

## Benefit of Consolidative Radiation Therapy in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP Chemotherapy

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### A B S T R A C T

#### Purpose

The current standard therapy for patients with diffuse large B-cell lymphoma (DLBCL) is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The role of consolidative radiation therapy (RT) in the setting of R-CHOP chemotherapy is not well reported. This retrospective analysis is an attempt to clarify this role.

#### Patients and Methods

Subjects were 469 patients with histologically confirmed DLBCL treated between January 2001 and December 2007. Variables including age, sex, Ann Arbor disease stage, bulky disease status, standardized uptake values (SUVs) on positron emission tomography (PET), International Prognostic Index (IPI), and Ki67 staining (proliferation).

#### Results

Of 469 patients, 190 (40.5%) had stage I or II disease and 279 (59.5%) had stage III or IV disease, 327 (70%) had at least six cycles of R-CHOP, and 142 (30.2%) had involved-field RT (dose, 30 to 39.6 Gy) after complete response to chemotherapy. Median follow-up was 36 months (range, 8 to 85 months). Multivariate analysis showed that RT ( $P < .0001$ ), IPI score ( $P = .001$ ), response to therapy ( $P = .001$ ), use of six to eight cycles of R-CHOP ( $P < .001$ ), and combined presence ( $P = .006$ ) or absence ( $P = .025$ ) of high Ki67, high PET SUV, and bulky disease influenced overall survival (OS) and progression-free survival (PFS). Matched-pair analyses of patients who received six to eight cycles of R-CHOP with stage I or II disease (44 pairs) and all stages (74 pairs) indicated that RT improved OS (hazard ratio [HR], 0.52 and 0.29, respectively) and PFS (HR, 0.45 and 0.24, respectively) compared with no RT.

#### Conclusion

This study showed significant improvements in OS and PFS among patients who received consolidation RT after R-CHOP chemotherapy for DLBCL.

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### INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of non-Hodgkin's lymphoma (NHL) that constitutes 30% to 40% of all adult NHLs.<sup>1,2</sup> Over the past few decades, chemotherapy consisting of the anti-CD20 antibody rituximab combined most often with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been established as the standard of care for patients with DLBCL, although the number of cycles delivered varies among institutions.<sup>3-6</sup> Although many patients initially respond to this therapeutic approach, the 5-year overall survival (OS) rates for patients

with DLBCL vary from 45% to 82%,<sup>7-9</sup> reflecting the heterogeneous nature of this disease as well as the need to identify prognostic factors that will allow further tailoring of therapy, including alternative chemotherapy or supplements to this therapy such as radiotherapy.

Although radiation therapy (RT) was the first curative therapy for aggressive lymphomas, whether it continues to have a role in the treatment of DLBCL is controversial, with some studies supporting its use and others not. Four randomized trials were unable to conclusively determine the benefit of RT for patients with DLBCL: the Southwest Oncology Group (SWOG) 8736 trial,<sup>7</sup> the Groupe d'Etudes des Lymphomes de

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l'Adulte (GELA) LNH 93-1 trial,<sup>10</sup> the Eastern Cooperative Oncology Group (ECOG) 1484 study,<sup>11</sup> and the GELA LNH 93-4 trial.<sup>12</sup> However, these four studies focused on patients with stage I or II disease and there is a general paucity of information available for patients with advanced-stage disease, with the exception being a prospective trial by Aviles et al<sup>13</sup> of 341 patients with bulky stage IV aggressive lymphoma in complete remission after chemotherapy. The results of this study showed that patients who received consolidative RT had better 5-year event-free survival rates (82% v 55%;  $P < .001$ ) and OS rates (87% v 66%;  $P = .01$ ) than patients who did not receive RT. Rituximab has not been part of the chemotherapy regimen in all the previously mentioned studies.

In an attempt to clarify the issue of whether RT is helpful in patients with DLBCL treated with the current standard of care and what subset of patients would benefit from its use, we undertook this retrospective study of DLBCL patients treated mostly with R-CHOP regimen, with or without consolidative RT, at The University of Texas M. D. Anderson Cancer Center.

## PATIENTS AND METHODS

This study was approved by the institutional review board at M. D. Anderson Cancer Center. We retrospectively reviewed the records of 491 patients who were referred to M. D. Anderson with DLBCL between January 2001 and December 2007. Twenty-two patients were excluded either for lack of pathology confirmation or because they were not treated at M. D. Anderson. The following pretreatment patient characteristics were extracted: age, sex, Ann Arbor clinical disease stage,<sup>14</sup> bulky disease status, standardized uptake values (SUVs) on positron emission tomography (PET) scans, and the International Prognostic Index (IPI) (13a). Bulky disease was defined as any mass greater than 5 cm in diameter; this was reviewed by three of the authors to confirm the disease measurements. PET SUVs were grouped as  $\leq 13$  or more than 13 based on a recent report from Noy et al<sup>15</sup> that an SUV more than 13 predicted aggressive behavior in NHL with greater than 90% certainty (see online-only Appendix for the rest of the Patients and Methods section).

## RESULTS

### Clinical Characteristics

A total of 469 patients with a histologically confirmed diagnosis of DLBCL were included in the analysis. Their clinical characteristics are summarized in Table 1, and a comparison of clinical characteristics of patients who received RT with those who did not is summarized in Table 2. The median age at diagnosis was 61 years (range, 20 to 92 years). Men slightly outnumbered women at 251 to 218. Ann Arbor clinical stage at diagnosis was as follows: 94 patients (20.0%) had stage I disease, 96 patients (20.5%) had stage II disease, 77 patients (16.4%) had stage III disease, and 202 patients (43.1%) had stage IV disease. Bulky disease was present in 175 patients (37%). Data on SUV were found in 467 patients; 292 patients had SUV  $\leq 13$  and 177 had an SUV more than 13. Proliferation index was reported in 306 patients, with Ki67  $\geq 50\%$  in 230 patients. The median follow-up interval was 36 months (range, 4 to 85 months).

Complete remission (CR) was achieved in 73% of stage I patients, 68% of stage II patients, 79% of stage III patients, and 75% of stage IV patients. Across all stages, CR was achieved in 74% of patients, CR unconfirmed (CRu) in 9%, partial response (PR) in 12%, and progressive disease/stable disease in 5% of patients. Radiation therapy was

**Table 1.** Demographic and Clinical Characteristics

Characteristic	No.	%
Sex		
Female	218	46.5
Male	251	53.5
Stage		
I	94	20.0
II	96	20.5
III	77	16.4
IV	202	43.1
Chemotherapy		
6-8 cycles of R-CHOP	327	69.7
Other	142	30.3
Radiotherapy		
Yes	142	30.3
No	327	69.7
Bulky disease status, cm		
$\leq 5$	260	55.4
$> 5$	207	44.1
Missing	2	0.4
PET standardized uptake values		
$\leq 13$	284	60.6
$> 13$	177	37.5
Missing	8	1.9
Ki67		
$< 50$	76	16.2
$\geq 50$	230	49.0
Missing	163	34.8
Triple negative		
No	268	57.1
Yes	38	8.1
Missing	163	34.8
Triple positive		
No	247	52.7
Yes	59	12.6
Missing	163	34.8
IPI score		
0	77	16.4
1-2	274	58.4
$\geq 3$	118	25.2

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PET, positron emission tomography; IPI, International Prognostic Index.

delivered to 96 of the 347 patients who achieved a CR by both PET and diagnostic computed tomography (CT; 28%), and to 43 patients who achieved CRu (9%), whereas patients with PR received salvage chemotherapy with and without high-dose chemotherapy.

### Treatment and Survival

**Univariate analysis.** A total of 394 patients (84%) were given R-CHOP: 327 patients received six to eight cycles of R-CHOP (121 patients had stage I or II disease), and 67 patients received fewer than six cycles of R-CHOP. Other chemotherapy regimens administered include rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone in 53 patients (11.3%) and other regimens in 20 patients (4%). One hundred forty-two (30.2%) of 469 patients were given RT. Of the 190 patients with stage I or II disease, RT was given to 103 patients (49 of 103 had bulky disease). RT was given to 39 of 279 patients with stage III or IV (23 of 39 patients had bulky disease).

**Table 2.** Comparison of Characteristics of Patients Who Received RT With Those Who Did Not

Characteristic	No RT		Yes RT		P*
	No.	%	No.	%	
Median age, years	61.5		60.5		.84
Sex					
Female	153	46.8	77	54.2	.46
Male	174	53.2	65	45.8	
Disease stage					
I	39	11.9	55	38.7	.005
II	48	14.7	48	33.8	
III	69	21.1	8	5.6	
IV	171	52.3	31	21.8	
IPI score					
0	37	11.3	40	28.2	.005
1-2	194	59.3	81	57	
≥ 3	96	29.4	21	14.8	
Chemotherapy					
6-8 cycles of R-CHOP	229	70	98	69	.83
Other	98	30	44	31	
Bulky disease					
No	221	69	70	49.3	.001
Yes	104	32	72	50.7	
PET standardized uptake values					
≤ 13	195	84.9	89	63.1	.068
> 13	125	39.1	52	39.9	
Ki67					
≤ 50	58	26.5	18	20.7	.31
>50	161	74.5	69	78.3	
Triple negative					
No	189	86.3	79	90.8	.34
Yes	30	13.7	8	9.2	
Triple positive					
No	186	84.9	61	70.1	.06
Yes	33	15.1	26	29.9	

Abbreviations: RT, radiation therapy; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PET, positron emission tomography.  
\*P value based on  $\chi^2$  analysis.

**Table 3.** Univariate Analysis of OS and PFS for All Patients

Variable	5-Year OS (%)	95% CI	P	5-Year PFS (%)	95% CI	P
Age, years						
≤ 60	75	71 to 79	.15	64	60 to 68	.301
> 60	75	71 to 79		67	62 to 72	
Disease stage						
I-II	83	75 to 89	.0029	76	72 to 80	.0001
III-IV	70	62 to 76		59	54 to 64	
Chemotherapy						
6-8 cycles of R-CHOP	82	76 to 88	< .0001	71	68 to 74	< .0001
Other	59	53 to 65		54	41 to 60	
Radiotherapy						
Yes	91	82 to 96	.0029	82	74 to 90	< .0001
No	68	61 to 74		59	51 to 65	
Bulky disease status, cm						
≤ 5	80	73 to 84	.60	74	66 to 79	.229
> 5	71	62 to 78		58	56 to 72	
PET standardized uptake values						
≤ 13	76	71 to 82	.82	69	65 to 73	.131
> 13	75	63 to 84		61	56 to 66	
Ki67						
< 50	82	76 to 86	.28	81	75 to 88	.11
≥ 50	79	75 to 83		72	68 to 76	
Triple negative						
Yes	95	91 to 99	.024	71	67 to 75	.013
No	75	71 to 78		95	92 to 98	
Triple positive						
No	82	78 to 86	.042	78	74 to 82	
Yes	66	59 to 73		58	59 to 73	.020
Missing				56	59 to 73	.020
IPI score						
0	94	88 to 98		84	79 to 89	
1-2	76	68 to 82	< .001	68	62 to 78	.001
≥ 3	62	52 to 72	< .0001	49	45 to 62	.001
Response						
No response	31	13 to 51		24	21 to 27	
Partial remission	58	48 to 68	< .0001	39	33 to 45	< .0001
Complete remission	83	74 to 91	.0010	77	74 to 80	< .0001

Abbreviations: OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PET, positron emission tomography; IPI, International Prognostic Index.

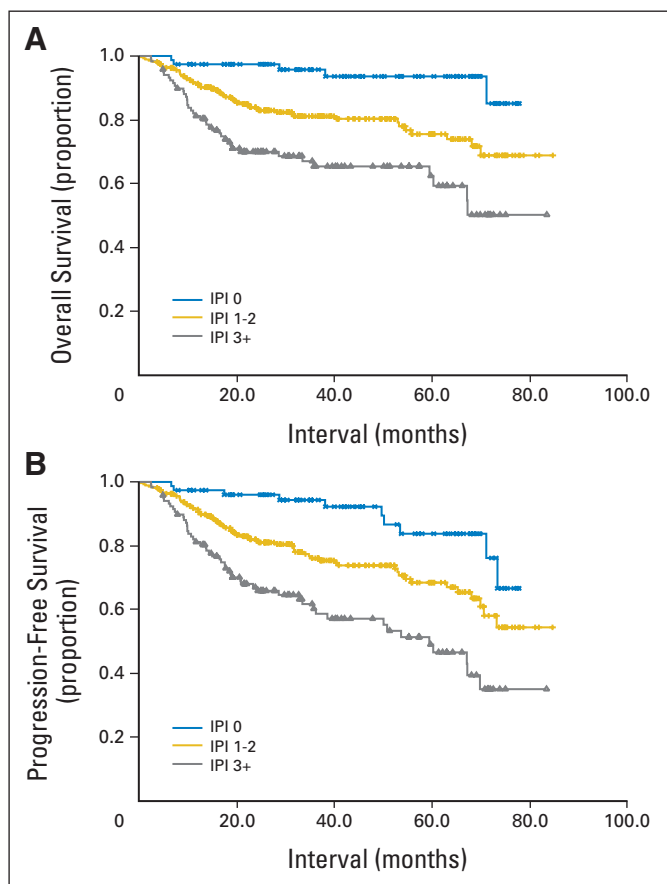
On univariate analysis of all patients, six factors were found to significantly affect both OS and progression-free survival (PFS): disease stage at presentation, type and number of cycles of chemotherapy, administration of RT, IPI score, response to chemotherapy, and the presence or absence of the three adverse factors (triple negative, triple positive; Table 3). The 5-year OS and PFS rates for those with limited-stage disease (stage I or II) were 83% and 81%, respectively, whereas the OS and PFS rates for those with advanced-stage disease (stage III or IV) were 70% ( $P = .0029$ ), and 60% ( $P = .0001$ ), respectively. The 5-year OS and PFS rates for those treated with six to eight cycles of R-CHOP chemotherapy were 82% and 71%, respectively, and the OS and PFS rates for those treated with other regimens were 59% ( $P < .0001$ ) and 54% ( $P < .0001$ ), respectively.

The 5-year OS and PFS rates for those treated with RT were 91% and 82%, respectively, whereas the OS and PFS for those not treated with RT were 68% ( $P < .0001$ ) and 59% ( $P < .0001$ ), respectively. The role of RT was still significant when looking at patients with limited- and advanced-stage disease. The 5-year OS and PFS rates for stage I and II disease treated with RT were 92%

and 82%, respectively, whereas the OS and PFS rates for those not treated with RT were 73% ( $P = .0007$ ) and 68% ( $P = .0003$ ), respectively. The 5-year OS and PFS rates for stage III and IV disease treated with RT were 89% and 76%, respectively, whereas the OS and PFS rates for those not treated with RT were 66% ( $P = .008$ ) and 55% ( $P = .003$ ), respectively.

Compared with patients who presented with IPI of 0 and had 5-year OS and PFS of 94% and 84%, respectively, the 5-year OS and PFS rates were lower for patients who presented with an IPI score of 1 to 2—76% ( $P = .001$ ) and 68% ( $P = .001$ ), respectively—and were significantly lower for patients with IPI  $\geq 3$ : 62% ( $P < .0001$ ) and 49% ( $P = .001$ ), respectively (Figs 1A and 1B).

The 5-year OS and PFS rates were lower, although statistically not significant, for patients with an SUV  $\geq 13$ , Ki67  $\geq 50\%$ , and bulky status looked at separately. We looked at the combination of these adverse factors, and we found that patients who presented with none of these risk factors (triple negative)—that is, SUV less than 13, Ki67 less than 50%, and nonbulky tumors—had a significantly higher OS



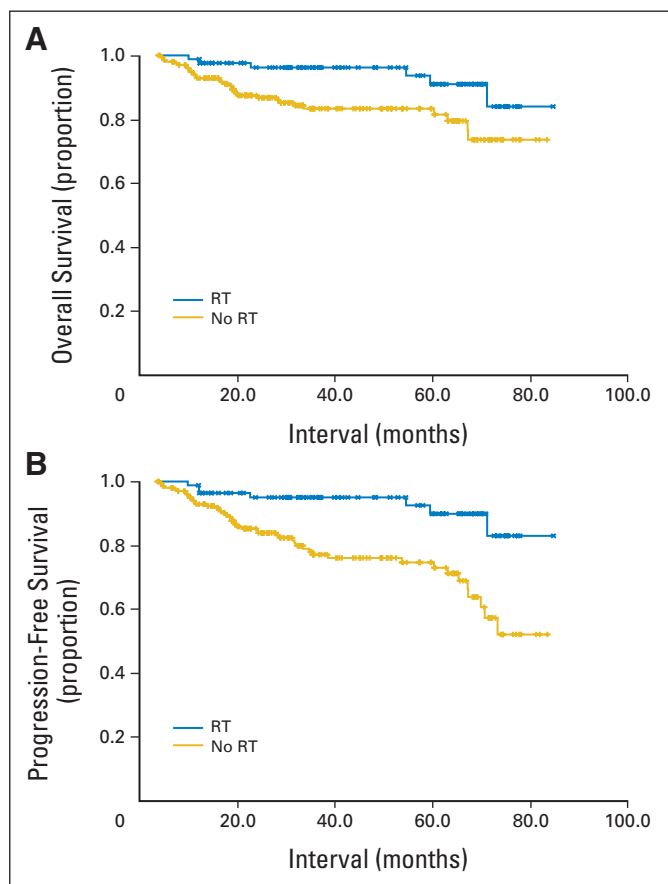
**Fig 1.** Five-year overall and progression-free survival rates. (A) Overall survival by International Prognostic Index (IPI) score. (B) Progression-free survival by IPI score.

and PFS of 95% and 95%, respectively, compared with 66% ( $P = .023$ ) and 58% ( $P = .009$ ), respectively, for those who had all three of these adverse factors.

Because the aim of the study was to look at the role of RT in the setting of using R-CHOP chemotherapy, we analyzed this group of patients separately. We performed the analysis on 327 patients who received six to eight cycles of R-CHOP, and we found the same six factors to be significant on univariate analysis. We further performed the analysis on 291 patients who received six to eight cycles of R-CHOP and achieved a documented CR. The role of RT was still significant in addition to the stage, triple-negative versus triple-positive status, and IPI score (Figs 2A and 2B). This is summarized in Table 4.

Finally, the 43 patients who achieved CRu (defined as CR only by PET with a residual mass on diagnostic CT) and received consolidation RT had a comparable OS (95%) and PFS (61%) to those who achieved CR by both modalities ( $P < .001$ ).

**Multivariate analysis.** In a multivariate analysis of prognostic factors (Table 5), the OS and PFS were significantly associated with age ( $P = .05$  for OS and  $P = .01$  for PFS), administration of RT ( $P < .0001$  for both OS and PFS), IPI score ( $P = .001$  for both OS and PFS), response to therapy ( $P = .001$  for both OS and PFS), and triple negative ( $P = .025$  for OS and  $P = .038$  for PFS)/triple positive ( $P = .006$  for OS and  $P = .037$  for PFS). In a



**Fig 2.** (A) Overall and (B) progression-free survival of patients achieving complete remission after treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, with and without radiotherapy (RT).

multivariate analysis of patients who achieved CR after six to eight cycles of R-CHOP, the OS and PFS were significantly associated with radiotherapy ( $P = .023$  for OS and  $P = .009$  for PFS) and triple negative ( $P = .042$  for OS and  $P = .042$  for PFS)/triple positive ( $P = .001$  for OS and  $P = .003$  for PFS).

**Matched-pair analysis.** We also performed matched-pair analyses of patients with stage I or II disease who received six to eight cycles of R-CHOP chemotherapy. We matched patients in this subset who received RT and those who did not receive RT based on three factors: bulky status, response to therapy defined as resolution of original tumors, and IPI score. A total of 44 matched pairs were found. The results were analyzed to determine the benefit of RT for patients with stage I or II disease. The estimate of the effect of RT from the matched pair analysis was similar to the results of the univariate analysis of OS and PFS: patients who underwent RT had a longer OS (hazard ratio [HR], 0.52) and PFS (HR, 0.45) than those who did not receive RT.

A second matched-pair analysis was performed using the same matching criteria but including only patients with stage III or IV disease who received six to eight cycles of R-CHOP chemotherapy. The 30 matched pairs identified with stage III or IV disease were then combined with the 44 pairs of patients with stage I or II disease, and the results were analyzed to determine the benefit of RT for patients who received six to eight cycles of R-CHOP chemotherapy regardless of

**Table 4.** Univariate Analysis of OS and PFS for Patients Who Achieve Complete Remission After Being Treated With Six to Eight Cycles of R-CHOP

Variable	5-Year OS (%)			5-Year PFS (%)		
	OS (%)	95% CI	P	PFS (%)	95% CI	P
Age, years						
≤ 60	88	84 to 92	.050	81	76 to 86	.217
> 60	84	79 to 88		87	83 to 91	
Stage						
I-II	91	88 to 94	.024	90	86 to 94	.001
III-IV	82	78 to 86		72	67 to 77	
Chemotherapy						
6-8 cycles of R-CHOP	86	83 to 89	.308	80	83 to 89	.56
< 6 cycles of R-CHOP	84	75 to 93		80	75 to 93	
Radiotherapy						
Yes	91	87 to 95	.015	90	86 to 94	< .001
No	83	67 to 96		75	71 to 79	
Bulky disease status, cm						
≤ 5	90	86 to 94	.214	86	82 to 90	.153
> 5	78	73 to 84		70	64 to 76	
PET standardized uptake values						
≤ 13	87	83 to 91	.430	83	79 to 87	.017
> 13	84	78 to 90		71	64 to 78	
Ki67						
< 50	94	89 to 99	.045	92	86 to 98	.023
≥ 50	89	95 to 93		81	76 to 86	
Triple negative						
Yes	97	95 to 99	.012	97	95 to 99	.032
No	88	83 to 93		81	72 to 90	
Triple positive						
No	93	90 to 96	.001	87	83 to 91	.002
Yes	70	60 to 80		65	45 to 76	
IPI score						
0	98	96 to 100		98	96 to 100	
1-2	87	83 to 91	.001	81	77 to 85	.001
≥ 3	74	67 to 81	< .0001	64	57 to 71	< .0001

Abbreviations: OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PET, positron emission tomography; IPI, international prognostic index.

**Table 5.** Multivariate Analysis of Overall and Progression-Free Survival for All Patients

Variable	Overall Survival			Progression-Free Survival		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
Age, years						
≤ 60	1.00		.051	1.00		.010
> 60	1.34	0.98 to 2.02		1.42	1.00 to 2.15	
Chemotherapy						
6-8 cycles of R-CHOP	0.42	0.27 to 0.65	< .0001	0.57	0.39 to 0.84	.0050
Other	1.00			1.00		
Radiotherapy						
No	1.00		< .0001	1.00		< .0001
Yes	0.19	0.10 to 0.38		0.32	0.17 to 0.51	
Triple negative						
No	1.00		.025	1.00		.038
Yes	0.16	0.03 to 0.79		0.24	0.06 to 0.92	
Triple positive						
No	1.00		.006	1.00		.037
Yes	4.96	1.58 to 15.61		1.39	1.58 to 9.87	
IPI score						
0	1.00			1.00		
1-2	2.53	1.32 to 4.84	.005	2.12	1.34 to 3.69	.001
≥ 3	5.41	2.24 to 8.28	.001	6.03	3.11 to 9.19	.001
Response						
No response	1.00			1.00		
Partial remission	1.96	0.91 to 2.05	< .0001	0.27	0.16 to 0.56	< .0001
Complete remission	3.35	2.33 to 4.59	< .001	0.42	0.33 to 0.72	.0055

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; IPI, international prognostic index.

disease stage. Patients who underwent RT had longer OS (HR, 0.29) and PFS (HR, 0.24) than those who did not undergo RT.

### Pattern of Failure

Relapse was documented in 63 patients who originally achieved CR. Failure occurred outside of the radiation fields in patients who originally received consolidative RT, thus achieving 100% local control at the sites that received involved-field RT.

## DISCUSSION

Our findings indicate that even in the era of R-CHOP chemotherapy, the use of RT was associated with significant improvements in OS and PFS for all patients with DLBCL. The benefit was seen in both univariate and multivariate analysis, across all disease stages and regardless of disease bulk. Although both the type and number of chemotherapy cycles administered varied somewhat, most patients (84%) received what is considered to be the current standard of care. Moreover, RT in all cases was delivered only to involved fields and not to

adjacent uninvolved lymph node stations; this was done to minimize unnecessary toxicity. In contrast, the GELA 93-4 trial involved the use of large RT fields, which may have influenced the conclusion in that report that RT should not be used in patients older than 60 years of age. In addition, some patients in that trial did not receive the RT as intended, and quality control with regard to treatment fields was less than optimal as well. We also used a lower RT dose than that used in any of the four randomized trials by SWOG, ECOG, and GELA, again to minimize potential toxicity.

The benefit in OS and PFS observed in our study was comparable to that observed in the initial SWOG 8736 study, which also found that RT had a beneficial effect on OS. The results of our study are in accord with a recent Surveillance, Epidemiology, and End Results analysis by Ballonoff et al<sup>8</sup> that also supports a benefit from RT in terms of OS for patients with DLBCL.

We also verified our previously published results by Wilder et al<sup>16</sup> on the benefit of involved-field RT in patients with stages I to IV disease. It is worthwhile to mention that our current dose of radiation is lower than our recommended practice previously published, and this is mainly a consequence of using rituximab-based chemotherapy as the current standard of care, which was not the case before 1996, the time frame for our previously published data. Additionally, three cycles of R-CHOP is not commonly used at our institution either. Therefore, with the improvement in systemic chemotherapy, the dose was appropriately changed.

We previously reported on the role of involved-field RT in patients with PR,<sup>17</sup> showing that they have a comparable outcome to those who received salvage chemotherapy. The definition of CRu in that article was based on the percentage of tumor reduction, defined as more than 76% to 99%. In our current data, patients with CRu were those who had negative PET with residual disease on the diagnostic

CT. Interestingly, and as one would expect, this later group had a comparable outcome to those who achieved CR with both PET and CT. Unfortunately, we could not evaluate the potential role of RT in patients who achieved PR, because according to our institutional guidelines, once PR is documented, then salvage chemotherapy is given, with the radiation reserved only as a palliative measure.

Our findings further show that adding rituximab to the current chemotherapy regimen does not obviate the need for RT in general, in contrast with the results of all four randomized trials (GELA 93-1, GELA93-4, SWOG, and ECOG).<sup>7,10-12</sup> Two conclusions are evident from the patterns of failure in these four randomized trials. First, RT achieved local control at the original disease site when used in combination with abbreviated chemotherapy, and second, abbreviated chemotherapy failed to control disease at distant sites and thus was responsible for an inferior outcome. Theoretically, use of a more aggressive chemotherapy regimen would control systemic microscopic disease but would still not eliminate the need for RT; indeed, we found that even though most of our patients received six to eight cycles of R-CHOP, a benefit from RT was still evident in terms of both OS and PFS. This finding is in contrast to the results of the GELA LHN-93-1 trial, in which intensive therapy with doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone was compared with abbreviated CHOP chemotherapy and RT. The combination of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone was found to be associated with higher toxicity and is no longer considered the standard of care by the GELA.<sup>7,10-12</sup>

The presence of bulky disease is perceived by most clinicians as a reason to deliver RT. However, in our matched-pair analysis, bulky disease status (defined here as the presence or absence of disease > 5 cm in diameter) did not affect outcome, especially in relation to the role of RT; patients with and without bulky disease benefited equally from RT. This is an important finding that contrasts with what is practiced by most oncologists and signifies the importance of RT as complementary to chemotherapy.

When comparing our findings with the body of literature, we confirmed many of the known prognostic factors and their association with OS and PFS, namely the influence of stage, response to therapy, IPI score, and age more than 60 years. PET SUV, Ki67, and bulky disease did not affect OS and PFS when examined separately. Because these criteria are commonly used to indicate aggressive disease, we combined the three factors and designated cases as triple negative or triple positive. The presence or absence of all three factors was associated significantly with OS and PFS. The failure of each individual factor to show significance could be due to the specificity/sensitivity of each test as well as to the lack of standard reading of both the PET SUV and Ki67 index. Another factor could be the insufficient numbers in the subset analysis to determine the effect of these factors. A minority of our patients were treated with what is considered a more

aggressive regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. This regimen is usually offered to patients with obvious aggressive features. In view of the small number of patients, we could not examine the influence of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone on the OS or PFS and particularly the role of RT in this subgroup of patients.

Our study was retrospective and thus our results constitute a lower level of evidence than those generated from prospective trials. A larger number of patients will be needed to address questions about which patients with early-stage disease might benefit from less aggressive therapy so that the therapy can be better tailored according to expected outcome. Future trials should address the role of RT in view of the current standard of care, R-CHOP, and recent advances in RT delivery, improved techniques, smaller fields of treatment, and lower total dose.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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