	Survival Estimate	95% CI	Log-Rank *P*	Survival Estimate	95% CI	Log-Rank *P*
Overall survival: radiotherapy									
No	Baseline		.32	Baseline		.89	Baseline		.07
Yes	0.76	0.45-1.30		0.94	0.38-2.34		0.53	0.27-1.06	
Failure-free survival: radiotherapy									
No	Baseline		.69	Baseline		.15	Baseline		.34
Yes	0.92	0.60-1.40		1.81	0.81-4.02		0.77	0.46-1.32	

Abbreviation: CI, confidence interval.

same presenting disease site in 23% of those who did not receive RT versus only 8% of those who did receive RT. These findings suggest that RT was helpful for minimizing the number of failure sites and preventing local recurrence.

DISCUSSION

Recent clinical reports indicate that RT may have merit for the treatment of patients with DLBCL during the rituximab era. The published report of the RICOVER-60 trial,[21] in which 166 elderly patients with DLBCL of all stages of disease were treated, compared the results of the best arm of immunochemotherapy [6RCHOP+2R] (2R = 2 additional cycles of Rituximab) plus 36 Gy to initial bulky sites (≥7.5 cm) with the results of a cohort treated without radiation. Although the radiation treatment decision was not randomized, those treated with radiation showed statistically significant improvements in OS (90% for the RT group versus 65% for the group with no RT, $P = .00$]) and event-free survival (80% for the RT group versus 54% for the group with no RT, $P = .001$). On the other hand, the UNFOLDER trial, which was

TABLE 6. Sites of Failure Versus Receipt of Radiation

Failure Site	Treatment Group		
	All	R-CHOP	R-CHOP+RT
Failures, n (%)	181 (100)	126 (69.6)	55 (30.4)
Distant site only, n (%)	47 (26.0)	31 (17.1)	16 (8.8)
Row %		66.0	34.0
Column %		24.6	29.1
Same site, n (%)	55 (30.4)	41 (22.6)	14 (7.7)
Row %		74.5	25.4
Column %		32.5	25.4
Same and distant site, n (%)	37 (20.4)	24 (13.3)	13 (7.2)
Row %		64.9	35.1
Column %		19.0	23.6
No sites of failure, n (%)	28 (15.5)	20 (11.0)	8 (4.4)
Row %		71.4	28.6
Column %		15.9	14.5
Unknown, n (%)	14 (7.7)	10 (5.5)	4 (2.2)
Row %		71.4	28.6
Column %		7.9	7.2

Abbreviations: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiation therapy.
Data were missing for 660 patients.

conducted by the German High-Grade Non-Hodgkin's Lymphoma Study Group, randomized 450 patients with DLBCL of all stages to receive either R-CHOP-14 (given every 14 days) or R-CHOP-21 (given every 21 days) with a second randomization to radiation or observation for patients with extranodal or bulky disease. Similar to the patients of the RICOVER trial, these were patients with all stages of disease. Final results have not yet been published. However, the RT randomization arms were closed when the second interim analysis showed a higher failure rate in the no-RT arm (data presented at the 2012 Annual Meeting of the American Society of Hematology).

Since rituximab became part of the standard of care for DLBCL, other trials have also addressed the role of radiation treatment for DLBCL of all stages, albeit indirectly or retrospectively. The MabThera International Trial[17] evaluated the benefit of adding rituximab to CHOP for patients with stages II-IV or bulky stage I DLBCL. Rituximab minimized but did not eliminate the adverse prognostic effects of tumor bulk on outcomes, and this suggested that RT could have merit for patients with bulky disease, regardless of the stage. A retrospective study from the MD Anderson Cancer Center in which most patients had received 6 or more cycles of R-CHOP showed that the addition of radiation improved both OS and progression-free survival (PFS) across all disease stages: the 5-year OS and PFS rates were 90% and 91% for those who received radiation and 75% and 83% for those who did not ($P < .001$). A matched pair analysis based on the disease stage and accounting for the number of cycles of R-CHOP, radiation, IPI score, tumor response to therapy, and disease bulk confirmed the benefit of radiation, with longer OS and PFS times for those who received radiation (HR for OS, 0.52; HR for PFS, 0.45).[20]

The present observational analysis of outcomes includes a large cohort of patients with DLBCL of all stages who were treated with R-CHOP chemotherapy with or without radiation. Radiation was predominantly given to patients with limited-stage disease and those with extranodal and/or bulky tumor sites. The decision for RT referral for treatment was at the discretion of the treating medical oncologist, and this in turn represented an uncontrolled selection bias for the radiation treatment group. In addition, patients were treated across several institutions, and compliance with the intended treatment might have been unaccounted. The use of radiation varied among the institutions (5%-31%), and this heterogeneity was also inherently difficult to control.

A Kaplan-Meier survival analysis of the whole group of patients indicated overall improvements in both OS and FFS. The multivariate analysis, however, did not show FFS improvement, and there was no significant difference in outcomes by institution. Given the heterogeneity of factors in the patient cohort, however, we performed a matched pair analysis including 217 pairs of patients. In the matched pair analysis, there was no statistically different outcome for those who received radiation. A possible explanation for RT not having an overall positive benefit in the matched cohorts is that these were predominantly patients with early-stage disease. The number of failure events seen overall in the limited-stage group was very low (with only 26 failures out of 402 patients or 6%). When we analyzed outcomes by subsets with the worst prognostic factors (a high IPI score, bulky disease, and a less than complete response to chemotherapy), a benefit of RT was seen for those with stage III/IV disease and those with stage I/II who had received abbreviated chemotherapy (<6 cycles of chemotherapy).

The results of this analysis in general align with those observed in previously noted studies suggesting that RT may contribute to improved outcomes for certain subsets of patients with DLBCL. The challenge remains of defining the criteria by which the patients most likely to benefit can be identified. It is evident from practice patterns that, despite observed variations, medical and radiation oncologists are applying radiation treatment in combination with chemotherapy for DLBCL in select patients. Radiation, however, is not without adverse effects, particularly

when it is combined with chemotherapy. Hence, to obtain the most benefit with the fewest side effects, it is essential to incorporate technological innovations in the field of radiation oncology planning and delivery to substantially reduce the acute and long-term side effects of RT. In addition, to prevent unnecessary treatment and potential harm, it is critical to prospectively study and definitively identify the factors that define the unique subsets of patients for whom combined modality therapy would be most appropriate.

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CONFLICT OF INTEREST DISCLOSURES

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