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Scientific Article

Patient Survival With and Without Radiation Therapy for Early-Stage Diffuse Large B-Cell Lymphoma in the Era of PET and Rituximab

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Abstract

Purpose: The benefit of radiation therapy (RT) becomes uncertain in the treatment of early stage diffuse large B-cell lymphoma (DLBCL) in the era of rituximab, positron emission topography (PET), and computed tomography (CT). We sought to retrospectively review modern patients with early stage I-II DLBCL treated with rituximab and staged by PET-CT to better define which patients benefit from consolidative RT.

Methods and Materials: Patients with early stage I-II DLBCL from 1998 to 2017 were reviewed coinciding with our institutional utilization of rituximab with the standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone and PET-CT. Relevant clinical information was used to calculate National Comprehensive Cancer Network international prognostic index (IPI) scores. Kaplan-Meier survival analysis and a Cox proportional hazards model were used for overall survival (OS).

Results: Seventy-seven patients received chemoimmunotherapy alone, and 41 received chemoimmunotherapy plus RT. Median follow-up time was 9.5 years. On univariate analysis, extranodal disease ($P = .04$) and National Comprehensive Cancer Network IPI ($P < .001$) were significantly correlated with OS. Five-year OS was 87% versus 67%, and 10-year OS was 67% versus 58%, numerically higher favoring RT ($P = .16$). On multivariate Cox regression analysis of OS controlling for IPI and extranodal disease, the addition of RT was associated with improved OS (hazard ratio of 0.4, $P = .01$).

Conclusions: The current analysis supports the use of consolidative RT in early stage DLBCL given an OS benefit on multivariate analysis. Further prospective randomized data are needed to confirm these findings.

Introduction

The use of radiation therapy (RT) in early stage diffuse large B-cell lymphoma (DLBCL) was considered the standard of care, but its benefit has recently become uncertain in the positron emission tomography (PET), computer

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tomography (CT), and rituximab era. Before the advent of these modalities, major cooperative group trials established the role of RT but given variations in patient populations and trial design, the benefit spans from overall survival (OS),[1] to progression-free survival (PFS),[2] to only local control.[3] After the advent and addition of rituximab to the standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) among others, RT use declined given concerns over late toxicity and inconclusive data. However, more recent institutional retrospective studies, large database studies, and prospective trials continue to show benefit with the use of consolidative RT in specific subgroups of early stage DLBCL even in the rituximab era.[4-8]

In an attempt to add further data and clarification to this question, we undertook a single institution retrospective review of patients with early stage DLBCL treated with chemoimmunotherapy, with or without consolidative RT. Given heterogeneity in practice patterns regarding the delivery of consolidative RT at our own institution, modern patients evaluated with PET-CT and treated with rituximab were examined to determine whether consolidative RT leads to an OS benefit.

Methods and Materials

An institutional review board−approved retrospective review was undertaken of all patients treated at our institution for early-stage DLBCL from 1998 to 2017, at which time utilization of PET-CT and R-CHOP was routine. Inclusion criteria were patients ≥18 years old with stage I-II DLBCL with any size tumor who received chemoimmunotherapy as first-line management. Patients were required to have received at least 3 cycles of a combination chemoimmunotherapy regimen that included rituximab and an anthracycline. Patients required a staging PET/CT. Exclusion criterion included multiple malignancies, prior receipt of RT, and active pregnancy.

The records of 1040 patients with lymphoma were identified and reviewed, with 118 patients meeting study criteria. The majority of patients were excluded due to having other forms of non-Hodgkin lymphoma. The following pretreatment and treatment patient characteristics were extracted: age, sex, stage based on Ann Arbor clinical disease stage,[9] National Comprehensive Cancer Network (NCCN) international prognostic index (IPI),[10] Eastern Cooperative Oncology Group (ECOG) performance status (PS), bulky disease status, bony involvement status, number of chemoimmunotherapy cycles, and RT dose. Bulky disease was defined as a mass greater than 7.5 cm in maximum diameter per NCCN guidelines as well as German studies and as reviewed by a single radiation oncologist. In addition, available postchemoimmunotherapy PET-CT radiologic reports documenting response were reviewed and stratified by complete response (CR; Deauville 1-3), partial response (PR; Deauville 4-5), stable disease (Deauville 4-5 without significant fluorodeoxyglucose [FDG] change compared with prechemoimmunotherapy), or progressive disease (Deauville 4-5 with increasing intensity compared with prechemoimmunotherapy scan and/or any new FDG-avid focus consistent with malignant lymphoma).[11] Given the retrospective nature of this study, comparison had to be made to average mean liver standardized uptake value (SUV) of 2.0, as supported by the literature.[12] The clinical outcome of interest was OS, counting all causes of death as events and censoring times of living patients at their dates of last contact. Survival from the start of first-line chemoimmunotherapy was estimated using the Kaplan-Meier method, and the log-rank test was used to compare groups in univariate analyses (UVAs). We used a forward entry parsimonious method for selection of independent variables that were significant ($P < .05$) on UVA into a Cox-proportional hazards model for multivariate analysis (MVA).

Results

Clinical characteristics

A summary of patient characteristics in the cohort examined can be found in Table 1. A total of 118 patients meeting the previously mentioned eligibility criteria were included in the analysis. Seventy-seven (65%) patients received chemoimmunotherapy alone and 41 (35%) received chemoimmunotherapy followed by consolidative RT. The mean age, stage, presence of bony or bulky disease, B symptoms, NCCN IPI score, and extranodal involvement were well-balanced between the groups in this analysis. However, ECOG PS was 0 to 1 in 87% versus 59% in the chemoimmunotherapy alone versus consolidation RT groups, respectively. This was the only prognostic factor that correlated with receipt of RT; patients with worse PS were more likely to receive RT, as determined by the Fisher exact test ($P < .01$). Maximal average dimensions of tumor were 6.0 cm (1.8-20 cm) versus 6.2 cm (0.9-21 cm) in the consolidation RT versus chemoimmunotherapy alone cohorts, respectively. The median RT dose in the consolidative group was 36 Gy (20-45 Gy, Q1-Q3 30.6-39.6 Gy). Of the patients who received consolidative RT, 52% were treated with involved-field RT, while the remaining 48% received involved-site RT. Forty (34%) patients had bulky disease. Ten (9%) patients had bony involvement at diagnosis.

Median cycles of chemoimmunotherapy were 3 for the chemoimmunotherapy alone and consolidative RT groups (range, 3-8 cycles vs 3-8 cycles, respectively). Patients received various chemoimmunotherapy regimens, the most common of which was R-CHOP (60%); 82% received either R-CHOP or R-EPOCH (rituximab,

Table 1 Patient characteristics

	Consolidative RT (n = 41)	Chemotherapy alone (n = 77)	Overall (n = 118)	*P* value on Fisher exact test
Stage				.70
I	21 (51%)	36 (47%)	57 (48%)	
II	20 (49%)	41 (53%)	61 (52%)	
Age at diagnosis				1
Mean (SD)	57 (17)	55 (17)	56 (17)	
Median [min, max]	60 [20, 91]	57 [22, 94]	57 [20, 94]	
ECOG performance status				< .01
0-1	24 (59%)	67 (87%)	91 (77%)	
2-3	17 (42%)	10 (13%)	27 (23%)	
Bony involvement				.45
Yes	4 (10%)	4 (5%)	8 (7%)	
No	37 (90%)	73 (95%)	110 (93%)	
Bulky disease				.21
Yes	9 (22%)	27 (35%)	36 (31%)	
No	32 (78%)	50 (65%)	82 (70%)	
B symptoms				.33
Yes	2 (5%)	9 (12%)	11 (9%)	
No	36 (88%)	64 (83%)	93 (79%)	
Missing	3 (7%)	4 (5%)	14 (12%)	
NCCN IPI score				.49*
Low	6 (15%)	20 (26%)	26 (22%)	
Low-int	24 (59%)	41 (53%)	65 (55%)	
High-int	10 (24%)	15 (19%)	25 (21%)	
High	1 (2%)	1 (1%)	2 (2%)	
Extranodal disease				.85
Yes	20 (49%)	40 (52%)	60 (51%)	
No	21 (51%)	37 (48%)	58 (49%)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPI = international prognostic index; NCCN = National Comprehensive Cancer Network; RT = radiation therapy; SD = standard deviation.
* If categorized as low/low-int versus high-int/high.

etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin). All patients received rituximab as part of their initial chemoimmunotherapy regimen. Thus, we did not identify any significant difference in the intensity of chemoimmunotherapy or in the choice of chemoimmunotherapy agents in patients who received chemoimmunotherapy alone versus consolidative RT.

Although all patients were required to have a staging PET-CT, 62 patients (43%) had postchemoimmunotherapy PET-CT radiologic reports that included mention of Deauville response, whereas the remainder of the reports were insufficiently detailed. Of those with adequate reports, 49 (79%) patients achieved a CR, 7 (11%) achieved a PR, 1 (2%) had stable disease, and 5 (8%) had progressive disease. Of those that received RT, 83% had achieved a CR before RT, while 75% of those that did not receive RT achieved a CR with chemoimmunotherapy alone. Of these 62 patients, only 24 (39%) had documented SUVs. Median documented SUV after chemoimmunotherapy before RT was 3.65 (2.1-81, Q1-Q3 2.4-6.6).

Prognostic factors associated with OS

The median follow-up time for patients in this analysis was 9.5 years, as determined by the reverse Kaplan-Meier method. The 5-year and 10-year OS rates among the entire cohort were 75% (95% confidence interval [CI],

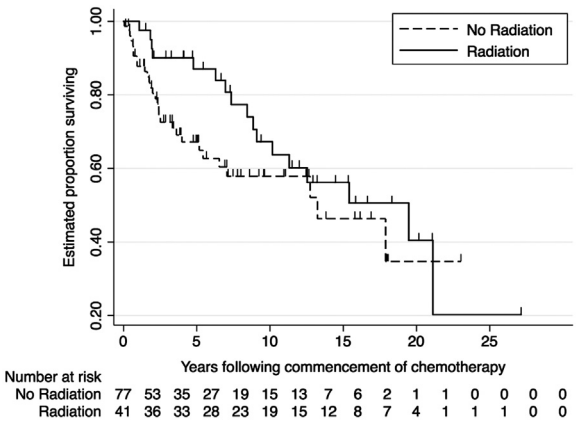

Fig. 1 Overall survival of the entire cohort.

65%-82%) and 61% (95% CI, 49%-70%), respectively (Fig 1). UVA of various prognostic factors is summarized in Table 2, with both NCCN IPI score ($P < .01$) and extranodal disease ($P = .04$) found to be significantly correlated with OS.

Potential OS benefit of RT

OS was numerically higher among those receiving consolidative RT compared with chemoimmunotherapy alone, but the difference was not statistically significant (log-rank $P = .16$, Fig 2). The 5-year OS for those treated with consolidative RT was 87% (95% CI, 72%-94%), compared with 67% (95% CI, 54%-77%) for those treated with chemoimmunotherapy alone. Ten-year OS was 67% versus 58% (Fig 2), numerically higher for those treated with consolidative RT. On UVA, consolidative RT was associated with improved OS for patients with intermediate-high to high IPI (log-rank $P = .04$) but not for patients with low to low-intermediate IPI (log-rank $P = .30$). In patients with low to low-intermediate IPI, the 5-year OS with consolidative RT was 97% (95% CI, 79%-99%), compared with 80% (95% CI, 66%-89%) for those treated with chemoimmunotherapy alone. Ten-year OS in this group was 79% (95% CI, 56%-91%) with consolidative RT versus 71% (95% CI, 55%-82%) with chemoimmunotherapy alone. In patients with intermediate-high to high IPI, 5-year OS with consolidative RT was 58% (95% CI, 23%-

Table 2 Univariate analysis of prognostic factors

	5-year OS (95% CI)	10-year OS (95% CI)	*P* value on log-rank test	HR on MVA (95% CI)	*P* value on MVA
Consolidative RT			.16	0.4 (0.2-0.8)	.01
Yes	87% (72%-94%)	67% (48%-81%)			
No	67% (54%-77%)	58% (44%- 70%)			
Stage					
I	70% (55%-81%)	65% (49%-77%)	.61	-	-
II	78% (61%-87%)	59% (43%- 72%)	.40	-	-
ECOG PS					
0-1	75% (64%-83%)	63% (50%-74%)			
2-3	73% (52%-86%)	54% (31%-72%)			
Bony disease			.97	-	-
Yes	33% (13%-98%)	N/A			
No	75% (65%-82%)	62% (50%-71%)			
Bulky disease			.90	-	-
Yes	76% (58%-87%)	68% (43%-83%)			
No	75% (63%-84%)	59% (46%-70%)			
NCCN IPI score			< .01	2.8 (2.0-3.9)	< .01
Low or low-int	86% (76%-92%)	73% (60%-83%)			
High-int or high	37% (19%-56%)	21% (7%-40%)			
Extranodal disease			.04	0.9 (0.5-1.8)	.76
Yes	68% (53%-78%)	52% (37%-66%)			
No	84% (70%-92%)	71% (53%-83%)			

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPI = international prognostic index; MVA = multivariate analysis; NCCN = National Comprehensive Cancer Network; OS = overall survival; PS = performance status; RT = radiation therapy.

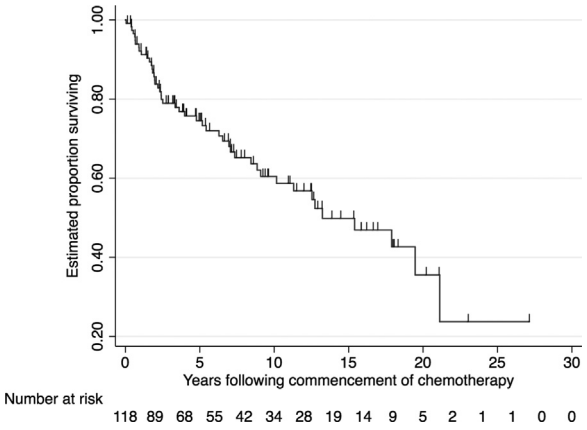

Fig. 2 Overall survival stratified by radiation therapy delivery.

82%) compared with 25% (95% CI, 8%-47%) for those treated with chemoimmunotherapy alone. Ten-year OS was 35% (95% CI, 9%-64%) versus 13% (95% CI, 1%-39%), in favor of consolidated RT. On MVA when controlling for NCCN IPI and presence or absence of extranodal disease, receipt of RT (hazard ratio, 0.4; 95% CI, 0.2-0.8; P = .01) was significantly associated with improved OS.

Discussion

The current study indicates that in contemporary practice, with rituximab-based chemoimmunotherapy and PET-CT staging, the addition of consolidative RT may improve OS. On MVA, our data suggest a benefit to consolidative RT across all NCCN IPI risk groups.

Although the standard of care with consolidative RT was set initially by the SWOG 8736 study in the pre-rituximab era, the only phase III trial (published in full manuscript form) to specifically examine R-CHOP versus R-CHOP plus RT for early stage DLBCL in the modern era was the Lymphoma Study Association/French Acute Leukemia and Blood Diseases West-East Group (LYSA/GOELAMS) 02 to 03 trial. This trial reported similar outcomes for both arms in a highly selected treatment group, with 5-year event-free survival (EFS) of 89% versus 92% in the RT arm and 5-year OS of 92% and 96% in the RT arm.[13] The patient cohort consisted of quite favorable patients, with 64% of patients <60 years old and 56% of patients having an IPI of 0. Perksy argues that the majority of patients in this study would be classified into the most favorable risk stratum, which historically has had, in the prerituximab era, a 5-year OS of 90%+.[14,15] We performed a subset analysis of patients who would have been included in the LYSA/GOELAMS trial (NCCN IPI low/low-int risk and nonbulky) and also found no significant difference in OS with the delivery of RT, though absolute numbers at 10 years favor RT (81.2% vs 68.2%).

Another recent randomized study, FLYER, also looked at this favorable group. Poeschel et al reported that 4 cycles of R-CHOP were noninferior to 6 cycles; patients did not receive consolidative RT unless they had testicular involvement, and PFS at 3 years was 96% in the experimental arm. These were stage I-II patients with ECOG PS of 0 to 1, without bulky disease, and this group historically has had excellent outcomes, even before rituximab.[16]

Subgroups of other prospective trials have clarified higher risk patients who may benefit from RT. Included in these is the RICOVER-noRTh cohort, a subset of the RICOVER-60 trial of 61- to 80-year-old patients achieving a CR or PR after 6 cycles of R-CHOP without RT compared with those who received RT for bulky disease. Inferior outcomes were seen in patients who did not receive RT (3-year PFS 88% vs 62%, $P < .001$; 3-year OS 90% vs 65%, $P = .001$), demonstrating the ability of RT to overcome the adverse risk factor of bulky disease.[7] The UNFOLDER (unfavorable low-risk patients treated with densification of R-chemo regimens) 21/14 trial, published in abstract form, also confirmed a PFS and OS benefit in bulky early-stage DLBCL after there were excess failures in the arm without RT causing its premature closing.[5] In contrast, there have been more limited data on the benefit of RT in extranodal disease in early-stage DLBCL. Extranodal patients consist of 40% to 50% of patients in trials/series in the rituximab era.[4,13] In previous trials, RT has generally been recommended for sites of extranodal disease[6,7] and reduces the risk of local failure.[17] In our cohort, 10-year OS rates for patients with extranodal disease who received consolidative RT were numerically higher (63% vs 44%, P = .09), potentially identifying another high-risk group suitable for RT.

Another higher risk subgroup of patients who appear to derive benefit from consolidative RT are those with osseous involvement. A recent meta-analysis of 9 prospective trials evaluated patients with DLBCL with osseous involvement as determined by CT imaging.[6] This study showed that osseous involvement became a risk factor for patients treated in the rituximab era with worsened EFS and a trend toward worse OS, which had not been present prerituximab, who at that time were receiving standard-of-care consolidative RT. This analysis also determined that in patients treated with rituximab, consolidative RT provided nearly a doubling of 3-year EFS rate compared with those patients not receiving RT (75% vs 36%, $P < .001$).[6] Benefit was seen even in stage III/IV patients, age > 60, with bulky disease, ECOG PS > 1, and extranodal involvement. In our study, only 10 patients (7%) had bony disease and therefore conclusions are difficult to make.

Despite these and similar findings, the use of RT in early-stage DLBCL remains controversial. A minority of

patients receive consolidative RT, with rates peaking at 47% in 2000 and falling to a nadir of 32% in 2012.[4] It is felt that the historic long-term toxicity seen in patients with Hodgkin lymphoma, the majority of whom were treated at a young age with high RT dose and large field sizes, has negatively affected the utilization of RT for lymphoma, even for newer techniques with less expected toxicity.[18] The long-term consequences of cardiac toxicity and secondary malignancy risk are well known in patients with Hodgkin lymphoma,[19,20] but these results should not be extrapolated to patients with DLBCL. Data suggest that secondary malignancy risk in older patients with DLBCL is much lower and equivalent to chemoimmunotherapy alone.[21,22]

Although our analysis reached statistical significance for our stated primary outcome, there were insufficient cases eligible for analysis to show valid differences among various subgroups. Furthermore, due to the retrospective nature of this study, there are multiple resulting limitations. Potential limitations of a retrospective design include selection bias, information bias, and changes to disease classification and management during the wide study period, as well as a heterogenous cohort. There was also heterogeneity in regard to treatment, as patients received differing numbers of chemoimmunotherapy cycles and different radiation planning approaches. The differences in radiation treatment planning are likely the result of the wide study period (1998-2017), during which involved-site RT became available. Unfortunately, treatment toxicity was not well-documented and thus could not be analyzed. There was a lack of detailed postchemoimmunotherapy PET-CT data for the majority of patients, which would have allowed us to examine if the outcomes differed by PET response. Of note, a PET-directed concept has been published previously by a group in British Columbia, where PET-negative patients received an additional cycle of R-CHOP, and those who were PET-positive received involved site radiation therapy (ISRT). Only 18% of patients were PET-positive after 3 cycles of R-CHOP, but that group had worse survival, and PET status was an independent predictor of time-to-progression on MVA.[23] In addition, had this been a prospective study, central review of PET-CT findings would have been possible and could have improved the quality of these data. Nonetheless, our patients were PET-staged and received contemporary chemoimmunotherapy regimens.

As written in a recent editorial, there is a sentiment among medical oncologists that results are favorable enough in early-stage DLBCL to avoid further study of consolidative RT.[24] However, it appears that RT continues to find OS benefit, particularly in the higher IPI risk groups, according to our analysis. To quote the article, it is not time "to quit." Although our study does not provide a definitive answer on the benefit for consolidative RT in this patient population, it adds to the available data and existing literature. Taken as a whole, these suggest that consolidative RT can offer meaningful improvement in oncologic outcomes, such as OS. It is therefore difficult to justify avoiding consolidative RT.

Our analysis demonstrates a survival benefit with the use of consolidation RT for early- stage DLBCL, when controlled for IPI score. Although utilization of RT in this setting has declined, both historic and emerging modern series support its continued use, including our study. Until prospective, randomized data prove the noninferiority of chemoimmunotherapy alone compared with combined modality treatment, combined modality should remain the standard of care.

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