*Leukemia & Lymphoma*, October 2011; 52(10): 1867–1872

informa
healthcare

**ORIGINAL ARTICLE: CLINICAL**

# Radiation therapy improves treatment outcome in patients with diffuse large B-cell lymphoma

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*(Received 1 February 2011; revised 27 April 2011; accepted 30 April 2011)*



**Abstract**

The effects of radiotherapy (RT) after chemotherapy in patients with diffuse large B-cell lymphoma (DLBCL) remain unclear; several trials have yielded conflicting results. This study examined the effect of RT after cyclophosphamide, doxorubicin, vincristine, and prednisone + rituximab (R-CHOP) treatment on event-free (EFS) and overall (OS) survival. Data from 216 patients with DLBCL who were enrolled in two clinical trials at Italian Lymphoma Study Group sites and were subjected to six R-CHOP cycles and involved-field radiotherapy (IFRT) were retrospectively analyzed. IFRT treatment yielded significant EFS benefit, with a 66% reduction in the risk of death and/or disease progression. Cox analysis, when adjusted for age, gender, stage, performance status (PS), lactate dehydrogenase (LDH), and disease bulk, confirmed the significant EFS benefit of IFRT. The role of RT in DLBCL in the rituximab era is unclear. Future studies must take into account new radiation techniques and the response to chemotherapy based on functional imaging. Prospective randomized trials incorporating response-adapted therapy and modern radiation techniques are needed.

**Keywords:** *DLBCL, R-CHOP, radiotherapy, OS, EFS, NHL*

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently occurring subtype of non-Hodgkin lymphoma (NHL), and constitutes 30–40% of all adult NHLs [1,2]. For more than 20 years, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard treatment for these patients. The addition of rituximab (R) [3,4] and a reduction in the cycle interval [5] have improved survival outcomes. Although the majority of patients initially respond to this therapeutic approach, some patients relapse and eventually die from their disease. Outcome variability could reflect either the heterogeneous nature of the disease or the need, in the R era, for new prognostic factors that are able to discriminate patients with high-risk disease who need alternative chemotherapy or supplemental treatment such as radiation therapy (RT).

The issue of whether the administration of RT after chemotherapy is beneficial to patients with DLBCL remains unresolved. Therefore, the aim of this study was to determine whether RT was of benefit in our set of patients.

## Patients and methods

Our study is a retrospective analysis of patients with DLBCL. Cases were retrieved from the Gruppo

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**There is an accompanying commentary that discusses this paper. Please refer to the issue Table of Contents.**

ISSN 1042-8194 print/ISSN 1029-2403 online © 2011 Informa UK, Ltd.
DOI: 10.3109/10428194.2011.585526

Italiano Studio Linfomi (GISL) archive. Patients were included in this study if they fulfilled the following criteria: histologically confirmed diagnosis of CD20+ DLBCL, which was previously untreated; age >18 years; no primary central nervous system involvement; no human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection; no severe coincident illnesses; and data on their clinical and laboratory characteristics, treatments, outcome, and follow-up were available. Patients included in this study were enrolled in two GISL clinical trials [6,7] (Anzinter3, ClinicalTrials.gov Identifier NCT01148446, and LA05, ClinicalTrials.gov Identifier NCT00866203) that complied with the requirements of the Declaration of Helsinki and its amendments and were conducted in accordance with Good Clinical Practice guidelines, including the acquisition of written informed consent. All patients were treated with six cycles of R-CHOP with or without involved-field radiotherapy (IFRT) at GISL sites. All patients included in these trials completed six cycles of chemotherapy. At the completion of chemotherapy, consolidative or adjuvant IFRT was allowed, at the treating physician's discretion, in patients who had obtained complete (CR) or partial (PR) remission, because the trial protocols did not specify how RT was to be used. It is assumed that IFRT was more likely to be given to patients with previously bulky disease, disease with extranodal involvement, and disease that failed to achieve CR upon chemotherapy. Final approval of the present retrospective study was obtained from the GISL review board. A total of 216 patients with a median follow-up of 30 months (range, 1–81 months) who were treated between 2003 and 2007 met the eligibility criteria.

### *Statistical methods*

Clinical parameters were registered prospectively at the time of each patient's entry into the clinical trial. Differences in baseline characteristics between patients treated with IFRT and those left untreated were evaluated using Fisher's exact test for variables in categorized form or Mann–Whitney *U*-test for age. Length of event-free survival (EFS) was defined as the time from the end of chemotherapy to the last follow-up or to one of the following events: progression, relapse, or death from any cause. OS was defined from the date of the end of chemotherapy to the date of the last observation or death from any cause. The survival function was estimated using the Kaplan–Meier method [8]. Comparisons between survival curves were checked with Cox proportional hazards (PH) regression [9], using both univariate and multivariate analysis, and the estimated effects were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). The proportional hazards assumption was checked by means of graphical analysis of Schoenfeld residuals [10]. For this study we did not plan a sample size, and in all analyses the *p*-values were two-sided. The International Prognostic Index (IPI) [11] was calculated for 172 (95%) of the 182 patients who were the target cohort of the study.

## Results

A total of 216 patients with a median follow-up of 30 months (range, 1–81 months) were enrolled in the two GISL protocols between 2003 and 2007. Thirty-four patients (16%) received <6 cycles of R-CHOP or obtained less than a PR and were excluded from the study. The remaining 182 patients, of whom 153 (84%) and 29 (16%) obtained CR or PR, respectively, were the target cohort of our study.

The clinical characteristics of these 182 patients were as follows: median age, 69 years; 51% male; 65% stage III–IV; 5% performance status (PS) >1; 73% IPI >1; bulky disease, 26%. Comparisons between the characteristics of patients who received IFRT and those who did not showed that younger patients, patients with bulky disease, and patients with stage I–II disease received IFRT more frequently; these differences were statistically significant (Table I).

After chemotherapy, 40 of 182 patients (22%) who achieved CR or PR were treated with consolidative (31 patients) or adjuvant (nine patients) IFRT. IFRT was delivered to 21 of 63 (33%) patients with stage I–II disease and 19 of 119 (16%) patients with stage III–IV disease. In 50% of patients, the sites of IFRT were supradiaphragmatic (28% mediastinal), and in 30% they were subdiaphragmatic. Extranodal sites were irradiated in 20% of patients. The median dose delivered was 34 Gy (range, 20–40 Gy) (Table II). We do not have information about the criteria used by physicians when deciding to use IFRT. Comparison between the survival outcome of the 40 patients who obtained CR or PR and were treated with consolidative or adjuvant IFRT and the outcome of the 142 non-irradiated patients showed a 5-year overall survival (OS) of 86% (95% confidence interval [CI] 66–95%) and 74% (95% CI 65–81%), respectively (HR = 0.44; 95% CI 0.15–1.24, $p = 0.118$), and an EFS of 85% (95% CI 67–94%) and 56% (95% CI 42–68%), respectively (HR = 0.34; 95% CI 0.13–0.85, $p = 0.021$) (Figure 1). When the 31 of 153 patients who obtained CR and were treated with consolidative IFRT were considered, comparison with the 122 non-irradiated patients showed a 5-year OS of 91% (95% CI 68–98%) and 79% (95% CI 69–86%), respectively

Table I. Important characteristics of 182 patients who obtained CR/PR after six cycles of R-CHOP.

| Variable | RT no, *n* (%) | RT yes, *n* (%) | Total, *n* (%) | *p*-Value‡ |
|---|---|---|---|---|
| Median age, years (IQR) | 69 (64–74) | 69 (48–74) | 69 (62–74) | 0.265 |
| Age | | | | |
| ≤60 years | 24 (17) | 17 (42) | 41 (22) | 0.001 |
| >60 years | 118 (83) | 23 (58) | 141 (78) | |
| Gender | | | | |
| Male | 72 (51) | 20 (50) | 92 (51) | >0.50 |
| Female | 70 (49) | 20 (50) | 90 (49) | |
| AA stage | | | | |
| I–II | 42 (30) | 21 (52) | 63 (35) | 0.009 |
| III–IV | 100 (70) | 19 (48) | 119 (65) | |
| PS | | | | |
| 0–1 | 136 (96) | 37 (92) | 173 (95) | 0.414 |
| >1 | 6 (4) | 3 (8) | 9 (5) | |
| LDH* | | | | |
| ≤UNL | 68 (50) | 18 (50) | 86 (50) | >0.50 |
| >UNL | 68 (50) | 18 (50) | 86 (50) | |
| IPI* | | | | |
| 0–1 | 32 (24) | 14 (39) | 46 (27) | 0.086 |
| 2 | 41 (30) | 12 (33) | 53 (31) | |
| 3–5 | 63 (46) | 10 (28) | 73 (42) | |
| Bulky† | | | | |
| No | 116 (82) | 19 (48) | 135 (74) | <0.001 |
| Yes | 26 (18) | 21 (52) | 47 (26) | |

*LDH and IPI values were missing in 10 cases out of 182.
†Bulky disease: mediastinal bulk diameter >6 cm or other nodal sites diameter >10 cm.
‡Fisher's exact test (age in continuous form by means of Mann–Whitney test).
CR, complete remission; PR, partial remission; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; IFRT, involved-field radiotherapy; IQR, interquartile range (25° to 75°); AA stage, Ann Arbor staging; PS, performance status; LDH, lactate dehydrogenase; UNL, upper normal limit; IPI, international prognostic index.

Table II. Sites irradiated with IFRT* in 40 patients.

| Site | Response after six R-CHOP | |
|---|---|---|
| | CR (*n* = 31) | PR (*n* = 9) |
| Supradiaphragmatic | | |
| Mediastinal mass | 8 | 3 |
| Lateral cervical node | 4 | 2 |
| Supraclavicular node | 1 | 1 |
| Oropharynx | 1 | – |
| Total | 14 | 6 |
| Subdiaphragmatic | | |
| Mesenteric node | – | 1 |
| Celiac node | 1 | – |
| Para-renal right | 1 | – |
| Inguinal nodes | 4 | 1 |
| Lumbo-aortic region | 3 | – |
| Lumbo-sacral region | – | 1 |
| Total | 9 | 3 |
| Extranodal | | |
| Frontal temporal right | 1 | – |
| Face | 1 | – |
| Breast | 2 | – |
| Skin | 3 | – |
| Femoral lesion left | 1 | – |
| Total | 8 | |

*Consolidative or adjuvant IFRT was delivered in 31 and nine patients, respectively. Median dose IFRT delivered was 34 Gy (range, 20–40 Gy).
IFRT, involved-field radiotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. CR, complete remission; PR, partial remission.

(HR = 0.34; 95% CI 0.08–1.43, $p = 0.141$), and an EFS of 88% (95% CI 67–96%) and 59% (95% CI 43–72%), respectively (HR = 0.28; 95% CI 0.10–0.91, $p = 0.035$) (Figure 2).

Univariate analysis showed that a poorer EFS was associated with increasing age, Ann Arbor (AA) stage III–IV, PS >1, and LDH >UNL (upper normal limit), whereas a reduction of risk was associated with IFRT treatment. We observed the same results for both cohorts (182 patients with CR/PR and 153 patients with CR after chemotherapy) under examination. In multivariate analysis, IFRT had a favorable effect for both the 182 patients with CR/PR (HR 0.33; 95% CI 0.11–0.97, $p = 0.044$) and the 153 patients with CR (HR 0.24; 95% CI 0.06–0.92, $p = 0.037$). In addition to IFRT, increasing age and stage III–IV remained the principal variables associated with EFS. The results of uni- and multivariate analyses for EFS are reported in Table III. The effect of IFRT on OS in the 182 patients with CR/PR after chemotherapy adjusted for age, AA stage, LDH >UNL, and PS >1 remained almost unchanged (HR = 0.39; 95% CI 0.13–1.17, $p = 0.096$), whereas OS tended to increase in the 153 patients with CR after chemotherapy (HR = 0.23; 95% CI 0.05–1.03, $p = 0.054$). However, the upper bound of the 95% CI for the HR was not less than one.

## Discussion

Whether the administration of RT after chemotherapy is of benefit in patients with DLBCL has not been completely resolved, in part due to conflicting results from several trials. Recognizing the lack of definitive evidence, the National Comprehensive Cancer Network (NCCN) guidelines recommend three cycles of R-CHOP plus IFRT for early-stage, non-bulky disease, but also allow the administration of 6–8 cycles of R-CHOP with or without IFRT.

Four randomized trials have evaluated the effect of RT following chemotherapy in patients with DLBCL [12–15], although these studies focused on patients with early-stage disease. The results of the Southwest Oncology Group (SWOG) 8736 trial [12] showed that adding RT to a short regimen of only three

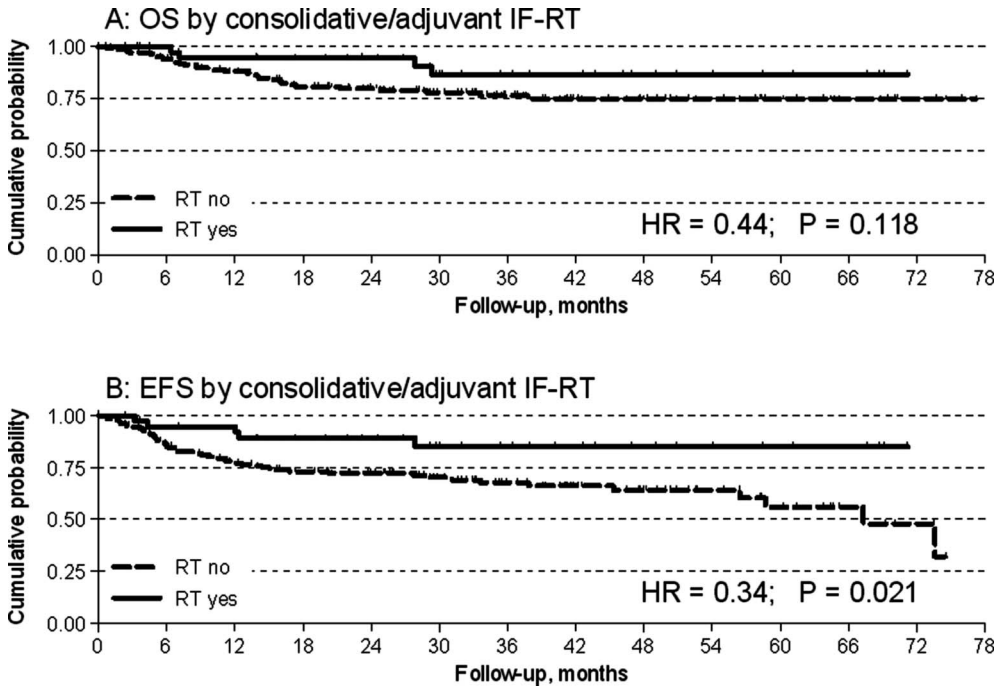


Figure 1. Comparison of (A) overall survival (OS) and (B) event-free survival (EFS) of patients who achieved complete or partial remission after chemotherapy and consolidative or adjuvant IFRT. Solid line: received involved-field radiotherapy (IFRT); dashed line: received no IFRT.



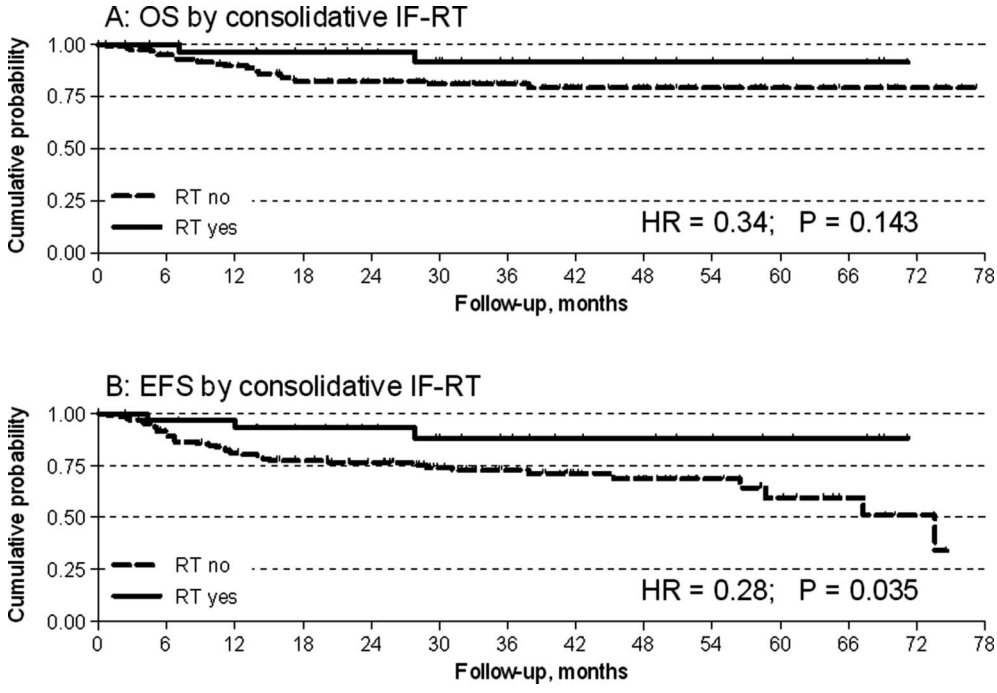


Figure 2. Comparison of (A) overall survival (OS) and (B) event-free survival (EFS) of patients who achieved complete remission after chemotherapy and consolidative IFRT. Solid line: received involved-field radiotherapy (IFRT); dashed line: received no IFRT.

cycles of CHOP reduced chemotherapy-related toxicity while maintaining the same efficacy as eight cycles of CHOP. However, a 2001 update [16] showed an excess of lymphoma relapses in the group receiving RT with fewer rounds of chemotherapy. A GELA (Groupe d'Etudes des Lymphomes de l'Adulte) trial in patients older than 60 years showed no advantage for the arm treated with four cycles of

Table III. Univariate and multivariate analysis of event-free survival (EFS) for 182 and 153 patients who obtained CR/PR or CR, respectively, after six R-CHOP cycles.

| | CR/PR ($n = 182$) | | CR ($n = 153$) | |
|---|---|---|---|---|
| Variable | Univariate, HR (95% CI) | Multivariate, HR (95% CI) | Univariate, HR (95% CI) | Multivariate, HR (95% CI) |
| Age*, years | 1.64 (1.15–2.34) | 2.36 (1.39–4.05) | 2.04 (1.26–3.32) | 3.00 (1.56–5.78) |
| Gender, F | 0.84 (0.49–1.45) | | 1.04 (0.55–1.96) | |
| AA stage, III–IV | 3.52 (1.70–7.28) | 3.14 (1.40–7.10) | 3.71 (1.62–8.49) | 3.56 (1.48–8.60) |
| PS, >1 | 3.86 (1.52–9.79) | 2.96 (0.98–8.84) | 4.57 (1.09–19.2) | 5.48 (1.06–28.2) |
| LDH†, >UNL | 2.14 (1.21–3.80) | 1.77 (0.95–3.31) | 2.22 (1.15–4.27) | 1.84 (0.93–3.64) |
| Bulky‡, yes | 0.83 (0.44–1.59) | | 0.80 (0.36–1.74) | |
| IFRT, yes | 0.34 (0.13–0.85) | 0.33 (0.11–0.97) | 0.28 (0.10–0.91) | 0.24 (0.06–0.92) |

*Age in continuous form divided by 10.
†LDH and IPI values were missing in 10 cases out of 182.
‡Bulky disease: mediastinal bulk diameter >6 cm or other nodal sites diameter >10 cm.
EFS, event-free survival; CR, complete remission; PR, partial remission; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; AA stage, Ann Arbor staging; PS, performance status; LDH, lactate dehydrogenase; UNL, upper normal limit; IFRT, involved-field radiotherapy; HR, hazard ratio; 95% CI, 95% confidence interval.



CHOP plus RT compared with the group who received only four cycles of CHOP [15]. A retrospective study of 168 patients with localized DLBCL [17] suggested that other anthracycline-containing regimens plus IFRT could produce excellent results, in terms of efficacy or safety, in early-stage disease. Avilés *et al.* [18] examined patients with stage III–IV and bulky disease and showed a clear survival benefit for patients who received RT on residual masses after CHOP. However, it is unclear whether the RT delivered should be considered adjuvant or consolidative. All these trials were done before R and positron emission tomography (PET) were available. Because R is very active against DLCBL, and PET is a useful prognostic tool for evaluating response, it could be argued that the role of IFRT needs to be re-examined in the context of modern disease management. However, this hypothesis has not yet been tested.

The results of the phase II SWOG 0014 trial that integrated R into three cycles of CHOP plus IFRT [19] in the treatment of limited-stage DLBCL are encouraging, but a longer follow-up period is needed. The results of a retrospective study recently published by Phan *et al.* [20] suggest a benefit for all patients treated with IFRT, even in the R era. Outcome improvement was observed in all disease stages, regardless of the presence of bulky disease.

The present retrospective study showed that IFRT delivered after six cycles of R-CHOP was associated with improved EFS. Indeed, for patients treated with IFRT we observed an approximately 70% reduction in the risk of events. Furthermore, the survival benefit of IFRT after R-CHOP in EFS was also maintained after adjustment for age, LDH level, and AA stage in Cox proportional hazards analysis, whereas the effect of IFRT on OS was moderate and not statistically significant. Unfortunately, because the number of patients treated with IFRT was low, we could not stratify them by the presence of bulky disease or disease stage. In our group of patients, we collected information regarding the site of irradiation. However, the criteria used by physicians to decide whether to use IFRT remain unclear, because of the retrospective nature of the study. Finally, we believe that our results strongly support the hypothesis that IFRT has a clinically useful role, even in the R era.

In conclusion, the role of RT in the treatment of DLBCL, at either early or advanced stages, is still unclear. The introduction of new treatments and technologies must be taken into account to define the value of RT. Only a program of prospective randomized clinical trials can produce high-quality data and address questions about which patients with DLBCL are most likely to benefit from IFRT.

## Acknowledgements

This study was supported in part by the Associazione Angela Serra per la Ricerca sul Cancro, Modena, Italy.

***Potential conflict of interest:*** Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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