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Scientific Article

# Are Higher Doses of Consolidation Radiation Therapy Necessary in Diffuse Large B-cell Lymphoma Involving Osseous Sites?

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**Abstract**

**Purpose:** This study aimed to evaluate whether higher doses of consolidation radiation therapy (RT), which have been traditionally recommended for osseous sites in diffuse large B-cell lymphoma (DLBCL), are still necessary.

**Methods and materials:** Patients with DLBCL with osseous involvement treated with first-line chemotherapy followed by consolidation RT between 1995 and 2016 were reviewed. The primary endpoint was 5-year freedom from local recurrence, estimated using the Kaplan-Meier method. Outcomes based on the RT dose received were also assessed.

**Results:** A total of 51 patients were identified. The most common chemotherapy regimens were rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (80%) and cyclophosphamide, doxorubicin, vincristine, and prednisone (12%) with a median of 6 cycles (range, 3-8 cycles). After chemotherapy, 82% of patients achieved a complete response (CR), and 18% achieved a partial response (PR). All patients in PR were deemed appropriate for consolidation RT. The median dose was 29 Gy (24 Gy for CR; 36 Gy for PR). After a median follow-up of 86 months, 8 patients relapsed, with 2 relapses in the RT field after consolidation RT of 30 and 39.6 Gy, respectively. Overall, the 5-year freedom from local recurrence was 96% (95% confidence interval [CI], 91%-100%), disease-free survival was 76% (95% CI, 65%-89%), and overall survival was 86% (95% CI, 76%-96%). No dose-response relationship was observed.

**Conclusions:** In patients with DLBCL with osseous involvement who achieved a CR after first-line chemotherapy, 20 to 30 Gy of consolidation RT led to high rates of local control. Higher doses should be reserved for patients in PR.



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## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma.[1] Approximately 30% to 60% of patients present with extranodal disease. Approximately 2% to 7% present with osseous involvement.[2,3] The standard of care for DLBCL is chemoimmunotherapy, followed by response evaluation with functional imaging and consideration of consolidation radiation therapy (RT), particularly for early stage disease. Studies have suggested that consolidation RT may be especially important in the setting of osseous involvement.[4,5]

For patients with a complete response (CR) to chemoimmunotherapy, the recommended dose of consolidation RT is 30 to 36 Gy per the National Comprehensive Cancer Network guidelines.[6] After a partial response (PR), higher doses of 40 to 50 Gy are recommended. Historically, higher doses of consolidation RT have also been used in the setting of osseous involvement, in part because of early series reporting improved rates of local control with higher doses as well as the challenges of assessing radiographic response in bone.[7-10] A recent study of consolidation RT for primary bone DLBCL from MD Anderson reported a median dose of 44 Gy.[4]

In the current era of improved systemic therapy and diagnostic imaging modalities such as positron emission tomography (PET)-computed tomography (CT) to assess response, these higher doses of RT may be unnecessary. Furthermore, long-term risks of treatment are an important consideration in DLBCL because most patients are ultimately cured of their disease. Lower doses are expected to be associated with lower risks of acute and long-term toxicity and lower financial costs.

Our institution has consistently used doses of 20 to 30 Gy for consolidation RT in patients with DLBCL who achieved CR, including sites of osseous involvement. Herein, we report the results of this experience.

## Methods and Materials

We identified all patients with DLBCL, not otherwise specified, with osseous involvement who received first-line systemic therapy and consolidation RT between 1995 and 2016 at Duke University. Patients with disease refractory to systemic therapy were not considered appropriate candidates for consolidation RT and were excluded. This study was approved by the institutional review board.

Between 1995 and 2016, 252 patients received chemotherapy followed by consolidation RT for DLBCL. Of these patients, 51 had osseous involvement and were included in the present analysis. The baseline patient characteristics are shown in Table 1.

Patients were staged using PET-CT, gallium, or CT. A total of 16 patients (31%) had stage I disease, 15 patients (29%) had stage II disease, and 20 patients (39%) had stage IV disease. Overall, 35 patients (69%) had a single site of osseous involvement. Of the remaining patients, 7 (14%) had 2 osseous sites, 4 (8%) had 3 to 4 sites, and 5 (10%) had ≥5 sites. Among osseous sites only, the

**Table 1** Patient demographic and clinical characteristics

| Characteristic | n (%) |
|---|---|
| Median age, y | 58 |
| Sex | |
| Male | 24 (47) |
| Female | 27 (53) |
| Age, y | |
| ≤60 | 31 (61) |
| >60 | 20 (39) |
| Stage | |
| I-II | 31 (61) |
| IV | 20 (39) |
| International Prognostic Index score | |
| 0-1 | 28 (55) |
| 2-3 | 20 (39) |
| 4-5 | 3 (6) |
| No. of osseous sites | |
| 1 | 35 (69) |
| >1 | 16 (31) |
| Maximum diameter of any site | |
| <7.5 cm | 29 (57) |
| ≥7.5 cm | 22 (43) |
| No. of chemotherapy cycles | |
| <6 | 11 (22) |
| ≥6 | 40 (78) |
| Type of chemotherapy | |
| R-CHOP | 41 (80) |
| Other | 10 (20) |
| Rituximab | |
| Yes | 44 (86) |
| No | 7 (14) |
| Response to chemotherapy | |
| Complete response | 42 (82) |
| Partial response | 9 (18) |
| Response assessment | |
| PET-CT | 47 (92) |
| Gallium | 5 (10) |
| CT | 1 (2) |
| Radiation dose | |
| 19.8-24 Gy | 25 (49) |
| 25-31 Gy | 15 (29) |
| 32-40 Gy | 11 (22) |
| Radiation sites | |
| All bony sites | 46 (90) |
| Select bony sites | 5 (10) |
| Radiation technique | |
| 2D | 20 (39) |
| 3D | 23 (45) |
| IMRT | 8 (16) |

*Abbreviations:* 2D = 2-dimensional; 3D = 3-dimensional; CT = computed tomography; IMRT = intensity modulated radiation therapy; PET = positron emission tomography; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

median size was 5 cm (range, 1-39 cm). When considering all DLBCL sites, the median size was 6 cm (range, 1-39 cm); bulky disease (≥7.5 cm) was present in 22 patients (43%).

Treatment decisions were made at the discretion of the patient's medical and radiation oncologists. The most common chemotherapy regimens were rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n = 41; 80%) and CHOP (n = 6; 12%). The other 4 patients received R with mitoxantrone replacing doxorubicin (CNOP), R-bendamustine, or CNOP. The majority of patients received rituximab (n = 44; 86%). The median number of chemotherapy cycles was 6 (range, 3-8 cycles). Response to chemotherapy was based on metabolic imaging in nearly all patients (n = 50; 98%), with 47 (92%) evaluated with PET-CT and 3 (6%) evaluated with gallium. One patient had a CT-based response evaluation only. CR was defined as resolution of 18F-fluorodeoxyglucose (FDG) avidity on metabolic imaging, and PR was defined as residual FDG avidity that was reduced compared with baseline. The Deauville criteria were not formally used during this time frame.

CR was achieved in 42 patients (82%) and PR in the remaining 9 patients (18%). Of these 9 patients, 3 had persistent FDG avidity at the involved nodal sites but had achieved CR at osseous sites. The remaining 6 patients had residual FDG avidity at osseous sites. All patients in PR were thought to have responded to chemotherapy and were considered appropriate candidates for consolidation RT.

For consolidation RT dose, the standard approach at our institution has been to treat patients with stage I or II disease in CR to 30 Gy. Patients with stage III or IV disease typically receive 20 Gy to minimize toxicity.[11] Patients in PR receive approximately 40 Gy. Between 2010 and 2016, a separate phase 2 trial was initiated at our institution to evaluate 20 Gy of consolidation RT for patients with all stages of DLBCL in CR.[12] Twelve of these trial patients had osseous involvement and were included in the present analysis.

After chemotherapy, 41 patients (80%) received consolidation RT to all sites of involvement. The remaining 10 patients (20%), all with stage IV disease, received consolidation RT to select osseous sites only. The dose per fraction was 1.8 to 2 Gy in 50 patients (98%) and 3 Gy in 1 patient (2%). The median total dose was 29 Gy (range, 19.8-40 Gy). The dose distributions were as follows: 25 (49%) received 19.8 to 24 Gy, 15 (29%) received 25 to 31 Gy, and 11 (22%) received 32 to 40 Gy. Patients with stage I or II disease received a median dose of 30 Gy, and patients with stage IV disease received a median dose of 20 Gy. Patients in CR received a median dose of 24 Gy, and patients in PR received a median dose of 36 Gy. The radiation technique was 2-dimensional in 20 patients (39%), 3-dimensional in 23 (45%), and intensity modulated RT in 8 (16%).

## Statistics

The primary endpoint was freedom from local recurrence (FFLR). The secondary endpoints were disease-free survival (DFS) and overall survival (OS). We use the term DFS rather than progression-free survival because the latter typically includes all patients at the start of any therapy and thus would include patients who fail to respond to induction systemic therapy. FFLR was defined from the date of pathologic diagnosis to the date of in-field recurrence. DFS was defined from the date of pathologic diagnosis to the date of any recurrence or death. OS was defined from the date of pathologic diagnosis to the date of death. Patients were censored at the date of last follow-up. Time-to-event analyses were calculated with the Kaplan-Meier method. Statistical analysis was done with R, version 3.5.0 (The R Foundation, Vienna, Austria).

## Results

With a median follow-up of 86 months (range, 10-249 months), 8 patients relapsed, with 2 patients relapsing within the RT field and at distant sites and 6 patients relapsing at distant sites only. Of these 8 patients, 5 patients had stage I or II disease and 3 patients had stage IV disease at diagnosis. Six patients had achieved a CR and 2 patients had achieved a PR to systemic therapy. Overall, the median time to relapse was 18 months (range, 8-41 months).

With regard to the 2 patients who relapsed within the RT field, 1 patient had stage II disease with a 10 cm mass centered in the left iliac bone with soft tissue extension and retroperitoneal lymphadenopathy. A very good PR was achieved after 6 cycles of R-CHOP with resolution of the retroperitoneal lymphadenopathy and soft-tissue component of the pelvic mass, but several small foci of increased FDG uptake remained within the mottled iliac bone. The patient then received 39.6 Gy to all involved sites. The patient relapsed 9 months after completing RT within the left iliac bone and at sites not originally involved and ultimately died of lymphoma. The second patient had stage IV disease, including an obstructing soft-tissue mass in the left chest, a bulky mass involving T6-T10 with soft-tissue extension, and numerous other foci of osseous disease. The patient developed dyspnea after 2 cycles of R-CHOP and received 12 Gy to the thorax with rapid symptomatic improvement and ultimately achieved a CR after 6 cycles of R-CHOP. The patient then received an additional 18 Gy to the thorax (total dose, 30 Gy) and 20 Gy to other sites. The patient relapsed 1 year later in the mediastinum where she had received 30 Gy. There was no evidence of disease progression at osseous sites that had received 20 to 30 Gy.

Of the 6 patients who relapsed only at distant sites, 3 patients died of disease. The remaining 3 patients all

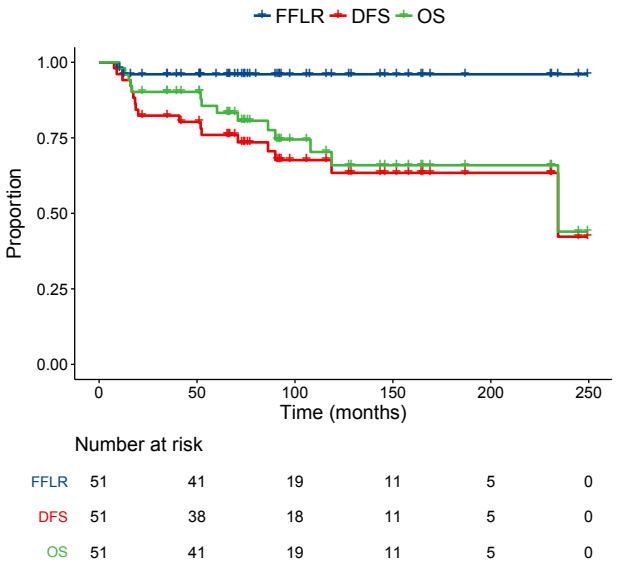


**Figure 1** Kaplan-Meier estimates of freedom from local recurrence (FFLR; blue), disease-free survival (DFS; red), and overall survival (OS; green) across all patients, calculated from the date of the pathologic diagnosis.

received salvage chemoimmunotherapy and autologous hematopoietic stem cell transplantation and were alive without evidence of disease at the time of last follow-up.

Overall, the 5-year FFLR was 96% (95% confidence interval [CI], 91%-100%), DFS was 76% (95% CI, 65%-89%), and OS was 86% (95% CI, 76%-96%; Fig 1). In patients with stage I or II disease, the 5-year FFLR was 97% (95% CI, 91%-100%), DFS was 77% (95% CI, 63%-94%), and OS was 90% (95% CI, 79%-100%). In patients with stage IV disease, the 5-year FFLR was 95% (95% CI, 85%-100%), DFS was 75% (95% CI, 58%-97%), and OS was 80% (95% CI, 64%-100%). Patients with nonbulky disease had a 5-year FFLR of 100% (95% CI, 100%-100%), DFS of 75% (95% CI, 61%-93%), and OS of 85% (95% CI, 73%-100%). Patients with bulky disease had a 5-year FFLR of 91% (95% CI, 79%-100%), DFS of 77% (95% CI, 62%-97%), and OS of 86% (95% CI, 73%-100%). The number of patients in each subgroup was small; thus, the differences in endpoints were not statistically significant between patients with stage I/II versus stage IV disease, nonbulky versus bulky presentations, or CR versus PR to chemotherapy.

Overall, 14 patients died. The cause of death was relapsed DLBCL in 5 patients, second cancers in 4 patients, treatment-related toxicity (pancytopenia and infection) in 1 patient, a late infection in 1 patient (6 years after treatment), stroke in 1 patient, and unknown in 2 patients.

Long-term toxicities of chemoimmunotherapy and radiation included second neoplasms, hypothyroidism, dental complications, and cardiovascular disease. A second neoplasm developed in 7 patients (14%; Table 2). Only 1 patient developed a second solid tumor inside the RT field, a perirectal paraganglioma within a previously irradiated pelvis. Two patients developed myelodysplastic syndromes after receiving an alkylating agent and RT. Three patients developed hypothyroidism after treatment, but none of these patients had RT within the head and neck region. Two patients who did receive RT to the head and neck developed dental complications. One of these patients had received 4 cycles of R-CNOP followed by 30 Gy to the nasopharynx, and required hyperbaric oxygen for osteoradionecrosis. The patient later also developed nonischemic cardiomyopathy that was attributed to chemotherapy toxicity.

## Discussion

Historically, doses of ≥45 Gy were used when RT alone was used for the treatment of localized DLBCL based on the observation that DLBCL appeared to be more radioresistant than other subtypes of lymphoma. Several studies suggested that such doses were particularly important in the presence of osseous disease.[7-10] Lower doses of RT are now used in combined modality treatment programs, but the tradition of using higher doses in the setting of osseous disease persists. For example, a recent retrospective series of 102 patients with primary bone DLBCL examined the outcome of 67 patients who received consolidation RT versus 35 patients who did not.[4] The median RT dose was 44 Gy. Survival outcomes were improved in those who received RT compared with those who did not, with 5-year DFS at 88% versus 63% and 5-year OS at 91% versus 68%, respectively. With respect to dose response, no differences in local control were observed between patients who received 30 to 35 Gy versus ≥36 Gy, and no in-field failures were observed. However, only 3 patients received a dose <30 Gy.

The German High Grade Non-Hodgkin's Lymphoma Study Group examined patients with DLBCL with osseous involvement of all stages from 9 prospective randomized trials of that group.[5] Of the 161 patients with a CR or PR to systemic therapy, 133 received consolidation RT in a nonrandomized fashion. The median radiation dose was 36 Gy with a range of 30 to 47.5 Gy. DFS was improved in those who received RT compared with those who did not, with 3-year DFS at 75% versus 36%, respectively. A trend toward improved OS was also observed, with 3-year OS at 86% versus 71%, respectively.

Good prospective randomized RT dose-response data for lymphoma have recently been published by the British National Lymphoma Investigation.[13] For aggressive-histology lymphoma, principally DLBCL, 30 Gy was compared with 40 to 45 Gy in 640 patients. Virtually identical outcomes were seen for local control, progression-free survival, and OS. The great majority of patients received systemic therapy as well, although

**Table 2** Secondary malignancies after first-line combined modality therapy

| Initial treatment | Secondmalignancy | In-field RT? | Interval between and second malignancy | Outcome |
|---|---|---|---|---|
| R-CHOP × 6, 40 Gy | HCC | No | 5 y | Death from HCC |
| R-CNOP × 6, 19.8 Gy | NSCLC | No | 3.5 y | Death from NSCLC |
| R-CHOP × 6, 30.6 Gy | Squamous cell cancer of the right leg | No | 8 y | Mohs surgery, NED |
| R-CHOP × 6, 20 Gy | Squamous cell cancer of the oral tongue | No | 4 y | Partial glossectomy, NED |
| R-CNOP × 4, 30 Gy | MDS with conversion to AML | NA | 4 y | Death from MDS/AML |
| R-CHOP × 4, 30 Gy | MDS | NA | 0.5 y | Death from MDS |
| CHOP × 6, 30 Gy | Paraganglioma of left carotid body and rectum | Yes | 13 y | Resection and post-operative RT, NED |

*Abbreviations:* AML = acute myeloid leukemia; HCC = hepatocellular carcinoma; MDS = myelodysplastic syndrome; NA = not assessable; NED = no evidence of disease; NSCLC = non-small cell lung cancer; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT = radiation therapy.

usually not including rituximab, so this trial was really an investigation of dose response in the setting of consolidation RT after systemic therapy. Of interest, however, no differences were observed in the small subset of patients who did not receive systemic therapy. This study did not comment on bulky disease or site of disease (eg, osseous disease) and their relationships to outcome, if any.

At our institution, we have long had a policy of using RT consolidation doses of 30 Gy for localized disease and 20 Gy for advanced disease, assuming a CR to systemic therapy, based on our own experience and data from British Columbia.[14] A recent protocol has lowered the dose even further for localized disease to 20 Gy.[12] The choice of 20 Gy for advanced disease warrants further explanation. First, our objective with advanced disease is to consolidate all areas of disease detected before the onset of chemotherapy, if feasible. Higher doses will increase the difficulty of accomplishing this. Second, with generalized disease, a successful outcome is much more dependent on the effectiveness of systemic therapy and less so on the consolidation RT. Third, patients typically receive 6 cycles of chemotherapy. In essence, we assume a greater cell kill from the systemic therapy and hence need a lesser dose of RT.

This current study supports the hypothesis that lower doses of RT achieve excellent local control after effective systemic therapy, even in patients with osseous involvement. Of the 51 study patients, there were only 2 in-field failures (only 1 of which involved an osseous site), for a 5-year actuarial local control of 96%. With a range of doses from 19.8 to 40 Gy, and 1 failure after 30 Gy and the other after 39.6 Gy, no dose response could be demonstrated. Furthermore, there was no obvious difference between the 42 patients in CR and the 9 patients in PR, with 1 failure in each group, but patients in PR tended to receive higher doses of RT. Interpretation of our data is limited by the relatively small numbers of patients in the study, which is expected given the low incidence of osseous DLBCL.

Recent guidelines from the International Lymphoma Radiation Oncology Group recommend a dose range of 30 to 40 Gy depending on the certainty that a CR has been achieved by metabolic imaging.[15,16] Thus, if a CR is achieved, a dose of 30 Gy would be deemed appropriate.

## Conclusions

This study supports the use of relatively modest doses of consolidation RT for osseous DLBCL. Specifically, we advocate 30 Gy in the setting of localized disease and 20 Gy in advanced disease, similar to doses used for other sites, after CR to chemoimmunotherapy by metabolic imaging. Even lower doses of RT may be appropriate for localized disease, which is an area of active investigation at our center and elsewhere.

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