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Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive Non-Hodgkin's Lymphoma: Eastern Cooperative Oncology Group Study 1484

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ABSTRACT

Purpose
To compare low-dose (30 Gy) radiotherapy (RT) with observation (OBS) in limited-stage aggressive lymphoma patients achieving complete remission (CR) after chemotherapy, and to measure conversion from partial response (PR) to CR with high-dose (40 Gy) RT.

Patients and Methods
From 1984 to 1992, stage I (with risk factors) and II adults with diffuse aggressive lymphoma in CR after eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were randomly assigned to 30 Gy involved-field RT or OBS. PR patients received 40 Gy RT.

Results
Among 172 CR patients, the 6-year disease-free survival (DFS) was 73% for low-dose RT versus 56% for OBS (two-sided $P = .05$). Failure-free survival (two-sided $P = .06$), and time to progression (two-sided $P = .06$) also favored RT. Intent-to-treat analyses yielded similar results. No survival differences were observed. Three RT versus 15 OBS patients relapsed in initial disease sites. At 6 years, failure-free survival was 63% in PR patients; conversion to CR did not significantly influence clinical outcome.

Conclusion
For patients in CR after CHOP, low-dose RT prolonged DFS and provided local control, but no survival benefit was observed. The majority of PR patients were event-free at 6 years despite residual radiographic abnormalities. Future efforts should be directed toward improved imaging and more effective systemic therapies.

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INTRODUCTION

Throughout the past 25 years, the treatment of limited-stage diffuse aggressive non-Hodgkin's lymphoma has evolved from surgical staging and radiotherapy (RT) to primary chemotherapy and limited RT.[1-5] Because excellent results were achieved with chemotherapy alone or in combination with RT in the experience of Miller and Jones, the cooperative groups sought to evaluate chemotherapy versus combined-modality treatment in phase III trials.[2,6] The Eastern Cooperative Oncology Group undertook a study (E1484) to determine the ability of low-dose RT to improve disease-free survival (DFS) in patients achieving complete remission (CR) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy in a randomized trial. The conversion of partial responders to complete responders with high-dose RT was also assessed. In addition to DFS, the study sought to define sites of relapse, survival, and toxicity in CR patients treated with combined-modality therapy versus chemotherapy alone.

Recent reports of late relapses from the Southwest Oncology Group (SWOG) experience with brief chemotherapy and RT, and

results from more recent randomized trials conducted in Europe have increased interest in the mature results of clinical trials testing full-course chemotherapy and RT in early-stage aggressive lymphoma.[7-9] Herein, we report results from the E1484 study.

PATIENTS AND METHODS

Treatment

Eligible patients were older than 16 years, with early-stage diffuse aggressive lymphoma according to the Working Formulation (diffuse large-cell, diffuse mixed-large, and small-cleaved cell, and diffuse small-cleaved cell).[10] All cases were centrally reviewed. Limited stages included in this study were: stage I with mediastinal or retroperitoneal involvement or bulky disease greater than 10 cm in diameter, and stage IE, II, or IIE disease. Patients with complete surgical resection of lymphoma were not eligible. Patients with the following extranodal sites of disease were deemed eligible: Waldeyer's ring (nasopharynx, tonsil or base of tongue), thyroid, lung, pleura, breast, gastrointestinal (stomach, small bowel or colon), and gynecologic (ovary, uterus, cervix). Bone or skin involvement was allowed when there was extension from a nodal mass.

No prior chemotherapy or RT was allowed before study entry. All patients were required to have preserved hematologic, renal, and hepatic functions, and to provide written informed consent. Minimal staging included chest radiograph, computed tomography of the abdomen and pelvis, and single percutaneous bone marrow biopsy and blood studies.

The treatment schedule and dosage for CHOP chemotherapy and consolidative RT are outlined in Figure 1. Patients were restaged after eight cycles of chemotherapy. CR was defined as regression of all palpable nodes ($< 1 \times 1$ cm and of normal consistency) and radiographic disease. Partial response (PR) was defined as $\geq 50\%$ reduction in the sum of the products of the dimensions of all measurable lesions. All PRs were verified by blinded review by the study chairman, cochairman, and an independent observer. Attempts were made to obtain histologic confirmation of stable, residual radiographic abnormalities.

CR patients were randomly assigned to 30 Gy RT to initial disease sites, administered in 2-Gy fractions or observation. PR patients received 40 Gy RT. Four weeks after the completion of RT, PR patients were restaged to determine conversion to CR.

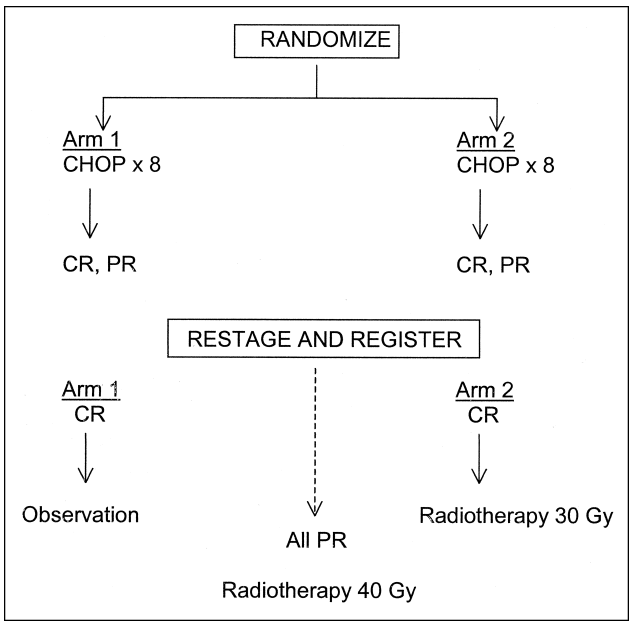

Fig 1. Schema for E1484. Stratification: performance status (0 to 1), diameter of largest mass (< 10 cm $v \geq 10$ cm), number of sites (< 3 $v \geq 3$). CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete remission; PR, partial remission.

Statistical Considerations

Patients were randomly assigned according to a balanced permutated block design with stratification for performance status (0 to 1 or 2 to 4), tumor mass (< 10 cm or ≥ 10 cm), and number of disease sites (< 3 or ≥ 3). The sample size was planned with a one-sided 5% significance test with 74% to 84% power to detect a 20% improvement in 2-year DFS with consolidative RT in CR patients. In the current analysis, however, treatment comparisons were made using two-sided tests.

Fisher's exact test was used for comparison of binary data, and the log-rank test of Mantel-Haenszel was used for comparison of failure-time data. The survival distribution for time to event data such as DFS (time to relapse or death in CR patients), time to progression ([TTP] time to lymphoma progression that censors deaths without progression), failure-free survival ([FFS] failure is lymphoma progression or death regardless of cause) and overall survival (OS) were estimated according to Kaplan and Meier. To evaluate the effects of prognostic factors simultaneously, the logistic regression model was employed for dichotomous outcome, and a proportional hazards regression model was used for time-to-event data.

RESULTS

Patient Characteristics

From October 1984 to August 1992, 399 patients were registered. Forty-seven patients (12%) were excluded from analysis due to withdrawal of consent (n = 4), ineligibility (n = 18), incorrect histology (n = 24), and inadequate data for response evaluation (n = 1). Among the 352 patients eligible and assessable, 179 were randomly assigned to observation, and 173, to low-dose RT. Selected patient characteristics are presented in Table 1. More than two-thirds of the study population had stage II disease. Extranodal involvement was present at diagnosis in 166 patients, with head and neck sites constituting the vast majority. Few patients had an impaired performance status or systemic symptoms. As expected, more than 80% of patients had diffuse large-cell lymphoma. A minority of patients (19%) had three or more Ann Arbor sites of disease. The tumor mass was ≥ 10 cm in 31%. Mediastinal adenopathy was recorded in 68 patients.

Response to CHOP Induction and Toxicity

With application of the above criteria, 215 patients achieved CR (61%; 95% CI, 55.8 to 66.2%), and 98 (28%) achieved PR. Two factors significantly associated with lack

Table 1. Patient Characteristics

Characteristic	No. of Patients	%
Age, years		
Median	59	
Range	19-84	
Performance status		
0-1	325	92
2-3	27	8
Stage		
I	49	14
IE	62	18
II	137	39
IIE	104	29
Extranodal disease	166	47
Systemic symptoms		
No	267	76
Yes	85	24
No. of sites		
< 3	286	81
≥ 3	66	19
Largest tumor size, cm		
< 10	244	69
≥ 10	108	31
Mediastinal lymph nodes	68	19
Histologic subtype		
Large cell	287	82
Mixed	39	11
Small cleaved	26	7

of achievement of CR were tumor mass $\geq$ 10 cm (43% *v* 69%; $P < .001$) and mediastinal adenopathy (50% *v* 64%; $P = .039$). Age, stage, extranodal disease, number of sites, and performance status did not significantly influence the CR rate ($P > .58$). Data on serum lactate dehydrogenase at diagnosis were not available. Using a logistic regression model with forward selection, only bulky disease was statistically associated with the lower CR rate ($P < .0001$).

Among 394 patients for whom toxicity date were reported, CHOP chemotherapy was administered for eight cycles in 324, nine and 11 cycles in one each, and one to seven cycles in 68. There were four treatment-related deaths due to infection (n = 2, one combined with hemorrhage) and congestive heart failure (n = 2). Grade 4 neutropenia was recorded for 128 patients (32%). Other grade 4 toxicities were rare and included thrombocytopenia (two patients); hemorrhage (two patients); infection (five patients); cardiac (five patients); and one case each of genitourinary, neurologic, and gastrointestinal (diarrhea) toxicity.

Consolidation

Of 282 patients registered for the consolidation step, 39 were not assessable (11 ineligible, 13 pathology exclusion, two without induction response, three induction PR on central review, and 10 did not receive the assigned or correct treatment). Among the 243 subsequent eligible and assessable responders, 93 CR patients were on observation, 79 CR patients received low-dose RT, and 71 PR patients received high-dose RT. To avoid potential bias, an intent-to-treat analysis involving all 215 eligible and assessable CR patients (112 on observation and 103 on RT) was performed. Table 2 summarizes the distribution of selected patient characteristics according to actual consolidation treatment and on an intent-to-treat basis. A single imbalance among randomly assigned patients occurred in the higher proportion of patients with mediastinal adenopathy in the low-dose RT arm in the intent-to-treat population ($P = .04$). There was a higher proportion, though not statistically significant, of patients with bulky disease in the low-dose RT arm ($P = .13$). Nearly half of the patients in the

Table 2. Selected Patient Characteristics and Consolidation Therapy

	% of Patients				
	CR As-Treated		CR Intent-to-Treat		
	OBS (n = 93)	LD-RT (n = 79)	OBS (n = 112)	LD-RT (n = 103)	PR HD-RT (n = 71)
Median age, years	60	58	60	58	59
Sex, male	55	57	57	57	54
Performance status 2-3	8	5	7	4	9
Stage II	73	70	70	68	68
Extranodal disease	50	43	52	45	48
Symptomatic	19	17	20	22	25
Largest tumor $\geq$ 10 cm	16	25	17*	26*	49
No. of sites $\geq$ 3	20	18	21	17	18
Mediastinal lymph nodes	13	19	11†	21†	24
Large-cell histology	81	87	82	85	75

Abbreviations: CR, complete remission; PR, partial remission; OBS, observation; LD-RT, low-dose radiotherapy; HD-RT, high-dose radiotherapy.
*$P = .13$.
†$P = .04$.

PR group had large tumor masses, compared with 16% and 25% in the as-treated observation and RT arms, respectively. The distribution of stage II bulky patients was CR observation (n = 6), CR low-dose RT (n = 13), and PR high-dose RT (n = 20).

Treatment with either low-dose or high-dose RT was tolerated well. There were no treatment-related deaths. Only three grade 4 toxicities were recorded: one each thrombocytopenia and cardiac toxicity on high-dose RT and one thrombocytopenia on low-dose RT.

CR Patients

The Kaplan-Meier estimate for DFS at 6 years was significantly greater for CR patients who received low-dose RT (73% *v* 56% for observed patients; two-sided $P = .05$). In the intent-to-treat analysis of 215 patients, RT patients had a significantly longer DFS compared with observed patients (69% *v* 53%, respectively; two-sided $P = .04$). In the as-treated analysis, 6-year FFS was 75% for RT patients and 56% for observed patients, (two-sided $P = .06$). Similarly, in the intent-to-treat analysis, FFS was longer for RT than observed patients (70% *v* 53%, respectively; two-sided $P = .05$). These data are summarized together in Table 3, and survival curves are illustrated in Figures 2A and 2b. Because half or more of the observed deaths occurred without disease progression and the follow-up in this older population exceeded 10 years, we evaluated an end point restricted to tumor progression. TTP was longer for as-treated CR patients consolidated with RT than for observed patients, (two-sided $P = .06$; Fig 2C). The TTP estimates for RT and observed patients at 5, 10, and 15 years were 82%, 78%, and 78%, compared with 71%, 67%, and 64%, respectively. The data are similar when evaluated as intent-to-treat. In the proportional hazards regression analysis, the most important predictor of TTP was number of disease sites followed by treatment (Table 4). Similar results were achieved when the analysis was applied to the intent-to-treat consolidation patients (data not shown).

The median follow-up for CR patients in the intent-to-treat analysis was 12 years. The Kaplan-Meier estimates of OS for consolidated patients (n = 172) in the as-treated analysis are illustrated in Figure 3. At 5, 10, and 15 years, the estimated OS rates were 87%, 68%, and 60% for CR patients consolidated with RT, versus 73%, 65%, and 44% for CR patients who were observed (two-sided $P = .24$). There was no significant difference in OS among the 215 CR patients according to consolidation in an intent-to-treat analysis. The following factors were statistically significantly associated with prolonged survival among induction CR patients: age less than 60 years ($P < .001$), and fewer than three disease sites ($P = .01$). Data relating cause of death were not available for this study. However, among the 215 CR patients, 26% of observation patients and 18% of RT patients died with progressive disease ($P = .15$).

In the as-treated population, treatment failed in 17 RT patients and 31 observed patients. Only three patients treated with RT progressed in previously involved sites, compared with 15 observed patients ($P = .06$). New disease sites were involved in 16 of 31 relapses among observed patients, and in 14 of 17 relapses among RT patients ($P = .06$).

PR Patients

Of the 71 induction PR patients, 22 (31%; 95% CI, 21% to 43%) converted to CR with high-dose RT. Ten of the 33 relapses in PR patients occurred in patients who had converted. The rate of relapse was virtually the same between those who did (46%) and those who did not (47%) convert. The median OS was 9.9 years; median FFS was 8.7 years; and median TTP was not reached for PR patients. Kaplan-Meier estimates at 6 years were 63% for FFS, 66% for TTP, and 69% for OS, with no statistically significant differences between those converted to CR compared with those remaining as PR patients ($P = .074$). These data are graphically represented in Figure 4.

Table 3. Six-Year Results Among Induction CR Patients

	Disease-Free Survival %	Failure-Free Survival %	Time to Progression %	Overall Survival
As-treated analysis (n = 172)				
CR after induction CHOP				
Observation	56	56	67	71
Low-dose RT	73	75	80	82
Two-sided *P* value*	.05	.06	.06	.24
Intent-to-treat analysis (n = 215)				
CR after induction CHOP				
Observation	53	53	63	67
Low-dose RT	69	70	75	79
Two-sided *P* value*	.05	.05	.07	.23

Abbreviations: CR, complete remission; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiotherapy.
*Log-rank statistic.

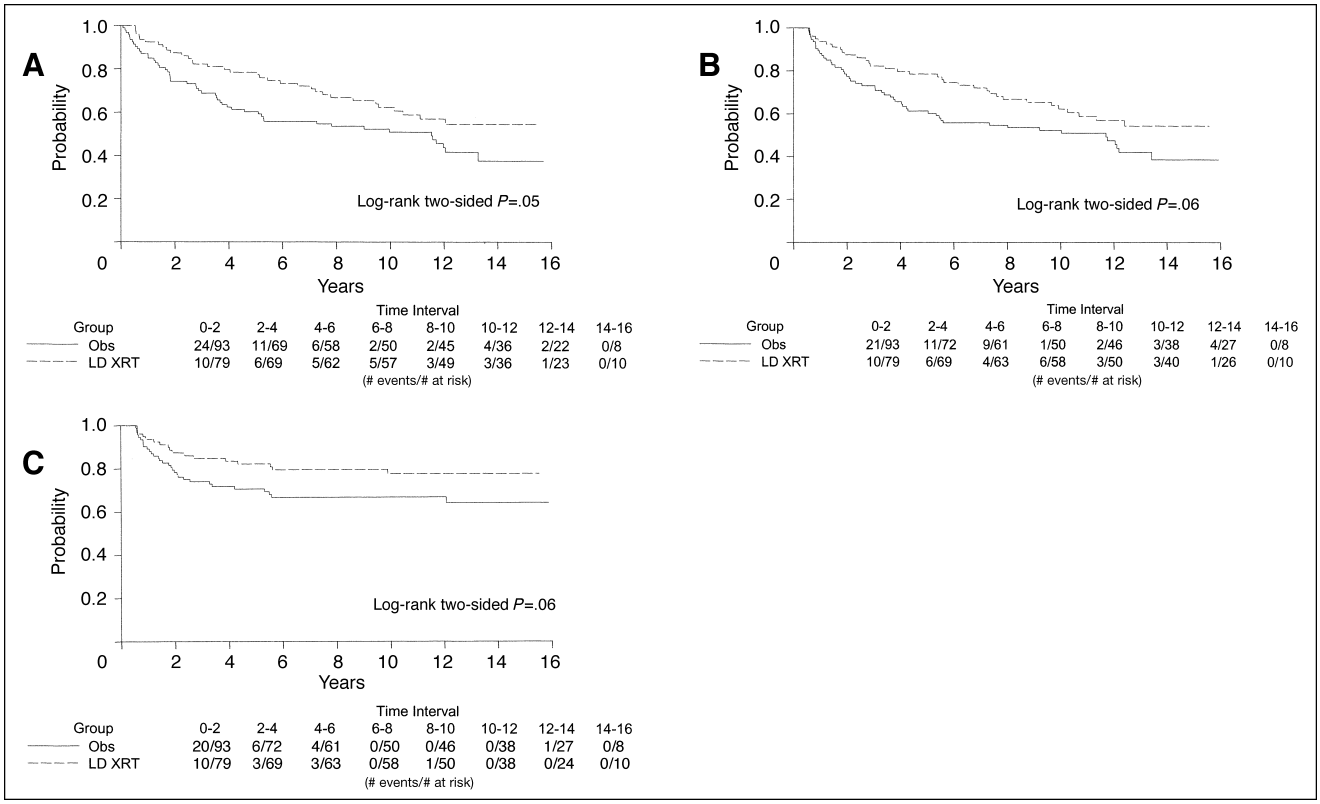

Fig 2. (A) Disease-free survival, (B) failure-free survival, and (C) time to progression for complete remission patients. Observation (Obs; n = 93, solid line) and low-dose radiotherapy (LD XRT; n = 79, dotted line) are shown, along with two-sided *P* values.

DISCUSSION

In the E1484 study, the addition of RT reduced the number of relapses and altered the pattern of relapse in patients with limited-stage diffuse aggressive (> 80% large-cell) lymphoma who achieved a CR with CHOP chemotherapy. Despite a small sample size, a greater proportion of bulky disease in the RT arm, and the use of a two-sided *P* value in the analysis, the observed improvement in DFS for combined modality patients was statistically significant (two-sided $P = .05$). An estimated 78% of chemotherapy and RT patients achieving a CR were free of disease progression after more than 10 years—an excellent outcome. The number of disease sites was the most significant variable associated with TTP. We did not observe a corresponding, significant survival benefit from the addition of low-dose consolidative RT after CR in this study. It is unlikely that consolidative RT contributed to late treatment-related deaths in a major way because the proportion of deaths without disease recurrence was slightly greater among patients receiving chemotherapy only.

Table 4. Time to Progression for Consolidation (as-treated) Patients

Characteristic	Parameter Estimate	SE*	Wald *P* Value	Risk Ratio
RT treatment	−0.604	0.309	.051	0.55
≥ 3 sites	1.225	0.3908	.0002	3.40
Performance status 2-3	0.367	0.556	.509	1.44
Bulky disease	0.290	0.368	.431	1.34
Age > 60 years	0.437	0.300	.144	1.55
Sex, female	0.204	0.295	.488	1.23
Stage II	−0.305	0.343	.374	0.74
Extranodal disease	−0.361	0.312	.247	0.70

Abbreviation: RT, radiotherapy.
*Standard error of the parameter estimate.

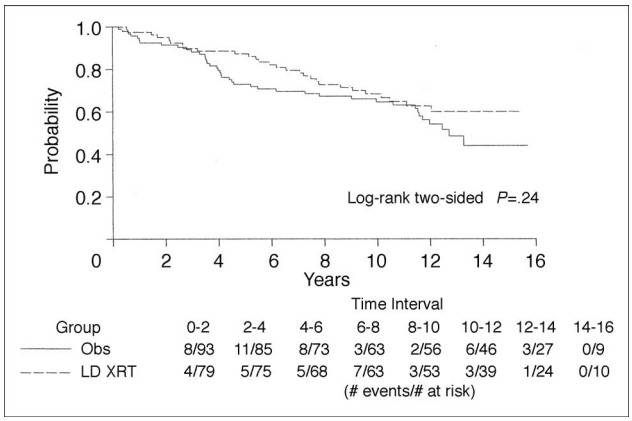

Fig 3. Overall survival for complete remission patients. Observation (Obs; n = 93, solid line) and low-dose radiotherapy (LD XRT; n = 79, dotted line) are shown, along with two-sided *P* value.

PR patients in this study had an excellent 63% FFS at 6 years, which is a fact that may reflect the efficacy of higher-dose RT. However, patients with bulky disease were less likely to achieve CR, and the greater probability of residual radiographic abnormalities that do not contain viable tumor is well established in these patients.[11] Conversion from PR to CR did not significantly influence FFS or TTP in this study. Rather than demonstrating the lack of effect of RT, this finding supports the use of functional imaging in future studies.

Although E1484 was conducted some time ago, the study question remains highly relevant. In fact, a number of recent observations and studies have created new interest in the role of consolidative RT in limited diffuse aggressive lymphoma. These include the report of late relapses in the SWOG study,[7] the lack of benefit for adding RT to brief chemotherapy alone in a European study of elderly patients,[8] and the reported advantage of an intensive chemotherapy regimen over brief CHOP plus RT in younger patients studied in Europe also.[9] Further questions have been raised by the recent report of mature results of brief chemotherapy and RT by the Vancouver group, who reported durable remissions and the importance of selected extranodal disease sites.[12] It is important to note that the E1484 study, distinct from these studies in fundamental design, included predominantly stage II patients (specifically excluding the very favorable stage I patients included in the SWOG and Vancouver studies) and a subset of patients with bulky disease. Despite inclusion of a less favorable population, the E1484 results with a full course of chemotherapy and RT are excellent.

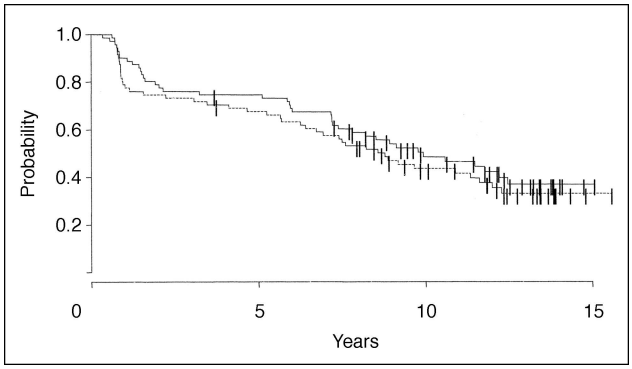

Fig 4. Overall (solid line) and failure-free (dotted line) survival for partial remission patients consolidated with high-dose radiotherapy (n = 71).

Differences in outcomes of various studies are always challenging to explain. In contrast to the SWOG study, E1484 and the Vancouver experience excluded patients with follicular large-cell and Burkitt's lymphoma. More than half of E1484 patients had extranodal disease as was true in the Vancouver study, whereas the proportion with extranodal disease in the SWOG study was 37%. The stage-adjusted international index is an important contribution from the SWOG group[7]; we were unable to assess the index in our patients due to absence of lactate dehydrogenase data. A remarkable aspect of E1484 was central review of responses and proper assignment of RT. In the recent study from Europe in which older patients were randomly assigned to four cycles of CHOP alone or followed by involved-field RT, the quality control of the RT was uncertain.[8] The second study from Europe, limited to younger patients, demonstrated the superiority of an intensive chemotherapy regimen over three cycles of CHOP plus RT. However, this European study included patients with bulky disease—a group specifically excluded from brief chemotherapy and RT trials in the United States.[9] Among the 40 bulky stage II consolidation patients on E1484, 33 received RT (40 Gy, n = 20; 30 Gy, n = 13) after eight cycles of CHOP. It is noteworthy that patients with bulky disease did not have an adverse outcome in our study.

The E1484 study and others indicate that involved-field RT provides excellent local control, but also demonstrates that systemic relapse represents the major cause of treatment failure. To that end, alternative chemotherapy, chemoimmunotherapy, and systemic RT approaches deserve evaluation. Older patients with stage II disease were included in studies of diffuse aggressive lymphoma in which rituximab-CHOP was found to be superior to CHOP.[13,14] Radioimmunotherapy offers a potential alternative delivery of systemic RT, and this approach is being investigated in phase II studies.[15]

Functional imaging with positron emission tomography has greater predictive accuracy in staging and restaging of lymphoma.[16] This diagnostic procedure has the potential to identify more extensive disease at diagnosis. To that end, it is notable that the number of involved sites was the most important prognostic factor for TTP in the E1484 study. Positron emission tomography scanning can also provide early

assessment of treatment response, and, theoretically, can be used to guide further systemic and local therapies.[17-19]

Clinicians have long recognized differences in limited disease presenting in different sites such as the mediastinum, testis, sinus, skin, epidural space, bone, and other sites. In theory, these differences, which are now being understood at the level of gene expression, can be exploited with biologically tailored therapies.[20,21]

In conclusion, E1484 demonstrated that low-dose consolidative RT provided excellent local control and yielded a higher DFS, FFS, and TTP at 5, 10, and 15 years for patients with limited-stage diffuse aggressive lymphoma who attained CR after eight cycles of CHOP. Median FFS for PR patients consolidated with 40 Gy RT was not reached in this study—a result that was better than expected. Future efforts should be directed toward more precise imaging for staging and response determination, more effective systemic therapy, and treatments based on greater understanding of the underlying biology of limited-stage disease.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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